

STATE OF NORTH CAROLINA
DEPARTMENT OF ENVIRONMENT AND NATURAL RESOURCES
DIVISION OF AIR QUALITY

REPORT OF PROCEEDINGS OF PUBLIC HEARING
ON PROPOSED AMENDMENTS TO
15A NCAC 02D .1104, TOXIC AIR POLLUTANT GUIDELINES, AND
15A NCAC 02Q .0711, EMISSION RATES REQUIRING A PERMIT

MAY 14, 2013
RALEIGH, NC

ENVIRONMENTAL MANAGEMENT COMMISSION

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CHAPTER I

Summaries and Recommendations

Proposed amendment to 15A NCAC 02D .1104, and 02Q .0711.

BACKGROUND AND SUMMARY

A public hearing was held in Raleigh, NC on May 14, 2013, to take public comments on amendments to the state air toxics rules to revise the health-based acceptable ambient level in 15A NCAC 02D .1104 and associated emission rate requiring a permit and 02Q .0711 for arsenic and inorganic arsenic compounds. Mr. Christopher Ayers and Mr. Donnie Redmond were appointed as the hearing officers for this hearing. After Mr. Ayers recused himself at the start of the hearing as a result of a potential conflict of interest, Mr. Redmond acted as the sole hearing officer.

North Carolina's health risk-based air toxics rules provide for local scale evaluation of the maximum impact of air toxic emissions from a facility at or beyond its property boundary through site-specific emissions estimates and modeling. Under the air toxics rules with the statutory exceptions enacted by S.L. 2012-91, a facility must demonstrate through modeling that predicted concentrations at or beyond the property boundary are below acceptable ambient levels (AALs) for the affected toxic air pollutants (TAPs) as defined in the Toxic Air Pollutant Guidelines. The emission rates requiring a permit, also referred to as "toxics permitting emission rates" (TPERs), are screening levels to which facility-wide TAP emissions levels are compared to determine whether further dispersion modeling analysis is necessary. The TPER is a conservatively set threshold below which, even under the worst case air pollutant dispersion conditions, impacts at the property boundary would not be expected to approach the health based AALs.

The Division of Air Quality (DAQ) identified the need for a re-evaluation of the values for arsenic and arsenic-containing inorganic compounds (AsC) in 15A NCAC 02D .1104, Toxic Air Pollutant Guidelines, and in 02Q .0711, Emission Rates Requiring a Permit. In response to a request made by DAQ, the North Carolina Science Advisory Board (NCSAB) has reassessed AsC and recommends a change to the AAL for these compounds based on review of the updated toxicological and epidemiological literature. The NCSAB reviews of scientific information are focused on recommending safe exposure concentrations for toxic air pollutants that allow an ample margin of safety for people with potential exposures. Through its public process, the NCSAB chose a lung cancer health endpoint based on human health studies of arsenic inhalation exposure as the basis for its recommendation. NCSAB's final recommendations go through the normal rulemaking process, with the Environmental Management Commission (EMC) making the final decision. The EMC accepted the recommendation of the NCSAB to revise the AAL for AsC based upon widely accepted risk assessment methods. The final recommendation from the NCSAB is to increase the AAL for AsC from 2.3×10^{-7} milligram per cubic meter (mg/m^3) to $2.1 \times 10^{-6} \text{ mg}/\text{m}^3$. The TPER must likewise be changed because its value is derived directly from the AAL value. The amendment replaces the current annual TPER for AsC of 0.016 pounds per year with an annual TPER of 0.053 pounds per year.

PUBLIC COMMENTS AND RESPONSES THERETO

Five sets of written comments on the proposed rules were submitted during the comment period after the public hearing. During the public hearing Mr. Bill Lane of Kilpatrick Townsend & Stockton, LLP made oral comments offered in behalf of Jackson Paper Manufacturing Company (Jackson Paper) and Evergreen Packaging Company (Evergreen Packaging). Mr. Lane's oral comments are reflected in the written comments made by Jackson Paper and Evergreen Packaging that are summarized below. In addition,

- North Carolina Manufacturers Alliance submitted comments on behalf of its members,
- Blue Ridge Environmental Defense League submitted comments on behalf of its members, and
- Southern Environmental Law Center submitted written comments on behalf of itself, Clean Air Carolina and Medical Advocates for Healthy Air.

Comment: Preston Howard of the North Carolina Manufacturers Alliance, Tammy Francis of Jackson Paper, and Dane Griswold of Evergreen Packaging commented that each strongly supports the NCSAB recommendation to relax the arsenic AAL. Each also stated the NCSAB relied on a more robust data set than what was available for the original arsenic AAL calculation.

Response: The commenters agree with the amendments proposed by the EMC. No change to the rule.

Comment: Preston Howard of the North Carolina Manufacturers Alliance, Tammy Francis of Jackson Paper, and Dane Griswold of Evergreen Packaging commented that each agrees with the DAQ's economic analysis indicating that revising the arsenic AAL will result in millions of dollars in savings to the regulated industries that would otherwise be incurred to comply with the existing AAL.

Response: The commenters agree with the amendments proposed by the EMC. No change to the rule.

Comment: Tammy Francis of Jackson Paper, and Dane Griswold of Evergreen Packaging commented that they each believe the actual compliance costs will be significantly higher than the estimated cost savings of \$2 million to \$3 million.

Response: The commenters believe that more than a few million dollars will be saved with the amendments proposed by the EMC. No change to the rule.

Comment: Preston Howard of the North Carolina Manufacturers Alliance, Tammy Francis of Jackson Paper, and Dane Griswold of Evergreen Packaging noted that the measured arsenic concentrations across the state being above the existing AAL incorrectly suggests that North Carolina's air is unhealthy, given that the existing AAL is based on an outdated analysis. In addition, the NCSAB report indicated that industrial sources only contribute a small fraction of the ambient arsenic level compared to background levels.

Response: The commenters agree with the amendments proposed by the EMC. No change to the rule.

Comment: Preston Howard of the North Carolina Manufacturers Alliance and Dane Griswold of Evergreen Packaging each indicated that the EMC should proceed with adopting the NCSAB recommendations without delay. Preston Howard stated that the arsenic AAL is outdated and the misperception that arsenic levels in our ambient air are unhealthy needs to be corrected immediately. According to EPA's proposed schedule, they will not complete their review before 2016.

Response: The commenters agree with the amendments proposed by the EMC. No change to the rule.

Comment: Dane Griswold of Evergreen Packaging commented that adoption of the revised arsenic AAL would be consistent with the ongoing reform of the air toxics program that began with Session Law 2012-99. In a separate rulemaking, the DAQ has proposed several amendments to the air toxics rules. As required by the legislation, the DAQ's proposed reforms are intended to reduce the unnecessary regulatory burden on regulated industries, increase the efficient use of the DAQ resources, and maintain protection of public health. The proposed revision to the arsenic AAL easily satisfies these three statutory criteria.

Response: The commenter agrees with the amendments proposed by the EMC. No change to the rule.

Comment: Ms. Terese Vick of the Blue Ridge Environmental Defense League stated that the impetus to change the AsC AAL came from industry's unwillingness to meet the existing AsC AAL and not public health related issues. She also pointed out that the DAQ had reported the median arsenic concentrations measured across the state in 2009 exceeded the arsenic AAL by 3 to 4-fold times. She also noted that several facilities are having difficulty complying with the arsenic AAL.

Response: The impetus for reviewing the existing arsenic AAL of 2.3×10^{-7} mg/m³ was three-fold, including the points raised by the commenter:

1. The arsenic AAL, originally effective and expanded in scope in 1990 to also include arsenic inorganic compounds, is based on a nearly 30-year old health data analysis by the U.S. Environmental Protection Agency (EPA). The arsenic AAL was overdue to be re-evaluated, given that much more health data is available now than at the time of EPA's analysis in 1984 which was the basis for the original AAL.
2. In addition to DAQ data on arsenic concentrations exceeding the arsenic AAL by 3 to 4 times, the EPA National Air Toxics Assessment 2011 report (based on 2005 data) showed that the mean ambient air concentration statewide in North Carolina was nearly two times the arsenic AAL. If the current AAL were accurately established and the mean ambient concentration were two to four times the AAL, then there would be widespread evidence of adverse health effects in North Carolina (and in other industrialized states) from arsenic inhalation exposure. The absence of such evidence warranted investigation of the AAL.

3. Several facilities in North Carolina did show results from dispersion modeling analysis of the maximum impact of arsenic emissions at its property boundary to be above the arsenic AAL. Concurrently, DAQ had observed that the mean statewide ambient arsenic concentration was well above the arsenic AAL. Also EPA was in the process of setting National Emission Standards for Hazardous Air Pollutants (NESHAPs) for these same facilities likely to require multi-million dollar expenditures to comply with multi-pollutant emission standards. Such national standards force all affected facilities to comply and reduce emissions for several (not just one) hazardous air pollutants (HAPs). The combination of these facts posed difficult questions in terms of how to respond to this information:
- Were arsenic emissions from several facilities posing a public health hazard that was going un-noticed by the communities close to these facilities, or was the current arsenic AAL based on 1984 information set too low and outdated?
 - With EPA in the process of setting NESHAPs to control multiple HAPs, would it be prudent to require expensive emission controls for several NC facilities to comply with a state-only rule for one pollutant that may or may not be compatible with and the most cost effective choice for subsequent EPA multi-pollutant standards?
 - Would it be wise to take the time to re-assess the arsenic AAL in order to assure it was set with updated information and in the meantime to let EPA complete its NESHAPs rulemaking process to see what affect they would have on arsenic emissions and control requirements?

After deliberation, the decision taken by DAQ was to recommended that the NCSAB reassess the arsenic AAL while EPA completed its NESHAPs rulemaking process.

Comment: Ms. Terese Vick of the Blue Ridge Environmental Defense League made the following four interrelated comments on the methodology utilized by the NCSAB in developing the arsenic AAL.

- **Comment A.** The methodology used by the NCSAB relied heavily on a model used by only one state in the country, Texas. The NCSAB did not utilize the 1984 EPA model to calculate the arsenic AAL. Instead, a model recommended by Flores and Sielken was used to calculate its arsenic AAL.

Response: The NCSAB did not utilize an Inhalation Unit Risk Factor (IUR) derived by EPA to calculate a revised arsenic AAL. The EPA IUR for arsenic was derived more than 30 years ago from occupational epidemiological data from two US copper smelters (Anaconda in Butte, Montana and Asarco in Tacoma, Washington). The NCSAB is not limited to exclusively relying on data analysis from EPA. The board uses their collective scientific judgment and expertise to identify the most robust and relevant data upon which to base candidate AALs.

- **Comment B.** Only the Anaconda and Asarco epidemiology studies should have been included for the NCSAB's As AAL calculation, which would be consistent with EPA's approach.

Response: The IUR proposed by Texas Commission on Environmental Quality (TCEQ) was based on respiratory and lung cancer mortality in an occupational cohort comprised of the Anaconda and Asarco workers as well as a Swedish cohort. The IUR proposed by TCEQ included enhanced analysis and an additional occupational site as well as updated and more accurate exposure estimates than the 1984 EPA effort. The NCSAB's scientific reviews and assessments are not limited in their scope to what has been done previously.

- **Comment C.** The unit risk factors calculated in the peer-reviewed publication by Viren and Silvers, 1994, should have been considered for the calculation of the AAL for arsenic. It appears that the unit risk factors utilized by the NCSAB were not peer-reviewed and published unit risk factors.

Response: The data used by the NCSAB to recommend updated candidate AALs for arsenic has been recently published as an article in a peer-review journal.¹ The article describes a thorough and comprehensive analysis of the epidemiological data acquired at the three work sites.

- **Comment D.** Lastly, the EPA is currently performing a "Toxicological Review of Inorganic Arsenic". The rule changes before you now may be obsolete in the future.

Response: The EPA has recently embarked on re-evaluating the inhalation toxicity of arsenic and inorganic arsenic compounds. Their draft Integrated Risk Information System (IRIS) assessment is tentatively scheduled for initial publication in 2016. Given the volume of research on the carcinogenicity of arsenic since the original EPA IRIS assessment was published, it is highly unlikely that the new arsenic inhalation unit risk factor will be based on a nearly 30-year old data analysis.

Comment: Myra Blake and John Suttles of the Southern Environmental Law Center commented that the NCSAB failed to consider the impacts of arsenic through ingestion, the primary exposure pathway for arsenic.

Response: NCSAB exposure assessments generally take into account potential inhalation exposures only, although dermal exposure may also be considered. Consideration of exposure due to deposition of airborne compounds onto soil or water may be important for some compounds, and may be considered when available data indicate deposition may lead to significant exposure. Each compound is considered individually, though consideration of mixtures of compounds with similar mechanisms of action may be necessary.

Comment: Myra Blake and John Suttles of the Southern Environmental Law Center commented that the DAQ should not consider increasing the permissible levels of arsenic before EPA completes its study of potential arsenic risks. In order to take advantage of EPA's information gathering process, the DAQ should postpone any revisions to the arsenic AAL until EPA concludes its investigation.

¹ Erraguntla, NK, Sileken RL, Valdez-Flores, C, and Grant, RL, "An updated inhalation unit risk factor for arsenic and inorganic arsenic compounds based on a combined analysis of epidemiology studies." In *Regulatory Toxicology and Pharmacology*, 64:329-341, 2012. <http://www.ncbi.nlm.nih.gov/pubmed/22813725>.

Response: As mentioned above, EPA is re-evaluating the toxicity of arsenic with their draft IRIS assessment tentatively scheduled for initial publication in (no sooner than) 2016. The NCSAB re-assessment of the arsenic AAL is considered timely for the reasons stated above. Additionally, the EMC has the authority to amend the air toxics rules at any time to revise the arsenic AAL if new evidence indicates an appropriate change.

Comment: Myra Blake and John Suttles of the Southern Environmental Law Center commented that the DAQ should not relax the arsenic AAL guideline at this time, when it is also considering overhauls to the Air Toxics Program. The DAQ is currently considering a number of changes to its Air Toxics Program, many of which would weaken the human health protection that the program provides. The DAQ should not consider making changes to the arsenic AAL and TPER until the full effects of these proposed changes are known.

Response: The DAQ has been responsible for implementing the Air Toxics Program and changes in AALs and TPERs for several TAPs since its inception in 1990, and as a result is familiar with the scope, details and interplay of the Program and its amendments. As such, the change in the arsenic AAL and TPER is recognized as a single variable in the Toxics Program equation and will be implemented independent of the other proposed changes.

Comment: Myra Blake and John Suttles of the Southern Environmental Law Center commented that if the DAQ does relax the arsenic AAL, the DAQ should not consider making the arsenic AAL less protective at this time. If the DAQ does revise the arsenic AAL, however, it must ensure that no facility or combination of facilities will exceed the AAL. The DAQ must also consider background levels of arsenic when setting the TPER. With one exception all the monitoring locations reveal that the mean annual arsenic concentration exceeds the current AAL for every year sampling was performed.

Response: Responding to this comment requires clarification of several aspects of the toxics program, including:

- a) How AALs are developed,
- b) Who is responsible for approving changes to AALs and TPERs, and
- c) What AALs and TPERs actually represent.

Regarding the statement that “DAQ should not consider making the arsenic AAL less protective”, the proposed arsenic AAL is designed to be *equally protective* as the existing level, since the proposed level still meets the same definition and metrics as the existing one. An AAL is defined as an airborne concentration above which a toxic air pollutant may be considered to have an adverse effect on human health. For substances known to cause cancer in humans such as arsenic, AALs are set at levels calculated to represent an increment of “one-in-a-million” risk. That is, if one million individuals are exposed continuously for a lifetime to a carcinogen at the concentration of the AAL, one of those million would be expected to contract cancer as a result of that exposure. Since scientific data shows that arsenic is not as toxic as indicated to be in 1984, the concentration above which arsenic may be considered to have an adverse health effect is proposed to be higher. While set at a higher level, the arsenic AAL is still calculated to represent the same risk increment and the same protection in human health as before.

Additionally, the DAQ does not make final decisions on rulemaking issues, but instead provides a technical support role in collecting, organizing, and presenting relevant information on such issues to the EMC. It is the responsibility of the EMC in their risk management capacity to make rulemaking decisions.

The comment that the DAQ must also consider background levels of arsenic when setting the TPER also requires clarification on the structure of the air toxics program. Unlike in the federal National Ambient Air Quality Standards (NAAQS) program which addresses only six criteria pollutants, since there is not enough monitoring information to know the general ambient concentrations for each of the many TAPs, the NC program focuses on what a facility adds to the existing environment. The program is structured on predicted concentrations from dispersion modeling that are independent of measured background levels. AALs are calculated to represent the incremental increase in ambient concentration only from site-specific emissions for the facility in question at its property line. A facility must demonstrate through modeling that predicted maximum ambient concentrations at the property boundary are below the AALs. Thus, the predicted ambient concentration is a model estimate not to be confused with actual measured ambient levels.

The emission rates requiring a permit, also referred to as TPERs, are screening levels to which facility-wide emissions levels are compared to determine whether further modeling is necessary. The TPER is a conservatively set threshold below which, even under the worst case air pollutant dispersion conditions, impacts at the property boundary are not expected to approach the AAL. Similarly, TPERs are mathematically derived incremental emissions levels independent of background levels.

In terms of the comment that the DAQ must ensure that no facility or combination of facilities will exceed the AAL, Rule 15A NCAC 02D .1107, Multiple Facilities, is available and in effect.

In summary, the comment to consider background levels in setting AALs and TPERs is asking for provisions beyond the current structure and scope of the toxics program.

SUMMARY OF COMMENTS AND RESPONSES

15A NCAC 02D .1104, Toxic Air Pollutant Guidelines, and 15A NCAC 02Q .0711, Emission Rates Requiring a Permit	
Comments	Responses
Strongly supports the NCSAB recommendation to relax the arsenic AAL.	No change to the rule.
Agrees with DAQ's economic analysis indicating that revising the arsenic AAL will result in millions of dollars in savings to the regulated industries.	No change to the rule.
Actual compliance costs will be significantly higher than the estimate of \$2 to \$3 million.	No change to the rule.
Measured arsenic levels across the state being above the existing AAL incorrectly suggests that	No change to the rule.

North Carolina's air is unhealthy, given the existing AAL is based on a outdated analysis.	
EMC should proceed with adopting the NCSAB recommendations without delay.	No change to the rule.
Revising the arsenic AAL is consistent with the ongoing reform of the toxics program under Session Law 2012-99 to reduce the unnecessary regulatory burden on regulated industries and to maintain protection of public health.	No change to the rule.
The impetus to change the arsenic AAL came from industry's reluctance to meet the existing AAL and that several facilities are having difficulty complying with the arsenic AAL.	The arsenic AAL was based on 30-year old health data analysis by EPA. Several facilities would face a multi-million dollar cost to comply with a state-only rule for one pollutant, disadvantaging their economic position. EPA recently set National Emission Standards for Hazardous Air Pollutants (HAPs) requiring multi-million dollar costs to comply with standards for several HAPs across a level playing field.
The NCSAB relied heavily on a model used by only one state and did not utilize the EPA model to calculate the arsenic AAL.	The NCSAB did not use an Inhalation Unit Risk Factor (IUR) derived by EPA more than 30 years ago. Instead, they used their collective scientific judgment and expertise to identify the most robust, relevant and recent data to calculate a range of AALs.
The unit risk factors utilized by the NCSAB to recommend updated candidate AALs for arsenic were not peer-reviewed and published unit risk factors.	The data used for the candidate AALs for arsenic has been recently published as an article in a peer-review journal.
EPA is currently performing a toxicological review of arsenic, so the rule changes may be obsolete in the future.	EPA has recently started to re-evaluate the inhalation toxicity of arsenic, with their draft assessment tentatively scheduled to be available for review no sooner than 2016.
The NCSAB failed to consider the impacts of through ingestion, the primary exposure pathway for arsenic.	NCSAB exposure assessments take into account potential inhalation exposures only, although dermal exposure may also be considered. Each compound is considered individually, though consideration of mixtures of compounds with similar mechanisms of action may be necessary.
The DAQ should not consider increasing the arsenic AAL before EPA completes its study of potential arsenic risks. In order to take advantage of EPA's effort, the DAQ should postpone any revisions until EPA concludes its investigation.	The NCSAB re-assessment of the arsenic AAL is considered timely for the reasons stated above. Additionally, the EMC has the authority to amend the air toxics rules at any time to revise the arsenic AAL if new evidence indicates an appropriate change.

<p>The DAQ should not relax the arsenic AAL at this time, when it is also considering overhauls to the Air Toxics Program. The DAQ is currently considering a number of changes to its toxics program, many of which would weaken the protection that the program provides.</p>	<p>The DAQ has been responsible for implementing the toxics program and changes in AALs and TPERs for several TAPs since 1990, and is familiar with the scope, details and interplay of the Program. The change in the arsenic AAL is recognized as a single variable in a complex program and will be implemented independent of the other program changes.</p>
<p>If the DAQ does relax and revise the arsenic AAL, it must ensure that no facility or combination of facilities will exceed the AAL. The DAQ must also consider the high background levels of arsenic when setting the TPER.</p>	<p>The proposed arsenic AAL is designed to be <i>equally protective</i> as the existing level, since the proposed level meets the same definition and metrics as the existing one. The comment to consider background levels in setting AALs and TPERs is asking for measures beyond the current structure and scope of the toxics program defined in State statutes.</p>

CONCLUSION

One person presented oral comments at the hearing on behalf of two entities who later submitted written comments. Five sets of written comments on the two proposed rules were submitted during the comment period for the hearing record. Three commenters supported the changes to the arsenic AAL and TPER and encouraged the adoption of the changes without delay. Two commenters had concerns over changing the arsenic AAL and TPER. One opposing comment was that the new data and its analysis, on which the proposed revised arsenic AAL was based, had not undergone peer review. Since the NCSAB issued their revised risk assessment, the data and analysis used by the NCSAB as a basis to recommend an updated arsenic AAL was recently published in a peer-review journal. A second opposing comment was that arsenic background ambient levels were above the existing AAL. To consider background levels in setting AALs and TPERs is asking for measures beyond the current structure and scope of the toxics program. While set at a higher level, the arsenic AAL is still calculated to represent the same risk increment and the same protection in human health as before. No changes were made to the rules as a result of these comments.

HEARING OFFICERS' RECOMMENDATION

The Hearing Officer recommends that the proposed amendments as presented in Chapter II of this hearing report be adopted by the Environmental Management Commission.

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1 15A NCAC 02D .1104 is proposed for amendment as follows:

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3 **15A NCAC 02D .1104 TOXIC AIR POLLUTANT GUIDELINES**

4 A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute
5 beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely
6 affect human health. In determining these significant ambient air concentrations, the Division shall be guided by the
7 following list of acceptable ambient levels in milligrams per cubic meter at 77° F (25° C) and 29.92 inches (760
8 mm) of mercury pressure (except for asbestos):

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
acetaldehyde (75-07-0)				27
acetic acid (64-19-7)				3.7
acrolein (107-02-8)				0.08
acrylonitrile (107-13-1)		0.03	1	
ammonia (7664-41-7)				2.7
aniline (62-53-3)			1	
arsenic and inorganic arsenic compounds	2.3×10^{-7} 2.1×10^{-6}			
asbestos (1332-21-4)	2.8×10^{-11} fibers/ml			
aziridine (151-56-4)		0.006		
benzene (71-43-2)	1.2×10^{-4}			
benzidine and salts (92-87-5)	1.5×10^{-8}			
benzo(a)pyrene (50-32-8)	3.3×10^{-5}			
benzyl chloride (100-44-7)			0.5	
beryllium (7440-41-7)	4.1×10^{-6}			
beryllium chloride (7787-47-5)	4.1×10^{-6}			
beryllium fluoride (7787-49-7)	4.1×10^{-6}			
beryllium nitrate (13597-99-4)	4.1×10^{-6}			
bioavailable chromate pigments, as chromium (VI) equivalent	8.3×10^{-8}			
bis-chloromethyl ether (542-88-1)	3.7×10^{-7}			
bromine (7726-95-6)				0.2

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
1,3-butadiene (106-99-0)	4.4×10^{-4}			
cadmium (7440-43-9)	5.5×10^{-6}			
cadmium acetate (543-90-8)	5.5×10^{-6}			
cadmium bromide (7789-42-6)	5.5×10^{-6}			
carbon disulfide (75-15-0)		0.186		
carbon tetrachloride (56-23-5)	6.7×10^{-3}			
chlorine (7782-50-5)		0.0375		0.9
chlorobenzene (108-90-7)		2.2		
chloroform (67-66-3)	4.3×10^{-3}			
chloroprene (126-99-8)		0.44	3.5	
cresol (1319-77-3)			2.2	
p-dichlorobenzene (106-46-7)				66
dichlorodifluoromethane (75-71-8)		248		
dichlorofluoromethane (75-43-4)		0.5		
di(2-ethylhexyl)phthalate (117-81-7)		0.03		
dimethyl sulfate (77-78-1)		0.003		
1,4-dioxane (123-91-1)		0.56		
epichlorohydrin (106-89-8)	8.3×10^{-2}			
ethyl acetate (141-78-6)			140	
ethylenediamine (107-15-3)		0.3	2.5	
ethylene dibromide (106-93-4)	4.0×10^{-4}			
ethylene dichloride (107-06-2)	3.8×10^{-3}			
ethylene glycol monoethyl ether (110-80-5)		0.12	1.9	
ethylene oxide (75-21-8)	2.7×10^{-5}			
ethyl mercaptan (75-08-1)			0.1	
fluorides		0.016	0.25	
formaldehyde (50-00-0)				0.15
hexachlorocyclopentadiene (77-47-4)		0.0006	0.01	
hexachlorodibenzo-p-dioxin (57653-85-7)	7.6×10^{-8}			

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
n-hexane (110-54-3)		1.1		
hexane isomers except n-hexane				360
hydrazine (302-01-2)		0.0006		
hydrogen chloride (7647-01-0)				0.7
hydrogen cyanide (74-90-8)		0.14	1.1	
hydrogen fluoride (7664-39-3)		0.03		0.25
hydrogen sulfide (7783-06-4)		0.12		
maleic anhydride (108-31-6)		0.012	0.1	
manganese and compounds		0.031		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.0006		
manganese tetroxide (1317-35-7)		0.0062		
mercury, alkyl		0.00006		
mercury, aryl and inorganic compounds		0.0006		
mercury, vapor (7439-97-6)		0.0006		
methyl chloroform (71-55-6)		12		245
methylene chloride (75-09-2)	2.4×10^{-2}		1.7	
methyl ethyl ketone (78-93-3)		3.7		88.5
methyl isobutyl ketone (108-10-1)		2.56		30
methyl mercaptan (74-93-1)			0.05	
nickel carbonyl (13463-39-3)		0.0006		
nickel metal (7440-02-0)		0.006		
nickel, soluble compounds, as nickel		0.0006		
nickel subsulfide (12035-72-2)	2.1×10^{-6}			
nitric acid (7697-37-2)				1
nitrobenzene (98-95-3)		0.06	0.5	
n-nitrosodimethylamine (62-75-9)	5.0×10^{-5}			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	8.3×10^{-8}			

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
pentachlorophenol (87-86-5)		0.003	0.025	
perchloroethylene (127-18-4)	1.9×10^{-1}			
phenol (108-95-2)			0.95	
phosgene (75-44-5)		0.0025		
phosphine (7803-51-2)				0.13
polychlorinated biphenyls (1336-36-3)	8.3×10^{-5}			
soluble chromate compounds, as chromium (VI) equivalent		6.2×10^{-4}		
styrene (100-42-5)			10.6	
sulfuric acid (7664-93-9)		0.012	0.1	
tetrachlorodibenzo-p-dioxin (1746-01-6)	3.0×10^{-9}			
1,1,1,2-tetrachloro-2,2-difluoroethane (76-11-9)		52		
1,1,2,2-tetrachloro-1,2-difluoroethane (76-12-0)		52		
1,1,2,2-tetrachloroethane (79-34-5)	6.3×10^{-3}			
toluene (108-88-3)		4.7		56
toluene diisocyanate, 2,4- (584-84-9) and 2,6- (91-08-7) isomers		0.0002		
trichloroethylene (79-01-6)	5.9×10^{-2}			
trichlorofluoromethane (75-69-4)			560	
1,1,2-trichloro-1,2,2-trifluoroethane (76-13-1)				950
vinyl chloride (75-01-4)	3.8×10^{-4}			
vinylidene chloride (75-35-4)		0.12		
xylene (1330-20-7)		2.7		65

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2 *History Note:* Authority G.S. 143-215.3(a)(1); 143-215.107(a)(3),(4),(5); 143B-282; S.L. 1989, c. 168, s. 45;3 *Eff. May 1, 1990;*

1 *Amended Eff. September 1, 1992; March 1, 1992;*
2 *Temporary Amendment Eff. July 20, 1997;*
3 *Amended Eff. November 1, 2013; March 1, 2010; June 1, 2008; April 1, 2005; April 1, 2001; July*
4 *1, 1998.*

1 15A NCAC 02Q .0711 is proposed for amendment as follows:

3 **15A NCAC 02Q .0711 EMISSION RATES REQUIRING A PERMIT**

4 (a) A permit to emit toxic air pollutants is required for any facility whose actual (or permitted if higher) rate of
 5 emissions from all sources are greater than any one of the following toxic air pollutant permitting emissions rates:

Pollutant (CAS Number)	Carcinogens lb/yr	Chronic Toxicants lb/day	Acute Systemic Toxicants lb/hr	Acute Irritants lb/hr
acetaldehyde (75-07-0)				6.8
acetic acid (64-19-7)				0.96
acrolein (107-02-8)				0.02
acrylonitrile (107-13-1)		0.4	0.22	
ammonia (7664-41-7)				0.68
aniline (62-53-3)			0.25	
arsenic and inorganic arsenic compounds	0.016 0.053			
asbestos (1332-21-4)	1.9×10^{-6}			
aziridine (151-56-4)		0.13		
benzene (71-43-2)	8.1			
benzidine and salts (92-87-5)	0.0010			
benzo(a)pyrene (50-32-8)	2.2			
benzyl chloride (100-44-7)			0.13	
beryllium (7440-41-7)	0.28			
beryllium chloride (7787-47-5)	0.28			
beryllium fluoride (7787-49-7)	0.28			
beryllium nitrate (13597-99-4)	0.28			
bioavailable chromate pigments, as chromium (VI) equivalent	0.0056			
bis-chloromethyl ether (542-88-1)	0.025			
bromine (7726-95-6)				0.052
1,3-butadiene (106-99-0)	11			
cadmium (7440-43-9)	0.37			
cadmium acetate (543-90-8)	0.37			
cadmium bromide (7789-42-6)	0.37			
carbon disulfide (75-15-0)		3.9		

carbon tetrachloride (56-23-5)	460			
chlorine (7782-50-5)		0.79		0.23
chlorobenzene (108-90-7)		46		
chloroform (67-66-3)	290			
chloroprene (126-99-8)		9.2	0.89	
cresol (1319-77-3)			0.56	
p-dichlorobenzene (106-46-7)				16.8
dichlorodifluoromethane (75-71-8)		5200		
dichlorofluoromethane (75-43-4)		10		
di(2-ethylhexyl)phthalate (117-81-7)		0.63		
dimethyl sulfate (77-78-1)		0.063		
1,4-dioxane (123-91-1)		12		
epichlorohydrin (106-89-8)	5600			
ethyl acetate (141-78-6)			36	
ethylenediamine (107-15-3)		6.3	0.64	
ethylene dibromide (106-93-4)	27			
ethylene dichloride (107-06-2)	260			
ethylene glycol monoethyl ether (110-80-5)		2.5	0.48	
ethylene oxide (75-21-8)	1.8			
ethyl mercaptan (75-08-1)			0.025	
fluorides		0.34	0.064	
formaldehyde (50-00-0)				0.04
hexachlorocyclopentadiene (77-47-4)		0.013	0.0025	
hexachlorodibenzo-p-dioxin (57653- 85-7)	0.0051			
n-hexane (110-54-3)		23		
hexane isomers except n-hexane				92
hydrazine (302-01-2)		0.013		
hydrogen chloride (7647-01-0)				0.18
hydrogen cyanide (74-90-8)		2.9	0.28	
hydrogen fluoride (7664-39-3)		0.63		0.064
hydrogen sulfide (7783-06-4)		1.7		
maleic anhydride (108-31-6)		0.25	0.025	
manganese and compounds		0.63		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.013		
manganese tetroxide (1317-35-7)		0.13		

mercury, alkyl		0.0013		
mercury, aryl and inorganic compounds		0.013		
mercury, vapor (7439-97-6)		0.013		
methyl chloroform (71-55-6)		250		64
methylene chloride (75-09-2)	1600		0.39	
methyl ethyl ketone (78-93-3)		78		22.4
methyl isobutyl ketone (108-10-1)		52		7.6
methyl mercaptan (74-93-1)			0.013	
nickel carbonyl (13463-39-3)		0.013		
nickel metal (7440-02-0)		0.13		
nickel, soluble compounds, as nickel		0.013		
nickel subsulfide (12035-72-2)	0.14			
nitric acid (7697-37-2)				0.256
nitrobenzene (98-95-3)		1.3	0.13	
n-nitrosodimethylamine (62-75-9)	3.4			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	0.0056			
pentachlorophenol (87-86-5)		0.063	0.0064	
perchloroethylene (127-18-4)	13000			
phenol (108-95-2)			0.24	
phosgene (75-44-5)		0.052		
phosphine (7803-51-2)				0.032
polychlorinated biphenyls (1336-36- 3)	5.6			
soluble chromate compounds, as chromium (VI) equivalent		0.013		
styrene (100-42-5)			2.7	
sulfuric acid (7664-93-9)		0.25	0.025	
tetrachlorodibenzo-p-dioxin (1746- 01-6)	0.00020			
1,1,1,2-tetrachloro-2,2,- difluoroethane (76-11-9)		1100		
1,1,2,2-tetrachloro-1,2- difluoroethane (76-12-0)		1100		
1,1,2,2-tetrachloroethane (79-34-5)	430			
toluene (108-88-3)		98		14.4
toluene diisocyanate,2,4-(584-84-9) and 2,6- (91-08-7) isomers		0.003		

trichloroethylene (79-01-6)	4000			
trichlorofluoromethane (75-69-4)			140	
1,1,2-trichloro-1,2,2-trifluoroethane (76-13-1)				240
vinyl chloride (75-01-4)	26			
vinylidene chloride (75-35-4)		2.5		
xylene (1330-20-7)		57		16.4

(b) For the following pollutants, the highest emissions occurring for any 15-minute period shall be multiplied by four and the product shall be compared to the value in Paragraph (a). These pollutants are:

- (1) acetaldehyde (75-07-0);
- (2) acetic acid (64-19-7);
- (3) acrolein (107-02-8);
- (4) ammonia (7664-41-7);
- (5) bromine (7726-95-6);
- (6) chlorine (7782-50-5);
- (7) formaldehyde (50-00-0);
- (8) hydrogen chloride (7647-01-0);
- (9) hydrogen fluoride (7664-39-3); and
- (10) nitric acid (7697-37-2).

History Note: Authority G.S. 143-215.3(a)(1); 143-215.108; 143B-282; S L. 1989, c. 168, s. 45;

Rule originally codified as part of 15A NCAC 02H .0610;

Eff. July 1, 1998;

Amended Eff. November 1, 2013; January 1, 2010; June 1, 2008; April 1, 2005; February 1, 2005; April 1, 2001.

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CHAPTER III

REPORT OF PROCEEDINGS

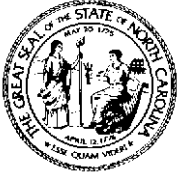
Introduction

The Department of Environmental and Natural Resources, Division of Air Quality, held a public hearing on May 14, 2013 at 6:00pm at the Training Room #1210, DENR Green Square Office Building, 217 West Jones Street, Raleigh, NC 27603.

The hearing considered the proposed amendment to Rule 15A NCAC 02D .1104 Toxic Air Pollutant Guidelines and 02Q .0711 Emission Rates Requiring a Permit for arsenic compounds.

The proposed effective date for these rules is projected to be September 1, 2013.

A public notice announcing this hearing was mailed to each person on the official mailing list for rule-making hearings. The public notice was also published in the North Carolina Register at least 20 days before the public hearing.



ENVIRONMENTAL MANAGEMENT COMMISSION

NORTH CAROLINA
DEPARTMENT OF ENVIRONMENT AND NATURAL RESOURCES

Stephen T. Smith
Chairman
Charles Peterson
Vice Chairman

Pat McCrory, Governor
John Skvarla, Secretary

Christopher J. Ayers
Yvonne C. Bailey
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Kevin Martin
Jeffrey V. Morse
Darryl D. Moss
David B. Peden
Dickson Phillips III
Amy E. Pickle
Clyde E. Smith, Jr.
Steve W. Tedder

March 27, 2013

MEMORANDUM

TO: Christopher J. Ayers and Donnie Redmond, Hearing Co-Officers

From: Stephen T. Smith

Subject: Hearing Officer Appointment

A public hearing has been scheduled for May 14, 2013 at 6:00 PM at the Division of Air Quality central office in Raleigh to receive public comments on the Revision of the Arsenic Acceptable Ambient Level (AAL). The attached public notice describes the hearing's purpose.

I am hereby appointing each of you to serve as hearing co-officers for this hearing. Please receive all relevant public comment and report your findings and recommendations to the Environmental Management Commission. Ms. Joelle Burleson will provide staff support for you.

If you have any questions, please feel free to contact Joelle Burleson at (919) 707-8720, or me.

SCH/jb

Attachment

cc: Sheila Holman
Lois Thomas
Hearing Record File

NORTH CAROLINA ENVIRONMENTAL MANAGEMENT COMMISSION

PUBLIC NOTICE

Notice is hereby given for one public hearing to be heard by the North Carolina Department of Environment and Natural Resources, Division of Air Quality concerning the proposed amendments to air quality rules.

PURPOSE: To revise the acceptable ambient level (AAL) for arsenic in 15A NCAC 02D .1104 and the corresponding emission rate requiring a permit in 15A NCAC 02Q .0711. The AAL value for arsenic and inorganic arsenic compounds (arsenic compounds) is proposed to be changed from 2.3×10^{-7} milligrams per cubic meter (mg/m^3) to 2.1×10^{-6} mg/m^3 on an annual average basis. The corresponding value for the toxic air pollutant permitting emissions rate (TPER) for arsenic compounds is proposed to be changed from 0.016 pounds per year to 0.053 pounds per year.

NOTE: The proposed amendments considered in this hearing, if adopted, will be effective statewide if they are later adopted by a local air pollution control agency, then that agency will enforce them in its area of jurisdiction.

DATES AND LOCATION: May 14, 2013, 6:00 P.M.
Training Room (#1210), Green Square Building,
217 West Jones Street, Raleigh, NC

COMMENT PROCEDURES: All persons interested in these matters are invited to attend the public hearings. **Any person desiring to comment is requested to submit a written statement for inclusion in the record of proceedings at the public hearing.** The hearing officer may limit oral presentation lengths if many people want to speak. The hearing record will remain open until June 14, 2013 to receive additional written statements. To be included, the statement must be received by the Division by June 14, 2013.

INFORMATION: Copies of the proposed rule changes may be downloaded at <http://daq.state.nc.us/Rules/Hearing/>. Copies of the proposals may also be reviewed at the regional offices of the North Carolina Department of Environment and Natural Resources, Division of Air Quality, located at the following cities:

Asheville	828/296-4500
Fayetteville	910/433-3300
Mooreville	704/663-1699
Raleigh	919/791-4200
Washington	252/946-6481
Wilmington	910/796-7215
Winston-Salem	336/771-5000

Comments should be sent to and additional information concerning the hearings or the proposals may be obtained by contacting:

Ms. Joelle Burleson
Division of Air Quality
1641 Mail Service Center
Raleigh, North Carolina 27699-1641
(919) 707-8720 Phone/Fax
joelle.burleson@ncdenr.gov

DATE: _____

Sheila Holman,
DAQ Director

Transcript

A transcript of the May 14, 2013 hearing has not been prepared; however, an audio recording of the proceeding will be kept on file with the Division of Air Quality (DAQ) for one year from the date of the final actions by the Environmental Management Commission.

A list of those attending the hearing as follows:

Hearing Officers

Mr. Christopher J. Ayers, member of Environmental Management Commission, recused
Mr. Donnie Redmond, DAQ, DENR, Environmental Program Supervisor IV

Staff Members

Ms. Joelle Burleson, DAQ, DENR
Mr. Glenn Sappie, DAQ, DENR
Mr. Steve Schliesser, DAQ, DENR
Mr. Vladimir Zaytsev, DAQ, DENR
Ms. Candace Prusiewicz, DAQ, DENR
Mr. Tom Mather, DAQ, DENR

Members of the General Public

Mr. Chet Chiles, Evergreen Packaging Company, Canton Paper Mill, Canton, NC
Mr. Bill Lane, Kilpatrick Townsend Stockton, LLP, Raleigh, NC
Ms. Marion Deerhake, member of the Environmental Management Commission

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CHAPTER IV

EXHIBITS

<u>EXHIBIT</u>	<u>PAGE</u>
Proposed Regulations as Published in the North Carolina Register and Presented at the Hearing	IV-2
Hearing Officer Comments at the Public Hearing	IV-8

TITLE 15A – DEPARTMENT OF ENVIRONMENT AND NATURAL RESOURCES

IV-2 concerning the submission of objections to the Commission, please call a Commission staff attorney at 919-431-3000. A-32

Notice is hereby given in accordance with G.S. 150B-21.2 that the Environmental Management Commission intends to amend the rules cited as 15A NCAC 02D .1104 and 02Q .0711.

Agency obtained G.S. 150B-19.1 certification:

- ☒ OSBM certified on: January 31, 2013
☐ RRC certified on:
☐ Not Required

Link to agency website pursuant to G.S. 150B-19.1(c):
<http://www.nair.org/rules/hearing/>

Proposed Effective Date: November 1, 2013

Public Hearing:

Date: May 14, 2013

Time: 6:00 p.m.

Location: Training Room #1210, DENR Green Square Office Building, 217 West Jones Street, Raleigh, NC 27603

Reason for Proposed Action: *To revise the acceptable ambient level (AAL) for arsenic and inorganic arsenic compounds in 15A NCAC 02D .1104 and the corresponding emission rate requiring a permit in 15A NCAC 02Q .0711 based upon recommendation of the Department of Environment and Natural Resources (DENR) Secretary's Science Advisory Board (SAB) on Toxic Air Pollutants. The AAL value for arsenic and inorganic arsenic compounds is proposed to be changed from 2.3×10^{-7} milligrams per cubic meter (mg/m^3) to 2.1×10^{-6} mg/m^3 on an annual average basis. The corresponding value for toxic air pollutant permitting emissions rates (TPER) for arsenic compounds is proposed to be changed from 0.016 pounds per year to 0.053 pounds per year.*

Procedure by which a person can object to the agency on a proposed rule: *If you have any objections to the proposed rules, please mail a letter including your specific reasons to: Ms. Joelle Burleson, Division of Air Quality, 1641 Mail Service Center, Raleigh, NC, 27699-1641.*

Comments may be submitted to: *Joelle Burleson, Division of Air Quality, 1641 Mail Service Center, Raleigh, NC 27699-1641; phone (919) 707-8720; fax (919) 707-8720; email joelle.burleson@ncdenr.gov*

Comment period ends: June 14, 2013

Procedure for Subjecting a Proposed Rule to Legislative

Review: If an objection is not resolved prior to the adoption of the rule, a person may also submit written objections to the Rules Review Commission after the adoption of the Rule. If the Rules Review Commission receives written and signed objections after the adoption of the Rule in accordance with G.S. 150B-21.3(b2) from 10 or more persons clearly requesting review by the legislature and the Rules Review Commission approves the rule, the rule will become effective as provided in G.S. 150B-21.3(b1). The Commission will receive written objections until 5:00 p.m. on the day following the day the Commission approves the rule. The Commission will receive those objections by mail, delivery service, hand delivery, or facsimile transmission. If you have any further questions

Fiscal impact (check all that apply).

- ☒ State funds affected
☐ Environmental permitting of DOT affected
Analysis submitted to Board of Transportation
☐ Local funds affected
Date submitted to OSBM:
☒ Substantial economic impact ($\geq \$500,000$)
☒ Approved by OSBM
☐ No fiscal note required by G.S. 150B-21.4

CHAPTER 02 - ENVIRONMENTAL MANAGEMENT COMMISSION

SUBCHAPTER 02D - AIR POLLUTION CONTROL REQUIREMENTS

SECTION .1100 - CONTROL OF TOXIC AIR POLLUTANTS

15A NCAC 02D .1104 TOXIC AIR POLLUTANT GUIDELINES

A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health. In determining these significant ambient air concentrations, the Division shall be guided by the following list of acceptable ambient levels in milligrams per cubic meter at 77° F (25° C) and 29.92 inches (760 mm) of mercury pressure (except for asbestos):

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
acetaldehyde (75-07-0)				27
acetic acid (64-19-7)				3.7
acrolein (107-02-8)				0.08
acrylonitrile (107-13-1)		0.03	1	
ammonia (7664-41-7)				2.7
aniline (62-53-3)			1	
arsenic and inorganic arsenic compounds	2.3×10^{-7} 2.1×10^{-6}			
asbestos (1332-21-4)	2.8×10^{-11} fibers/ml			
aziridine (151-56-4)		0.006		
benzene (71-43-2)	1.2×10^{-4}			
benzidine and salts (92-87-5)	1.5×10^{-8}			
benzo(a)pyrene (50-32-8)	3.3×10^{-5}			
benzyl chloride (100-44-7)			0.5	
beryllium (7440-41-7)	4.1×10^{-6}			
beryllium chloride (7787-47-5)	4.1×10^{-6}			
beryllium fluoride (7787-49-7)	4.1×10^{-6}			
beryllium nitrate (13597-99-4)	4.1×10^{-6}			
bioavailable chromate pigments, as chromium (VI) equivalent	8.3×10^{-8}			
bis-chloromethyl ether (542-88-1)	3.7×10^{-7}			
bromine (7726-95-6)				0.2
1,3-butadiene (106-99-0)	4.4×10^{-4}			
cadmium (7440-43-9)	5.5×10^{-6}			
cadmium acetate (543-90-8)	5.5×10^{-6}			
cadmium bromide (7789-42-6)	5.5×10^{-6}			
carbon disulfide (75-15-0)		0.186		
carbon tetrachloride (56-23-5)	6.7×10^{-3}			
chlorine (7782-50-5)		0.0375		0.9
chlorobenzene (108-90-7)		2.2		
chloroform (67-66-3)	4.3×10^{-3}			
chloroprene (126-99-8)		0.44	3.5	
cresol (1319-77-3)			2.2	
p-dichlorobenzene (106-46-7)				66
dichlorodifluoromethane (75-71-8)		248		
dichlorofluoromethane (75-43-4)		0.5		
di(2-ethylhexyl)phthalate (117-81-7)		0.03		
dimethyl sulfate (77-78-1)		0.003		
1,4-dioxane (123-91-1)		0.56		
epichlorohydrin (106-89-8)	8.3×10^{-2}			
ethyl acetate (141-78-6)			140	
ethylenediamine (107-15-3)		0.3	2.5	
ethylene dibromide (106-93-4)	4.0×10^{-4}			
ethylene dichloride (107-06-2)	3.8×10^{-3}			
ethylene glycol monoethyl ether (110-80-5)		0.12	1.9	

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
ethylene oxide (75-21-8)	2.7×10^{-5}			
ethyl mercaptan (75-08-1)			0.1	
fluorides		0.016	0.25	
formaldehyde (50-00-0)				0.15
hexachlorocyclopentadiene (77-47-4)		0.0006	0.01	
hexachlorodibenzo-p-dioxin (57653-85-7)	7.6×10^{-8}			
n-hexane (110-54-3)		1.1		
hexane isomers except n-hexane				360
hydrazine (302-01-2)		0.0006		
hydrogen chloride (7647-01-0)				0.7
hydrogen cyanide (74-90-8)		0.14	1.1	
hydrogen fluoride (7664-39-3)		0.03		0.25
hydrogen sulfide (7783-06-4)		0.12		
maleic anhydride (108-31-6)		0.012	0.1	
manganese and compounds		0.031		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.0006		
manganese tetroxide (1317-35-7)		0.0062		
mercury, alkyl		0.00006		
mercury, aryl and inorganic compounds		0.0006		
mercury, vapor (7439-97-6)		0.0006		
methyl chloroform (71-55-6)		12		245
methylene chloride (75-09-2)	2.4×10^{-2}		1.7	
methyl ethyl ketone (78-93-3)		3.7		88.5
methyl isobutyl ketone (108-10-1)		2.56		30
methyl mercaptan (74-93-1)			0.05	
nickel carbonyl (13463-39-3)		0.0006		
nickel metal (7440-02-0)		0.006		
nickel, soluble compounds, as nickel		0.0006		
nickel subsulfide (12035-72-2)	2.1×10^{-6}			
nitric acid (7697-37-2)				1
nitrobenzene (98-95-3)		0.06	0.5	
n-nitrosodimethylamine (62-75-9)	5.0×10^{-5}			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	8.3×10^{-8}			
pentachlorophenol (87-86-5)		0.003	0.025	
perchloroethylene (127-18-4)	1.9×10^{-1}			
phenol (108-95-2)			0.95	
phosgene (75-44-5)		0.0025		
phosphine (7803-51-2)				0.13
polychlorinated biphenyls (1336-36-3)	8.3×10^{-5}			
soluble chromate compounds, as chromium (VI) equivalent		6.2×10^{-4}		
styrene (100-42-5)			10.6	

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
sulfuric acid (7664-93-9)		0.012	0.1	
tetrachlorodibenzo-p-dioxin (1746-01-6)	3.0×10^{-9}			
1,1,1,2-tetrachloro-2,2,-difluoroethane (76-11-9)		52		
1,1,2,2-tetrachloro-1,2-difluoroethane (76-12-0)		52		
1,1,2,2-tetrachloroethane (79-34-5)	6.3×10^{-3}			
toluene (108-88-3)		4.7		56
toluene diisocyanate, 2,4- (584-84-9) and 2,6- (91-08-7) isomers		0.0002		
trichloroethylene (79-01-6)	5.9×10^{-2}			
trichlorofluoromethane (75-69-4)			560	
1,1,2-trichloro-1,2,2- trifluoroethane (76-13-1)				950
vinyl chloride (75-01-4)	3.8×10^{-4}			
vinylidene chloride (75-35-4)		0.12		
xylene (1330-20-7)		2.7		65

Authority G.S. 143-215.3(a)(1); 143-215.107(a)(3),(4),(5); 143B-282; S.L. 1989, c. 168, s. 45.

SUBCHAPTER 02Q - AIR QUALITY PERMITS PROCEDURES

SECTION .0700 - TOXIC AIR POLLUTANT PROCEDURES

15A NCAC 02Q .0711 EMISSION RATES REQUIRING A PERMIT

(a) A permit to emit toxic air pollutants is required for any facility whose actual (or permitted if higher) rate of emissions from all sources are greater than any one of the following toxic air pollutant permitting emissions rates:

Pollutant (CAS Number)	Carcinogens lb/yr	Chronic Toxicants lb/day	Acute Systemic Toxicants lb/hr	Acute Irritants lb/hr
acetaldehyde (75-07-0)				6.8
acetic acid (64-19-7)				0.96
acrolein (107-02-8)				0.02
acrylonitrile (107-13-1)		0.4	0.22	
ammonia (7664-41-7)				0.68
aniline (62-53-3)			0.25	
arsenic and inorganic arsenic compounds	0.016 0.053			
asbestos (1332-21-4)	1.9×10^{-6}			
aziridine (151-56-4)		0.13		
benzene (71-43-2)	8.1			
benzidine and salts (92-87-5)	0.0010			
benzo(a)pyrene (50-32-8)	2.2			
benzyl chloride (100-44-7)			0.13	
beryllium (7440-41-7)	0.28			
beryllium chloride (7787-47-5)	0.28			
beryllium fluoride (7787-49-7)	0.28			

beryllium nitrate (13597-99-4)	0.28			
bioavailable chromate pigments, as chromium (VI) equivalent	0.0056			
bis-chloromethyl ether (542-88-1)	0.025			
bromine (7726-95-6)				0.052
1,3-butadiene (106-99-0)	11			
cadmium (7440-43-9)	0.37			
cadmium acetate (543-90-8)	0.37			
cadmium bromide (7789-42-6)	0.37			
carbon disulfide (75-15-0)		3.9		
carbon tetrachloride (56-23-5)	460			
chlorine (7782-50-5)		0.79		0.23
chlorobenzene (108-90-7)		46		
chloroform (67-66-3)	290			
chloroprene (126-99-8)		9.2	0.89	
cresol (1319-77-3)			0.56	
p-dichlorobenzene (106-46-7)				16.8
dichlorodifluoromethane (75-71-8)		5200		
dichlorofluoromethane (75-43-4)		10		
di(2-ethylhexyl)phthalate (117-81-7)		0.63		
dimethyl sulfate (77-78-1)		0.063		
1,4-dioxane (123-91-1)		12		
epichlorohydrin (106-89-8)	5600			
ethyl acetate (141-78-6)			36	
ethylenediamine (107-15-3)		6.3	0.64	
ethylene dibromide (106-93-4)	27			
ethylene dichloride (107-06-2)	260			
ethylene glycol monoethyl ether (110-80-5)		2.5	0.48	
ethylene oxide (75-21-8)	1.8			
ethyl mercaptan (75-08-1)			0.025	
fluorides		0.34	0.064	
formaldehyde (50-00-0)				0.04
hexachlorocyclopentadiene (77-47-4)		0.013	0.0025	
hexachlorodibenzo-p-dioxin (57653- 85-7)	0.0051			
n-hexane (110-54-3)		23		
hexane isomers except n-hexane				92
hydrazine (302-01-2)		0.013		
hydrogen chloride (7647-01-0)				0.18
hydrogen cyanide (74-90-8)		2.9	0.28	
hydrogen fluoride (7664-39-3)		0.63		0.064
hydrogen sulfide (7783-06-4)		1.7		
maleic anhydride (108-31-6)		0.25	0.025	
manganese and compounds		0.63		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.013		
manganese tetroxide (1317-35-7)		0.13		
mercury, alkyl		0.0013		
mercury, aryl and inorganic compounds		0.013		
mercury, vapor (7439-97-6)		0.013		
methyl chloroform (71-55-6)		250		64
methylene chloride (75-09-2)	1600		0.39	
methyl ethyl ketone (78-93-3)		78		22.4

methyl isobutyl ketone (108-10-1)		52		7.6
methyl mercaptan (74-93-1)			0.013	
nickel carbonyl (13463-39-3)		0.013		
nickel metal (7440-02-0)		0.13		
nickel, soluble compounds, as nickel		0.013		
nickel subsulfide (12035-72-2)	0.14			
nitric acid (7697-37-2)				0.256
nitrobenzene (98-95-3)		1.3	0.13	
n-nitrosodimethylamine (62-75-9)	3.4			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	0.0056			
pentachlorophenol (87-86-5)		0.063	0.0064	
perchloroethylene (127-18-4)	13000			
phenol (108-95-2)			0.24	
phosgene (75-44-5)		0.052		
phosphine (7803-51-2)				0.032
polychlorinated biphenyls (1336-36-3)	5.6			
soluble chromate compounds, as chromium (VI) equivalent		0.013		
styrene (100-42-5)			2.7	
sulfuric acid (7664-93-9)		0.25	0.025	
tetrachlorodibenzo-p-dioxin (1746-01-6)	0.00020			
1,1,1,2-tetrachloro-2,2,-difluoroethane (76-11-9)		1100		
1,1,2,2-tetrachloro-1,2-difluoroethane (76-12-0)		1100		
1,1,2,2-tetrachloroethane (79-34-5)	430			
toluene (108-88-3)		98		14.4
toluene diisocyanate, 2,4- (584-84-9) and 2,6- (91-08-7) isomers		0.003		
trichloroethylene (79-01-6)	4000			
trichlorofluoromethane (75-69-4)			140	
1,1,2-trichloro-1,2,2-trifluoroethane (76-13-1)				240
vinyl chloride (75-01-4)	26			
vinylidene chloride (75-35-4)		2.5		
xylene (1330-20-7)		57		16.4

(b) For the following pollutants, the highest emissions occurring for any 15-minute period shall be multiplied by four and the product shall be compared to the value in Paragraph (a). These pollutants are:

- (1) acetaldehyde (75-07-0);
- (2) acetic acid (64-19-7);
- (3) acrolein (107-02-8);
- (4) ammonia (7664-41-7);
- (5) bromine (7726-95-6);
- (6) chlorine (7782-50-5);
- (7) formaldehyde (50-00-0);
- (8) hydrogen chloride (7647-01-0);
- (9) hydrogen fluoride (7664-39-3); and
- (10) nitric acid (7697-37-2).

Authority G.S. 143-215.3(a)(1); 143-215.108; 143B-282; S.L. 1989, c. 168, s. 45.

Hearing Officer's Suggested Hearing Comments
Raleigh, NC – May 14, 2013

INTRODUCTION

[Christopher Ayers and Donnie Redmond, hearing officers]:

Good evening ladies and gentlemen. My name is Christopher Ayers. I am a member of the Environmental Management Commission. My role as hearing officer is to listen to all relevant comment on these proceedings and report them to the full commission. Sitting with me is Mr. Redmond and Ms. Joelle Burleson. They are with the North Carolina Division of Air Quality (DAQ), Planning Section.

Some of the staff from the Division of Air Quality is here to assist. Ms. Burleson, please introduce the staff present.

Ms. Burleson. (Introduce staff)

[hearing officer]:

This evening we are conducting a public hearing to take comments on two Rules. These hearings will be held according to the North Carolina Administrative Procedures Act. The public notice for these hearings has been advertised in the North Carolina Register. Copies of the notice have also been sent to those on the official DAQ mailing list. I will enter the public notice and the proposed amendments and adoptions into the hearing record without reading them at this time.

I will now open the hearing and take relevant comments on these two rules. Any person desiring to comment is requested to submit a written statement for inclusion into the hearing record. Once called to speak, please come to the podium and state your name clearly, identify the rule or rules you are commenting on, and whom you represent.

Optional Time Limit: Many people have requested to speak at this hearing. Due to time constraints, speakers' presentations will be limited to **5** minutes. Speakers are requested to submit a written statement by the close of the comment period for inclusion into the hearing record.

[hearing officer]: **First Rule**

I will now take relevant comments on Rule **15A NCAC 02D .1104** – Toxic Air Pollutant Guidelines. Being considered are amendments to:

The first amendment is to *change the annual acceptable ambient level* (AAL) of arsenic and arsenic containing inorganic compounds (arsenic compounds) from 2.3×10^{-7} milligrams per cubic meter (mg/m^3) to $2.1 \times 10^{-6} \text{ mg}/\text{m}^3$ on an average annual basis. The Rule states that a facility must not emit any toxic air pollutant listed that may contribute to any significant ambient air concentration that may adversely affect human health. An AAL is an established airborne concentration of a toxic pollutant “above which the substance may be considered to have an adverse effect on human health.” AALs are expressed in weight per unit volume as milligrams per cubic meter of air (mg/m^3). For substances known to cause cancer in humans, AALs are set at levels calculated to represent an increment of “one in a million” risk. That is, if one million individuals are exposed continuously for 70 years to a carcinogen at the concentration of the AAL, only one might be expected to contract cancer as a result of that exposure.

The amendments to the Rules are proposed based upon recommendation of the Department of Environment and Natural Resources Secretary’s Science Advisory Board (SAB) which studies the toxicological effects of toxic air pollutants. After completing the study on arsenic compounds, the SAB advised the Environmental Management Commission regarding the necessary level of control of those pollutants for protection of human health. A fiscal note is being prepared by DAQ estimating the economic impacts of the rule change. The U.S. Environmental Protection Agency (EPA) staff has been working on an arsenic toxicity assessment for more than a decade, striving to update a previous assessment which assessed only ingestion risks.¹ EPA plans to complete their arsenic assessment no sooner than 2016.

The second amendment is to *change the annual emission rate* for arsenic compounds from 0.016 pounds per year to 0.053 pounds per year as previously calculated for carcinogens for a Toxic Permitting Exemption Rate (TPER) for a facility requiring a permit. TPERs are expressed as an emission rate in weight per unit of time as pounds per hour (lb/hr).

¹ U.S. EPA, “Toxicological Review of Inorganic Arsenic,” <http://www.epa.gov/iris/publicmeeting/arsenic/iAs%20Workshop%20Introduction%20Slides.pdf>

The North Carolina toxic air pollutant rules apply to all facilities that emit a toxic air pollutant required to have a permit. The permit application must include an evaluation for all toxic air pollutants covered in the rules for all sources at the facility, excluding those sources exempt from evaluation. Computerized air dispersion modeling is the means by which facilities evaluate whether the facility emission rates and other parameters will prevent any of the AALs from being exceeded, with allowable exceptions. Dispersion modeling is the mathematical simulation of how air pollutants disperse in the atmosphere. The dispersion models are used to estimate the downwind concentration of air pollutants at the facility property line using facility-specific emission rates and release parameters.

To reduce the burden of modeling, the toxics rules include a *threshold* provision to exempt modeling for toxic pollutant emission rates at such a low level relative to its toxicity that permitting would not be needed. This provision is referred to as the Toxic Permitting Exemption Rate (TPER). To establish the TPER, DAQ applies modeling to calculate the threshold value from each AAL using conservative release parameters and meteorological data. Given that TPERs are derived from AALs which represent acceptable concentrations, TPERs likewise represent emission rate levels demonstrated to be acceptable and therefore do not need modeling. Since the AAL value for arsenic compounds is proposed to be amended, the corresponding TPER value is proposed to be amended as well.

[SPEAKERS]

[hearing officer]: **Second Rule**

I will now take relevant comments on rule **15A NCAC 02Q .0711** – Emission Rates Requiring a Permit. Being considered is an amendment to:

[SPEAKERS]

[hearing officer]:

Is there anyone else who would like to comment? If there are no more comments, then the hearing is closed. The hearing record will remain open until June 6, 2013 for additional written comments.

CHAPTER V

COMMENTS DURING THE COMMENT PERIOD

INDEX OF COMMENTERS

NAME	REPRESENTING	PAGE
Tammy Francis	Jackson Paper Manufacturing Company	V-2
Dane Griswold	Evergreen Packaging Company	V-4
Bill Lane	Kilpatrick Townsend & Stockton (made only oral comments on behalf of Jackson Paper and Evergreen Packaging reflected in their written comments)	
Preston Howard	North Carolina Manufacturers Alliance	V-6
Terese Vick	Blue Ridge Environmental Defense League	V-8
Myra Blake, John Suttles	Southern Environmental Law Center, Clean Air Carolina, and Medical Advocates for Healthy Air	V-14



JACKSON PAPER MANUFACTURING

June 12, 2013

VIA ELECTRONIC MAIL AND FIRST CLASS MAIL

Ms. Joelle Burleson
North Carolina Division of Air Quality
1641 Mail Service Center
Raleigh, North Carolina 27699-1641

**Re: Comments on Proposed Revisions to AAL and TPER for Arsenic
(15A NCAC 02D .1104 and 02Q .0711)**

Dear Ms. Burleson:

On behalf of Jackson Paper Manufacturing Company (Jackson Paper), I am writing to submit comments in support of the proposed revisions to the Acceptable Ambient Level (AAL) and the Toxic Permitting Emissions Rate (TPER) for arsenic.

Jackson Paper owns and operates a paper mill in Sylva, North Carolina. Jackson Paper employs approximately 120 people and is one of the largest employers in Jackson County. We operate the mill in a manner that minimizes impacts to the environment. Jackson Paper produces 100 percent recycled corrugated medium for cardboard boxes. This material is produced by recycling approximately 120,000 tons per year of used cardboard that would otherwise enter the solid waste stream destined for disposal at a landfill.

The mill boiler combusts only high-quality renewable wood fuel that is produced at sawmills, and at furniture and flooring manufacturing facilities. Jackson Paper combusts no fossil fuels. In addition, Jackson Paper recycles all of its process wastewater and therefore has no process wastewater discharge.

Jackson Paper strongly supports the recommendation from the Science Advisory Board (SAB) for revision of the arsenic AAL to 2.1×10^{-6} mg/m³ (on an annual basis) and the corresponding revision of the arsenic TPER to 0.053 lb/year. We urge the Environmental Management Commission (EMC) to defer to the scientific expertise of the SAB and adopt these recommended changes. The current AAL was adopted in 1990 and, to our knowledge, it has not been reviewed by the SAB since then. In making its recommendation, the SAB relied on a more robust epidemiological data set compared with the EPA data upon which the current AAL was established 23 years ago. In addition, the SAB conducted a thorough review of the current peer-reviewed literature data. Using these data, the SAB applied its conservative risk assessment methodology. Their recommended adoption of the central estimate is reasonable and appropriate.

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We believe the EMC, in its role as a risk manager, should accept the scientific judgment of the SAB and adopt their recommendation. The SAB's scientific analysis, by itself, is sufficient to justify a change in the AAL. If cost is considered, however, the DAQ economic analysis provides additional reasons for updating the AAL. Revising the AAL will result in millions of dollars in savings that would otherwise be incurred as compliance costs by Jackson Paper and other regulated industries. (We believe the actual costs that will be incurred are much higher than the estimated costs of \$2 million to \$3 million.) We agree with DAQ's conclusion that if those costs are incurred, there would be no commensurate benefit to the public. In fact, as DAQ points out, public health would not be impacted by adoption of the revised AAL.

We also believe that there should not be any bias towards retention of the current AAL. If the EMC were developing an initial AAL today, the SAB's recommendation would likely be the same. But even if there were unequal weight given to the current standard, it would be far outweighed by the scientific and economic information in the record before the EMC now.

Finally, we note that the SAB report indicates that arsenic levels in ambient air throughout the state are above the current AAL. This is an important reason for review of the AAL. This information creates a false impression that North Carolina's air is unhealthy. However, the risk assessment by the SAB shows that is not the case. Moreover, the SAB report shows that arsenic levels in ambient air are not caused by stationary sources. Instead, emissions contribute only a small fraction compared to background levels. These data confirm that continued regulation of stationary sources under the current AAL is inappropriate. It diverts resources of the regulated community and the state government towards achievement of an obsolete standard.

Therefore, we urge the EMC to adopt the SAB's recommendation. Thank you for your consideration of these comments.

Sincerely,

Jackson Paper Manufacturing Company

A handwritten signature in cursive script that reads "Tammy Francis".

Tammy Francis
Controller

Signing for: Tim Campbell CEO/President



Canton Office
175 Main Street • Canton, NC 28716

14 June 2013

Certified Mail Return Receipt Requested
7099 3220 0007 0372 2267

CCC# 39-13

Ms. Joelle Burleson
North Carolina Division of Air Quality
1641 Mail Service Center
Raleigh, NC 27699-1641

**Re: Comments on Proposed Revisions to AAL and TPER for Arsenic
(15A NCAC 02D .1104 and 02Q .0711)**

Dear Ms. Burleson:

On behalf of Blue Ridge Paper Products, Inc. d/b/a Evergreen Packaging (Evergreen), I am writing to submit comments in support of the proposed revisions to the Acceptable Ambient Level (AAL) and the Toxic Permitting Emissions Rate (TPER) for arsenic. Evergreen operates a kraft pulp and paper mill in Canton, North Carolina and a related facility in Waynesville, North Carolina. The Canton mill has been in operation for approximately 105 years. Evergreen currently employs approximately 1,150 people and it is an economic engine for Haywood County and the rest of western North Carolina.

Evergreen strongly supports the recommendation from the Science Advisory Board (SAB) for revision of the arsenic AAL to $2.1 \times 10^{-6} \text{ mg/m}^3$ (on an annual basis) and the corresponding revision of the arsenic TPER to 0.053 lb/year. We urge the Environmental Management Commission (EMC) to adopt these recommended changes.

There are several compelling reasons for revising the AAL. First, the current AAL was adopted in 1990 and, to our knowledge, it has not been reviewed by the SAB since then. The SAB has conducted a thorough review of the current peer-reviewed literature data. In making its recommendation, the SAB relied on a more robust epidemiological data set compared with the EPA data upon which the current AAL was established 23 years ago.

Second, the SAB report indicates that arsenic levels in ambient air throughout the state are above the current AAL. This information incorrectly suggests that North Carolina's air is unhealthy. The risk assessment by the SAB shows that arsenic levels in ambient air do not pose a public health issue. Rather, the misperception is due to the existence of an outdated regulatory standard.

fresh by design.

Third, DAQ's economic analysis indicates that revising the AAL will result in millions of dollars in savings that would otherwise be incurred as compliance costs by Evergreen and other regulated industries. We believe the actual costs will be significantly higher than the estimated costs of \$2 million to \$3 million. Most importantly, DAQ states that these savings can be secured without any adverse impact to public health.

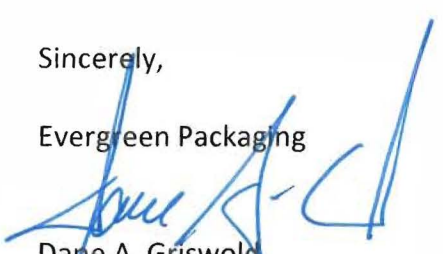
Finally, the adoption of the revised AAL and TPER would be consistent with the ongoing reform of the air toxics program that began with Session Law 2012-91. In a separate rulemaking, DAQ has proposed several amendments to the air toxics rules. As required by the legislation, DAQ's proposed reforms are intended to reduce unnecessary regulatory burden on regulated industries, increase the efficient use of DAQ resources, and maintain protection of public health. The proposed revision to the arsenic AAL easily satisfies these three statutory criteria.

In addition, we believe that the EMC should proceed with adoption of the SAB's recommendation, rather than deferring any decision-making pending the outcome of EPA's toxicological review of arsenic. According to EPA's proposed schedule, they will not complete their review for at least three more years. The SAB's recommendation is grounded in current scientific data and should be adopted now.

Therefore, we urge the EMC to adopt the SAB's recommendation. Thank you for your consideration of these comments. Should you have questions or require additional information, please contact Chet Chiles, C/W EHS&S Manager at (828) 646-2381 or by email at chet.chiles@everpack.com.

Sincerely,

Evergreen Packaging



Dane A. Griswold
Canton/Waynesville
General Manager

CCC\



14 June 2013

Ms. Joelle Burleson
North Carolina Division of Air Quality
1641 Mail Service Center
Raleigh, NC 27699-1641

Subject: **Comments on Proposed Revisions to the
Acceptable Ambient Level and Toxic
Permitting Emissions Rate for Arsenic
(15A NCAC 02D .1104 and 02Q .0711)**

Dear Ms. Burleson:

I write to you today on behalf of the North Carolina Manufacturers Alliance (NCMA) and our many member companies who have a significant interest in the subject rulemaking action. Amendments to the Acceptable Ambient Level (AAL) and the Toxic Permitting Emissions Rate (TPER) for arsenic are long overdue, and we congratulate the Environmental Management Commission and the Division of Air Quality (DAQ) for initiating this rulemaking action to accomplish those amendments.

NCMA strongly supports the recommendation submitted by the North Carolina Science Advisory Board (SAB) which calls for revision of the arsenic AAL to 2.1×10^{-6} mg/m³ (on an annual basis), as well as the corresponding revision of the arsenic TPER to 0.053 lb/year. We urge the Environmental Management Commission (EMC) to adopt these recommended changes.

NCMA has followed the SAB's review of the Arsenic AAL, which was last reviewed over two (2) decades ago. The SAB's current proposal is based on a thorough review of the available peer-reviewed data, including a more robust epidemiological data set for arsenic exposures that was not available when the original AAL was determined.

As you know, the SAB's report on arsenic indicates that arsenic levels in excess of the existing AAL are currently being measured in the ambient air throughout North Carolina. Thus, while the SAB's risk assessment demonstrates that arsenic levels found in our ambient air does not pose a health risk, our out-dated AAL suggests just the opposite – that our ambient air is unhealthy. Therefore, it is imperative that the EMC move as expeditiously as possible to correct the misperception that arsenic levels in our air are unhealthy.

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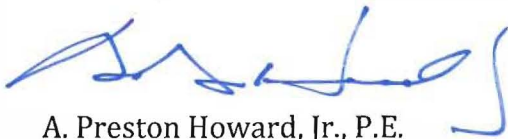
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It is also important to note that the proposed revision of the arsenic AAL will result in millions of dollars in savings by manufacturers and other regulated industries across North Carolina. Both DAQ and many regulated sources (including NCMA member companies) have already expended tens of thousands of dollars on modeling, design, and other efforts in attempts to demonstrated compliance with the outdated AAL.

Finally, we recognize that there are some who would suggest that the EMC should defer its amendment to the arsenic AAL until completion of a pending toxicological review of arsenic that is currently underway at EPA. However, according to EPA's proposed timeline, completion of that study is not expected until 2016 (or later). Postponing action on the AAL will not only lead to regulatory compliance issues for some of our member companies; it also will continue to promote the erroneous perception that arsenic levels in our ambient are unsafe. NCMA therefore urges the EMC to act immediately to adopt the SAB's recommendations on amendment to the arsenic AAL and TPER.

Thank you for the opportunity to participate in this rulemaking action, and for your thoughtful consideration of our comments and recommendations. If you have any questions, please contact me.

Sincerely,

A handwritten signature in blue ink, appearing to read 'A. Preston Howard, Jr.', with a stylized flourish at the end.

A. Preston Howard, Jr., P.E.
President

Blue Ridge Environmental Defense League

www.BREDL.org 4617 Pearl Rd. Raleigh N.C. 27610 (919) 345-3673 therese.vick@gmail.com

Ms. Joelle Burleson

Division of Air Quality

1641 Mail Service Center

Raleigh, North Carolina 27699-1641

June 13, 2013

Re: Draft Rule for Revision of the Arsenic AAL

Dear Ms. Burleson:

On behalf of the members and Directors of Blue Ridge Environmental Defense League (BREDL), I appreciate the opportunity to offer the following comments on the proposed revision of the acceptable ambient level (AAL), and corresponding toxic air pollutant permitting emissions (TPERs) rate for arsenic. BREDL opposes these changes, as they are not in the best interest of public health or the environment.

In 2011, when the North Carolina Division of Air Quality posted notice of the Science Advisory Board's "Draft Risk Assessment for Arsenic and Inorganic Arsenic Compounds", it was clear that the impetus to re-assess arsenic came from industry's unwillingness to meet North Carolina's more protective standards. BREDL submitted comments opposing the SAB's

Blue Ridge Environmental Defense League

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recommendation pointing out arsenic's toxic effects as well as asking the question, "What industry (or industries) are behind the impetus" (to change the acceptable ambient level of arsenic).¹ Upon review of Division of Air Quality files, it is clear that public health was not the driving force behind the changes.

For example:

- The SAB's recommendation was scheduled to be voted on by the Board November 30, 2011 at the 161st meeting, which was held by teleconference. Because of BREDL comments, it was decided to postpone the decision until the January 2012 meeting. During the public comment portion of the teleconference, BREDL inquired as to where this request initially came from. Dr. Starr answered that the request had come from the North Carolina Division of Air Quality. It was explained that certain areas in North Carolina "routinely exceed the current AAL for arsenic."^{2,3} The "2009 Annual Air Toxics Report" states that: "...median arsenic concentrations measured across the state in 2009 exceed the AAL for arsenic by 3–4 times."⁴ More troubling, members of the SAB pointed out that the lower bound of the proposed AAL was "coincidentally close to the measured concentrations at monitoring sites around NC."⁵
- In the "PSD Preliminary Review – modification 300 construction/operation permit (Draft Revision 8, July 2011 – Assistant Secretary)" for Carolinas Cement Company LLC (aka Titan Cement) proposed to be located in Castle Hayne, North Carolina, the modeled

¹ [BREDL Comments Arsenic AAL](#)

² From Therese Vick's notes of the 161st meeting of the Director's Science Advisory Board, November 30, 2011.

³ [One Hundred Fifty-Fourth Meeting of the Science Advisory Board on Toxic Air Pollutants-Proceedings of the October 27, 2010 Teleconference](#)

⁴ ["2009 Annual Air Toxics Report" Division of Air Quality Toxics Protection Branch October 2010](#)

⁵ [Comment by Dr. Ivan Rusyn, SAB member, One hundred Sixtieth Meeting of the Science Advisory Board on Toxic Air Pollutants-Proceedings of the October 11, 2011 Teleconference](#)

Blue Ridge Environmental Defense League

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arsenic levels are at 30% of the AAL— according to the company’s own modeling and after pollution control. The amount of arsenic potentially emitted into the air of the surrounding community is significant and dangerous. In the Draft Revision, DAQ attempts to diminish the potential concern over these levels by saying “Finally, the Scientific⁶ Advisory Board is considering adjusting the Arsenic AAL.”⁷ As troubling as 30% is, it pales in comparison to the almost 48% of the AAL modeled in an earlier draft.⁸

- Industry admits that sources are having problems meeting the arsenic AAL. Trinity Consultants, a North Carolina environmental consulting firm posted this on their website:

“For a variety of emission source(s), particularly combustion sources, the arsenic AAL has often been problematic in TAP air dispersion modeling. *In some cases, affected facilities have had to improve pollution control systems, increase stack heights or place operational limits to demonstrate compliance with the arsenic AA (L)* [emphasis added].”⁹

- At the November 2010 meeting of the SAB, Brendan Davey, DAQ staff from the Asheville Regional Office, remarked that “there are a few combustion sources in the Asheville region that are having difficulty complying with the AAL for arsenic given current regulations”,¹⁰ and that “the control technology for these emissions is

⁶ Historical Note: The “Science Advisory Board” was known as “The Scientific Advisory Board” prior to 2004.

⁷ [North Carolina Division of Air Quality: PSD Preliminary Review Draft Revision 8 July 2011](#)

⁸ “The air toxics modeling indicated that arsenic was at 47.83% of the Significant Ambient Air Concentration (SAAC) at some locations along the facility property line.” [North Carolina Division of Air Quality: PSD Preliminary Review Draft Revision 9 September 2009](#)

⁹ [Trinity Consultants News: Increased AAL for Arsenic](#)

¹⁰ In a January 5, 2012 email to Therese Vick, Brendan Davey listed these three companies as exceeding the arsenic AAL: **Blue Ridge Paper in Canton, Jackson Paper Manufacturing Company in Silva, and Zickgraf Hardwood Flooring Company in Franklin**

Blue Ridge Environmental Defense League

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insufficient...”¹¹ Mr. Davey was speaking of Blue Ridge Paper in Canton, Jackson Paper Manufacturing Company in Silva, and Zickgraf Hardwood Flooring Company in Franklin, NC. At a later meeting, SAB member Dr. Woodhall Stopford ask why the arsenic AAL was being reviewed. He was told that “DAQ needs to have the arsenic AAL reviewed because ambient concentrations are above the AAL across the state and the DAQ has been tasked by the EMC (Environmental Management Commission) to do a combustion source evaluation because *boilers have been exempt from Toxics regulations.*”¹²

- Operating facilities are not the only companies which have an interest in higher arsenic AAL’s. The North Carolina Legislature requires that power companies generate a certain percentage of electricity from poultry manure.¹³ Several large-scale biomass incinerators have been proposed in North Carolina. The Division of Air Quality performed a “Toxics Emissions Evaluation from Poultry/Turkey Litter.”¹⁴ The modeling DAQ evaluated based on a 50 megawatt facility showed that:
 - “*The model results provide that the arsenic emissions are the limiting pollutant with NC Toxics based on the estimated emissions. **For the given plant characteristics, the arsenic emissions resulted in an ambient concentration that is 277% of the AAL*** [emphasis added].”

¹¹ [One Hundred Fifty-Fifth Meeting of the Science Advisory Board on Toxic Air Pollutants- Proceedings of the November 17, 2010 Teleconference](#)

¹² Dr. Reginald Jordan, DAQ Toxics Protection Branch [One Hundred Fifty-Sixth Meeting of the Science Advisory Board on Toxic Air Pollutants- Proceedings of the January 26, 2011 Teleconference](#)

¹³ ["NC poultry litter-fired generating plants under consideration"](#)

¹⁴ [Agenda Item 13 March 2009](#)

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At the November 16, 2011 meeting of the Air Quality Committee of the EMC, DAQ Director Sheila Holman remarked that directed by the Chairs of the Environmental Review Commission, DAQ was meeting with industry looking at the air toxics regulations. Meeting attendees included representatives from Duke Energy and the Manufacturers and Chemical Industry Council of North Carolina (MCIC). Former NC DENR employees; George Everett, currently with Duke Power (formerly with MCIC), was the Director of the North Carolina Division of Environmental Management, and Preston Howard, currently with MCIC, was the Director of the Division of Water Quality and a DENR employee for over 20 years.¹⁵ Legislative staff facilitates these meetings. By statute, the meetings can be private, and some documents held confidential. However, notes from obtained by BREDL reveal an interest in the arsenic revisions. On October 26, 2011, DAQ Director Sheila Holman made note of this question:

“How many sources would have exceeded the AAL’s- w/new As AAL?”¹⁶

Of additional concern, methodology used by the SAB to support their recommendation did not utilize US EPA’s model. Their decision relied heavily on a model used by only one state in the country, Texas.

- The Scientific Advisory Board did not utilize the United States Environmental Protection Agency (USEPA) model to calculate the arsenic AAL. Instead, a model recommended by Flores and Sielken in a January, as presented to the SAB in January 2011, was used to calculate its arsenic ambient air level. Only one other state in the country that uses this modeled approach to calculate the arsenic ambient air level is Texas.
- Only the Tacoma and Montana epidemiology studies should have been included for the SAB’s As AAL calculation, which would be consistent with EPA’s approach.
- The unit risk factors calculated in the peer-reviewed publication by Viren and Silvers, 1994, should have been considered for the calculation of the AAL for arsenic. It appears

¹⁵ [Preston Howard](#) ,[George Everett](#)

¹⁶ Notes provided to BREDL by the North Carolina Division of Air Quality

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that the unit risk factors utilized by the SAB were not peer-reviewed and published unit risk factors

Lastly, the United States Environmental Protection Agency is currently performing a “Toxicological Review of Inorganic Arsenic”. The rule changes before you now may be obsolete in the future.

I appreciate the opportunity to comment.

Sincerely,

A handwritten signature in cursive script that reads "Therese Vick".

Therese Vick

North Carolina Healthy, Sustainable Communities Campaign Coordinator

SOUTHERN ENVIRONMENTAL LAW CENTER

Telephone 919-967-1450

601 WEST ROSEMARY STREET, SUITE 220
CHAPEL HILL, NC 27516-2356

Facsimile 919-929-9421

June 14, 2013

Joelle Burleson
Division of Air Quality
1641 Mail Service Center
Raleigh, North Carolina 27699-1641

VIA ELECTRONIC MAIL (joelle.burleson@ncdenr.gov)

**Re: Comments on Proposed Revisions to the Acceptable Ambient Level and
Toxic Pollutant Emission Rate for Arsenic**

Dear Ms. Burleson:

The Southern Environmental Law Center, on behalf of itself, Clean Air Carolina, and Medical Advocates for Healthy Air, respectfully submits the following comments on proposed changes to the arsenic standards in the North Carolina Air Toxics Program. The Division of Air Quality ("DAQ") has published notice of its intent to increase the acceptable ambient level ("AAL") of arsenic. DAQ also proposes to allow facilities to emit higher levels of arsenic without obtaining a permit, and without demonstrating that their emissions, individually or in combination with other nearby emission sources, will not contribute to a violation of the AAL. In the public notice, DAQ stated that it would accept written comments through June 14, 2013. These comments are therefore timely.

As described in the comments below, DAQ should not increase the acceptable ambient level of arsenic for a number of reasons:

- (1) Arsenic is a potent carcinogen that puts the public at risk for cancers of the bladder, liver, lung, and skin, as well as numerous other adverse health effects;
- (2) DAQ and the NCSAB have not investigated public health risks from arsenic ingestion;
- (3) EPA will complete its comprehensive assessment of the health effects of arsenic by 2016, at which time more information will be available to guide DAQ's decision; and
- (4) DAQ is currently considering other changes that would weaken the Air Toxics Program, and should not allow greater arsenic emissions before the effects of these changes are known.

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If DAQ does increase the acceptable ambient level of arsenic, it should account for cumulative effects from other facilities and background levels of arsenic when setting the revised arsenic TPER.

I. Background

A. DAQ's proposed changes

By raising the acceptable ambient level of arsenic from 2.3×10^{-7} to 2.1×10^{-6} milligrams per cubic meter, DAQ's proposal would allow 11 times more arsenic in the ambient air. By increasing the toxic permitting pollutant emission rate ("TPER") from 0.016 to 0.053 pounds per year, DAQ's proposal would also allow facilities to emit over three times more arsenic without obtaining a permit, and without modeling to determine whether these increases would exceed the arsenic AAL. Because of these changes, 137 currently covered facilities would be exempted from showing that their arsenic emissions will not endanger public health, and could—in some or all cases—increase their arsenic emissions as a result of DAQ's proposed changes.

B. Health effects of arsenic

Arsenic is a naturally occurring heavy metal. While arsenic is released to the environment from some natural sources, releases from anthropogenic sources far exceed those from natural sources.¹ In North Carolina, the vast majority of anthropogenic arsenic emissions come from electric power generating facilities, followed by paper and pulp mills and other manufacturers.² Although most anthropogenic releases of arsenic are to land or soil (primarily in the form of pesticides or solid wastes), substantial amounts are also released into the air and water.³

Once released, arsenic persists and accumulates in the environment, in drinking water, and in the food chain.⁴ Food consumption is the primary source of arsenic exposure for most people, while smaller exposures occur through drinking water and air.⁵ In foods, the highest levels of arsenic are found in seafood, rice and rice cereal, mushrooms, and poultry.⁶

Short- and long-term exposures to arsenic are known to elevate the risk of a number of adverse health effects, including cancer. Ingestion of inorganic arsenic has been linked to

¹ See U.S. Dep't of Health and Human Servs., Agency for Toxic Substances and Disease Registry, Toxicological Profile for Arsenic at 313 (Aug. 2007), Att. 1 (hereinafter "ATSDR Arsenic Profile").

² NCSAB Recommendation Pending Review by NC Environmental Management Commission, Risk Assessment for Arsenic and Inorganic Arsenic Compounds at 3, Attachment 2.

³ ATSDR Arsenic Profile at 313.

⁴ *Id.* at 327-30.

⁵ *Id.* at 4; U.S. EPA, Air Toxics Web Site: Arsenic Compounds, <http://www.epa.gov/ttnatw01/hlthef/arsenic.html> (last updated Jan. 24, 2013).

⁶ ATSDR Arsenic Profile at 4-5. Fish and shellfish usually contain an organic form of arsenic that is much less harmful; however, seaweed contains an inorganic form that is more damaging. *Id.*

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bladder, liver, lung, and skin cancer.⁷ Studies show that inhalation of inorganic arsenic is strongly associated with lung cancer.⁸ Based on these findings, the U.S. Environmental Protection Agency has classified inorganic arsenic as a human carcinogen.⁹

Arsenic exposure is also linked to a number of non-cancerous health effects. Arsenic ingestion has been associated with cardiovascular, pulmonary, immunological, neurological, endocrine, and reproductive and developmental effects.¹⁰ Chronic inhalation of organic arsenic can cause irritation of the skin and mucous membranes, such as dermatitis, conjunctivitis, pharyngitis, and rhinitis.¹¹ Oral exposure is known to cause gastrointestinal effects, anemia, peripheral neuropathy, skin lesions, hyperpigmentation, and liver and kidney damage in humans.¹² Recent studies show an association between elevated arsenic levels in drinking water and neurocognitive or behavioral test results in children.¹³ Ingested arsenic can cross the placenta in humans, exposing the fetus to the chemical.¹⁴ Animal studies show ingestion of arsenic at very high doses is toxic to fetuses and causes birth defects.¹⁵ Inhalation is also associated with effects on the brain and nervous system.¹⁶

Acute, high-level inhalation exposure to arsenic dust or fumes has resulted in gastrointestinal effects, including nausea, diarrhea, and abdominal pain.¹⁷ Central and peripheral nervous system disorders have occurred in workers acutely exposed to inorganic arsenic.¹⁸

Gaps remain in the current research and understanding of the health effects of arsenic.¹⁹ For example, no chronic inhalation exposure studies have been performed in animals for inorganic arsenic compounds.²⁰ EPA is currently investigating the full health effects of arsenic through multiple exposure pathways, including ingestion and inhalation, as discussed below.

⁷ U.S. EPA, Air Toxics Web Site: Arsenic Compounds, <http://www.epa.gov/ttnatw01/hlthef/arsenic.html> (last updated Jan. 24, 2013).

⁸ *Id.*

⁹ *Id.*

¹⁰ U.S. EPA, National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring, 66 Fed. Reg. 37,617, 37,623 (proposed July 19, 2001).

¹¹ U.S. EPA, Air Toxics Web Site: Arsenic Compounds, <http://www.epa.gov/ttnatw01/hlthef/arsenic.html> (last updated Jan. 24, 2013).

¹² *Id.*

¹³ *Id.*

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ *Id.*

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II. The NCSAB failed to consider the impacts of arsenic through ingestion, even though ingestion is the primary exposure pathway for humans.

DAQ's proposal to allow additional arsenic emissions is based on a report prepared by the North Carolina Science Advisory Board ("NCSAB"). In its report, the NCSAB summarizes the studies on which it based its recommendation to relax the arsenic AAL.²¹ Yet none of the studies cited in the report appears to have considered the effects of exposure to arsenic through ingestion.²² Instead, the studies focus on inhalation of arsenic.²³ This is particularly troubling, since food ingestion is the primary way in which humans are exposed to arsenic.²⁴ Arsenic in the ambient air is eventually deposited, and makes its way into the food chain.²⁵ Limits on ambient concentrations of arsenic are therefore essential for curbing the presence of arsenic in food sources.

Under the North Carolina Air Toxics Program, AALs must prevent concentrations of pollutants that "may adversely affect human health." 15A N.C. Admin. Code 02D .1104; *see also* 15A N.C. Admin. Code 02D .1101 (explaining that the purpose of the Air Toxics regulations is to "set[] forth the rules for the control of toxic air pollutants *to protect human health*" (emphasis added)). In order to prevent potential adverse effects on human health, AALs must be defined based on all relevant transmission pathways, not just inhalation.

To ensure that ambient levels of arsenic will not "adversely affect human health," 15A N.C. Admin. Code 02D .1104, DAQ must request that the NCSAB fully explore the impacts of arsenic through all exposure pathways—including ingestion—before considering any changes to the arsenic AAL.

III. DAQ should not consider increasing the permissible levels of arsenic before EPA completes its study of potential arsenic risks.

As DAQ recognizes, EPA is currently investigating the effects of arsenic exposure as part of the Agency's review of its arsenic toxicity assessment.²⁶ The review will analyze arsenic risks from all exposure pathways, including inhalation and ingestion.²⁷ EPA plans to complete its

²¹ NCSAB Recommendation Pending Review by NC Environmental Management Commission, Risk Assessment for Arsenic and Inorganic Arsenic Compounds at 5-21, Attachment 2.

²² *Id.*

²³ *Id.*; *see also* Secretary's Science Advisory Board on Toxic Air Pollutants, Internal Guidelines for Toxicological Evaluation of Chemicals Released to the Air, <http://daq.state.nc.us/toxics/risk/sab/sabtoxra.shtml> (explaining that the SAB's exposure assessments "generally take into account potential inhalation exposures only").

²⁴ U.S. EPA, Air Toxics Web Site: Arsenic Compounds, <http://www.epa.gov/ttnatw01/hlthef/arsenic.html> (last updated Jan. 24, 2013).

²⁵ *See* ATSDR Arsenic Profile at 313-15.

²⁶ DAQ, Rules in the Hearing Process, <http://www.ncair.org/rules/hearing/> (last updated Mar. 28, 2013); *see also* Public Stakeholder Workshop to Inform EPA's Upcoming IRIS Toxicological Review of Inorganic Arsenic (Jan. 8-9, year unknown), Attachment 3.

²⁷ *Id.*

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review by 2016. In order to take advantage of EPA's information-gathering process and assessment of all arsenic exposure pathways, including ingestion, DAQ should postpone any revisions to the arsenic AAL until EPA has concluded its investigation.

At the very least, DAQ should require the NCSAB to reassess the arsenic AAL after EPA releases the results of its study, and on a periodic basis going forward.

IV. DAQ should not relax the arsenic standard at this time, when it is also considering overhauls to the Air Toxics Program.

DAQ is currently considering a number of changes to the N.C. Air Toxics Program, many of which would weaken the human health protections that the program provides. *See* SELC, Clean Air Carolina, and Medical Advocates for Healthy Air Comment Letters (Oct. 2012, Apr. 2013), Attachments 4, 5. DAQ should not consider making changes to the arsenic AAL and TPER until the full effects of these proposed changes to the Air Toxics Program are known.

V. If DAQ does relax the arsenic AAL, DAQ must consider cumulative effects and background levels of arsenic when setting the revised arsenic TPER.

As described above, DAQ should not consider making the arsenic AAL less protective at this time. If DAQ does revise the arsenic AAL, however, it must ensure that no facility or combination of facilities will exceed the revised AAL. *See* 15A N.C. Admin. Code 02D .1104 ("A facility shall not emit any of the following toxic air pollutants in such quantities that may cause *or contribute* beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health." (emphasis added)); *id.* 02D .1107. To do so, DAQ must take into account the possible effects of multiple emitters of arsenic in the same area when setting the toxic air pollutant permitting emission rate ("TPER") for arsenic. If a facility's emissions are below the arsenic TPER, the facility would not have to obtain a permit limit or model to determine whether the facility will contribute to a violation of the AAL. *See* 15A N.C. Admin. Code 02Q .0711; *id.* 02Q .0709(a). Therefore, DAQ must set the arsenic TPER low enough so that any facility that might exceed the AAL, even in combination with other facilities, will need to obtain a permit limit and demonstrate that its emissions will not contribute to an AAL violation.

DAQ must also consider background levels of arsenic when setting the TPER. DAQ does not currently consider background pollution concentrations when setting TPERs.²⁸ DAQ's reason for ignoring background pollutant levels is that "[s]ince there is not enough monitoring information to be able to know the general ambient concentrations for each of the 97 TAPs, the North Carolina program focuses on what a facility adds to the existing environment."²⁹ Yet there is ample monitoring data available for ambient concentrations of arsenic. The NCSAB

²⁸ *See* Air Toxics Program, Acceptable Ambient Levels (AALs), <http://daq.state.nc.us/toxics/aal-disc.pdf>.

²⁹ *Id.*

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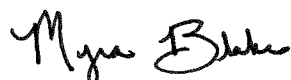
report on arsenic references state-wide monitoring data for mean annual arsenic concentrations.³⁰ With one exception, all of the monitoring locations reveal that the mean annual arsenic concentrations “exceed the [current] AAL for every year in which sampling was performed.”³¹ DAQ therefore has sufficient information to take these high background levels of arsenic into account when determining the arsenic TPER, and ultimately when determining whether a facility will cause or contribute to a violation of the AAL.

In sum, DAQ must consider the elevated background levels of arsenic, as well as arsenic emissions from other facilities, and set the arsenic TPER low enough so that no facility will contribute to a violation of the AAL.

VI. Conclusion

DAQ should not increase the acceptable ambient level of arsenic—a potent carcinogen with numerous other dangerous health effects—without investigating the public health risks from arsenic ingestion and other exposure pathways. DAQ’s proposal to amend the arsenic standard at this time is particularly concerning, since DAQ is currently considering other changes that would weaken the Air Toxics Program, and should not allow facilities to increase their arsenic emissions before the effects of these changes are known. If DAQ does increase the acceptable ambient level of arsenic, it should account for cumulative effects from other facilities and background levels of arsenic when setting the revised arsenic TPER.

Respectfully submitted,



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³⁰ NCSAB Recommendation Pending Review by NC Environmental Management Commission, Risk Assessment for Arsenic and Inorganic Arsenic Compounds at 4, Attachment 2.

³¹ *Id.*

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JS/MB/lap

Attachments:

1. ATSDR Toxicological Profile for Arsenic
2. NCSAB Recommendation Pending Review by NC Environmental Management Commission
3. EPA Toxicological Review Workshop
4. SELC Oct. 2012 Comments on Air Toxics Rules
5. SELC April 2013 Comments on Air Toxics Rules

TOXICOLOGICAL PROFILE FOR ARSENIC

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 2007

ATTACHMENT 1 TO SELC'S COMMENTS ON AAL AND TPER FOR ARSENIC
JUNE 14, 2013

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Arsenic, Draft for Public Comment was released in September 2005. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-32
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

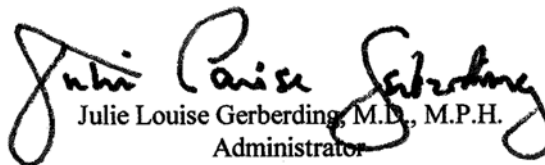
The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Howard Frumkin, M.D., Dr. P.H.
Director

National Center for Environmental Health/
Agency for Toxic Substances and
Disease Registry



Julie Louise Gerberding, M.D., M.P.H.
Administrator

Agency for Toxic Substances and
Disease Registry

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	How Can (Chemical X) Affect Children?
Section 1.7	How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7	Children's Susceptibility
Section 6.6	Exposures of Children

Other Sections of Interest:

Section 3.8	Biomarkers of Exposure and Effect
Section 3.11	Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) **Fax:** (770) 488-4178
E-mail: cdcinfo@cdc.gov **Internet:** <http://www.atsdr.cdc.gov>

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental*

Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

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Syracuse Research Corporation, North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for arsenic. The panel consisted of the following members:

1. Toby Rossman, Ph.D., Professor of Environmental Medicine, New York University School of Medicine, Nelson Institute of Environmental Medicine, Tuxedo, New York;
2. Rosalind Schoof, Ph.D., DABT, Integral Consulting, Inc., Mercer Island, Washington; and
3. Allan Smith, M.D., Ph.D., Professor of Epidemiology, School of Public Health, University of California, Berkeley, California.

Draft for Public Comment:

1. Alan Hall, M.D., Toxicology Consulting and Medical Translating Services, Inc. (TCMTS, Inc.), Elk Mountain, Wyoming;
2. Gary Pascoe, Ph.D., Pascoe Environmental Consulting, Port Townsend, Washington; and
3. Toby Rossman, Ph.D., Professor of Environmental Medicine, New York University School of Medicine, Nelson Institute of Environmental Medicine, Tuxedo, New York.

These experts collectively have knowledge of arsenic's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about arsenic and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Arsenic has been found in at least 1,149 of the 1,684 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which arsenic is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to arsenic, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ARSENIC?

Arsenic is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. Elemental arsenic (sometimes referred to as metallic arsenic) is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with

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these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic.

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. Thus, you usually cannot tell if arsenic is present in your food, water, or air.

Inorganic arsenic occurs naturally in soil and in many kinds of rock, especially in minerals and ores that contain copper or lead. When these ores are heated in smelters, most of the arsenic goes up the stack and enters the air as a fine dust. Smelters may collect this dust and take out the arsenic as a compound called arsenic trioxide (As_2O_3). However, arsenic is no longer produced in the United States; all of the arsenic used in the United States is imported.

Presently, about 90% of all arsenic produced is used as a preservative for wood to make it resistant to rotting and decay. The preservative is copper chromated arsenate (CCA) and the treated wood is referred to as “pressure-treated.” In 2003, U.S. manufacturers of wood preservatives containing arsenic began a voluntary transition from CCA to other wood preservatives that do not contain arsenic in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; however, wood treated prior to this date could still be used and existing structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications. It is not known whether, or to what extent, CCA-treated wood products may contribute to exposure of people to arsenic.

In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved

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properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic compounds is in semiconductors and light-emitting diodes.

To learn more about the properties and uses of arsenic, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT?

Arsenic occurs naturally in soil and minerals and it therefore may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching. Volcanic eruptions are another source of arsenic. Arsenic is associated with ores containing metals, such as copper and lead. Arsenic may enter the environment during the mining and smelting of these ores. Small amounts of arsenic also may be released into the atmosphere from coal-fired power plants and incinerators because coal and waste products often contain some arsenic.

Arsenic cannot be destroyed in the environment. It can only change its form, or become attached to or separated from particles. It may change its form by reacting with oxygen or other molecules present in air, water, or soil, or by the action of bacteria that live in soil or sediment. Arsenic released from power plants and other combustion processes is usually attached to very small particles. Arsenic contained in wind-borne soil is generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Arsenic that is attached to very small particles may stay in the air for many days and travel long distances. Many common arsenic compounds can dissolve in water. Thus, arsenic can get into lakes, rivers, or underground water by dissolving in rain or snow or through the discharge of industrial wastes. Some of the arsenic will stick to particles in the water or sediment on the bottom of lakes or rivers, and some will be carried along by the water. Ultimately, most arsenic ends up in the soil or sediment. Although some fish and shellfish take in arsenic, which may build up in tissues, most of this arsenic is in an organic form called arsenobetaine (commonly called "fish arsenic") that is much less harmful.

For more information on how arsenic behaves in the environment, see Chapter 6.

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1.3 HOW MIGHT I BE EXPOSED TO ARSENIC?

Since arsenic is found naturally in the environment, you will be exposed to some arsenic by eating food, drinking water, or breathing air. Children may also be exposed to arsenic by eating soil. Analytical methods used by scientists to determine the levels of arsenic in the environment generally do not determine the specific form of arsenic present. Therefore, we do not always know the form of arsenic a person may be exposed to. Similarly, we often do not know what forms of arsenic are present at hazardous waste sites. Some forms of arsenic may be so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals.

The concentration of arsenic in soil varies widely, generally ranging from about 1 to 40 parts of arsenic to a million parts of soil (ppm) with an average level of 3–4 ppm. However, soils in the vicinity of arsenic-rich geological deposits, some mining and smelting sites, or agricultural areas where arsenic pesticides had been applied in the past may contain much higher levels of arsenic. The concentration of arsenic in natural surface and groundwater is generally about 1 part in a billion parts of water (1 ppb), but may exceed 1,000 ppb in contaminated areas or where arsenic levels in soil are high. Groundwater is far more likely to contain high levels of arsenic than surface water. Surveys of U.S. drinking water indicate that about 80% of water supplies have less than 2 ppb of arsenic, but 2% of supplies exceed 20 ppb of arsenic. Levels of arsenic in food range from about 20 to 140 ppb. However, levels of inorganic arsenic, the form of most concern, are far lower. Levels of arsenic in the air generally range from less than 1 to about 2,000 nanograms (1 nanogram equals a billionth of a gram) of arsenic per cubic meter of air (less than 1–2,000 ng/m³), depending on location, weather conditions, and the level of industrial activity in the area. However, urban areas generally have mean arsenic levels in air ranging from 20 to 30 ng/m³.

You normally take in small amounts of arsenic in the air you breathe, the water you drink, and the food you eat. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine that is much less harmful. Some seaweeds may

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contain arsenic in inorganic forms that may be more harmful. Children are likely to eat small amounts of dust or soil each day, so this is another way they may be exposed to arsenic. The total amount of arsenic you take in from these sources is generally about 50 micrograms (1 microgram equals one-millionth of a gram) each day. The level of inorganic arsenic (the form of most concern) you take in from these sources is generally about 3.5 microgram/day. Children may be exposed to small amounts of arsenic from hand-to-mouth activities from playing on play structures or decks constructed out of CCA-treated wood. The potential exposure that children may receive from playing in play structures constructed from CCA-treated wood is generally smaller than that they would receive from food and water. Hand washing can reduce the potential exposure of children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water.

In addition to the normal levels of arsenic in air, water, soil, and food, you could be exposed to higher levels in several ways, such as the following:

- Some areas of the United States contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water. If you live in an area like this, you could take in elevated amounts of arsenic in drinking water. Children may be taking in higher amounts of arsenic because of hand-to-mouth contact or eating soil in areas with higher than usual arsenic concentrations.
- Some hazardous waste sites contain large quantities of arsenic. If the material is not properly disposed of, it can get into surrounding water, air, or soil. If you live near such a site, you could be exposed to elevated levels of arsenic from these media.
- If you work in an occupation that involves arsenic production or use (for example, copper or lead smelting, wood treating, or pesticide application), you could be exposed to elevated levels of arsenic during your work.
- If you saw or sand arsenic-treated wood, you could inhale some of the sawdust into your nose or throat. Similarly, if you burn arsenic-treated wood, you could inhale arsenic in the smoke.
- If you live in a former agricultural area where arsenic was used on crops, the soil could contain high levels of arsenic.

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- In the past, several kinds of products used in the home (rat poison, ant poison, weed killer, some types of medicines) had arsenic in them. However, most of these uses of arsenic have ended, so you are not likely to be exposed from home products any longer.

You can find more information on how you may be exposed to arsenic in Chapter 6.

1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY?

If you swallow arsenic in water, soil, or food, most of the arsenic may quickly enter into your body. The amount that enters your body will depend on how much you swallow and the kind of arsenic that you swallow. This is the most likely way for you to be exposed near a waste site. If you breathe air that contains arsenic dusts, many of the dust particles settle onto the lining of the lungs. Most of the arsenic in these particles is then taken up from the lungs into the body. You might be exposed in this way near waste sites where arsenic-contaminated soils are allowed to blow into the air, or if you work with arsenic-containing soil or products. If you get arsenic-contaminated soil or water on your skin, only a small amount will go through your skin into your body, so this is usually not of concern.

Both inorganic and organic forms leave your body in your urine. Most of the inorganic arsenic will be gone within several days, although some will remain in your body for several months or even longer. If you are exposed to organic arsenic, most of it will leave your body within several days.

You can find more information on how arsenic enters and leaves your body in Chapter 3.

1.5 HOW CAN ARSENIC AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

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One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Inorganic arsenic has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in water which is 10,000 times higher than 80% of U.S. drinking water arsenic levels) can result in death. If you swallow lower levels of inorganic arsenic (ranging from about 300 to 30,000 ppb in water; 100–10,000 times higher than most U.S. drinking water levels), you may experience irritation of your stomach and intestines, with symptoms such as stomachache, nausea, vomiting, and diarrhea. Other effects you might experience from swallowing inorganic arsenic include decreased production of red and white blood cells, which may cause fatigue, abnormal heart rhythm, blood-vessel damage resulting in bruising, and impaired nerve function causing a "pins and needles" sensation in your hands and feet.

Perhaps the single-most characteristic effect of long-term oral exposure to inorganic arsenic is a pattern of skin changes. These include patches of darkened skin and the appearance of small "corns" or "warts" on the palms, soles, and torso, and are often associated with changes in the blood vessels of the skin. Skin cancer may also develop. Swallowing arsenic has also been reported to increase the risk of cancer in the liver, bladder, and lungs. The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen (a chemical that causes cancer). The International Agency for Research on Cancer (IARC) has determined that inorganic arsenic is carcinogenic to humans. EPA also has classified inorganic arsenic as a known human carcinogen.

If you breathe high levels of inorganic arsenic, then you are likely to experience a sore throat and irritated lungs. You may also develop some of the skin effects mentioned above. The exposure level that produces these effects is uncertain, but it is probably above 100 micrograms of arsenic

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per cubic meter ($\mu\text{g}/\text{m}^3$) for a brief exposure. Longer exposure at lower concentrations can lead to skin effects, and also to circulatory and peripheral nervous disorders. There are some data suggesting that inhalation of inorganic arsenic may also interfere with normal fetal development, although this is not certain. An important concern is the ability of inhaled inorganic arsenic to increase the risk of lung cancer. This has been seen mostly in workers exposed to arsenic at smelters, mines, and chemical factories, but also in residents living near smelters and arsenical chemical factories. People who live near waste sites with arsenic may have an increased risk of lung cancer as well.

If you have direct skin contact with high concentrations of inorganic arsenic compounds, your skin may become irritated, with some redness and swelling. However, it does not appear that skin contact is likely to lead to any serious internal effects.

Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms. In animals, ingestion of methyl compounds can result in diarrhea, and lifetime exposure can damage the kidneys. Lifetime exposure to dimethyl compounds can damage the urinary bladder and the kidneys.

You can find more information on the health effects of inorganic and organic arsenic in Chapters 2 and 3.

1.6 HOW CAN ARSENIC AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Children are exposed to arsenic in many of the same ways that adults are. Since arsenic is found in the soil, water, food, and air, children may take in arsenic in the air they breathe, the water they drink, and the food they eat. Since children tend to eat or drink less of a variety of foods and beverages than do adults, ingestion of contaminated food or juice or infant formula made

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with arsenic-contaminated water may represent a significant source of exposure. In addition, since children often play in the soil and put their hands in their mouths and sometimes intentionally eat soil, ingestion of contaminated soil may be a more important source of arsenic exposure for children than for adults. In areas of the United States where natural levels of arsenic in the soil and water are high, or in areas in and around contaminated waste sites, exposure of children to arsenic through ingestion of soil and water may be significant. In addition, contact with adults who are wearing clothes contaminated with arsenic (e.g., with dust from copper- or lead-smelting factories, from wood-treating or pesticide application, or from arsenic-treated wood) could be a source of exposure. Because of the tendency of children to taste things that they find, accidental poisoning from ingestion of pesticides is also a possibility. Thus, although most of the exposure pathways for children are the same as those for adults, children may be at a higher risk of exposure because of normal hand-to-mouth activity.

Children who are exposed to inorganic arsenic may have many of the same effects as adults, including irritation of the stomach and intestines, blood vessel damage, skin changes, and reduced nerve function. Thus, all health effects observed in adults are of potential concern in children. There is also some evidence that suggests that long-term exposure to inorganic arsenic in children may result in lower IQ scores. We do not know if absorption of inorganic arsenic from the gut in children differs from adults. There is some evidence that exposure to arsenic in early life (including gestation and early childhood) may increase mortality in young adults.

There is some evidence that inhaled or ingested inorganic arsenic can injure pregnant women or their unborn babies, although the studies are not definitive. Studies in animals show that large doses of inorganic arsenic that cause illness in pregnant females can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues. Arsenic is found at low levels in breast milk.

In animals, exposure to organic arsenic compounds can cause low birth weight, fetal malformations, and fetal deaths. The dose levels that cause these effects also result in effects in the mothers.

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You can find more information about how arsenic can affect children in Sections 3.7 and 6.6.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ARSENIC?

If your doctor finds that you have been exposed to substantial amounts of arsenic, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Many communities may have high levels of arsenic in their drinking water, particularly from private wells, because of contamination or as a result of the geology of the area. The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. Wells used to provide water for drinking and cooking should be tested for arsenic. As of January 2006, EPA's Maximum Contaminant Level (MCL) for arsenic in drinking water is 10 ppb. If you have arsenic in your drinking water at levels higher than the EPA's MCL, an alternative source of water should be used for drinking and cooking should be considered.

If you use arsenic-treated wood in home projects, personal protection from exposure to arsenic-containing sawdust may be helpful in limiting exposure of family members. These measures may include dust masks, gloves, and protective clothing. Arsenic-treated wood should never be burned in open fires, or in stoves, residential boilers, or fire places, and should not be composted or used as mulch. EPA's Consumer Awareness Program (CAP) for CCA is a voluntary program established by the manufacturers of CCA products to inform consumers about the proper handling, use, and disposal of CCA-treated wood. You can find more information about this program in Section 6.5. Hand washing can reduce the potential exposure of children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water.

If you live in an area with a high level of arsenic in the water or soil, substituting cleaner sources of water and limiting contact with soil (for example, through use of a dense groundcover or thick lawn) would reduce family exposure to arsenic. By paying careful attention to dust and soil

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control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated soil. Some children eat a lot of soil. You should prevent your children from eating soil. You should discourage your children from putting objects in their mouths. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or engaging in other hand-to-mouth activities. Since arsenic may be found in the home as a pesticide, household chemicals containing arsenic should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number by the phone.

It is sometimes possible to carry arsenic from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in the fertilizer, pesticide, glass, or copper/lead smelting industries. You may contaminate your car, home, or other locations outside work where children might be exposed to arsenic. You should know about this possibility if you work with arsenic.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) for many chemicals used should be found at your place of work, as required by the Occupational Safety and Health Administration (OSHA) in the U.S. Department of Labor. MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion data, potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your state OSHA-approved occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or

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OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

You can find more information about how arsenic can affect children in Sections 3.7 and 6.6.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ARSENIC?

Several sensitive and specific tests can measure arsenic in your blood, urine, hair, or fingernails, and these tests are often helpful in determining if you have been exposed to above-average levels of arsenic in the past. These tests are not usually performed in a doctor's office. They require sending the sample to a testing laboratory.

Measurement of arsenic in your urine is the most reliable means of detecting arsenic exposures that you experienced within the last several days. Most tests measure the total amount of arsenic present in your urine. This can sometimes be misleading, because the nonharmful forms of arsenic in fish and shellfish can give a high reading even if you have not been exposed to a toxic form of arsenic. For this reason, laboratories sometimes use a more complicated test to separate "fish arsenic" from other forms. Because most arsenic leaves your body within a few days, analysis of your urine cannot detect if you were exposed to arsenic in the past. Tests of your hair or fingernails can tell if you were exposed to high levels over the past 6–12 months, but these tests are not very useful in detecting low-level exposures. If high levels of arsenic are detected, this shows that you have been exposed, but unless more is known about when you were exposed and for how long, it is usually not possible to predict whether you will have any harmful health effects.

You can find more information on how arsenic can be measured in your hair, urine, nails, and other tissues in Chapters 3 and 7.

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1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations *can* be enforced by law. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as “not-to-exceed” levels, that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for ARSENIC include the following:

The federal government has taken several steps to protect humans from arsenic. First, EPA has set limits on the amount of arsenic that industrial sources can release into the environment. Second, EPA has restricted or canceled many of the uses of arsenic in pesticides and is considering further restrictions. Third, in January 2001, the EPA lowered the limit for arsenic in drinking water from 50 to 10 ppb. Finally, OSHA has established a permissible exposure limit (PEL), 8-hour time-weighted average, of $10 \mu\text{g}/\text{m}^3$ for airborne arsenic in various workplaces that use inorganic arsenic.

You can find more information on regulations and guidelines that apply to arsenic in Chapter 8.

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1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: <http://www.ntis.gov/>

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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ARSENIC IN THE UNITED STATES

Arsenic is widely distributed in the Earth's crust, which contains ~3.4 ppm arsenic. In nature, arsenic is mostly found in minerals and only to a small extent in its elemental form. Arsenic is mainly obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores. Arsenic trioxide is the primary form in which arsenic is marketed and consumed. There has been no domestic production of arsenic since 1985. In 2003, the world's largest producer of arsenic compounds was China, followed by Chile and Peru.

In 2003, the United States was the world's largest consumer of arsenic. Production of wood preservatives, primarily copper chromated arsenate (CCA), $\text{CrO}_3 \cdot \text{CuO} \cdot \text{As}_2\text{O}_5$, accounted for >90% of domestic consumption of arsenic trioxide. In response to consumer concerns, U.S. manufacturers of arsenical wood preservative began a voluntary transition from CCA to other wood preservatives for certain residential wood products. This phase-out was completed on December 31, 2003; wood treated prior to this date could still be used and CCA-treated wood products continue to be used in industrial applications.

Other uses for arsenic compounds include the production of agricultural chemicals, as an alloying element in ammunition and solders, as an anti-friction additive to metals used for bearings, and to strengthen lead-acid storage battery grids. High-purity arsenic (99.9999%) is used by the electronics industry for gallium-arsenide semiconductors for telecommunications, solar cells, and space research. Various organic arsenicals are still used in the United States as herbicides and as antimicrobial additives for animal and poultry feed. However, the use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s. Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware. Arsenic compounds also have a long history of use in medicine, and have shown a re-emergence of late with the recent introduction of arsenic trioxide treatment for acute promyelocytic leukemia.

The principal route of exposure to arsenic for the general population is likely to be the oral route, primarily in the food and in the drinking water. Dietary exposures to total arsenic were highly variable, with a mean of 50.6 $\mu\text{g}/\text{day}$ (range of 1.01–1,081 $\mu\text{g}/\text{day}$) for females and 58.5 $\mu\text{g}/\text{day}$ (range of 0.21–1,276 $\mu\text{g}/\text{day}$) for males. U.S. dietary intake of inorganic arsenic has been estimated to range from 1 to 20 $\mu\text{g}/\text{day}$, with grains and produce expected to be significant contributors to dietary inorganic arsenic

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intake. Drinking water generally contains an average of 2 µg/L of arsenic, although 12% of water supplies from surface water sources in the North Central region of the country and 12% of supplies from groundwater sources in the Western region have levels exceeding 20 µg/L. Arsenic is also widely distributed in surface water, groundwater, and finished drinking water in the United States. Surveys of arsenic concentrations in rivers and lakes indicate that most values are below 10 µg/L, although individual samples may range up to 3,400 µg/L. Arsenic released to the land at hazardous waste sites is likely to be relatively immobile due to a high capacity for soil binding, particularly to iron and manganese oxides. Exposure to arsenic from other pathways is generally small, but may be significant for areas with high levels of arsenic contamination or in occupational settings. For a more complete discussion of possible exposures to arsenic, see Chapter 6 of the profile.

2.2 SUMMARY OF HEALTH EFFECTS

Arsenic is a potent toxicant that may exist in several oxidation states and in a number of inorganic and organic forms. Most cases of arsenic-induced toxicity in humans are due to exposure to inorganic arsenic, and there is an extensive database on the human health effects of the common arsenic oxides and oxyacids. Although there may be some differences in the potency of different chemical forms (e.g., arsenites tend to be somewhat more toxic than arsenates), these differences are usually minor. An exception would be arsine, which is highly toxic. However, because arsine and its methyl derivatives are gases or volatile liquids and are unlikely to be present at levels of concern at hazardous waste sites, health effect data for these compounds are not discussed in this document. Humans may be exposed to organic arsenicals (mainly methyl and phenyl derivatives of arsenic acid) that are used in agriculture and to organic arsenicals found in fish and shellfish (arsenobetaine and arsenocholine). Although the toxicity of organic arsenicals has not been as extensively investigated as inorganic arsenicals, there are sufficient animal data to evaluate the toxicity of methyl arsenates (e.g., monomethylarsonic acid [MMA] and dimethylarsinic acid [DMA]) and roxarsone. The so-called “fish arsenic” compounds (e.g., arsenobetaine) are not thought to be toxic and health effects data are not discussed in this document.

It is generally accepted that the arsenic-carbon bond is quite strong and most mammalian species do not have the capacity to break this bond; thus, inorganic arsenic is not formed during the metabolism of organic arsenicals. In most species, including humans, ingested (or exogenous) MMA(V) and DMA(V) undergo limited metabolism, do not readily enter the cell, and are primarily excreted unchanged in the urine. This is in contrast to inorganic arsenic, which undergoes sequential reduction and methylation reactions leading to the formation of MMA and DMA. Inorganic As(V) is readily reduced to inorganic

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As(III), which is taken up by the cell. Within the cell (primarily in the liver), As(III) is methylated to form MMA(V), which is reduced to MMA(III); MMA(III) subsequently undergoes oxidative methylations to form DMA(V). DMA(V) is the primary excretion product in humans. Because inorganic and organic arsenicals exhibit distinct toxicokinetic characteristics, the health effects and MRLs are considered separately.

Inorganic Arsenicals. Exposures of humans near hazardous waste sites could involve inhalation of arsenic dusts in air, ingestion of arsenic in water, food, or soil, or dermal contact with contaminated soil or water. Increased risk of lung cancer, respiratory irritation, nausea, skin effects, and neurological effects have been reported following inhalation exposure. There are only a few quantitative data on noncancer effects in humans exposed to inorganic arsenic by the inhalation route. Animal data similarly identify effects on the respiratory system as the primary noncancer effect of inhaled inorganic arsenic compounds, although only a few studies are available. Only limited data on the effects of inhaled organic arsenic compounds in humans or animals are available; these studies are generally limited to high-dose, short-term exposures, which result in frank effects.

Relatively little information is available on effects due to direct dermal contact with inorganic arsenicals, but several studies indicate that the chief effect is local irritation and dermatitis, with little risk of other adverse effects.

The database for the oral toxicity of inorganic arsenic is extensive, containing a large number of studies of orally-exposed human populations. These studies have identified effects on virtually every organ or tissue evaluated, although some end points appear to be more sensitive than others. The available data from humans identify the skin as the most sensitive noncancer target following long-term oral arsenic exposure. Typical dermal effects include hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Oral exposure data from studies in humans indicate that these lesions typically begin to manifest at exposure levels of about 0.002–0.02 mg As/kg/day, but one study suggests that lesions may appear at even lower levels. At these exposure levels, peripheral vascular effects are also commonly noted, including cyanosis, gangrene, and, in Taiwanese populations, the condition known as “Blackfoot Disease.” Other reported cardiovascular effects of oral exposure to inorganic arsenic include increased incidences of high blood pressure and circulatory problems. The use of intravenous arsenic trioxide as therapy for acute promyelocytic leukemia has raised further concerns about the cardiovascular effects of arsenic, including alterations in cardiac QT interval and the

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development of torsades de pointes. Decrements in lung function, assessed by spirometry, have been reported in subjects exposed to approximately 0.008–0.04 mg As/kg/day in the drinking water who exhibited skin lesions.

In addition to dermal, cardiovascular, and respiratory effects, oral exposure to inorganic arsenic may result in effects on other organ systems. Nausea, vomiting, and diarrhea are very common symptoms in humans following oral exposure to inorganic arsenicals, both after acute high-dose exposure and after repeated exposure to lower doses; these effects are likely due to a direct irritation of the gastrointestinal mucosa. Acute, high-dose exposure can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability, while long-term exposure to lower levels can lead to the development of peripheral neuropathy characterized by a numbness in the hands and feet that may progress to a painful "pins and needles" sensation. Recent studies also have reported neurobehavioral alterations in arsenic-exposed children.

Chronic exposure of humans to inorganic arsenic in the drinking water has been associated with excess incidence of miscarriages, stillbirths, preterm births, and infants with low birth weights. Animal data suggest that arsenic may cause changes to reproductive organs of both sexes, including decreased organ weight and increased inflammation of reproductive tissues, although these changes may be secondary effects. However, these changes do not result in a significant impact on reproductive ability. Animal studies of oral inorganic arsenic exposure have reported developmental effects, but generally only at concentrations that also resulted in maternal toxicity.

Arsenic is a known human carcinogen by both the inhalation and oral exposure routes. By the inhalation route, the primary tumor types are respiratory system cancers, although a few reports have noted increased incidence of tumors at other sites, including the liver, skin, and digestive tract. In humans exposed chronically by the oral route, skin tumors are the most common type of cancer. In addition to skin cancer, there are a number of case reports and epidemiological studies that indicate that ingestion of arsenic also increases the risk of internal tumors (mainly of bladder and lung, and to a lesser extent, liver, kidney, and prostate).

The Department of Health and Human Services (DHHS) has concluded that inorganic arsenic is known to be a human carcinogen. The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer. The IARC classification of arsenic is Group 1. The EPA has determined that inorganic arsenic is a human carcinogen by the

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inhalation and oral routes, and has assigned it the cancer classification, Group A. EPA has calculated an oral cancer slope factor of $1.5 \text{ (mg/kg/day)}^{-1}$ and a drinking water unit risk of $5 \times 10^{-5} \text{ (}\mu\text{g/L)}^{-1}$ for inorganic arsenic based on human dose-response data. The inhalation unit risk for cancer is calculated to be $0.0043 \text{ (}\mu\text{g/m}^3\text{)}^{-1}$. The unit risk is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of $1 \text{ }\mu\text{g/L}$ in water or $1 \text{ }\mu\text{g/m}^3$ in air. EPA is currently revising the assessment for inorganic arsenic; a more detailed discussion of the uncertainties associated with human cancer risk levels for arsenic is presented in Section 3.2.2.7.

The following sections discuss significant effects resulting from exposure to inorganic arsenic in greater detail: dermal, cardiovascular, respiratory, gastrointestinal, neurological, and cancer. Additional information on these effects and on other effects is discussed in Section 3.2.

Dermal Effects. The most characteristic effect of long-term oral exposure to inorganic arsenic compounds is the development of skin lesions; these lesions are often used as diagnostic criteria for arsenicosis. The three lesions most often associated with chronic arsenicosis are hyperkeratinization of the skin (especially on the palms and soles), formation of multiple hyperkeratinized corns or warts, and hyperpigmentation of the skin with interspersed spots of hypopigmentation. Numerous studies of long-term, low-level exposure to inorganic arsenic in humans have reported the presence of these lesions. In general, they begin to manifest at chronic exposure levels $>0.02 \text{ mg As/kg/day}$. Chronic oral studies of lower exposure levels, ranging from 0.0004 to $0.01 \text{ mg As/kg/day}$, have generally not reported dermal effects. However, in a study with detailed exposure assessment, all confirmed cases of skin lesions ingested water containing $>100 \text{ }\mu\text{g/L}$ arsenic (approximately $0.0037 \text{ mg As/kg/day}$) and the lowest known peak arsenic concentration ingested by a case was $0.115 \text{ }\mu\text{g/L}$ (approximately $0.0043 \text{ mg As/kg/day}$). Another large study reported increased incidence of skin lesions associated with estimated doses of $0.0012 \text{ mg As/kg/day}$ (0.023 mg As/L drinking water). The mechanism(s) by which inorganic arsenic causes dermal effects is not well-understood. Elucidating the mechanism of dermal effects has been particularly difficult because the dermal effects common in humans have not been seen in studies in animals.

Dermal effects have also been reported following inhalation exposures to inorganic arsenic, although they are not as diagnostic as for oral exposure. Several studies of arsenic-exposed workers have reported the development of dermatitis; exposure levels required to produce this condition are not well-established. Altered dermal pigmentation and hyperkeratosis have also been reported in studies of humans exposed to inorganic arsenic by inhalation, although exposure levels have varied considerably. Direct dermal contact

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with inorganic arsenicals may cause irritation and contact dermatitis. Usually, the effects are mild (erythema and swelling), but may progress to papules, vesicles, or necrotic lesions in extreme cases; these conditions tend to heal without treatment if exposure ceases.

Cardiovascular Effects. A large number of studies in humans have reported cardiovascular effects following oral exposure to inorganic arsenic compounds. The cardiac effects of arsenic exposure are numerous, and include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes), cardiac arrhythmias, and ischemic heart disease. These effects have been seen after acute and long-term exposure to inorganic arsenic in the environment, as well as side effects from intravenous therapy with arsenic trioxide for acute promyelocytic leukemia. Exposure levels for environmental exposures have not been well characterized, but intravenous doses for arsenic trioxide therapy are generally on the order of 0.15 mg As/kg/day.

Chronic exposure to inorganic arsenic has also been shown to lead to effects on the vascular system. The most dramatic of these effects is “Blackfoot Disease,” a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene. Blackfoot Disease is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm, corresponding to doses of about 0.014–0.065 mg As/kg/day. The results of another study suggested that individuals with a lower capacity to methylate inorganic arsenic to DMA have a higher risk of developing peripheral vascular disease in the Blackfoot Disease-hyperendemic area in Taiwan. Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular and microvascular diseases and ischemic heart disease. While Blackfoot Disease itself has not been reported outside of Taiwan, other vascular effects are common in areas with high arsenic exposures, and include such severe effects as increases in the incidences of Raynaud's disease and of cyanosis of fingers and toes as well as hypertension, thickening and vascular occlusion of blood vessels, and other unspecified cardiovascular conditions. However, while the majority of human studies have reported cardiovascular effects following exposure to inorganic arsenic, some have found no such effects.

Changes in cardiac rhythm and in some vascular end points have also been reported in animal studies of inorganic arsenicals, but generally only at higher exposure levels and not to the degree of severity seen in humans.

Respiratory Effects. While case reports and small cohort studies have routinely reported an increase in respiratory symptoms of humans exposed occupationally to inorganic arsenic, dose-response data for

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these symptoms are generally lacking. The only study that evaluated respiratory effects (changes in chest x-ray or respiratory performance) and reported an exposure estimate did not report significant changes at an exposure level of 0.613 mg As/m^3 . Exposed workers often report irritation of the mucous membranes of the nose and throat, which may lead to laryngitis, bronchitis, or rhinitis. Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association of these diseases with arsenic exposure has been presented. It is not known whether respiratory effects following inhaled inorganic arsenic compounds are due to a direct effect of arsenic on respiratory tissues, general effects of foreign material in the lungs, or an effect of arsenic on the pulmonary vasculature. Similar responses, including rales, labored breathing, and respiratory hyperplasia, have been noted in animal studies of inhaled or instilled inorganic arsenic compounds.

Respiratory effects have also been reported following oral exposure of humans to inorganic arsenic. Acute oral exposure to $\geq 8 \text{ mg As/kg}$ may result in serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema; however, it is not clear whether these are primary effects or are the result of damage to the pulmonary vascular system. In general, respiratory effects have not been widely associated with long-term oral exposure to low arsenic doses. However, some studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to $0.03\text{--}0.05 \text{ mg As/kg/day}$. More serious respiratory effects, such as bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed in patients chronically exposed to arsenic and at autopsy in some chronic poisoning cases. There are few animal data reporting respiratory effects of oral exposure to inorganic arsenic, and those studies generally found effects only at very high dose levels.

Gastrointestinal Effects. Both short-term and chronic oral exposures to inorganic arsenicals have been reported to result in irritant effects on gastrointestinal tissues. Numerous studies of acute, high-dose exposure to inorganic arsenicals have reported nausea, vomiting, diarrhea, and abdominal pain, although specific dose levels associated with the onset of these symptoms have not been identified. Chronic oral exposure to $0.01 \text{ mg As/kg/day}$ generally results in similar reported symptoms. For both acute and chronic exposures, the gastrointestinal effects generally diminish or resolve with cessation of exposure. Similar gastrointestinal effects have been reported after occupational exposures to inorganic arsenicals, although it is not known if these effects were due to absorption of arsenic from the respiratory tract or from mucociliary clearance resulting in eventual oral exposure.

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Neurological Effects. A common effect following both oral and inhalation exposure to inorganic is the development of peripheral neuropathy. Following occupational exposure to inorganic arsenic in pesticide plants or smelters, exposed workers have shown increased incidence of neurological changes, including altered nerve conduction velocities. One study reported that these effects were seen after 28 years of exposure to 0.31 mg As/m^3 . In another study, signs and symptoms of sensory and motor polyneuropathy on both upper and lower extremities were reported in workers at a power station in Slovakia. The average length of exposure was 22.3 years (standard deviation [SD] ± 8.4 years) and the average arsenic exposure in inhaled air ranged from 4.6 to $142.7 \text{ } \mu\text{g/m}^3$.

Following high-dose ($>2 \text{ mg As/kg/day}$) acute oral exposures to inorganic arsenicals in humans, reported effects include headache, lethargy, mental confusion, hallucination, seizures, and coma. Following longer-term exposure to $0.03\text{--}0.1 \text{ mg As/kg/day}$, peripheral neuropathy, characterized initially by numbness of the hands and feet and a “pins and needles” sensation and progressing to muscle weakness, wrist-drop and/or ankle-drop, diminished sensitivity, and altered reflex action. Histological features of the neuropathy include a dying-back axonopathy and demyelination. Following removal from exposure, the neuropathy is only partially reversible and what recovery does occur is generally slow. Reports of neurological effects at lower arsenic levels ($0.004\text{--}0.006 \text{ mg As/kg/day}$) have been inconsistent, with some human studies reporting fatigue, headache, depression, dizziness, insomnia, nightmare, and numbness while others reported no neurological effects. Some studies also have reported that exposure to arsenic may be associated with intellectual deficits in children. Neurological effects have also been reported in oral studies of arsenic toxicity in animals, although these were generally performed at higher doses ($0.4\text{--}26.6 \text{ mg As/kg/day}$) than has been reported in exposed human populations. The mechanism(s) of arsenic-induced neurological changes has not been determined.

Cancer. There is clear evidence from studies in humans that exposure to inorganic arsenic by either the inhalation or oral routes increases the risk of cancer. Numerous studies of copper smelters or miners exposed to arsenic trioxide have reported an increased risk of lung cancer. Increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate. Other studies suggest that residents living near smelters or arsenical chemical plants may have increased risk of lung cancer, although the reported increases are small and are not clearly detectable in all cases. In general, studies reporting long-term exposure to 0.07 mg As/m^3 or greater have shown an increased incidence of lung cancer, while at lower exposure levels, the association has been less clear or not present.

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There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer. The most common tumors seen are squamous cell carcinomas, which may develop from the hyperkeratotic warts or corns commonly seen as a dermal effect of oral inorganic arsenic exposure. Early studies of populations within the United States did not suggest an increased risk of cancer from oral inorganic arsenic exposure. Later studies have found suggestive evidence that the possibility of arsenic-induced skin cancers cannot be discounted based on an association between toenail arsenic levels and incidence of skin cancer.

There is increasing evidence that long-term exposure to arsenic can result in the development of bladder cancer, with transitional cell cancers being the most prevalent. While studies have noted statistical dose-response trends in arsenic-induced bladder cancers, reliable quantitative assessments of dose-response relationships have not been presented. Several studies have also shown that chronic oral exposure to arsenic results in the development of respiratory tumors, making lung cancer an established cause of death from exposure to arsenic in drinking water. Exposure levels in studies evaluating respiratory and bladder cancers have been comparable to those in studies evaluating skin tumors. Studies of U.S. populations have not identified an increased risk of bladder or respiratory tumors following oral exposure to inorganic arsenic.

Animal studies of both inhalation and oral exposure to inorganic arsenicals have not resulted in increased incidence of cancer formation in adult animals. However, a series of studies have shown that inorganic arsenic can induce cancer in the offspring from mice exposed to arsenic during gestation (transplacental carcinogen) and acts as a co-carcinogen with UV light and polycyclic aromatic hydrocarbons (PAHs).

Organic Arsenicals. Humans may be exposed to organic arsenicals via inhalation of dusts, ingestion of organic arsenic in water, food, soil, or dermal contact with contaminated soil, water or plants following pesticide application. There are limited data on the toxicity of organic arsenicals following inhalation exposure in humans and animals and these data do not allow for identification of critical effects. Keratosis was observed in workers exposed to 0.065 mg/m³ arsanilic acid (i.e., 4-aminophenyl arsenic acid); no alterations in gastrointestinal symptoms or hematological alterations were observed. In animals, very high concentrations (>3,000 mg/m³) of DMA results in respiratory distress, diarrhea, and erythematous lesions on the feet and ears. No adverse effects were observed in rats exposed to DMA concentrations as high as 100 mg DMA/m³ for 95 days.

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Similarly, the available dermal toxicity data do not allow for identification of critical effects. Contact dermatitis was observed in workers applying DMA (and its sodium salt) and mild dermal irritation was observed in a Draize test in rabbits (adverse effect level not reported). Intermediate duration (21 days) exposure studies in rabbits did not result in systemic toxicity or skin irritation following 5 day/week exposure to 1,000 mg/kg/day MMA or DMA.

The preponderance of toxicity data for organic arsenicals involves oral exposure. Human data are limited to three case reports of individuals intentionally ingesting pesticides containing organic arsenicals. Gastrointestinal irritation (vomiting, nausea, and diarrhea) were consistently reported in these cases. Animal data has primarily focused on the toxicity of MMA, DMA, and roxarsone; these data suggest that the targets of toxicity may differ between the compounds.

MMA. The gastrointestinal tract appears to be the most sensitive target of toxicity for MMA. Diarrhea and tissue damage in the large intestine have been reported in several animal species following dietary, gavage, and capsule exposure. For diarrhea, both the time of onset and incidence appear to be dose-related. In rats, diarrhea was observed in 100% of females exposed to 98.5 mg MMA/kg/day, 55% of females exposed to 33.9 mg MMA/kg/day, and 5.1% of females exposed to 3.9 mg MMA/kg/day. The increased incidence of diarrhea was observed after 3 weeks of exposure to 98.5 mg MMA/kg/day, 4 weeks at 33.9 mg MMA/kg/day, and 18 months at 3.9 mg MMA/kg/day. Histological damage consisting of squamous metaplasia of the epithelial columnar absorptive cells in the cecum, colon, and rectum was observed in rats and mice chronically exposed to 72.4 or 67.1 mg MMA/kg/day, respectively. Hemorrhagic, necrotic, ulcerated, or perforated mucosa were also observed in the large intestine of rats exposed to 67.1 mg MMA/kg/day for 2 years. In rats, the damage to the large intestine resulted in intestinal contents leaking into the abdominal cavity and the development of peritonitis. The available data provide suggestive evidence that there may be some species differences in the sensitivity to gastrointestinal damage; however, some of these differences may be due to the route of administration. The lowest adverse effect levels, regardless of duration of exposure, for gastrointestinal effects in rats, mice, rabbits, and dogs are 25.7, 67.1, 12, and 2 mg MMA/kg/day, respectively; the no adverse effect levels in rats and mice (NOAELs were not identified in rabbits and dogs) were 3.0 and 24.9 mg MMA/kg/day. However, the rabbit and dog studies involved bolus administration (gavage and capsule administration), which may have increased sensitivity; the rat and mouse studies involved dietary exposure.

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The kidney also appears to be a sensitive target in rats and mice chronically exposed to MMA. An increase in the severity of progressive glomerulonephropathy was observed in female rats exposed to 33.9 mg MMA/kg/day for 2 years and an increase in the incidence of progressive glomerulonephropathy was observed in male mice exposed to 6.0 mg MMA/kg/day for 2 years. Other adverse effects that have been observed in animals exposed to MMA include hypertrophy of the thyroid follicular cells in rats exposed to 33.9 mg MMA/kg/day in the diet for 2 years, reproductive toxicity, and developmental toxicity. Decreases in pregnancy rate and male fertility index were observed in F₀ and F₁ rats exposed to 76 mg MMA/kg/day for 14 weeks prior to mating and during the mating period; the findings were not significantly different than control values but were considered treatment-related because they were outside the range found in historical controls. This study also reported a decrease in pup survival in the F₁ and F₂ offspring of rats exposed to 76 mg MMA/kg/day; as with the reproductive effects, the incidence was not statistically different from controls but was considered biologically significant because survival in the MMA pups was outside the range found in historical controls. Another study reported impaired fetal growth (decreases in fetal weights and incomplete ossification) and minor skeletal defects (an increase in the number of fetuses with supernumerary thoracic ribs and eight lumbar vertebrae) in rat and rabbit fetuses exposed to 500 or 12mg MMA/kg/day, respectively; maternal toxicity was also observed at these dose levels and the effects may be secondary to maternal stress rather than a direct effect on the developing organisms. A 2-year bioassay did not result in significant increases in the incidence of neoplastic lesions in rats and mice exposed to doses as high as 72.4 and 67.1 mg MMA/kg/day, respectively.

DMA. The most sensitive targets of DMA toxicity in rats are the urinary bladder and kidneys. In the bladder, the effects progress from cytotoxicity to cellular necrosis to regenerative proliferation and hyperplasia. At dietary doses of 11 mg DMA/kg/day, cytotoxicity is observed as early as 6 hours after exposure initiation and cellular proliferation (as evident by increased BrdU labeling) was observed after 2 weeks of exposure. After 10 weeks of exposure, necrosis and hyperplasia were also observed. The lowest adverse effect levels for urinary bladder effects following intermediate or chronic duration exposure were 5 mg DMA/kg/day for evidence of regenerative proliferation and 3.1 mg DMA/kg/day for vacuolar degeneration of urothelium and hyperplasia. Vacuolization of the superficial cells of the urothelium was observed in mice exposed to 7.8 mg DMA/kg/day and higher for 2 years. However, unlike the vacuolar degeneration observed in rats, the vacuolization observed in mice was not associated with cytotoxicity, necrosis, inflammation, or hyperplasia.

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Kidney damage characterized by increased urinary calcium levels, calcification, nephrocalcinosis, and necrosis of the renal papillae have been observed in rats following intermediate- or chronic-duration exposure. Increases in urine calcium levels and corticomedullary junction calcification were observed in rats exposed to 5 or 10 mg DMA/kg/day for 10 weeks and cortical degeneration and necrosis were observed in rats exposed to 57 mg DMA/kg/day for 4 weeks. Chronic-duration exposure to 3.1 mg DMA/kg/day resulted in an increased incidence of nephrocalcinosis and necrosis of the renal papillae in rats; these lesions are typical in aged rats, although DMA exposure appeared to exacerbate them. An exacerbation of age-related kidney lesion (progressive glomerulonephropathy and nephrocalcinosis) has also been observed in male mice exposed to 37 or 94 mg DMA/kg/day, respectively, for 2 years. A consistent finding in intermediate and chronic rat studies is an increase in urine volume, which corresponds to an increase in water consumption; the toxicological significance of this finding is not known. The observed decreases in electrolyte levels and specific gravity are likely due to the higher urine volume.

Although gastrointestinal effects have been observed in animals exposed to DMA, it does not appear to be as sensitive a target compared to MMA. Diarrhea has been observed in rats exposed to a lethal dose of 190 mg DMA/kg/day for 4 weeks and in dogs administered via 16 mg DMA/kg/day. No gastrointestinal effects were observed in rats or mice chronically exposed to 7.8 or 94 mg DMA/kg/day.

Other adverse effects that have been observed in animals exposed to organic arsenicals include hypertrophy of thyroid follicular cells in rats exposed to 4.0 mg DMA/kg/day in the diet for 13 weeks and 7.8 mg DMA/kg/day in the diet for 2 years and developmental effects in rats and mice. Decreases in fetal growth and delays in ossification have been observed in rat fetuses exposed to ≥ 36 mg DMA/kg/day; these alterations typically occur at doses associated with decreases in maternal weight gain. Other developmental effects that have been reported include an increase in the incidences of irregular palatine rugae in rats exposed to 30 mg DMA/kg/day, diaphragmatic hernia in rats exposed to 36 mg DMA/kg/day, and cleft palate in mice exposed to 400 mg DMA/kg/day. No developmental effects were observed in rabbits exposed to 12 mg DMA/kg/day.

The available data provide strong evidence that DMA is carcinogenic in rats. A 2-year exposure to DMA resulted in significant increases in the incidence of neoplastic urinary bladder tumors in rats exposed to 7.8 mg DMA/kg/day in the diet or 3.4 mg DMA/kg/day in drinking water. No increases in neoplastic tumors were observed in mice exposed to doses as high as 94 mg DMA/kg/day for 2 years; however, a

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50-week exposure to 10.4 mg DMA/kg/day did result in an increased incidence of lung tumors in A/J mice.

The available data for DMA suggest that there are species differences in terms of the critical effects and sensitivity. In rats, the urinary bladder and kidneys are the most sensitive targets with effects occurring at 5 mg DMA/kg/day following intermediate-duration exposure and 3.1 mg DMA/kg/day following chronic-duration exposure. Although the urinary bladder and kidneys are also sensitive targets in mice with LOAELs of 7.8 and 37 mg DMA/kg/day, respectively, following chronic exposure, the effects are not associated with cytotoxicity or elevated urine calcium levels. In dogs, the most sensitive effect is gastrointestinal tract irritation (diarrhea), which occurs at 16 mg DMA/kg/day.

There is concern that the rat may not be a good model to predict the human risk associated with organic arsenic exposure due to the unique toxicokinetic properties of DMA in rats. In humans and most animal species, DMA is rapidly eliminated from the body; >90% of the dose is excreted 2–3 days after dosing. In contrast, DMA is slowly eliminated in rats. One study estimated that 45% of an initial oral DMA dose was eliminated with a half-time of 13 hours; the remaining 55% of the dose DMA dose had an elimination half-time of 50 days. In rats, DMA has a strong affinity for hemoglobin resulting in an accumulation of DMA in erythrocytes. Species differences in DMA metabolism have also been found. In particular, DMA undergoes further methylation to trimethylarsine oxide (TMAO) in rats. In most animal species, almost the entire oral DMA dose is excreted in the urine unchanged; however, in rats, about half of the dose is excreted in the urine as DMA and the other half as TMAO. During the metabolism of DMA to TMAO, DMA(III) is formed as a metabolic intermediate. The formation of this highly reactive intermediate and the excretion of small amounts of DMA(III) in urine may damage the urinary bladder.

There are limited data on the mode of action of DMA for most end points. Recently, there has been considerable research on the mode of action for the development of neoplastic urinary bladder tumors in rats. Although the mechanisms have not been fully elucidated, it has been proposed that the mode of action involves cytotoxicity leading to necrosis and subsequent regeneration of the urinary bladder urothelium. There is strong evidence to suggest that DMA(III) is the causative agent for the urothelial cytotoxicity. The strongest evidence comes from the finding that urinary concentrations of DMA(III) measured in rats exhibiting urothelial cytotoxicity are equivalent to DMA(III) concentrations that are cytotoxic to urothelial cells *in vitro*. Urothelial cytotoxicity, regenerative urothelial proliferation, and urothelial tumors have not been detected in other animal species. Other animal species, including

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humans, only metabolize a small percentage of ingested DMA to TMAO; thus, much lower levels of DMA(III) are produced, suggesting that rats may be very sensitive to toxicity of DMA and therefore are not an appropriate model for human risk assessment.

Roxarsone. The available data on the toxicity of roxarsone suggest that following bolus administration, the gastrointestinal tract, kidney, and nervous system are sensitive end points of roxarsone toxicity. Vomiting and gastrointestinal hemorrhage were observed in dogs receiving a single capsulized dose of 50 mg/kg roxarsone; no gastrointestinal effects were observed in rats or mice administered 4 or 42 mg/kg/day roxarsone for 2 years. Kidney effects included increases in kidney weight, minimal tubular epithelial cell degeneration, and focal mineralization in rats exposed to 32 mg roxarsone/kg/day for 13 weeks; no kidney effects were observed at 16 mg/kg/day or in mice exposed to doses as high as 136 mg/kg/day for 13 weeks or 43 mg/kg/day for 2 years. Hyperexcitability, ataxia, and/or trembling were observed in rats exposed to 20 mg/kg/day for 13 weeks or 64 mg/kg/day for 13 weeks. A 14-day study in rats reported slight inactivity in rats exposed to 32 mg/kg/day, but this was not observed in longer-term studies. Neurological effects were observed in mice exposed to doses as high as 136 mg/kg/day for 13 weeks or 43 mg/kg/day for 2 years, although a slight decrease in activity at 42 mg/kg/day was reported in a 14 day study. Pigs appear to be especially sensitive to the neurotoxicity of roxarsone. Muscle tremors have been observed at doses of ≥ 6.3 mg roxarsone/kg/day and myelin degeneration in the spinal cord was noted at 6.3 mg/kg/day. Both the clinical signs of neuropathy and the myelin degeneration followed a time-related pattern. Mild lethargy and ataxia were observed 7 days after exposure initiation, exercise-induced muscle tremors and clonic seizures were observed at day 11, paraparesis was observed at day 22, and paraplegia was observed at day 33. At day 11, equivocal lesions were observed in the cervical spinal cord, and the severity of these lesions increased with time; myelin degeneration was observed in the peripheral nerves and optic nerve starting at day 32 (2 days after exposure termination). Equivocal evidence of carcinogenicity (a slight increase in the incidence of pancreatic tumors) was found in male rats chronically exposed to roxarsone; no increases in neoplastic tumors were observed in female rats or male and female mice.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for arsenic. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive

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health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990i), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inorganic Arsenicals

Inhalation MRLs. No inhalation MRLs were derived for inorganic arsenic. Human data suggest that dermal or respiratory effects may be the most prevalent (Lagerkvist et al. 1986; Mohamed 1998; Perry et al. 1948); respiratory or immunological effects appeared to be the most common following inhalation exposure to inorganic arsenic in animals (Aranyi et al. 1985; Holson et al. 1999). Adequate human studies evaluating dose-response relationships for noncancer end points were not located for inorganic arsenic, and animal data on the health effects of inorganic arsenic following inhalation exposure are limited to studies that did not evaluate a suitable range of health effects. Lacking suitable studies upon which to base the MRLs, no inhalation MRLs were derived for inorganic arsenic.

Oral MRLs

- An MRL of 0.005 mg As/kg/day has been derived for acute-duration (14 days or less) oral exposure to inorganic arsenic.

Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). The duration of exposure was 2–3 weeks in most cases. The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed by skin lesions and neuropathy in

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some patients. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects. The MRL of 0.005 mg As/kg/day was calculated by applying an uncertainty factor of 10 (10 for use of a lowest-observed-adverse-effect level (LOAEL) and 1 for human variability) to the LOAEL of 0.05 mg As/kg/day (see Appendix A for MRL worksheets).

An intermediate-duration oral MRL for inorganic arsenic was not derived due to inadequacy of the database. The lowest LOAEL identified in a limited number of intermediate-duration human studies available was 0.05 mg As/kg/day in a study by Mizuta et al. (1956) (summarized above). While this study was considered appropriate to derive an acute-duration oral MRL for inorganic arsenic, there is considerable uncertainty regarding what the effects and severity might be beyond the relatively short 2–3 weeks of exposure that most subjects experienced. There are numerous studies in animals dosed for intermediate durations, but as indicated in Section 3.5.3, animals are not appropriate models for effects of inorganic arsenic in humans.

- An MRL of 0.0003 mg As/kg/day has been derived for chronic-duration (365 days or more) oral exposure to inorganic arsenic.

Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot Disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people, including one group in which arsenic exposure was “undetermined” and which included those villages where arsenic-contaminated wells were no longer used or the level could not be classified, and a control population of 7,500 people who consumed water from wells almost free of arsenic (0.001–0.017 ppm) was also examined. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 µg/L), medium (300–600 µg/L), or high (>600 µg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by IRIS (IRIS 2007). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The no-observed-adverse-effect level (NOAEL) identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was <20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are

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highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 $\mu\text{g/day}$ (mean=61 $\mu\text{g/day}$), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 $\mu\text{g/day}$ estimate would result in an approximate doubling of the NOAEL (0.0016 mg/kg/day) (see Appendix A for MRL worksheets). The MRL was derived by applying an uncertainty factor of 3 (for human variability) to the NOAEL of 0.0008 mg/kg/day.

The MRL is supported by a large number of well-conducted epidemiological studies that identify reliable NOAELs and LOAELs for dermal effects. EPA (1981b) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Guha Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Haque et al. (2003) identified a LOAEL of 0.002 mg As/kg/day for hyperpigmentation and hyperkeratosis in a case-control study in India. Cebrián et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in two regions in Mexico. Borgoño and Greiber (1972) and Zaldívar (1974) identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgoño et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyperpigmentation and hyperkeratosis is approximately 0.002 mg As/kg/day. While many of these studies also identified effects on other end points at these exposure levels, including effects on gastrointestinal (Borgoño and Greiber 1972; Cebrián et al. 1983; Guha Mazumder et al. 1988; Zaldívar 1974), cardiovascular (Tseng et al. 1995, 1996), hepatic (Hernández-Zavala et al. 1998), and neurological end points (Guha Mazumder et al. 1988; Lianfang and Jianzhong 1994; Tsai et al. 2003), the overall database for dermal effects is considerably stronger than for effects on other end points.

Organic Arsenicals

Inhalation MRLs. No inhalation MRLs were derived for organic arsenic. Human data are limited to an occupational exposure study of workers exposed to 0.065 mg/m³ anisilic acid (Watrous and McCaughey 1945). The exposed workers more frequently complained of keratosis than nonexposed workers. A limited number of animal studies have examined the toxicity of organic arsenicals following inhalation exposure. Respiratory distress and diarrhea were observed in rats and mice exposed to high concentrations of MMA and DMA (Stevens et al. 1979); at lower concentrations (1,540–3,150 mg DMA/m³), respiratory irritation, as evidenced by a decrease in respiration rate, was observed in animals

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exposed to MMA or DMA (Stevens et al. 1979). The acute-duration studies do not clearly identify the most sensitive targets of inorganic arsenical toxicity; the available studies are of limited scope and none included a comprehensive histological examination.

One study examined the toxicity of DMA in rats following intermediate-duration exposure. This study (Whitman 1994) found an increase in intracytoplasmic eosinophilic globules in the nasal turbinates of rats exposed to 34 or 100 mg/m³ DMA 6 hours/day, 5 days/week for 67–68 exposures; no other adverse effects were observed in this comprehensive study. As discussed in greater detail in the oral MRL section, the toxicokinetic properties of DMA in rats differ from other species and rats do not appear to be a good model for human exposure. The half-time of DMA in the body is much longer in rats compared to other species, including humans, and DMA is more extensively methylated in rats. In the absence of data to determine whether the observed effect is due to a direct interaction of DMA, derivation of an intermediate-duration MRL using rat data is not recommended at this time.

No studies examined the chronic toxicity of organic arsenicals precluding the derivation of a chronic-duration inhalation MRL.

Oral MRLs

MMA. A limited number of animal studies have examined the acute oral toxicity of MMA. These studies consisted of LD₅₀ studies in rats (Gur and Nyska 1990), mice (Kaise et al. 1989), and rabbits (Jaghabir et al. 1988) and developmental toxicity studies in rats (Irvine et al. 2006) and rabbits (Irvine et al. 2006); all studies administered MMA via gavage. Adverse effects reported in the LD₅₀ studies included diarrhea in rats at 2,030 mg monosodium methane arsonate (MSMA)/kg (Gur and Nyska 1990), mice at 2,200 mg MMA/kg (Kaise et al. 1989) and rabbits at 60 mg MSMA/kg (Jaghabir et al. 1988) and respiratory arrest in mice at 1,800 mg MMA/kg/day (Kaise et al. 1989). These doses were at or near the LD₅₀ levels of 2,449 mg MSMA/kg, 1,800 mg MMA/kg, 100 mg MSMA/kg for the rats, mice, and rabbits, respectively. In the developmental toxicity studies (Irvine et al. 2006), maternal effects included decreases in maternal body weight gain in rats (17% less than controls) and rabbits (70% less than controls) receiving gavage doses of 100 and 12 mg MMA/kg/day, respectively, and loose feces/diarrhea in rabbit does administered 12 mg MMA/kg/day. The NOAELs for maternal effects were 10 and 7 mg MMA/kg/day in the rats and rabbits, respectively. Minor developmental effects (decreased fetal weight, incomplete ossification, and supernumerary ribs) were also observed at the maternally toxic doses in the rats and rabbits (Irvine et al. 2006); these effects were probably secondary to the maternal stress. These

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data, coupled with the results of longer-term studies (Arnold et al. 2003; Waner and Nyska 1988), suggest that the gastrointestinal tract is a sensitive target of MMA toxicity. The rabbit developmental toxicity study (Irvine et al. 2006) identified the lowest LOAEL (12 mg MMA/kg/day) for gastrointestinal irritation. However, this study is not suitable for the derivation of an acute-duration oral MRL for MMA because the MMA was administered via bolus doses. It is likely that the observed gastrointestinal effect is a concentration-dependent effect; thus, at a given dose level, effects are more likely to occur following bolus administration. A marked decrease in body weight gain was also observed at this dose level.

- An MRL of 0.1 mg MMA/kg/day has been derived for intermediate-duration (15–364 days) oral exposure to MMA.

Three studies have examined the intermediate-duration toxicity of MMA; two of these are chronic-duration studies reporting diarrhea and decreases in body weight gain after MMA exposure for <1 year. Diarrhea was observed in rats exposed to 30.2 mg MMA/kg/day in the diet (Arnold et al. 2003) and in dogs exposed via a capsule to 2 mg MMA/kg/day (Waner and Nyska 1988). Decreases in body weight were observed at the next highest doses, 106.9 mg MMA/kg/day in rats and 8 mg MMA/kg/day in dogs. In the rat study (Arnold et al. 2003), diarrhea was observed in 16.7 and 40% of the males and females, respectively, exposed to 30.2/35.9 mg MMA/kg/day during the first 52 weeks of the study; diarrhea first occurred after 4 weeks of exposure. At the highest dose level (106.9 mg MMA/kg/day), diarrhea was observed in all exposed male and female rats. In dogs, the increased incidence of diarrhea first occurred during weeks 25–28; at the highest dose tested in the study (35 mg MMA/kg/day), vomiting was also observed. A NOAEL of 3.5 mg MMA/kg/day was identified in the rat study; a NOAEL was not identified in the dog study. The remaining study in the intermediate-duration database is a 2-generation study that reported reproductive (decreased pregnancy rate and male fertility index in F₀ and F₁ generations) and developmental (decreased pup survival in F₁ and F₂ generation) effects in rats exposed to 76 mg MMA/kg/day in the diet (Schroeder 1994). The lowest LOAEL identified in the intermediate-duration database is 2 mg MMA/kg/day for diarrhea in dogs (Waner and Nyska 1988). Although dogs appear to be more sensitive to the gastrointestinal effects of MMA, a direct comparison of the two studies is not possible due to the difference in the routes of exposure. It is possible that the bolus administration of MMA, in the form of a capsule, resulted in increased sensitivity of the dogs. Because the most likely route of exposure for humans would be ingestion and the critical effect appears to be irritation of the gastrointestinal tract, studies involving bolus administration (gavage or capsule) were not considered for derivation of oral MRLs. The Arnold et al. (2003) and Schroeder (1994) studies were considered as the basis for an intermediate-duration MRL. Of these two studies, Arnold et al. (2003) identified the lowest

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LOAEL, 30.2 mg MMA/kg/day, for gastrointestinal effects and was selected as the principal study for the intermediate-duration oral MRL.

Arnold et al. (2003) exposed groups of 60 male and 60 female Fischer 344 rats to 0, 50, 400, or 1,300 ppm MMA in the diet for 104 weeks. Using the average doses for weeks 1–50 reported in an unpublished version of this study (Crown et al. 1990), doses of 0, 3.5, 30.2, and 106.9 mg MMA/kg/day and 0, 4.2, 35.9, and 123.3 mg MMA/kg/day were calculated for males and females, respectively. Body weights, food consumption, and water intake were monitored regularly. Blood was taken at 3, 6, and 12 months for clinical chemistry measurements, and urine samples were collected at the same interval. Mortality was increased in high-dose males and females during the first 52 weeks of the study. Body weights were decreased in the mid- and high-dose groups of both sexes; however, at 51 weeks, only the body weight for the high-dose males was <10% of the control weight (14.5%). Food and water consumption was increased in the mid- and high-dose groups. Diarrhea was observed in 100% of the high-dose males and females and in 16.7 and 40% of the mid-dose males and females during the first 52 weeks of exposure. Diarrhea first occurred after 3 weeks of exposure to the high dose and 4 weeks of exposure to the mid-dose group; the severity of the diarrhea was dose-related. The gastrointestinal system was the primary target in animals dying early; numerous macroscopic and histological alterations were observed.

A benchmark dose (BMD) analysis of the incidence data for diarrhea was conducted; details of this analysis are presented in Appendix A. Using the female incidence data, a BMD (BMD₁₀) of 16.17 mg MMA/kg/day, which corresponds to a 10% increase in the incidence of diarrhea, was calculated; the 95% lower confidence limit on the BMD (BMDL₁₀) was 12.38 mg MMA/kg/day. The female incidence data were selected over the male data because the females may be more sensitive than the males. Thus, the intermediate-duration oral MRL of 0.1 mg MMA/kg/day is based on the BMDL₁₀ of 12.38 mg MMA/kg/day in female rats and an uncertainty factor of 100 (10 to account for animal to human extrapolation and 10 for human variability).

- An MRL of 0.01 mg MMA/kg/day has been derived for chronic-duration (365 days or longer) oral exposure to MMA.

The available data on the chronic toxicity of MMA in animals (no human data are available) suggest that the gastrointestinal tract and the kidney are the most sensitive targets. Diarrhea has been observed in rats and mice exposed to MMA in the diet for 2 years (Arnold et al. 2003). The NOAEL and LOAEL values for diarrhea are 3.0 and 25.7 mg MMA/kg/day in rats, respectively, and 24.9 and 67.1 mg MMA/kg/day

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in mice, respectively. At 72.4 mg MMA/kg/day, necrotic, ulcerated, or perforated mucosa and metaplasia were observed in the cecum, colon, and rectum of rats. Squamous metaplasia was also observed in the cecum, colon, and rectum of mice exposed to 67.1 mg MMA/kg/day. Diarrhea was observed in dogs exposed via capsule to 2 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988). The bolus administration used in the dog study probably increased the dog's sensitivity to MMA. In both the rats and mice, chronic administration of MMA resulted in an exacerbation of chronic progressive nephropathy. In female rats, significant increases in the severity of chronic progressive nephropathy were observed at 33.9 and 98.5 mg MMA/kg/day; the NOAEL was 3.9 mg MMA/kg/day (Arnold et al. 2003). In male mice, there was an increased incidence of slight progressive nephropathy at doses ≥ 6.0 mg MMA/kg/day; the NOAEL was 1.2 mg MMA/kg/day (Arnold et al. 2003; incidence data reported in Gur et al. 1991). Nephrocalcinosis was also observed in male mice exposed to ≥ 24.9 mg MMA/kg/day (Arnold et al. 2003). Other effects that have been observed following chronic exposure MMA include decreased weight gain in male and female rats exposed to 25.7/33.9 mg MMA/kg/day and higher (Arnold et al. 2003) and hypertrophy of the thyroid follicular epithelium in female rats exposed to ≥ 33.9 mg MMA/kg/day (Arnold et al. 2003). A variety of other lesions including peritonitis, pancreatitis, inflammation of the ureter, uterus, prostate, testes, epididymis, and seminal vesicles, hydronephrosis, pyelonephritis, and cortical tubular cystic dilation were also observed in rats; however, these alterations were probably secondary to the ulceration and perforation of the large intestine, which resulted in leaking of gastrointestinal contents into the abdominal cavity. Hyperplasia of the urinary bladder was also observed in rats exposed to 2.1 mg MMA/kg/day as MMA in drinking water for 2 years (Shen et al. 2003). Although hyperplasia of the urinary bladder is commonly observed in rats exposed to DMA, it was not observed in the Arnold et al. (2003) study at doses as high as 72.4 mg MMA/kg/day; thus, the significance of the results of the Shen et al. (2003) study is not known.

The lowest reliable LOAEL identified in the chronic oral MMA database was 6.0 mg MMA/kg/day for an increased incidence of progressive glomerulonephropathy in mice (Arnold et al. 2003). Although the investigators noted that the kidney lesions were consistent with the normal spectrum of spontaneous renal lesions and that there was no difference in character or severity of lesions between groups, ATSDR considers the dose-related increase in glomerulonephropathy to be treatment-related.

In the Arnold et al. (2003) study (incidence data reported in Gur et al. 1991), groups of 52 male and 52 female B6C3F₁ mice were exposed to 0, 10, 50, 200, or 400 ppm of MMA in the diet for 104 weeks. The average doses reported in Gur et al. (1991) were 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day for males and 0, 1.4, 7.0, 31.2, and 101 mg MMA/kg/day for females. Body weights, food consumption, and

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water intake were monitored regularly. Blood was taken at 3, 6, 12, 18, and 24 months for white cell counts. At sacrifice, complete necropsies were performed, including histological examination of at least 13 organs. No treatment-related increases in mortality were observed. Significant decreases in body weights were observed in males and females exposed to 67.1 or 101 mg MMA/kg/day, respectively; at week 104, the males and females weighed 17 and 23%, respectively, less than controls. Food consumption was increased in females exposed to 101 mg MMA/kg/day, and water consumption was increased in 67.1 mg MMA/kg/day males and 31.2 and 101 mg MMA/kg/day females. Loose and mucoid feces were noted in mice exposed to 67.1/101 mg MMA/kg/day. No changes were seen in white cell counts of either sex. Small decreases in the weights of heart, spleen, kidney, and liver weights were observed in some animals, but the decreases were not statistically significant. Squamous metaplasia of the cecum, colon, and rectum was observed at 67.1/101 mg MMA/kg/day. The incidence of metaplasia in the cecum, colon, and rectum were 29/49, 14/49, and 39/49 in males and 38/52, 17/52, and 42/52 in females; metaplasia was not observed in other groups of male or female mice. An increased incidence of progressive glomerulonephropathy (incidence of 25/52, 27/52, 38/52, 39/52, and 46/52 in the 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day males, respectively) was observed in males; the incidence was significantly higher (Fisher Exact Test) than controls at ≥ 6.0 mg MMA/kg/day. Significant increases in the incidence of nephrocalcinosis was observed in the males at 24.9 and 67.1 mg MMA/kg/day (Fisher Exact Test) (incidences of 25/52, 30/52, 30/52, 45/52, and 45/51 in males and 0/52, 1/52, 1/52, 2/52, and 5/52 in females). A reduction in the incidence of cortical focal hyperplasia in the adrenal gland of male mice exposed to 67.1 mg MMA/kg/day was possibly related to MMA exposure; the toxicological significance of this effect is not known. Thus, this study identifies a NOAEL of 1.2 mg MMA/kg/day and a LOAEL of 6.0 mg MMA/kg/day for progressive glomerulonephropathy in male mice.

As described in greater detail in Appendix A, BMD was applied to the incidence data for progressive glomerulonephropathy in male mice using all available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) to calculate predicted doses associated with a 10% extra risk. As assessed by the Akaike's Information Criteria (AIC), the log-logistic model provided the best fit to the data. The predicted BMD₁₀ and BMDL₁₀ are 2.09 and 1.09 mg MMA/kg/day. The BMDL₁₀ was selected as the point of departure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive a chronic-duration oral MRL of 0.01 mg MMA/kg/day.

DMA. As discussed in greater detail in Section 2.2, urinary bladder effects characterized by cytotoxicity and regenerative proliferation and hyperplasia have been observed in rats, but not in other species. The LOAELs for these effects are lower than the LOAELs for sensitive effects in other species. Additionally,

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rats have a much greater capacity than other species to metabolize ingested DMA to form DMA(III) (a reactive intermediate) and TMAO (Cohen et al. 2006; Marafante et al. 1987b; Yoshida et al. 1998). It is likely that DMA(III) is the causative agent for the urothelial cytotoxicity observed in rats (Cohen et al. 2006). Thus, rats were not considered a suitable model for humans and these data were not considered for derivation of MRLs for DMA.

There are limited data to assess the acute toxicity of DMA in species other than rats. Diarrhea, increased startle reflex, and ataxia were observed in mice exposed to a lethal gavage dose of 1,757 mg DMA/kg (Kaise et al. 1989); vomiting and diarrhea were also observed during the second week of a 52-week study in dogs exposed via capsule to 16 mg DMA/kg/day (Zomber et al. 1989). The remaining studies in the acute database are developmental toxicity studies in mice and rabbits. Rabbits appear to be more sensitive than mice to maternal and developmental effects. Gavage exposure to 48 mg DMA/kg/day on gestational days 7–19 resulted in maternal weight loss and abortion in approximately 75% of the does; no adverse effects were observed at 12 mg DMA/kg/day (Irvine et al. 2006). In mice, decreases in maternal body weight gain were observed at gavage doses of 200 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981), decreases in fetal body weight, delays in ossification, and increased incidence of cleft palate were observed at 400 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981) and fetal deaths, decreases in growth, and increased incidence of malformations were observed in mice administered 1,600 mg DMA/kg on gestational day 8 (Kavlock et al. 1985). The acute-duration database for DMA was not considered adequate for derivation of an oral MRL. The database is lacking a comprehensive toxicity study, which would be useful in establishing the critical target of toxicity. In a chronic-duration study in mice (Arnold et al. 2006), vacuolization was observed in the urinary bladder at ≥ 7.8 mg DMA/kg/day; it is not known if these effects would also be observed after acute-duration exposure. Thus, it is not known if systemic effects would occur at lower doses than the maternal developmental effects observed in rabbits exposed to 48 mg DMA/kg/day (Irvine et al. 2006); an acute-duration oral MRL for DMA is not recommended at this time.

Excluding rat studies, the database on the toxicity of DMA following intermediate-duration oral exposure is limited to a chronic study of dogs exposed to DMA via capsule 6 days/week for 52 weeks (Zomber et al. 1989). Diarrhea and vomiting were observed at 16 and 40 mg DMA/kg/day starting after the first week of exposure. A slight decrease in erythrocyte levels and increase in total leukocyte levels were observed in males exposed to 40 mg DMA/kg/day for 51 weeks. This dog study was not selected as the basis of an MRL because it is likely that bolus administration of DMA would increase sensitivity to the gastrointestinal effects.

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- An MRL of 0.02 mg DMA/kg/day has been derived for chronic-duration (365 days or longer) oral exposure to DMA.

Two studies investigated the chronic-duration toxicity of DMA in a species other than rats. In dogs, diarrhea and vomiting were observed after 52 weeks of exposure to 16 or 40 mg As/kg/day (Zomber et al. 1989); no histological alterations were observed. In mice exposed to DMA in the diet for 2 years, vacuolization of the urothelium in the urinary bladder was observed at ≥ 7.8 mg DMA/kg/day and progressive glomerulonephropathy was observed at ≥ 37 mg DMA/kg/day (Arnold et al. 2006). As noted in Section 2.2, the vacuolization was not associated with cytotoxicity or proliferation. Because the bladder effects in mice occurred at the lowest adverse effect level for the database, it was selected as the critical effect and Arnold et al. (2006) was selected as the principal study.

In the Arnold et al. (2006) study, groups of 56 male and 56 female B6C3F₁ mice were exposed to 0, 8, 40, 200, or 500 ppm DMA in the diet for 2 years; the results of this study were also reported in an unpublished paper (Gur et al. 1989b) submitted to EPA under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The investigators reported dietary doses of approximately 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day. The following parameters were used to assess toxicity: clinical observations, body weight, food consumption, water consumption, differential leukocyte levels measured at 12, 18, and 24 months in mice in the control and 94 mg DMA/kg/day groups, organ weights (brain, kidneys, liver, and testes), and histopathological examination of major tissues and organs. No deaths or treatment-related clinical signs were observed. Decreases in body weight gain were observed in the male mice exposed to 94 mg DMA/kg/day; the difference was $<10\%$ and not considered adverse. An increase in water consumption was observed in males exposed to 94 mg DMA/kg/day during weeks 60–96. In the female mice exposed to 51 mg As/kg/day, a statistically significant decrease in lymphocytes and an increase in monocytes were observed at 24 months. Treatment related nonneoplastic alterations were observed in the urinary bladder and kidneys. In the urinary bladder, increases in the vacuolization of the superficial cells of the urothelium were observed in males exposed to 37 or 94 mg DMA/kg/day (0/44, 1/50, 0/50, 36/45, 48/48) and in females exposed to 7.8, 37, and 94 mg DMA/kg/day (1/45, 1/48, 26/43, 47/47, 43/43); incidence data reported in Gur et al. (1989b). An increased incidence of progressive glomerulonephropathy was observed in males at 37 mg DMA/kg/day (16/44, 22/50, 17/50, 34/45, 30/50) and an increased incidence of nephrocalcinosis was also observed in male mice at 94 mg DMA/kg/day (30/44, 25/50, 27/50, 29/50, 45/50). Neoplastic alterations were limited to an increased incidence of fibrosarcoma of the skin in females exposed to 94 mg DMA/kg/day (the incidence of 3/56, 0/55, 1/56,

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1/56, and 6/56 in the 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day groups, respectively); however, it was concluded that this lesion was not related to DMA exposure.

As described in detail in Appendix A, BMD analysis was applied to the incidence data for vacuolization of the urothelium in the urinary bladder of female mice using all available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) to calculate predicted doses associated with a 10% extra risk. As assessed by the AIC, the multi-stage model provided the best fit to the data. The predicted BMD₁₀ and BMDL₁₀ are 2.68 and 1.80 mg DMA/kg/day. The BMDL₁₀ was selected as the point of departure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive a chronic-duration oral MRL of 0.02 mg DMA/kg/day.

Roxarsone. A series of three National Toxicology Program (NTP) studies in rats and mice (NTP 1989b) and a study in dogs (Kerr et al. 1963) have examined the acute toxicity of roxarsone; adverse effects have also been reported within the first 2 weeks of a longer-term study in pigs (Rice et al. 1985; Kennedy et al. 1986). A single exposure study reported diarrhea and ataxia in rats and mice exposed to doses that exceeded the LD₅₀ (NTP 1989b). In another study, no alterations in hematological parameters (only end point assessed) were found after 10 or 9 days of dietary exposure in rats and mice, respectively (NTP 1989b). In a 14-day study (NTP 1989b), a decrease in body weight gain and slight inactivity were observed in rats exposed to 32 mg roxarsone/kg/day and slight inactivity was observed in mice exposed to 42 mg roxarsone/kg/day; a decrease in body weight gain was also observed in mice exposed to 168 mg roxarsone/kg/day. The dog study was considered inadequate because a small number (n=3) of animals were tested and no control group was used. In a 30-day dietary exposure study in pigs (Rice et al. 1985; Kennedy et al. 1986), mild lethargy and ataxia were observed from day 7 forward and exercise-induced muscle tremors and clonic seizures were observed from day 11 forward in pigs exposed to 6.3 mg roxarsone/kg/day; equivocal evidence of myelin degeneration was also observed in pigs sacrificed after 11 days of exposure. These data clearly identify pigs as the most sensitive species following acute-duration oral exposure; in the absence of data to the contrary, it is assumed that pigs are a good model to predict the toxic potential of roxarsone in humans. Because the lowest dose tested in pigs was a serious LOAEL for neurotoxicity and a NOAEL for this effect was not identified, an acute-duration oral MRL cannot be derived for roxarsone.

As with the acute-duration database, pigs appear to be the most sensitive species; neurotoxicity has been observed at ≥ 6.3 mg roxarsone/kg/day. In a study reported by Rice et al. (1985) and Kennedy et al. (1986), exercise-induced muscle tremors and clonic convulsions were observed in pigs during the early

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part of the study; when the pigs returned to a recumbent position, the seizures and tremors stopped. Paraparesis, evidenced by reluctance to rise and the pigs dragging their hindquarters on the ground, was observed at day 22; paraplegia was observed 2 days after exposure termination. In addition to these clinical signs of neuropathy, histological alterations consisting of myelin degeneration was observed in the spinal cord, peripheral nerves, and optic nerve. The lesions were first detected in the spinal cord on day 15 and in the peripheral nerves and optic nerve 2 days after exposure termination. The Rice et al. (1985) and Kennedy et al. (1986) studies did not identify a NOAEL. Muscle tremors were also observed in pigs exposed to 10 mg roxarsone/kg/day for 28 days (Edmonds and Baker 1986). This study was not designed to assess neurotoxicity and did not include histological examination of the spinal cord or nerves. Trembling, ataxia, and hyperexcitability were also observed in rats exposed to 64 mg roxarsone/kg/day for 13 weeks (NTP 1989b). Other effects that have been observed include tubular degeneration and focal regenerative hyperplasia in the kidney and decreased body weight in rats exposed to 32 mg roxarsone/kg/day for 13 weeks (NTP 1989b) and decreased body weight in mice at 136 mg roxarsone/kg/day for 13 weeks (NTP 1989b). The lowest identified adverse effect level is 6.3 mg roxarsone/kg/day for serious neurological effects in pigs (Kennedy et al. 1986; Rice et al. 1985) and is not suitable for the derivation of an intermediate-duration oral MRL.

The chronic toxicity of roxarsone has been examined in rats (NTP 1989b; Prier et al. 1963), mice (NTP 1989b; Prier et al. 1963), and dogs (Prier et al. 1963) in 2-year dietary exposure studies. None of these studies reported adverse effects at the highest doses tested; the highest NOAELs for each species are 10, 43, and 5 mg roxarsone/kg/day for rats, mice, and dogs, respectively. The results from shorter duration studies suggest that pigs are more sensitive to the neurotoxic effects of roxarsone than rats, mice, or dogs. Because no chronic duration pig studies were identified and deriving an MRL using a potentially less sensitive species may not be protective of human health, a chronic-duration oral MRL is not recommended at this time.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of arsenic. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

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the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of arsenic are indicated in Tables 3-1 and 3-3 and Figures 3-1 and 3-3. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-3 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Chemical Forms of Concern. Analysis of the toxic effects of arsenic is complicated by the fact that arsenic can exist in several different oxidation states and many different inorganic and organic compounds. Most cases of human toxicity from arsenic have been associated with exposure to inorganic arsenic, so these compounds are the main focus of this profile.

The most common inorganic arsenical in air is arsenic trioxide (As_2O_3), while a variety of inorganic arsenates (AsO_4^{-3}) or arsenites (AsO_2^-) occur in water, soil, or food. A number of studies have noted differences in the relative toxicity of these compounds, with trivalent arsenites tending to be somewhat more toxic than pentavalent arsenates (Byron et al. 1967; Gaines 1960; Maitani et al. 1987a; Sardana et al. 1981; Willhite 1981). However, these distinctions have not been emphasized in this profile, for several reasons: (1) in most cases, the differences in the relative potency are reasonably small (about 2–3-fold), often within the bounds of uncertainty regarding NOAEL or LOAEL levels; (2) different forms of arsenic may be interconverted, both in the environment (see Section 6.3) and the body (see Section 3.4); and (3) in many cases of human exposure (especially those involving intake from water or soil, which are of greatest concern to residents near wastes sites), the precise chemical speciation is not known.

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Gallium arsenide (GaAs) is another inorganic arsenic compound of potential human health concern, due to its widespread use in the microelectronics industry. Available toxicokinetic data suggest that although gallium arsenide is poorly soluble, it undergoes slow dissolution and oxidation to form gallium trioxide and arsenite (Webb et al. 1984, 1986). Therefore, the toxic effects of this compound are expected to be attributable to the arsenite that is liberated, plus the additional effects of the gallium species.

It is beyond the scope of this profile to provide detailed toxicity data on other less common inorganic arsenic compounds (e.g., As_2S_3), but these are expected to be of approximately equal or lesser toxicity than the oxycompounds, depending mainly on solubility (see Section 3.4).

Although organic arsenicals are usually viewed as being less toxic than the inorganics, several methyl and phenyl derivatives of arsenic that are widely used in agriculture are of possible human health concerns based on their toxicity in animal species (Arnold et al. 2003, 2006; NTP 1989b). Chief among these are monomethylarsonic acid (MMA) and its salts (monosodium methane arsonate [MSMA] and disodium methane arsonate [DSMA]), dimethylarsinic acid (DMA, also known as cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). However, it should be noted that food is the largest contributor to background intakes of organic arsenicals. Estimates on the concentration of organic arsenicals in the diet were not located; Cohen et al. (2006) estimated that the intake of DMA from food and water is <1 ng/kg/day. As with the inorganic compounds, there are toxicological differences between these various organic derivatives; because of these differences, the discussion of the health effects of MMA, DMA, and roxarsone are discussed separately. As discussed below, animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans, but it is not known if this also applies to toxicity of organic arsenicals.

Several organic arsenicals are found to accumulate in fish and shellfish. These derivatives (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") have been studied by several researchers and have been found to be essentially nontoxic (Brown et al. 1990; Cannon et al. 1983; Charbonneau et al. 1978; Kaise et al. 1985; Luten et al. 1982; Siewicki 1981; Tam et al. 1982; Yamauchi et al. 1986). Thus, these compounds are not considered further here.

Arsine (AsH_3) and its methyl derivatives, although highly toxic, are also not considered in this profile, since these compounds are either gases or volatile liquids that are unlikely to be present at levels of concern at hazardous waste sites.

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Use of Animal Data. An additional complexity to the analysis of arsenic toxicity is that most laboratory animals appear to be substantially less susceptible to inorganic arsenic than humans. For example, chronic oral exposure of humans to inorganic arsenic at doses of 0.05–0.1 mg/kg/day is frequently associated with neurological (Barton et al. 1992; Goddard et al. 1992; Guha Mazumder et al. 1988; Hauptert et al. 1996; Hindmarsh et al. 1977; Huang et al. 1985; Sass et al. 1993; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Valentine et al. 1981) or hematological signs of arsenic toxicity (Glazener et al. 1968; Guha Mazumder et al. 1988; Prasad and Rossi 1995; Sass et al. 1993; Tay and Seah 1975), but no characteristic neurological or hematological signs of arsenism were detected in monkeys, dogs, or rats chronically exposed to arsenate or arsenite at doses of 0.7–2.8 mg As/kg/day (Byron et al. 1967; EPA 1980f; Heywood and Sortwell 1979). This may be because the studies were not conducted for a sufficient length of time, or because too few animals were used. Moreover, while there is good evidence that inorganic arsenic is carcinogenic in humans by both oral and inhalation routes, evidence of inorganic arsenic-induced carcinogenicity in animals is mostly negative, with the exception of studies in mice demonstrating transplacental carcinogenesis. For these reasons, quantitative dose-response data from animals are not judged to be reliable for determining levels of significant human exposure, and will be considered only briefly except when human data are lacking.

3.2.1 Inhalation Exposure

Most information on human inhalation exposure to arsenic derives from occupational settings such as smelters and chemical plants, where the predominant form of airborne arsenic is arsenic trioxide dust. One limitation to this type of study is that exposure data are usually difficult to obtain, especially from earlier time periods when exposure levels were higher than in recent years. This is further complicated by the fact that significant oral and dermal exposures are also likely to occur under these conditions and co exposure to other metals and chemicals is also common. Thus, studies of this type are, like virtually all epidemiological studies, subject to some limitations and uncertainties. Table 3-1 and Figure 3-1 summarize studies that provide the most reliable quantitative data on health effects in humans, along with several studies in animals exposed to arsenic trioxide and other inorganic arsenic compounds by the inhalation route. Data for DMA are shown in Table 3-2 and Figure 3-2. All exposure data are expressed as milligrams of arsenic (as the element) per cubic meter of air (mg As/m³). These studies and others that provide useful qualitative information on health effects of inorganic and organic arsenicals are discussed below.

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m³)	Serious (mg/m³)		
ACUTE EXPOSURE								
Immuno/ Lymphoret								
1	Mouse (CD-1)	3 hr		0.123 F	0.271 F (decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)	
2	Mouse (CD-1)	5 d 3 hr/d		0.259 F	0.519 F (decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)	
Developmental								
3	Mouse (CFLP)	Gd 9-12 4 hr/d		0.2	2.2 (10% decreased average fetal body weight)	21.6 (increased fetal deaths, skeletal malformations, and retarded growth)	Nagymajtenyi et al. 1985 As(+3)	
INTERMEDIATE EXPOSURE								
Death								
4	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d				20 F (5/10 dams died)	Holson et al. 1999 As(+3)	
Systemic								
5	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d	Resp	2 F	8 F (rales, dried red material around nose)		Holson et al. 1999 As(+3)	
			Bd Wt	2 F	8 F (decreased body weight gain during gestation)			

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m³)	Serious (mg/m³)		
6	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d	Resp	0.9 F	8 F (rales)	20 F (labored breathing, gasping)	Holson et al. 1999 As(+3)	
			Gastro	8 F	20 F (gross gastrointestinal lesions)			
			Bd Wt	8 F	20 F (drastic decrease body weight)			
Immuno/ Lymphoret								
7	Mouse (CD-1)	4 wk 5 d/wk 3 hr/d		0.126 F	0.245 F (decreased pulmonary bactericidal activity)		Aranyi et al. 1985 As(+3)	
Reproductive								
8	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		8 F			Holson et al. 1999 As(+3)	
9	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		20 F			Holson et al. 1999 As(+3)	
Developmental								
10	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		8			Holson et al. 1999 As(+3)	

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
11	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d		8		20 (marked increase in post- implantation loss and marked decrease in viable fetuses)	Holson et al. 1999 As(+3)	
CHRONIC EXPOSURE								
Systemic								
12	Human	23 yr (avg) (occup)	Cardio			0.36 M (increased incidence of vasospasticity and clinical Raynaud's phenomenon)	Lagerkvist et al. 1986 As(+3)	
13	Human	0.5-50 yr (occup)	Resp	0.613			Perry et al. 1948 As(+3)	
			Dermal		0.078 (mild pigmentation keratosis of skin)	0.613 (gross pigmentation with hyperkeratinization of exposed areas, wart formation)		
Neurological								
14	Human	28 yr (avg) (occup)			0.31 M (decreased nerve conduction velocity)		Lagerkvist and Zetterlund 1994 As(+3)	
Cancer								
15	Human	1- >30 yr (occup)				0.213 M (CEL: lung cancer)	Enterline et al. 1987a As(+3)	
16	Human	19.5 yr (avg) (occup)				0.069 M (CEL: lung cancer)	Enterline et al. 1987b As(+3)	

Table 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		
17	Human	3 mo- >30 yr (occup)				0.2 M (CEL: lung cancer)	Jarup and Pershagen 1991 As(+3)	
18	Human	3 mo- >30 yr (occup)				0.05 M (CEL: lung cancer)	Jarup et al. 1989 As(+3)	
19	Human	1- >30 yr (occup)				0.38 M (CEL: lung cancer)	Lee-Feldstein 1986 As(+3)	
20	Human	>25 yr (occup)				0.29 M (CEL: lung cancer)	Lubin et al. 2000 As(+3)	
21	Human	14.8 yr (avg) (occup)				0.3 M (CEL: lung cancer)	Welch et al. 1982 As(+3)	

^a The number corresponds to entries in Figure 3-1.

avg = average; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = female; Gastro = gastrointestinal; Gd = gestation day; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; occup = occupational; pmd = pre-mating day; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation

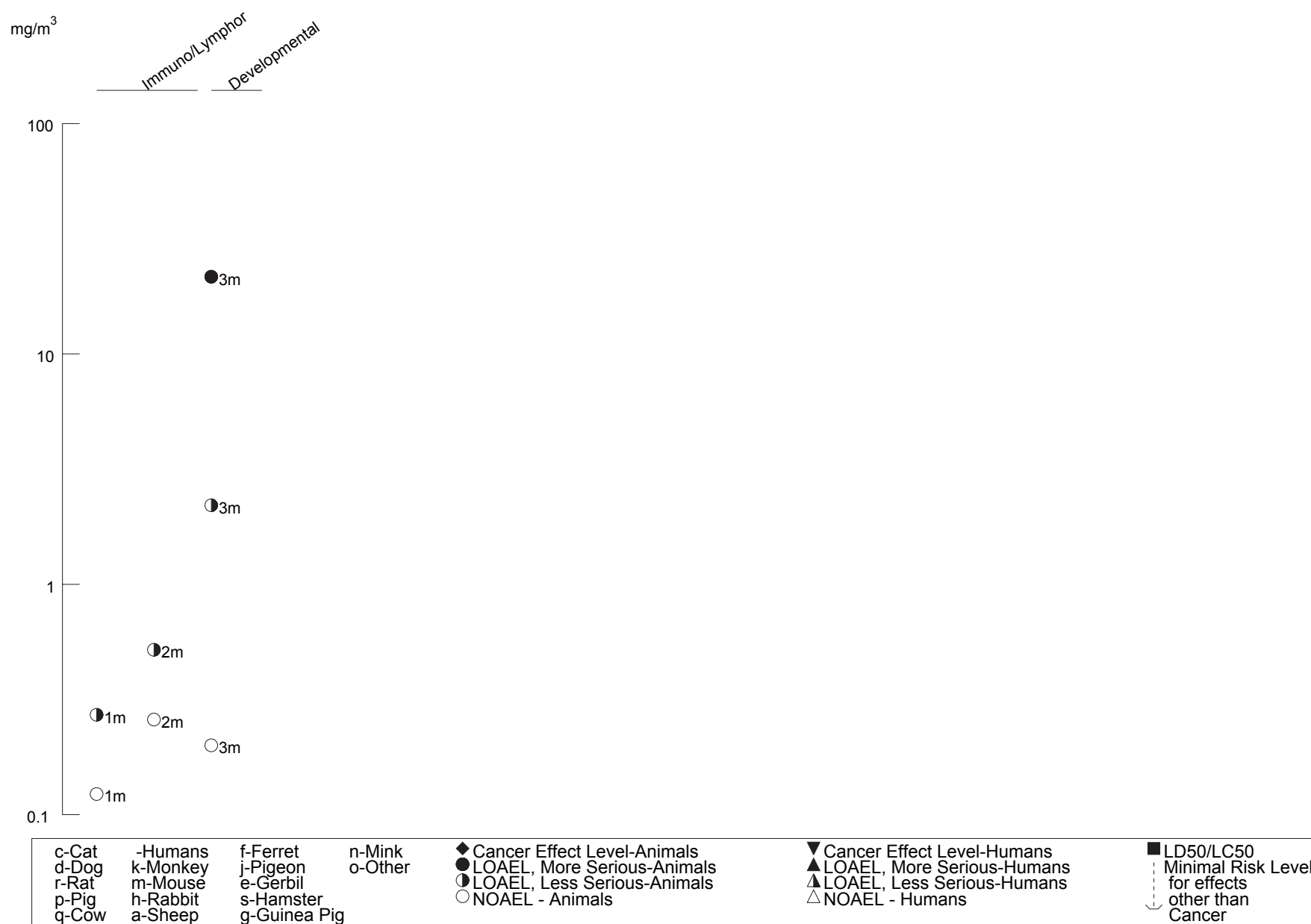
Acute (≤ 14 days)

Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation (*Continued*)

Intermediate (15-364 days)

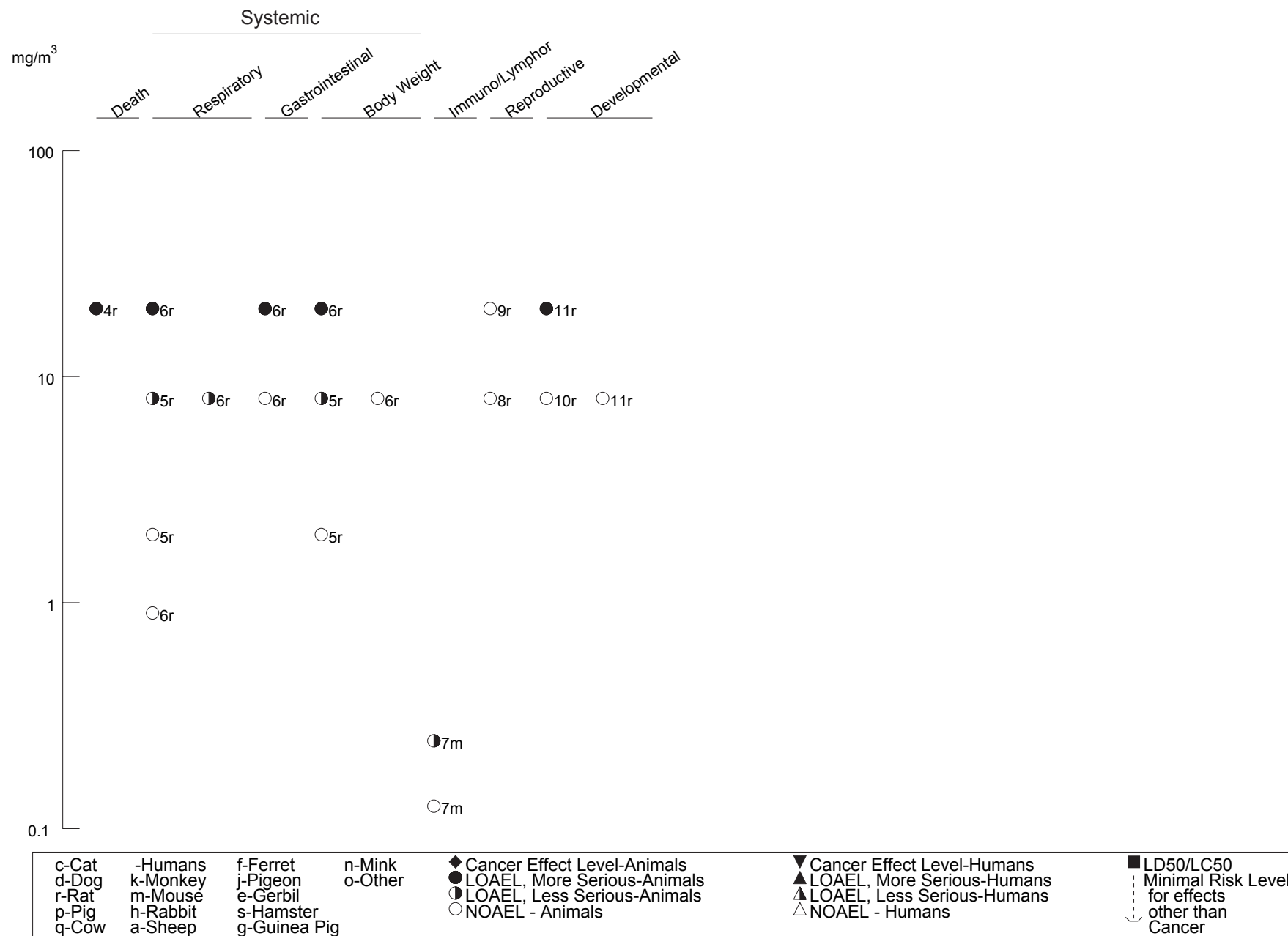


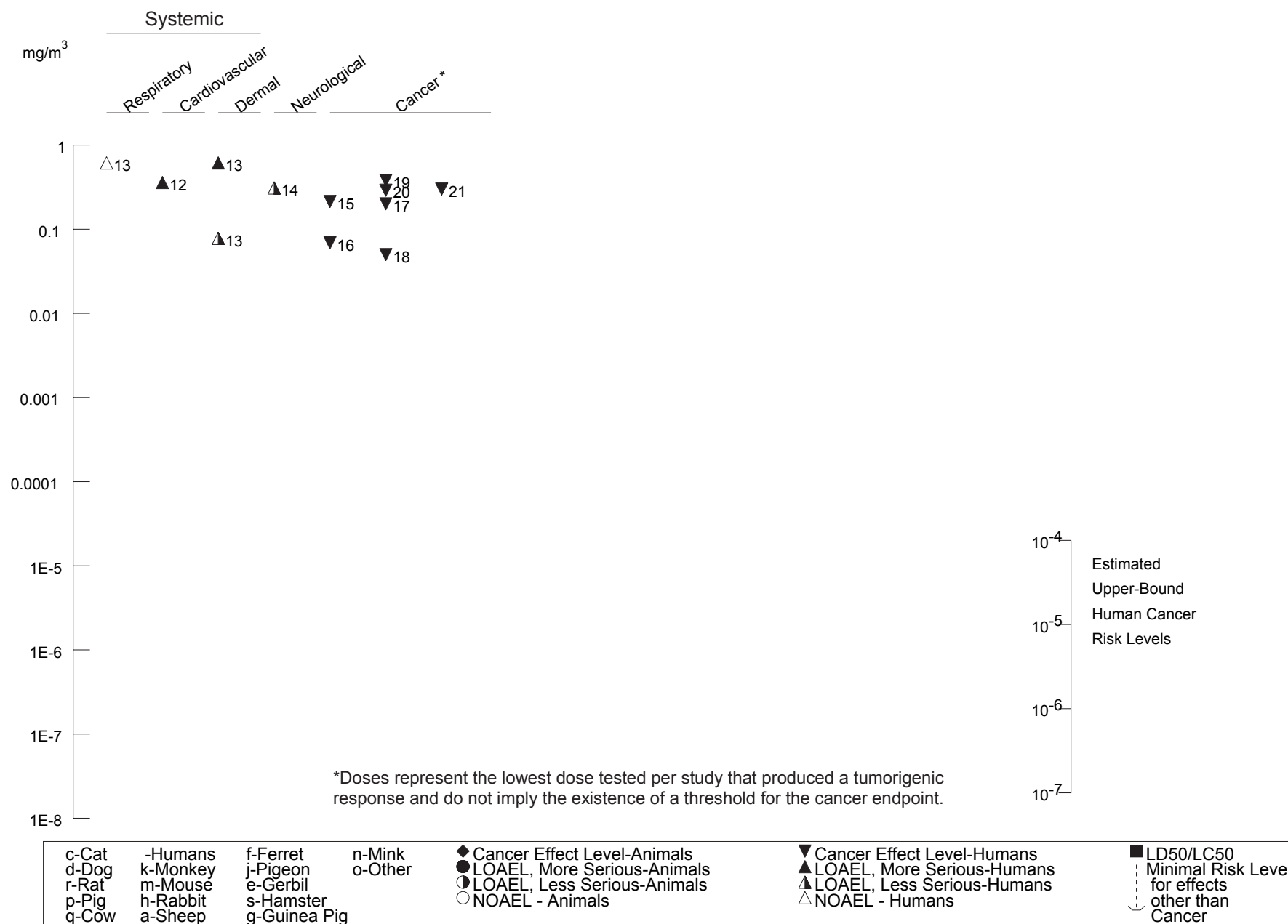
Figure 3-1 Levels of Significant Exposure to Inorganic Arsenic - Inhalation (*Continued*)Chronic (≥ 365 days)

Table 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m³)	Serious (mg/m³)		
ACUTE EXPOSURE								
Death								
1	Rat (Sherman)	2 hr				3900 F (LC50)	Stevens et al. 1979 DMA	
Systemic								
2	Rat (Sherman)	2 hr	Resp			4000 (respiratory distress)	Stevens et al. 1979 DMA	
			Gastro		4000 (diarrhea)			
			Dermal	4100	6900 F (erythematous lesions of ears and feet)			
			Ocular		4000 (eye encrustation)			
			Bd Wt		4000 (unspecified decrease in body weight)			
3	Mouse (Swiss-Webster)	5 min	Resp		3150 M (RD50)		Stevens et al. 1979 DMA	
INTERMEDIATE EXPOSURE								
Systemic								
4	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 67-68 exposures	Resp	10	34 (intracytoplasmic eosinophilic globules in nasal turbinates)		Whitman 1994 DMA	
			Cardio	100				
			Gastro	100				
			Hemato	100				
			Hepatic	100				
			Renal	100				
			Endocr	100				
			Dermal	100				

Table 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation

(continued)

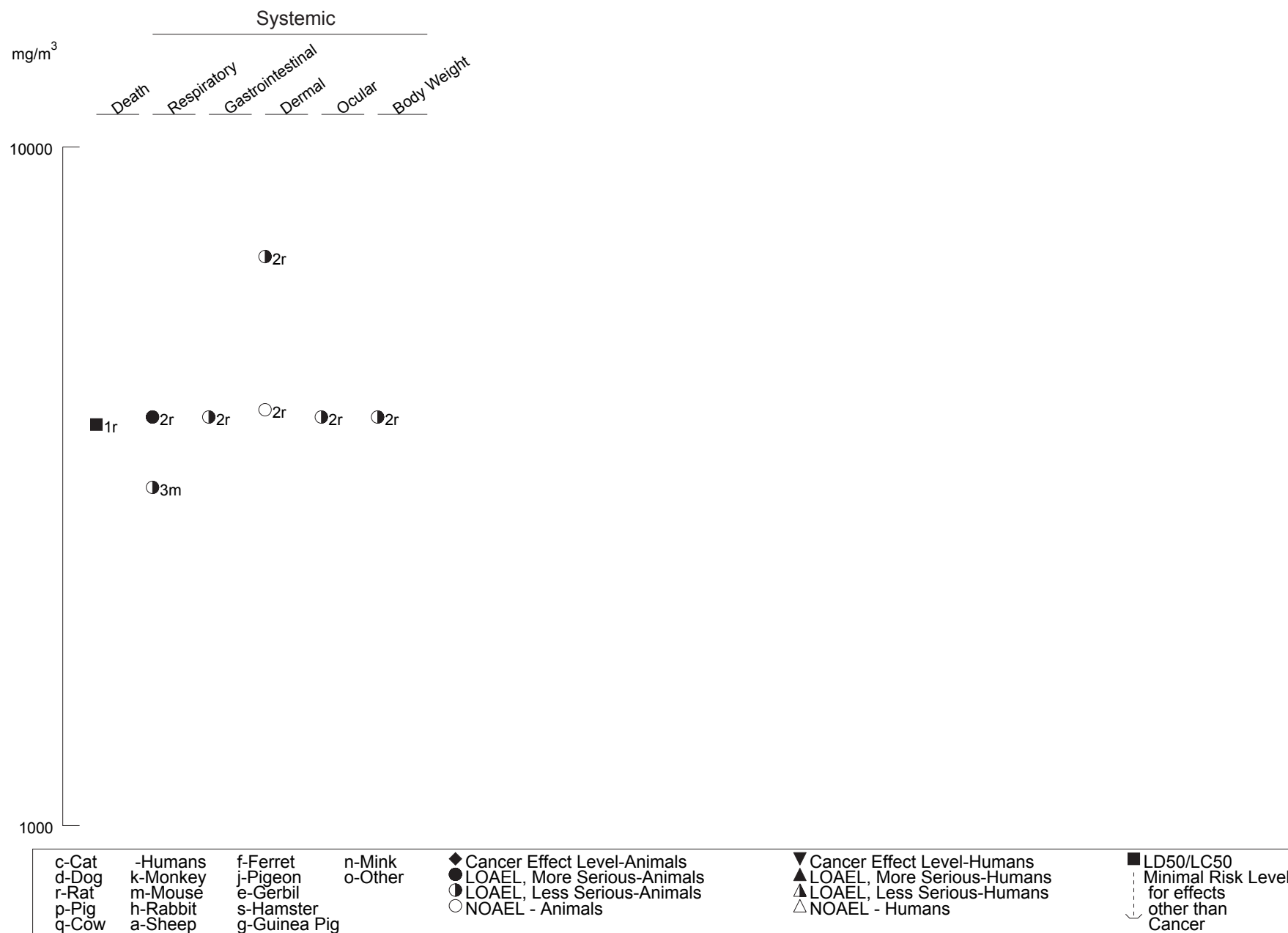
Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m ³)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/m ³)	Serious (mg/m ³)		

Bd Wt 100

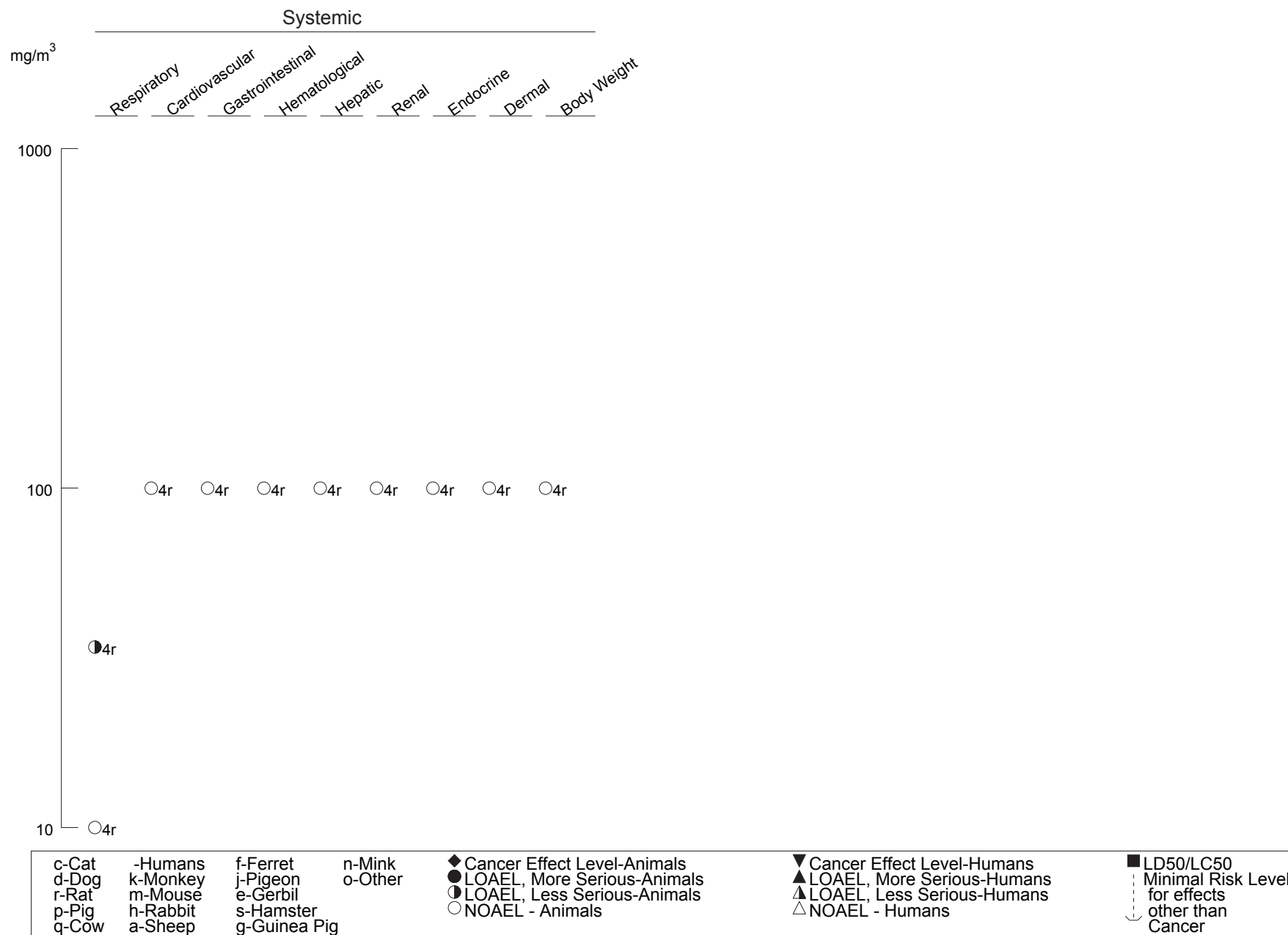
^a The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DMA = dimethylarsinic acid; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; min = minute(s); NOAEL = no-observable-adverse-effect level; RD50 = 50% decrease in respiration rate; Resp = respiratory; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Dimethylarsinic Acid - Inhalation

Acute (≤ 14 days)

Intermediate (15-364 days)



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3.2.1.1 Death

Inorganic Arsenicals. Although there are many studies of humans exposed to arsenic in air, no cases of lethality from short-term exposure were located. This suggests that death is not likely to be of concern following acute exposure, even at the very high exposure levels (1–100 mg As/m³) found previously in the workplace (e.g., Enterline and Marsh 1982; Järup et al. 1989; Lee-Feldstein 1986). Delayed lethality from chronic exposure attributable to increased risk of cardiovascular disease or lung cancer is discussed below in Sections 3.2.1.2 and 3.2.1.7, respectively. The only report of a lethal effect of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized in extremis, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m³ (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. In this same study, there was 100% mortality in groups of 10 pregnant rats after 1 day of exposure to concentrations ≥ 100 mg/m³ (76 mg As/m³).

Organic Arsenicals. No studies were located regarding death in humans after inhalation exposure to organic arsenicals. A 2-hour LC₅₀ of 3,900 mg DMA/m³ was calculated for DMA in female rats (Stevens et al. 1979). This LC₅₀ is shown in Table 3-2 and Figure 3-2. Male rats and mice of both sexes were less susceptible, with only a few deaths after 2-hour exposures as high as 6,900 mg DMA/m³ in rats and 6,400 mg DMA/m³ in mice (Stevens et al. 1979). The cause of death was not specified, but was probably due to lung injury (see Section 3.2.1.2). No deaths were observed among rats and mice exposed to DSMA (the disodium salt of MMA) at concentrations up to 6,100 mg DSMA/m³ in rats and 6,900 mg DSMA/m³ in mice (Stevens et al. 1979). Chamber atmospheres at these high concentrations were so dense that it was difficult to see the animals clearly. These data indicate that there is no significant risk of acute lethality from concentrations of DMA or MMA that might be encountered in the environment or the workplace.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from inhalation exposure to inorganic arsenicals in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1, while the corresponding data for DMA are shown in Table 3-2 and Figure 3-2.

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Respiratory Effects.

Inorganic Arsenicals. Workers exposed to arsenic dusts in air often experience irritation to the mucous membranes of the nose and throat. This may lead to laryngitis, bronchitis, or rhinitis (Dunlap 1921; Morton and Caron 1989; Pinto and McGill 1953), and very high exposures (characteristic of workplace exposures in the past) can cause perforation of the nasal septum (Dunlap 1921; Pinto and McGill 1953; Sandstrom et al. 1989). Despite the known respiratory irritant effects of arsenic, there have been few systematic investigations of respiratory effects in humans exposed to arsenic. Perry et al. (1948) found no difference in chest x-rays or respiratory performance (vital capacity and exercise-tolerance tests) between unexposed and exposed workers in a cross-sectional study at a factory where sodium arsenite was prepared. The NOAEL of 0.613 mg As/m³ for respiratory effects in this study is shown in Table 3-1 and plotted in Figure 3-1.

Increased mortality due to respiratory disease has been reported in some cohort mortality studies of arsenic-exposed workers, but no conclusive evidence of an association with arsenic has been produced. In studies of workers exposed to arsenic trioxide at the Anaconda copper smelter in Montana, mortality due to noncancer respiratory disease (e.g., emphysema) was significantly increased compared to the general population (Lee-Feldstein 1983; Lubin et al. 2000; Welch et al. 1982). However, the data were not adjusted for smoking (a well-known confounder for respiratory disease), and analysis of the data with respect to arsenic exposure level did not show a clear dose-response. Similarly, Enterline et al. (1995) found a significant excess of nonmalignant respiratory disease mortality in workers at the ASARCO copper smelter in Tacoma, Washington, but only a slight negative relation to cumulative arsenic exposure. Xuan et al. (1993) found an increase in the relative risk of mortality from pneumoconiosis associated with arsenic exposure in a cohort of tin miners in China. However, this finding was based on a small number of observations (n=32), a clear exposure-response relationship with arsenic was not established, and the miners experienced confounding exposures to dust (a known risk factor for pneumoconiosis) and to radon. These studies were all considered to be inconclusive as to the relationship between inhaled inorganic arsenic and respiratory disease.

Respiratory symptoms were observed in a study of developmental effects in rats. Pregnant female rats exposed to arsenic trioxide dust starting 14 days prior to mating and continuing through mating and gestation exhibited rales at 8 mg As/m³ and labored breathing and gasping at 20 mg As/m³, with no symptoms at 2 mg As/m³ (Holson et al. 1999). The lungs were examined by gross necropsy and no lesions were found. Intratracheal instillation of arsenic trioxide (13 mg As/kg) or gallium arsenide (1.5–

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52 mg As/kg) can cause marked irritation and hyperplasia in the lungs of rats and hamsters (Goering et al. 1988; Ohyama et al. 1988; Webb et al. 1986, 1987). Since this sort of response is produced by a number of respirable particulate materials, it is likely that the inflammatory response is not specifically due to the arsenic.

Organic Arsenicals. No studies were located regarding respiratory effects in humans exposed to organic arsenicals. Short-term exposure of rats and mice to high concentrations ($\geq 4,000$ mg/m³) of DMA caused respiratory distress, and necropsy of animals that died revealed bright red lungs with dark spots (Stevens et al. 1979). Respiratory distress was also observed in rats and mice exposed to high levels ($\geq 6,100$ mg/m³) of the disodium salt of MMA (Stevens et al. 1979), although none of the MMA-exposed animals died. Respiratory distress appears to be associated with inhalation of very high concentrations of organic arsenicals. In 5-minute whole-body plethysmography trials, DMA and the disodium salt of MMA had RD₅₀ (concentration calculated to produce a 50% decrease in respiration rate) values of 3,150 and 1,540 mg/m³, respectively (Stevens et al. 1979). Based on these RD₅₀ values, neither DMA nor MMA is considered to be a potent respiratory irritant. At low concentrations of DMA (34 or 100 mg DMA/m³), an increase in intracytoplasmic eosinophilic globules were found in the nasal turbinates of rats exposed to DMA 6 hours/day, 5 days/week for 67–68 exposures (Whitman 1994).

Cardiovascular Effects.

Inorganic Arsenicals. There is some evidence from epidemiological studies that inhaled inorganic arsenic can produce effects on the cardiovascular system. Cardiovascular effects following oral exposure to arsenic are well known (see Section 3.2.2.2). A cross-sectional study of workers exposed to an estimated time-weighted average of 0.36 mg As/m³ (as arsenic trioxide) at the Ronnskar copper smelter in Sweden for an average of 23 years showed that smelter workers had significantly increased incidences of Raynaud's phenomenon (a peripheral vascular disease characterized by spasm of the digital arteries and numbness of the fingers) and showed increased vasospasticity (constriction of blood vessels) in response to cold when tested in the fingers (Lagerkvist et al. 1986). A follow-up study conducted 2–3 years later found that vasospasticity measurements in exposed workers had improved concurrent with a reduction in arsenic exposure levels, although symptoms of peripheral vascular effects (cold hands or feet, white fingers, numbness in fingers or feet) were still common (Lagerkvist et al. 1988). A cross-sectional study including 46 workers in Denmark with varying, unquantified occupational exposure to arsenic in different occupations found that systolic blood pressure was significantly increased in the arsenic workers (median=125 mmHg) compared with controls (median=117 mmHg) (Jensen and Hansen 1998). Diastolic

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pressure was also increased in this study (77.9 vs. 74.7 mmHg), although the difference from controls was not statistically significant.

Cohort mortality studies of arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline et al. 1995), Anaconda copper smelter in Montana (Lee-Feldstein 1983; Welch et al. 1982), Ronnskar copper smelter in Sweden (Wall 1980), orchard workers in Washington state (Tollestrup et al. 1995), and tin miners in China (Qiao et al. 1997; Xuan et al. 1993) have all reported increased risk of mortality from cardiovascular disease, specifically ischemic heart disease and cerebrovascular disease, in the cohorts studied. However, none of these studies provided conclusive evidence that the observed increase in risk was due to arsenic exposure. The studies in the ASARCO and Anaconda copper smelter workers failed to find a clear dose-response relationship with arsenic (Enterline et al. 1995; Welch et al. 1982), while a follow-up study of the Ronnskar smelter workers not only found lack of a dose-response, but also that the risk of cardiovascular disease was no longer elevated in the cohort (Järup et al. 1989). The studies in orchard workers and tin miners were limited by confounding exposures to copper, lead, and radon, respectively (Qiao et al. 1997; Tollestrup et al. 1995). The risk of cardiovascular disease mortality in the tin miners not only showed no dose-response relationship with arsenic exposure, but was positively associated with radon exposure, suggesting that radon may have been responsible for the increased cardiovascular risk in this cohort (Xuan et al. 1993).

The LOAEL for Raynaud's phenomenon and vasospasticity identified by Lagerkvist et al. (1986) is shown in Table 3-1 and Figure 3-1. No studies were located regarding cardiovascular effects in animals after inhalation exposure to inorganic arsenic.

Organic Arsenicals. No studies were located regarding cardiovascular effects in humans after inhalation exposure to organic arsenicals. No histological alterations were observed in the hearts of rats exposed to 100 mg DMA/m³ for 67–68 exposures (Whitman 1994).

Gastrointestinal Effects.

Inorganic Arsenicals. Several case studies have reported nausea, vomiting, and diarrhea in workers with acute arsenic poisoning following occupational inhalation exposure (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Although gastrointestinal effects are not typically associated with arsenic poisoning by inhalation (Pinto and McGill 1953), such effects are a common feature of oral ingestion of high doses of arsenic (see Section 3.2.2.2),

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and it is possible that mucociliary transport of arsenic dust from the lungs to the gut could be responsible for the effects in these cases. Exposure levels were not reliably estimated for any of these cases.

The only report of gastrointestinal effects of inhaled inorganic arsenic in animals was a developmental toxicology study in which four of nine pregnant rats died, and one rat was euthanized *in extremis*, between days 12 and 19 of gestation after 30–35 days of exposure to an aerosol of arsenic trioxide at an exposure concentration of 20 mg As/m³ (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. Exposure to 8 mg As/m³ did not produce gross gastrointestinal lesions.

Organic Arsenicals. Data regarding gastrointestinal effects in people exposed to organic arsenic in the air are limited. The frequency of gastrointestinal complaints was no higher than controls in workers exposed to arsanilic acid (i.e., 4-aminophenyl arsonic acid) at mean concentrations up to 0.17 mg/m³ in a chemical factory (Watrous and McCaughey 1945). However, this sort of data might easily be biased by workers who chose not to complain about minor symptoms, so no conclusion can be reached. Rats and mice exposed to very high levels (above 3,000 mg/m³) of MMA (disodium salt) or DMA experienced diarrhea (Stevens et al. 1979). The diarrhea could be due to transport of inhaled particulate material from the lungs to the gastrointestinal system or to direct ingestion of the compound (e.g., from grooming of the fur). No gastrointestinal effects were observed in rats repeatedly exposed to 100 mg DMA/m³ 6 hours/day, 5 days/week for 67–68 exposures (Whitman 1994).

Hematological Effects.

Inorganic Arsenicals. Although anemia is a common feature of arsenic poisoning following oral exposure in humans (see Section 3.2.2.2), case studies of workers with arsenic poisoning from occupational inhalation exposure reported no effects on red blood cell count (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). The reason for this apparent route specificity is not clear, but might simply be related to dose. No studies were located regarding hematological effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No effect on levels of hemoglobin, red cells, or white cells was detected in the blood of manufacturing workers (323 counts in 35 workers) exposed to airborne arsanilic acid dusts at a mean concentration of 0.17 mg/m³ in the workplace (Watrous and McCaughey 1945). Controls were an unspecified number of unexposed manufacturing workers with 221 complete blood counts. No

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hematological alterations were observed in rats exposed to 100 mg DMA/m³ for an intermediate duration (Whitman 1994).

Musculoskeletal Effects.

Inorganic Arsenicals. Few data were located regarding musculoskeletal effects associated with inhalation exposure to inorganic arsenic, and none to suggest the existence of any such effects. Electromyographic examination of the calves and feet showed no differences between control and arsenic-exposed workers in a cross-sectional study of workers at the Ronnskar copper smelter in Sweden (Blom et al. 1985). No studies were located regarding musculoskeletal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to organic arsenicals.

Hepatic Effects.

Inorganic Arsenicals. There is no evidence that inhaled inorganic arsenic produces effects on the liver, although few data are available. Case studies of workers with inhalation arsenic poisoning that included liver function tests did not find any evidence of hepatic dysfunction (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). No studies were located regarding hepatic effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding hepatic effects in humans after inhalation exposure to organic arsenicals. No histological alterations were observed in the livers of rats exposed to 100 mg DMA/m³ for 67–68 exposures (Whitman 1994).

Renal Effects.

Inorganic Arsenicals. The limited data available do not suggest any relationship between inhalation of inorganic arsenic and kidney effects. A cross-sectional study of renal function parameters in glass factory workers exposed to arsenic (concentrations unknown) found no meaningful differences from controls in urinary levels of several proteins (albumin, retinol binding protein, β_2 -microglobulin, brush-border antigen) used as markers of glomerular damage or tubular cell exfoliation (Foà et al. 1987). Routine

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clinical urinalysis was normal when included in case studies of workers with inhalation arsenic poisoning (Ide and Bullough 1988; Morton and Caron 1989). No studies were located regarding renal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding renal effects in humans after inhalation exposure to organic arsenicals. No renal effects were reported in rats exposed to 100 mg DMA/m³ 6 hours/day, 5 days/week for 67–68 exposures (Whitman 1994).

Dermal Effects.

Inorganic Arsenicals. Dermatitis has frequently been observed in industrial workers exposed to inorganic arsenic in the air, with the highest rates occurring in the workers with the greatest arsenic exposure (Cöl et al. 1999; Dunlap 1921; Holmqvist 1951; Lagerkvist et al. 1986; Pinto and McGill 1953). Limited quantitative information is available regarding the exposure levels that produce dermatitis, and the high likelihood of co-exposure by the dermal route makes dose-response analysis difficult. A cross-sectional study of workers at a factory where sodium arsenite was prepared found that workers with the highest arsenic exposure (mean air levels ranging from 0.384 to 1.034 mg As/m³ and estimated to average 0.613 mg As/m³) tended to be grossly pigmented with hyperkeratinization of exposed skin and to have multiple warts (Perry et al. 1948). In the same study, workers with lower arsenic exposure (estimated to average 0.078 mg As/m³) were much less affected, but still had a higher incidence of pigmentation keratosis than controls. LOAEL values identified by Perry et al. (1948) and Mohamed (1998) are shown in Table 3-1 and Figure 3-1. NOAEL values for dermal irritation have not been identified. Dermal effects (hyperkeratoses, hyperpigmentation) are also very common in people exposed to inorganic arsenic by the oral route (see Section 3.2.2.2). No studies were located on dermal effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. Data regarding dermal effects in people exposed to organic arsenic in the air are limited. Complaints of keratosis were roughly 2-fold higher than unexposed controls in female packaging workers exposed to arsanilic acid at an average concentration of 0.065 mg/m³ and in male manufacturing workers exposed to an average concentration of 0.17 mg/m³ in a chemical factory (Watrous and McCaughey 1945). Limitations in study methodology (e.g., alternate sources of effects were not investigated, workers might choose not to report minor complaints to company officials) make the reliability of this observation uncertain. Female rats exposed to DMA at 6,900 mg/m³ developed erythematous lesions on the feet and ears (Stevens et al. 1979); these lesions did not develop in females

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exposed at lower concentrations ($4,100 \text{ mg/m}^3$) or males. It seems likely that these effects were due to direct irritation from dermal contact with the dust. No dermal effects were observed in rats repeatedly exposed to lower levels of DMA (100 mg/m^3) (Whitman 1994).

Ocular Effects.

Inorganic Arsenicals. Chemical conjunctivitis, characterized by redness, swelling, and pain, has been observed in workers exposed to arsenic dusts in air, usually accompanied by facial dermatitis (Dunlap 1921; Pinto and McGill 1953). No information was located regarding air levels of arsenic that produce this effect. No studies were located on ocular effects in animals after inhalation exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located on ocular effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA ($\geq 4,000 \text{ mg/m}^3$) developed an encrustation around the eyes (Stevens et al. 1979). It seems likely that these effects were due to direct irritation from ocular contact with the dust.

Body Weight Effects.

Inorganic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to inorganic arsenicals. Female rats exposed to arsenic trioxide dust starting 14 days before mating and continuing through mating and gestation showed a marked decrease in body weight and food consumption at 20 mg As/m^3 (preliminary study) and a smaller decrease at 8 mg As/m^3 (definitive study), with no effect at 2 mg As/m^3 (Holson et al. 1999).

Organic Arsenicals. No studies were located on body weight effects in humans after inhalation exposure to organic arsenicals. Rats and mice exposed to high concentrations of DMA ($\geq 4,000 \text{ mg/m}^3$) for 2 hours had an unspecified decrease in body weight gain during the subsequent 14 days (Stevens et al. 1979). No alterations in body weight gain were observed in rats exposed to 100 mg DMA/m^3 for 67–68 exposures (Whitman 1994).

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3.2.1.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. A single study was located regarding the immunological and lymphoreticular effects of inhaled inorganic arsenic in humans. Bencko et al. (1988) detected no abnormalities in serum levels of immunoglobins in 47 workers exposed to arsenic (exposure levels not measured) in a coal-burning power plant. However, serum levels of other proteins such as transferrin, orosomucoid, and ceruloplasmin were significantly elevated compared to levels in a group of 27 workers from a different plant in which the arsenic content in the coal was 10 times lower. The investigators suggested that the increased levels of ceruloplasmin might be related to higher cancer mortality rates found among these workers.

The immune effects of inhaled arsenic in animals were studied by Aranyi et al. (1985). Female mice exposed to arsenic trioxide aerosol for 3 hours showed a concentration-related decrease in pulmonary bactericidal activity (presumably as a result of injury to alveolar macrophages) and a corresponding concentration-related increase in susceptibility to introduced respiratory bacterial pathogens. Similar results were found when the exposure was repeated over 1- and 4-week periods. The NOAEL and LOAEL values for this study are shown in Table 3-1 and Figure 3-1.

Intratracheal studies in animals offer some support for an immune effect of inhaled inorganic arsenic. Decreases in humoral response to antigens and in several complement proteins were noted in mice given an intratracheal dose of 5.7 mg As/kg as sodium arsenite (Sikorski et al. 1989), although these changes were not accompanied by any decrease in resistance to bacterial or tumor cell challenges. Animals given an intratracheal dose of GaAs (25 mg As/kg or higher) also displayed a variety of changes in numerous immunological end points (some increased, some decreased) (Burns and Munson 1993; Sikorski et al. 1989). Whether these effects were due to a direct effect on the immune system or were secondary to the inflammatory effect of GaAs on the lung (see Section 3.2.1.2, above) is uncertain.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.4 Neurological Effects

Inorganic Arsenicals. There is evidence from epidemiological studies that inhaled inorganic arsenic can produce neurological effects. A study by Gerr et al. (2000) reported an elevated incidence of peripheral neuropathy in subjects who lived near an arsenic-using pesticide plant (13/85=15.3%; odds ratio

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[OR]=5.1, $p=0.004$), relative to subjects who lived farther from the plant ($4/118=3.4\%$). Concentrations of arsenic in soil and house dust were elevated ($\sim 30\text{--}300\text{ }\mu\text{g As/g}$) for residences near the plant, according to 1993–1995 monitoring data. Studies of copper smelter workers at the ASARCO smelter in Tacoma, Washington (Feldman et al. 1979), a power station in Slovakia (Buchancová et al. 1998), and the Ronnskar smelter in Sweden (Blom et al. 1985; Lagerkvist and Zetterlund 1994) have demonstrated peripheral neurological effects in workers associated with arsenic trioxide exposure. At the ASARCO smelter, the prevalence of clinically diagnosed peripheral neuropathy was markedly higher in arsenic-exposed workers ($26/61=43\%$) than controls ($4/33=12\%$), and although the difference in mean nerve conduction velocities (NCV) was not statistically significant, mean peroneal motor NCV was lower in arsenic-exposed workers than controls and all 12 cases of abnormally low NCV occurred in the arsenic group (Feldman et al. 1979). In the study of 70 workers in Slovakia, the investigators described 16 cases of arsenic intoxication. Among these, 13 had signs and symptoms of sensory and motor polyneuropathy on both upper and lower extremities, 10 were diagnosed with pseudoneurasthenic syndrome, and 6 suffered from toxic encephalopathy (Buchancová et al. 1998). The average length of exposure was 22.3 years ($\text{SD} \pm 8.4$ years) and the average arsenic exposure in inhaled air ranged from 4.6 to $142.7\text{ }\mu\text{g/m}^3$. Similar results were observed at the Ronnskar smelter, where Blom et al. (1985) reported significantly increased prevalence of workers with abnormally low NCV in the exposed group, and lower, but not statistically significant, mean NCV in five peripheral nerves. A follow-up study on the Ronnskar workers 5 years later found that the prevalence of abnormally low NCV remained significantly increased in the exposed workers, but that the decrease in mean NCV was now also statistically significant in the tibial (motor) and sural (sensory) nerves (Lagerkvist and Zetterlund 1994). Blood lead was monitored in this study as a potential confounder, but levels were low and not considered likely by the researchers to have had any influence on the results. The follow-up Ronnskar study provided enough information to estimate that mean arsenic exposure was 0.31 mg As/m^3 and lasted an average of 28 years in the exposed group, and this LOAEL is shown in Table 3-1 and Figure 3-1.

The literature also contains several case studies of workers with inhalation arsenic poisoning who developed neurological symptoms. Although these studies do not provide reliable information on exposure levels or conclusive evidence that the observed effects were related to arsenic, the findings are suggestive. Symptoms in these cases included not only indicators of peripheral neuropathy (numbness, loss of reflexes, muscle weakness, tremors) (Ide and Bullough 1988; Morton and Caron 1989), but also frank encephalopathy (hallucinations, agitation, emotional lability, memory loss) (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Morton and Caron 1989). Both peripheral neuropathy and encephalopathy are associated with oral exposure to inorganic arsenic (see Section 3.2.2.4).

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The possible association between arsenic in air and neurological effects in children has also been examined. A study by Bencko et al. (1977) reported that children of approximately 10 years of age ($n=56$) living near a power plant burning coal of high arsenic content showed significant hearing losses (increased threshold) compared to a control group of children ($n=51$) living outside the polluted area (Bencko et al. 1977). The effect was most marked at low frequencies. The precise site affected within the auditory pathway was not determined and could have been in the periphery, centrally-located, or both. A small study of children in Mexico reported a significant negative correlation between tests of verbal IQ and urinary arsenic in children ($n=41$) living in an urban area near a smelter complex (Calderón et al. 2001). Exposure concentrations were not available in either study.

No studies were located regarding neurological effects in animals after inhalation exposure to inorganic arsenicals. Mice given a single intratracheal dose of 200 mg/kg of GaAs displayed a decrease in overall activity 6–8 hours later, but no additional neurological evaluations were conducted on these animals (Burns and Munson 1993).

Organic Arsenicals. Data regarding neurological effects in people exposed to organic arsenic in the air are limited to a single study. The frequency of central nervous system complaints was no higher than controls in workers at a chemical factory exposed to arsanilic acid at mean concentrations up to 0.17 mg/m^3 (Watrous and McCaughey 1945). Although peripheral nerve complaints were higher in arsenic packaging workers (mean exposure= 0.065 mg/m^3) than in unexposed controls, this was not the case in manufacturing workers with higher arsenic exposure (mean= 0.17 mg/m^3). This suggests that the effects on the peripheral nerves in the exposed packaging workers were not due to arsenic. The reliability of these data is limited by shortcomings in the study methodology (e.g., the data might easily be biased by workers who chose not to complain about minor symptoms). No studies were located regarding neurological effects in animals after inhalation exposure to organic arsenicals.

3.2.1.5 Reproductive Effects

Inorganic Arsenicals. No studies were located regarding reproductive effects in humans after inhalation exposure to inorganic arsenicals. Reproductive performance was evaluated in female rats exposed to $0.08\text{--}20 \text{ mg As/m}^3$ (preliminary study) or $0.2\text{--}8 \text{ mg As/m}^3$ (definitive study) as As_2O_3 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). No changes occurred in the precoital interval (time to mating), mating index (percentage of rats mated), or fertility index (percentage

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of matings resulting in pregnancy). The NOAEL values for this study are shown in Table 3-1 and Figure 3-1.

Organic Arsenicals. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.6 Developmental Effects

Inorganic Arsenicals. Developmental effects associated with occupational and environmental exposure to airborne arsenic have been investigated in a series of studies at the Ronnskar copper smelter in northern Sweden (Nordström et al. 1978a, 1978b, 1979a, 1979b). In comparison to a northern Swedish reference population, female employees of the smelter had a significantly increased incidence of spontaneous abortion (Nordström et al. 1979a), and their children had a significantly increased incidence of congenital malformations (Nordström et al. 1979b) and significantly decreased average birth weight (Nordström et al. 1978a). Increased incidence of spontaneous abortion and decreased average birth weight of children were also found in populations living in close proximity to the smelter (Nordström et al. 1978a, 1978b, 1979b). While these data are suggestive of developmental effects associated with occupational and environmental exposure from the smelter, the reported effects are not large, the analyses include only limited consideration of potential confounders (e.g., smoking), and there are no data relating the apparent effects specifically to arsenic exposure.

Ihrig et al. (1998) conducted a case-control study of stillbirths in the vicinity of a Texas arsenic pesticide factory that included estimation of environmental arsenic exposures using atmospheric dispersion modeling and multiple regression analysis considering arsenic exposure, race/ethnicity, maternal age, median income, and parity as explanatory variables. There was a statistically significant increase in the risk of stillbirth in the highest exposure category ($>100 \text{ ng As/m}^3$, midpoint= 682 ng/m^3). Further analysis showed that this increase in risk was limited to people of Hispanic descent, who the researchers speculated may be an especially sensitive population due to a genetic impairment in folate metabolism. Interpretation of this study is limited by small numbers of cases and controls in the high exposure group, lack of data on smoking, potential confounding exposures to other chemicals from the factory, and failure to take into account previous years of deposition in the exposure estimates.

Arsenic has been shown to produce developmental effects by inhalation exposure in laboratory animals, although it is unclear whether or not the effects occur only at maternally toxic doses. Mice exposed to

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22 mg As/m³ (as As₂O₃) for 4 hours on days 9–12 of gestation had serious developmental effects (significant increases in the percentage of dead fetuses, skeletal malformations, and the number of fetuses with retarded growth), while those exposed to 2.2 mg As/m³ had only a 10% decrease in average fetal body weight, and those exposed to 0.20 mg As/m³ had no effects (Nagymajtényi et al. 1985). The study was limited by failure to quantify malformations on a litter basis, discuss the nature and severity of the observed malformations, or report on the occurrence of maternal effects. No increases in fetal resorptions, fetal mortality, or malformations, and no decreases in fetal body weight occurred when rats were exposed to 0.2–8 mg As/m³ (as As₂O₃), 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). At the 8 mg/m³ exposure level, toxicity was observed in the dams, including rales, a dried red exudate at the nose, and lower gains in net body weight than controls. In a preliminary dose-range study, there was a marked significant increase in postimplantation loss (primarily early resorptions) and consequent marked significant decrease in viable fetuses per litter at 20 mg As/m³, a concentration that also produced severe maternal effects including mortality (Holson et al. 1999).

The NOAEL and LOAEL values for increased risk of stillbirth in humans identified by Ihrig et al. (1998) and those for developmental effects in rodents found by Nagymajtényi et al. (1985) and Holson et al. (1999) are shown in Table 3-1 and Figure 3-1.

Organic Arsenicals. No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.1.7 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies that inhalation exposure to inorganic arsenic increases the risk of lung cancer. Most studies involved workers exposed primarily to arsenic trioxide dust in air at copper smelters (Axelson et al. 1978; Brown and Chu 1982, 1983a, 1983b; Enterline and Marsh 1982; Enterline et al. 1987a, 1987b, 1995; Ferreccio et al. 1996; Järup and Pershagen 1991; Järup et al. 1989; Lee and Fraumeni 1969; Lee-Feldstein 1983, 1986; Lubin et al. 2000; Mazumdar et al. 1989; Pinto et al. 1977, 1978; Sandstrom et al. 1989; Viren and Silvers 1999; Wall 1980; Welch et al. 1982) and mines (Liu and Chen 1996; Qiao et al. 1997; Taylor et al. 1989; Xuan et al. 1993), but increased incidence of lung cancer has also been observed at chemical plants where exposure was primarily to arsenate (Bulbulyan et al. 1996; Mabuchi et al. 1979; Ott et al. 1974; Sobel et al. 1988). In addition, several studies suggest that residents living near smelters or arsenical chemical plants may also have increased risk of lung cancer (Brown et al. 1984; Cordier et al. 1983; Matanoski et

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al. 1981; Pershagen 1985), although the increases are small and are not clearly detectable in all cases (e.g., Frost et al. 1987). The strongest evidence that arsenic is responsible for the observed lung cancer comes from quantitative dose-response data relating specific arsenic exposure levels to lung cancer risk. These data are available for arsenic-exposed workers at the ASARCO copper smelter in Tacoma, Washington (Enterline and Marsh 1982; Enterline et al. 1987a, 1995; Mazumdar et al. 1989), the Anaconda copper smelter in Montana (Lee-Feldstein 1986; Welch et al. 1982), eight other U.S. copper smelters (Enterline et al. 1987b), and the Ronnskar copper smelter in Sweden (Järup and Pershagen 1991; Järup et al. 1989). A common limitation of these studies is confounding exposure to other chemicals, such as sulfur dioxide, and cigarette smoking.

Enterline and Marsh (1982) reported a significant increase in respiratory cancer mortality (standard mortality ratio [SMR]=189.4) based on 104 observed respiratory cancer deaths and only 54.9 expected over the years 1941–1976 in a cohort of 2,802 male workers employed for ≥ 1 year between 1940 and 1964 at the ASARCO smelter. When the cohort was separated into low and high arsenic exposure groups, with mean estimated time-weighted average arsenic exposures of 0.054 and 0.157 mg As/m³, respectively (based on work history, historical urinary arsenic measurements, and an experimentally derived relationship between urinary and inhaled arsenic), respiratory cancer mortality was significantly increased in both groups in a concentration-related fashion (SMR=227.7 and 291.4 in the low and high groups, respectively). Enterline et al. (1987a) re-analyzed these data using improved exposure estimates that incorporated historical measurements of arsenic in the ambient air and personal breathing zone of workers. Respiratory cancer mortality was significantly increased in a concentration-related fashion in the low (SMR=213.0), medium (SMR=312.1), and high (SMR=340.9) arsenic exposure groups, which had mean estimated time-weighted average arsenic exposures of 0.213, 0.564, and 1.487 mg As/m³, respectively. An alternative analysis of these data by Mazumdar et al. (1989) produced similar results. Enterline et al. (1995) extended the mortality follow-up from 1976 to 1986, but reported findings similar to the earlier study in a less thorough analysis. The CEL from Enterline et al. (1987a), the most complete analysis of the ASARCO cohort with the best exposure estimates, is presented in Table 3-1 and Figure 3-1.

Respiratory cancer mortality was significantly increased (SMR=285) based on 302 observed respiratory deaths between 1938 and 1977 in a cohort of 8,045 white male workers employed for at least 1 year between 1938 and 1956 at the Anaconda smelter (Lee-Feldstein 1986). When workers were categorized according to cumulative arsenic exposure and date of hire, lung cancer mortality was significantly increased in all groups hired between 1925 and 1947. Workers in the lowest cumulative exposure group

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(<10 mg-mo/m³) were reported to have had <2 years of exposure at an average arsenic concentration of 0.38 mg/m³. An alternative analysis of a subset of the Anaconda cohort (n=1,800, including all 277 employees with heavy arsenic exposure and 20% of the others) that included information on smoking and other occupational exposures was performed by Welch et al. (1982). This analysis showed that lung cancer mortality increased with increasing time-weighted average arsenic exposure, with a small nonsignificant increase in the low group (SMR=138) exposed to 0.05 mg/m³ and significant increases in the medium (SMR=303), high (SMR=375), and very high (SMR=704) groups exposed to 0.3, 2.75, and 5.0 mg/m³, respectively. Cohort members were more likely to be smokers than U.S. white males, but smoking did not differ among the arsenic exposure groups. Exposure-response analysis of smokers was similar to the analysis based on the full subcohort, while analysis of nonsmokers (limited by small group sizes) also showed a similar pattern, but with lower SMRs. In a followup analysis of the same cohort, Lubin et al. (2000) re-weighted the exposure concentrations based on duration and time of exposure and re-evaluated the effects of exposure. Relative risks for respiratory cancer increased with increasing duration in each arsenic exposure area (light, medium, and heavy) after adjustment for duration in the other two exposure areas. SMRs were significantly elevated following exposure to 0.58 mg/m³ (medium; SMR=3.01, 95% CI=2.0–4.6) or 11.3 mg/m³ (high; SMR=3.68, 95% CI=2.1–6.4) for 10 or more years, and following exposure to 0.29 mg/m³ (low; SMR=1.86, 95% CI=1.2–2.9) for 25 or more years. The CELs from the analyses of the Anaconda cohort are presented in Table 3-1 and Figure 3-1.

Enterline et al. (1987b) studied the mortality experience from 1949 to 1980 of a cohort of 6,078 white males who had worked for 3 years or more between 1946 and 1976 at one of eight U.S. copper smelters in Arizona, Utah, Tennessee, and Nevada. Lung cancer mortality was significantly increased only in the Utah smelter (SMR=226.7), which had the highest average arsenic exposure concentration (0.069 mg/m³ vs. 0.007–0.013 mg/m³ in the other smelters) and also contributed the largest number of cohort members (n=2,288 vs. 189–965 from the other smelters). A nested case-control study showed that arsenic exposure and cigarette smoking were significant risk factors for lung cancer in the smelter workers. Smoking was lower in the Utah smelter workers than in the other smelter workers, but still higher than in the referent Utah population, suggesting that the risk attributable to arsenic in this study population is somewhat lower than indicated by the SMR reported above. The CEL from this study is presented in Table 3-1 and Figure 3-1.

Järup et al. (1989) reported significantly increased lung cancer mortality (SMR=372, 95% confidence interval [CI]=304–450) based on 106 lung cancer deaths in a cohort of 3,916 male workers employed for ≥3 months between 1928 and 1967 at the Ronnskar smelter and followed for mortality through 1981.

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Workers were separated into low, medium, and high arsenic exposure groups with mean time-weighted average exposure estimates of 0.05, 0.2, and 0.4 mg/m³, respectively. Lung cancer mortality was significantly increased in all three exposure groups in a concentration-related fashion (SMR=201, 353, and 480, respectively). A nested case-control analysis of 102 lung cancer cases and 190 controls from the cohort showed that lung cancer risk increased with increasing arsenic exposure in nonsmokers, light smokers, and heavy smokers (Järup and Pershagen 1991). The results demonstrated that arsenic is a risk factor for lung cancer in the smelter workers, but also suggested a greater-than-additive interaction between smoking and arsenic exposure. In this analysis, in contrast to the cohort study, lung cancer risk due to arsenic was increased only in the higher arsenic-exposure groups. Potential explanations for this difference between the cohort and case-control analyses include a higher proportion of smokers in the smelter workers than in the regional referent population in the cohort study, and limited power to detect increased risk in the case-control study due to small group sizes in the dose-response analysis. The CELs from both the cohort and case-control studies are presented in Table 3-1 and Figure 3-1.

Several researchers have examined the histological cell types of lung cancer (epidermoid carcinoma, small cell carcinoma, adenocarcinoma) in arsenic-exposed workers (e.g., Axelson et al. 1978; Newman et al. 1976; Pershagen et al. 1987; Qiao et al. 1997; Wicks et al. 1981). Although the incidence of the various cell types varied from population to population, all studies found an increase in several tumor types. This indicates that arsenic does not specifically increase the incidence of one particular type of lung cancer.

The studies of the ASARCO cohort (Enterline and Marsh 1982; Enterline et al. 1987a, 1995) noted a supralinear exposure-response relationship (i.e., steeper at lower doses) between arsenic exposure and lung cancer mortality. Hertz-Picciotto and Smith (1993) extended this observation to several other occupationally exposed cohorts with quantitative exposure information. The authors suggest that neither toxicokinetic mechanisms nor confounding from age, smoking, or other workplace carcinogens that differ by exposure level are likely explanations for the curvilinearity. Plausible explanations offered include: (1) synergism (with smoking), which varies in magnitude according to the level of arsenic exposure, (2) long-term survivorship at higher exposures among the healthier, less susceptible individuals, and (3) exposure estimate errors that were more prominent at higher-exposure levels as a result of past industrial hygiene sampling or worker protection practices.

Quantitative risk estimates for inhaled inorganic arsenic have been derived using the exposure-response data. EPA derived a unit risk estimate (the excess risk of lung cancer associated with lifetime exposure to

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1 $\mu\text{g}/\text{m}^3$) of 4.3×10^{-3} per ($\mu\text{g}/\text{m}^3$) based on the dose-response relationships between arsenic exposure and excess lung cancer mortality in workers at the Anaconda smelter in Montana (Brown and Chu 1982, 1983a, 1983b; Lee-Feldstein 1983; and an unpublished paper by Higgins and associates) and the ASARCO smelter in Tacoma, Washington (Enterline and Marsh 1982; EPA 1984a; IRIS 2007). In some cases, calculations of exposure, as well as the procedures for generating quantitative risk estimates, are quite complex and the interested reader is referred to the EPA documents (EPA 1981c, 1984a, 1987e, 1996b; IRIS 2007) for a detailed description. Viren and Silvers (1994) re-evaluated the unit risk estimate using the same methods as EPA, but incorporating updated results from the ASARCO smelter (Enterline et al. 1987a; Mazumdar et al. 1989) and the findings from the Swedish smelter (Järup et al. 1989). Their analysis yielded a revised unit risk of 1.28×10^{-3} per ($\mu\text{g}/\text{m}^3$) that, when pooled with the earlier estimate from the Montana smelter cohort, yielded a composite unit risk of 1.43×10^{-3} per ($\mu\text{g}/\text{m}^3$). This unit risk estimate is a factor of 3 smaller than the EPA's current estimate of 4.3×10^{-3} per ($\mu\text{g}/\text{m}^3$). Figure 3-1 shows the air concentrations that correspond to excess lifetime cancer risks of 10^{-4} – 10^{-7} based on the EPA unit risk estimate.

There have been occasional reports of other types of cancer (i.e., nonrespiratory cancer) potentially associated with inhalation exposure to inorganic arsenic, but there is no strong evidence for any of them. For example, Enterline et al. (1995) found significantly increased mortality due to cancer of the large intestine and bone cancer in the ASARCO cohort. However, neither cancer showed any relation to cumulative arsenic exposure, and the purported increase in bone cancer risk was based on a very small number of observations. Pesch et al. (2002) reported an increase in nonmelanoma skin cancers resulting from exposure from a Slovakian coal-burning power plant, but exposure levels associated with the lesions were not presented. Bencko et al. (2005) also reported an increase in the incidence of nonmelanoma skin cancer among workers of a power plant burning coal of a high arsenic content and in the population living in the vicinity of the power plant. Bulbulyan et al. (1996) reported an increase in risk of stomach cancer among workers exposed to the highest average arsenic concentrations at a Russian fertilizer plant, but this finding, which was based on a small number of observations and was only marginally statistically significant, was confounded by exposure to nitrogen oxides, which were more convincingly associated with stomach cancer in this study. Wingren and Axelson (1993) reported an association between arsenic exposure and stomach and colon cancer in Swedish glass workers, but this result was confounded by concomitant exposure to other metals. Lee-Feldstein (1983) observed a small, marginally significant increase in digestive tract cancer (SMR=125) in one study of the Anaconda cohort, but this was not found in other studies of this cohort (Lee and Fraumeni 1969; Lee-Feldstein 1986; Welch et al. 1982). Wulff et al. (1996) observed an apparent increase in the risk of childhood cancer (all types combined) in the

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population living within 20 km of the Ronnskar smelter, but the apparent increase was based on a small number of cases (13 observed vs. 6.7 expected) and was not statistically significant, and exposure to arsenic was confounded by exposure to lead, copper, cadmium, sulfur dioxide, and possibly other emissions such as nickel and selenium. A retrospective study of deaths due to unspecified types of malignancies among workers of power plants found no significant differences in death rate between two groups whose exposure levels to arsenic had a difference of one order of magnitude (Bencko et al. 1980). However, the mean age of those deceased due to cancer in the high-exposure group was 55.9 years compared to 61.2 years in the low-exposure group, and this difference was statistically significant ($p < 0.05$). Also, when the workers were stratified by exposure-duration, there was a significantly higher frequency of tumors in the high-exposure group after shorter employment periods (< 5 or $6-10$ years) than after a longer employment period (≥ 11 years). No information was provided regarding specific types of cancer. Various case reports have implicated occupational arsenic exposure as a potential contributing factor in workers who developed sinonasal cancer (Battista et al. 1996), hepatic angiosarcoma (Tsai et al. 1998a), and skin cancer (Cöl et al. 1999; Tsuruta et al. 1998), but provide no proof that inhaled arsenic was involved in the etiology of the observed tumors. Wong et al. (1992) found no evidence that environmental exposure to airborne arsenic produced skin cancer in residents living near the Anaconda smelter or an open pit copper mine.

No studies were located regarding cancer in animals after inhalation exposure to inorganic arsenicals, although several intratracheal instillation studies in hamsters have provided evidence that both arsenite and arsenate can increase the incidence of lung adenomas and/or carcinomas (Ishinishi et al. 1983; Pershagen and Björklund 1985; Pershagen et al. 1984; Yamamoto et al. 1987). These data support the conclusion that inhalation of arsenic may lead to lung cancer in humans.

Organic Arsenicals. No studies were located regarding cancer effects in humans or animals after inhalation exposure to organic arsenicals.

3.2.2 Oral Exposure

There are a large number of studies in humans and animals on the toxic effects of ingested arsenic. In humans, most cases of toxicity have resulted from accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions or by consumption of contaminated food or drinking water. In some cases, the chemical form is known (e.g., the most common arsenic medicinal was Fowler's solution, which contained 1% potassium arsenite or arsenic trioxide), but in many cases (e.g., exposures through

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drinking water), the chemical form is not known. In these cases, it is presumed that the most likely forms are either inorganic arsenate [As(+5)], inorganic arsenite [As(+3)], or a mixture. Table 3-3 and Figure 3-3 summarize a number of studies that provide reliable quantitative data on health effects in humans and animals exposed to inorganic arsenicals by the oral route. Similar data for MMA, DMA, and roxarsone are listed in Tables 3-4, 3-5, and 3-6, and shown in Figures 3-4, 3-5, and 3-6, respectively. All exposure data are expressed as milligrams of arsenic (as the element) per kilogram body weight per day (mg As/kg/day). These studies and others that provide useful qualitative information are summarized below.

3.2.2.1 Death

Inorganic Arsenicals. There are many case reports of death in humans due to ingestion of high doses of arsenic. In nearly all cases, the most immediate effects are vomiting, diarrhea, and gastrointestinal hemorrhage, and death may ensue from fluid loss and circulatory collapse (Levin-Scherz et al. 1987; Saady et al. 1989; Uede and Furukawa 2003). In other cases, death may be delayed and result from the multiple tissue injuries produced by arsenic (Campbell and Alvarez 1989). Some accounts of fatal arsenic poisoning describe both gastrointestinal effects soon after ingestion and extensive damage to multiple organ systems prior to death (Quatrehomme et al. 1992). A precise estimate of the ingested dose is usually not available in acute poisonings, so quantitative information on lethal dose in humans is sparse. The lethal doses ranged from 22 to 121 mg As/kg in four cases where known amounts were ingested as a single bolus (Civantos et al. 1995; Hantson et al. 1996; Levin-Scherz et al. 1987; Quatrehomme et al. 1992). Two people in a family of eight died from ingestion of water containing about 110 ppm of arsenic for a week (Armstrong et al. 1984). This corresponded to a dose of about 2 mg As/kg/day. Based on a review of clinical reports in the older literature, Holland (1904) estimated the minimum lethal dose to be about 130 mg (also about 2 mg/kg). A similar estimate of 70–180 mg (about 1–3 mg/kg) was provided by Vallee et al. (1960). Death due to chronic arsenic exposure has been reported at lower concentrations. Five children between the ages of 2 and 7 years died from late sequelae of chronic arsenic poisoning after drinking contaminated water throughout their lives at estimated average doses of 0.05–0.1 mg As/kg/day (Zaldívar and Guillier 1977). A 22-year-old man with chronic arsenical dermatosis died from arsenic-related effects after lifetime exposure to an estimated average dose of 0.014 mg As/kg/day in the drinking water (Zaldívar et al. 1981). Systematic studies of lethality from chronic exposure attributable to increased risk of cardiovascular disease or cancer are discussed below in Sections 3.2.2.2 and 3.2.2.7, respectively.

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Human	1 wk (W)				2 (death)	Armstrong et al. 1984 NS	
2	Human	once (IN)				121 M (death)	Civantos et al. 1995 As(+5)	
3	Human	once (IN)				108 M (death)	Hantson et al. 1996 As(+3)	
4	Human	once (IN)				22 M (death)	Levin-Scherz et al. 1987 As(+3)	
5	Human	once (IN)				93 M (death)	Quatrehomme et al. 1992 As(+3)	
6	Rat (wild Norway)	once (G)				104 (LD50)	Dieke and Richter 1946 As(+3)	
7	Rat (Sherman)	once (G)				112 F (LD50)	Gaines 1960 As(+5) calcium arsenate	
8	Rat (Sherman)	once (G)				44 F (LD50)	Gaines 1960 As(+3)	
9	Rat (Sherman)	once (G)				175 F (LD50)	Gaines 1960 As(+5) lead arsenate	
10	Rat (Sprague- Dawley)	once (GW)				15 M (LD50)	Harrisson et al. 1958 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
11	Rat (Sprague- Dawley)	once (F)				145 M (LD50)	Harrisson et al. 1958 As(+3)	
12	Rat (CD)	once Gd 9 (GW)				23 F (7/25 dams died)	Stump et al. 1999 As(+3)	
13	Mouse (Swiss- Webster)	once (GW)				39 M (LD50)	Harrisson et al. 1958 As(+3)	
14	Mouse (C57H46)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)	
15	Mouse (Dba2)	once (GW)				32 M (LD50)	Harrisson et al. 1958 As(+3)	
16	Mouse (C3H)	once (GW)				26 M (LD50)	Harrisson et al. 1958 As(+3)	
17	Mouse (ddY)	once (GW)				26 M (LD50)	Kaise et al. 1985 As(+3)	
18	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)				1.49 F (7/20 dams died)	Nemec et al. 1998 As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic								
19	Human	1 wk (W)	Gastro		0.2 (vomiting, diarrhea, abdominal pain)	2 M (diffuse inflammation of the GI tract)	Armstrong et al. 1984 NS	
			Hemato			0.2 (pancytopenia, leukopenia)		
			Hepatic			0.4 (hepatitis)		
			Renal			0.2 (nephropathy)		
			Ocular			0.2 (periorbital swelling)		
20	Human	once (IN)	Resp			121 M (respiratory distress, lung hemorrhage and edema)	Civantos et al. 1995 As(+5)	
			Cardio			121 M (hypotension, ventricular fibrillation, cardiac arrest)		
			Gastro			121 M (ulceration of upper gastrointestinal tract)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
21	Human	once (IN)	Cardio			19 F (tachycardia)	Cullen et al. 1995 As (+5)	
			Gastro			19 F (profuse vomiting and diarrhea)		
			Hemato	19 F				
			Hepatic	19 F				
			Renal	19 F				
22	Human	once (NS)	Resp			8 M (hemorrhagic bronchitis, pulmonary edema)	Fincher and Koerker 1987 As(+3)	
			Cardio			8 M (hypotension, tachycardia, massive cardiomegaly)		
			Gastro			8 M (gastrointestinal bleeding)		
			Hemato			8 M (hemolysis)		
			Musc/skel			8 M (marked atrophy of distal muscle groups)		
			Renal			8 M (acute renal failure)		
			Dermal		8 M (truncal macular rash)			
23	Human	1 or 2 x (W)	Gastro		0.05 (occasional nausea, diarrhea, and abdominal cramps)		Franzblau and Lilis 1989 As(+3) As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
24	Human	once (W)	Gastro			120 M (vomiting and diarrhea)	Goebel et al. 1990 NS	
			Renal			120 M (anuria)		
			Dermal		120 M (hyperkeratosis)			
25	Human	once (IN)	Gastro		2 F (vomiting)		Hantson et al. 1996 As(+3)	
			Hepatic		2 F (slight increase in serum bilirubin)			
			Renal		2 F (altered renal function tests)			
26	Human	once (IN)	Gastro			13 M (frequent vomiting, diarrhea)	Kamijo et al. 1998 As(+3)	
			Hepatic			13 M (large increase in serum bilirubin, ALT, AST, LDH)		
			Dermal		13 M (erythematous eruption)			
			Ocular		13 M (constricted vision)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
27	Human	once (IN)	Resp			22 M (tachypnea, respiratory failure)	Levin-Scherz et al. 1987 As(+3)	
			Cardio			22 M (cyanosis, hypotension, tachycardia, ventricular fibrillation)		
			Gastro			22 M (abdominal pain, nausea, diarrhea, massive vomiting, dysphagia, hemorrhage)		
			Hepatic			22 M (large increase in serum AST and LDH)		
			Renal			22 M (large increase in serum creatinine and BUN indicating acute renal failure)		
28	Human	once pregnancy wk 30 (IN)	Cardio			6 F (hypotension, rapid pulse)	Lugo et al. 1969 As(+3)	
			Gastro			6 F (abdominal pain, vomiting)		
			Hemato		6 F (high leukocyte count, low hematocrit)			
			Renal			6 F (acute renal failure)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
29	Human	2-3 wk (F)	Resp		0.05	(sore throat, rhinorrhea, cough, sputum)	Mizuta et al. 1956 As(+5)	
			Cardio			0.05 (abnormal electrocardiogram)		
			Gastro			0.05 ^b (nausea, vomiting, diarrhea, occult blood in feces and gastric and duodenal juice)		
			Hemato		0.05	(mild anemia, leukopenia)		
			Musc/skel		0.05	(tender calf muscle)		
			Hepatic		0.05	(mild hepatomegaly, impaired liver function, degenerative lesions)		
			Renal	0.05				
			Dermal		0.05	(pigmentation, itching, desquamation, exanthema)		
			Ocular		0.05	(edema of eyelids, conjunctivitis, central scotoma, neuro-retinitis)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
30	Human	once (IN)	Resp	11 M		43 M (shortness of breath, decreased oxygen saturation)	Moore et al. 1994a As(+3)	
			Cardio	11 M		43 M (hypotension, asystolic cardiac arrest)		
			Gastro			11 M (profuse diarrhea and vomiting, severe abdominal pain)		
			Hemato	43 M				
			Renal		11 M (increased serum creatinine)	43 M (acute renal failure)		
31	Human	once (IN)	Resp			93 M (pulmonary edema)	Quatrehomme et al. 1992 As(+3)	
			Gastro			93 M (ulcero-necrotic hemorrhagic gastritis)		
			Hepatic			93 M (hepatomegaly, diffuse fatty degeneration)		
			Renal			93 M (glomerular congestion)		
			Dermal			93 M (dermoepidermic separation)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
32	Monkey (Rhesus)	13 d 1 x/d (IN)	Gastro	3		6 (vomiting, unformed stool, "loss of condition")	Heywood and Sortwell 1979 As(+5)	
			Hepatic	3	6 (decreased liver glycogen, vacuolation of hepatocytes)			
			Renal	3	6 (dilation of proximal tubules)			
33	Rat (Wistar-Barby)	4-14 d 5 d/wk 1 x/d (G)	Cardio	2 F	11 F (decreased vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)	
			Gastro	2 F		11 F (diarrhea, bloody stools)		
34	Rat (Sprague-Dawley)	2 x (GW)	Resp	14 F			Brown and Kitchin 1996 As(+3)	
			Hepatic		0.9 F (slight increased ornithine decarboxylase and heme oxygenase activity in liver)			
			Dermal	14 F				
35	Rat (Sprague-Dawley)	2 x (GW)	Hepatic	8 F	24 F (increased heme oxygenase activity in liver)		Brown et al. 1997c As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
36	Rat (Sprague- Dawley)	1 x/d 15 d (G)	Bd Wt	10 M	20 M (20-25% decreased body weight)		Rodriguez et al. 2001 As(+3)	
37	Rat (CD)	once Gd 9 (GW)	Bd Wt	15 F	23 F (decreased body weight gain)		Stump et al. 1999 As(+3)	
38	Mouse (CD-1)	Gd 6-15 1 x/d (GW)	Bd Wt	12 F	24 F (decreased body weight gain during gestation)		Nemec et al. 1998 As(+5)	
39	Mouse (B6C3F1)	1 or 4 d 1 x/d (GW)	Hemato	3 M	6 M (decreased polychromatic erythrocytes in bone marrow)		Tice et al. 1997 As(+3)	
40	Gn Pig	1 x/d 8 d (G)	Cardio		3.8 M (prolongation of QT interval)		Chiang et al. 2002 As ₂ O ₃	
41	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)	Bd Wt	0.37 F	1.49 F (loss of body weight during treatment during gestation)		Nemec et al. 1998 As(+5)	
Neurological								
42	Human	1 wk (W)				2 (encephalopathy, peripheral neuropathy)	Armstrong et al. 1984 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
43	Human	once (IN)				121 M (confusion, brain edema)	Civantos et al. 1995 As(+5)	
44	Human	once (IN)				19 F (lethargy)	Cullen et al. 1995 As (+5)	
45	Human	once (NS)				8 M (severe, persistent encephalopathy and peripheral neuropathy)	Fincher and Koerker 1987 As(+3)	
46	Human	once (W)				120 M (severe polyneuropathy)	Goebel et al. 1990 NS	
47	Human	once (IN)				216 M (peripheral neuropathy)	Hantson et al. 1996 As(+3)	
48	Human	once (IN)				13 M (peripheral neuropathy)	Kamijo et al. 1998 As(+3)	
49	Human	once (IN)				22 M (agitation, disorientation, paranoia, violent reactions)	Levin-Scherz et al. 1987 As(+3)	
50	Human	2-3 wk (F)				0.05 (hypesthesia in legs, abnormal patellar reflex)	Mizuta et al. 1956 As(+5)	
51	Human	once (IN)		43 M			Moore et al. 1994a As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
52	Human	once (IN)				93 M (encephalopathy)	Quatrehomme et al. 1992 As(+3)	
53	Monkey (Rhesus)	13 d 1 x/d (IN)		3		6 (marked salivation, uncontrolled head shaking)	Heywood and Sortwell 1979 As(+5)	
54	Rat (Sprague- Dawley)	1 x/d 15 d (G)		10 M	20 M (altered spontaneous locomotor activity)		Rodriguez et al. 2001 As(+3)	
55	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)		0.37 F		1.49 F (prostration, ataxia)	Nemec et al. 1998 As(+5)	
Developmental								
56	Human	once pregnancy wk 30 (IN)				6 (severe pulmonary hemorrhage that may have contributed to death in premature neonate)	Lugo et al. 1969 As(+3)	
57	Rat (CD)	once Gd 9 (GW)		15		23 (increased post-implantation loss and decreased viable fetuses)	Stump et al. 1999 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
58	Mouse (CD-1)	once Gd 8-15 (GW)		11		23	(increased fetal mortality, exencephaly)	Baxley et al. 1981 As(+3)
59	Mouse (CD-1)	once Gd 7-15 (GW)				48	(increased fetal death, decreased fetal weight, gross and skeletal malformations)	Hood et al. 1978 As(+5)
60	Mouse (CD-1)	Gd 6-15 1 x/d (GW)		12		24	(increased resorptions per litter, decreased live fetuses per litter, decreased mean fetal weight)	Nemec et al. 1998 As(+5)
61	Hamster (Lak:LVG [SYR])	once Gd 8-12 (GW)		11		14	(increased fetal mortality, decreased fetal weight)	Hood and Harrison 1982 As(+3)
62	Rabbit (New Zealand)	Gd 6-18 1 x/d (GW)		0.37		1.49	(increased resorptions per litter, decreased live fetuses per litter)	Nemec et al. 1998 As(+5)

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer								
63	Mouse C3H	10 d (W)				9.55 M (CEL: liver and adrenal tumors)	Waalkes et al. 2003 As(+3)	
						19.13 F (CEL: ovarian and lung tumors)		
INTERMEDIATE EXPOSURE								
Systemic								
64	Human	3 mo (W)	Gastro			0.1 (severe nausea, diarrhea, pain, cramps, vomiting, traces of blood in stool)	Franzblau and Lilis 1989 As(+3) As(+5)	
			Hemato			0.1 (anemia, leukopenia)		
			Hepatic			0.1 (large increased AST and ALT)		
			Dermal	0.1	(diffuse erythematous and scaly rash)			
			Ocular	0.1	(swelling and irritation of the eyes, impaired peripheral vision)			
65	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
66	Human	4 mo (W)	Gastro			0.06 F (nausea, vomiting, diarrhea)	Wagner et al. 1979 NS	
			Hemato			0.06 F (anemia, leukopenia, erythroid hyperplasia of bone marrow)		
			Dermal			0.06 F (persistent extensive hyperkeratosis of palms and soles)		
			Bd Wt			0.06 F (40 lb weight loss)		
67	Rat (Wistar- Barby)	4 wk 5 d/wk 1 x/d (GW)	Cardio		11 F (decreased vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)	
68	Rat (Sprague- Dawley)	6 wk (W)	Renal		4.7 M (increased relative kidney weight, impaired renal mitochondrial respiration, ultrastructural changes in proximal tubule)			Brown et al. 1976 As(+5)
			Bd Wt	9.4 M	10.9 M (decreased body weight gain)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
69	Rat (Wistar)	1 x/d 28 d (G)	Bd Wt	0.14 F			Chattopadhyay et al. 2001 As(+3)	
70	Rat (CD)	6 wk (W)	Hepatic	3 M	6 M (ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)		Fowler et al. 1977 As(+5)	
			Bd Wt	6 M		12 M (final body weight 28% lower than controls)		
71	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d (GW)	Gastro	4 F		8 F (stomach adhesions, eroded luminal epithelium in the stomach)	Holson et al. 2000 As(+3)	
			Hepatic	2 F	4 F (increased liver weight)			
			Renal	4 F	8 F (increased kidney weight)			
			Bd Wt	4 F	8 F (decreased body weight gain)			
72	Rat (NS)	16 wk (W)	Hemato		0.92 M (decreased erythrocyte and leukocyte numbers)		Kannan et al. 2001 As(+3)	
			Hepatic	2.3 M				

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
73	Rat (Sprague- Dawley)	4 wk (W)	Hemato	0.12	0.3	(increased platelet aggregation)	Lee et al. 2002 As(+3)	
74	Rat (NS)	1 x/d 30 d (G)	Endocr		2.3 M	(decreased islet cells in pancreas, increased pancreatic SOD and catalase)	Mukherjee et al. 2003 As ₂ O ₃	
75	Rat (Wistar)	1 x/d 5 d/wk 12 wk (G)	Resp	19 M			Schulz et al. 2002 As(+3)	
			Renal	19 M				
			Bd Wt	9.5 M	19 M	(~17% decreased body weight gain)		
76	Mouse (C57BL)	6 wk (W)	Hepatic	5 M	10 M	(ultrastructural changes in hepatocytes, impaired liver mitochondrial respiration)	Fowler and Woods 1979 As(+5)	
			Bd Wt	5 M	10 M	(decreased body weight gain)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
77	Mouse (C57BL/6 B6)	14 wk (W)	Hepatic	25 M			Kerkvliet et al. 1980 As(+5)	
			Renal	25 M				
78	Gn Pig (NS)	16 wk (W)	Hemato		0.69 M (decreased erythrocyte number and leukocyte number, decreased ALAD levels)		Kannan et al. 2001 As(+3)	
			Hepatic		0.69 M (increased ALAS activity)			
79	Dog (Beagle)	26 wk ad lib (F)	Hemato	1.9 F			Neiger and Osweiler 1989 As(+3)	
			Hepatic		0.8 F (mild increased serum ALT/AST)			
			Renal	1.9 F				
			Bd Wt	0.8 F	1.5 F (decreased body weight gain)	1.9 F (25% decrease in body weight)		
Immuno/ Lymphoret								
80	Mouse (C57BL/6 B6)	14 wk (W)		25 M			Kerkvliet et al. 1980 As(+5)	
Neurological								
81	Human	3 mo (W)				0.1 (paresthesia of hands and feet; confusion, disorientation and mental sluggishness)	Franzblau and Lilis 1989 As(+3) As(+5)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
82	Human	4 mo (W)				0.06 F (weakness, paresthesia)	Wagner et al. 1979 NS	
83	Rat (NS)	16 wk (W)		0.92 M	2.3 M (decreased brain neurotransmitter levels)		Kannan et al. 2001 As(+3)	
84	Rat (Wistar)	1 x/d 5 d/wk 12 wk (G)		19 M			Schulz et al. 2002 As(+3)	
85	Gn Pig (NS)	16 wk (W)		0.69 M	1.7 M (changes in brain neurotransmitter levels)		Kannan et al. 2001 As(+3)	
Reproductive								
86	Rat (Wistar)	1 x/d 28 d (G)			0.14 F (changes in uterine and ovarian weights, decreased estradiol)		Chattopadhyay et al. 2001 As(+3)	
87	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d (GW)		8 F			Holson et al. 2000 As(+3)	
88	Mouse (CD)	3 gen (W)				1 (decreased litter size)	Schroeder and Mitchener 1971 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Developmental								
89	Rat (CD)	14 pmd- Gd 19 7 d/wk 6 hr/d (GW)		4	8 (decreased fetal body weight, increased skeletal variations)		Holson et al. 2000 As(+3)	
90	Rat (Sprague- Dawley)	Gd 15 or pnd 1- 4 mo (W)			2.93 M (impaired performance in postnatal neurobehavioral tests)		Rodriguez et al. 2002 As(+3)	
91	Mouse (CD)	3 gen (W)				1 (decreased litter size)	Schroeder and Mitchener 1971 As(+3)	
CHRONIC EXPOSURE								
Death								
92	Human	2-7 yr children (W)				0.05 (death)	Zaldivar and Guillier 1977 NS	
93	Human	22 yr (W)				0.014 M (death)	Zaldivar et al. 1981 NS	Cause of death was liver tumor.
94	Monkey (Rhesus)	1 yr (IN)				3 (2/7 died)	Heywood and Sortwell 1979 As(+5)	
95	Rat (Wistar)	27 mo (F)				30 (increased mortality)	Kroes et al. 1974 As(+5) lead arsenate	
96	Mouse (CD)	2 yr (W)				1 (increased mortality, decreased life span)	Schroeder and Balassa 1967 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
97	Dog (Beagle)	2 yr (F)				2.4 (6/6 died)	Byron et al. 1967 As(+3)	
98	Dog (Beagle)	2 yr (F)				2.4 (1/6 died)	Byron et al. 1967 As(+5)	
Systemic								
99	Human	NS (W)	Resp		0.032 (cough)		Ahmad et al. 1997 NS	
			Dermal			0.032 (melanosis, keratosis, hyperkeratosis, and depigmentation)		
			Ocular			0.032 (chronic conjunctivitis)		
100	Human	>8 yr (W)	Dermal		0.0012 (increased risk of premalignant skin lesions)		Ahsan et al. 2006 (NS)	
101	Human	4 yr (IN)	Dermal			0.1 F (de-pigmentation with hyperkeratosis, possibly pre-cancerous)	Bickley and Papa 1989 As(+3)	
102	Human	NS (W)	Cardio			0.014 (gangrene of feet)	Biswas et al. 1998 NS	
			Dermal			0.014 (melanosis and keratosis of hand palms and foot soles)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
103	Human	12 yr (W)	Cardio			0.02 (Raynaud's disease, gangrene of toes)	Borgono and Greiber 1972 NS	
			Gastro		0.02 (diarrhea, abdominal pain)			
			Dermal			0.02 (abnormal pigmentation with hyperkaratosis, possibly pre-cancerous)		
104	Human	11-15 yr (W)	Dermal		0.01 (hypo- and hyperpigmentation)		Borgono et al. 1980 NS	
105	Human	NS (W)	Gastro	0.0004	0.022 (gastrointestinal irritation, diarrhea, nausea)		Cebrian et al. 1983 As(+5)	
			Dermal	0.0004		0.022 (pigmentation changes with hyperkeratosis, possibly pre-cancerous)		
106	Human	1-11 yr (W)	Hepatic		0.046 (hepatomegaly)		Chakraborty and Saha 1987 NS	
			Dermal			0.046 (pigmentation changes with keratosis, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
107	Human	NS (W)	Cardio			0.064 (Blackfoot disease)	Chen et al. 1988b NS	
108	Human	>10 yr (W)	Cardio	0.0008		0.022 (increased risk of ischemic heart disease mortality)	Chen et al. 1996 NS	
109	Human	NS (W)	Cardio			0.002 (increased prevalence of cerebrovascular disease and cerebral infarction)	Chiou et al. 1997 NS	
110	Human	>5 yr (W)	Hemato	0.006 ^C M 0.007 F			EPA 1981b NS	
			Dermal	0.0009 ^C M 0.001 F				
111	Human	3-7 yr (W)	Cardio			0.05 (Blackfoot disease)	Foy et al. 1992 NS	
			Dermal			0.05 (melanosis with hyperkeratosis, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
112	Human	2-6 yr (IN)	Hepatic			0.08 M (cirrhosis, ascites)	Franklin et al. 1950 As(+3)	
			Dermal			0.08 M (pigmentation with hyperkeratosis, possibly pre-cancerous)		
113	Human	1-15 yr (W)	Hepatic		0.16 (portal fibrosis of the liver)		Guha Mazumder 2005 (NS)	
114	Human	NS (W)	Hepatic	0.004		0.014 (hepatomegaly)	Guha Mazumder et al. 1988 NS	
			Dermal	0.004		0.014 (pigmentation changes with hyperkaratosis, possibly pre-cancerous)		
115	Human	1-20 yr (W)	Gastro		0.06 (abdominal pain)		Guha Mazumder et al. 1988 NS	
			Hemato		0.06 (anemia)			
			Hepatic			0.06 (hepatomegaly, fibrosis)		
			Dermal			0.06 (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		
116	Human	NS (W)	Dermal	0.0016		0.009 (hyperpigmentation with keratosis, possibly pre-cancerous)	Guha Mazumder et al. 1998a NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
117	Human	(W)	Dermal	0.0014	(arsenical dermatosis)		Guo et al. 2001a (NS)	
118	Human	NS (W)	Dermal	0.0043	(hyperkeratosis, hyperpigmentation)		Haque et al. 2003 (NS)	dose listed is that associated with lowest known peak As concentration ingested by a case with complete water history
119	Human	10 yr (W)	Gastro	0.0046			Harrington et al. 1978 NS	
			Hemato	0.0046				
			Dermal	0.0046				
120	Human	NS (W)	Hepatic	0.0008	0.006	(increased serum alkaline phosphatase and bilirubin)	Hernandez-Zavala et al. 1998 NS	
121	Human	lifetime (W)	Hemato		0.002 F	(anemia during pregnancy)	Hopenhayn et al. 2006 (NS)	
122	Human	NS (W)	Cardio			0.067 (ischemic heart disease)	Hsueh et al. 1998b NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
123	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS	
124	Human	15 yr (IN)	Gastro			0.03 M (hematemesis, hemoperitoneum, melena)	Lander et al. 1975 As(+3)	
			Dermal			0.03 M (hyperkeratosis - possibly pre-cancerous)		
125	Human	NS (W)	Cardio	0.004		0.005 (cyanosis of extremities, palpitations/chest discomfort)	Lianfang and Jianzhong 1994 NS	
			Dermal	0.004		0.005 (keratosis, hyperpigmentation, depigmentation)		
126	Human	3-22 yr (IN)	Gastro			0.05 M (gastrointestinal hemorrhages)	Morris et al. 1974 As(+3)	
			Hepatic			0.05 M (vascular fibrosis, portal hypertension)		
			Dermal			0.05 M (hyperpigmentation with keratoses, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
127	Human	15 yr (IN)	Hepatic			0.05 F (central fibrosis)	Piontek et al. 1989 As(+3)	
			Dermal			0.05 F (hyperkeratosis, possibly pre-cancerous)		
128	Human	NS (W)	Endocr			0.11 (diabetes mellitus)	Rahman et al. 1998 NS	
129	Human	NS (W)	Cardio	0.018	0.055 (hypertension)		Rahman et al. 1999 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
130	Human	28 mo (IN)	Cardio	0.06 F			Silver and Wainman 1952 As(+3)	
			Gastro		0.06 F (intermittent, progressively severe nausea, cramps, and diarrhea)			
			Hemato	0.06 F				
			Hepatic		0.06 F (hepatomegaly, fatty liver)			
			Renal	0.06 F				
			Dermal			0.06 F (melanosis with hyperkeratosis, possibly pre-cancerous)		
131	Human	55 yr (IN)	Hepatic			0.03 M (portal fibrosis and hypertension, bleeding from esophageal varices)	Szuler et al. 1979 As(+3)	
			Dermal			0.03 M (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		
132	Human	45 yr (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1977 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
133	Human	NS (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1989 NS	
134	Human	>45 yr (W)	Dermal	0.0008 ^d M	0.014 M (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968 NS	
135	Human	>30 yr (W)	Cardio		0.064 M (deficits in cutaneous microcirculation of the toes)		Tseng et al. 1995 As(+3)	
136	Human	52.6 yr (avg) (W)	Cardio	0.016		0.031 (peripheral vascular disease)	Tseng et al. 1996 NS	
137	Human	16 mo (IN)	Resp	0.1 M			Wade and Frazer 1953 As(+3)	
			Cardio	0.1 M				
			Hemato	0.1 M				
			Hepatic		0.1 M (liver enlargement)			
			Dermal			0.1 M (hyperkeratosis, hyperpigmentation with hyperkeratosis, possibly pre-cancerous)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
138	Human	30-33 yr (W)	Dermal			0.015 M (hyperkeratosis of foot, possibly pre-cancerous)	Zaldivar 1974 NS	
139	Human	12 yr (W)	Resp		0.015 ^C M (bronchitis, bronchiectasis)		Zaldivar 1974 NS	
					0.018 F (bronchitis, bronchiectasis)			
			Cardio			0.015 ^C M (Raynaud's disease, thrombosis)		
						0.018 F		
			Gastro		0.015 ^C M (diarrhea)			
					0.018 F (diarrhea)			
			Dermal		0.015 ^C M (scaling of skin, hyperkeratosis, leukoderma, melanoderma)			
					0.018 F			
			Bd Wt		0.015 ^C M (unspecified decreased body weight)			
					0.018 F (unspecified decreased body weight)			

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
140	Human	NS (W)	Dermal			0.063 (hyperpigmentation with keratoses, possibly pre-cancerous)	Zaldivar 1977 NS	
141	Human	2-7 yr children (W)	Resp			0.08 (inflammation of bronchi and larynx, bronchopneumonia)	Zaldivar and Guillier 1977 NS	
			Cardio			0.05 (vascular spasms, thrombosis, ischemia, hypotension, cardiac failure)		
			Gastro			0.05 (nause, vomiting, diarrhea, intestinal hemorrhage)		
			Hemato			0.05 (anemia)		
			Hepatic			0.08 (cirrhosis)		
			Renal		0.08 (cloudy swelling in kidneys)			
			Dermal			0.05 (hyperkeratosis of palms and soles, melanoderma, leukoderma)		
142	Human	1-39 yr (W)	Cardio			0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977 NS	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
143	Rat (Osborne- Mendel)	2 yr (F)	Resp	20			Byron et al. 1967 As(+3)	
			Cardio	20				
			Gastro	20				
			Hemato	9	20	(slight transient decrease in Hb and Hct values)		
			Hepatic	4		9 (enlarged bile duct, bile duct proliferation)		
			Renal	9	20	(pigmentation)		
			Bd Wt	2	4	(decreased body weight gain)		
144	Rat (Osborne- Mendel)	2 yr (F)	Resp	30			Byron et al. 1967 As(+5)	
			Cardio	30				
			Gastro	30				
			Hemato	30				
			Hepatic	9	20	(enlarged bile duct)		
			Renal	9	20	(pigmentation, cysts)		
			Bd Wt		2	(decreased body weight gain in females)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
145	Rat (Wistar)	27 mo (F)	Resp	7			Kroes et al. 1974 As(+5)	
			Cardio	7				
			Gastro	7				
			Hemato	7				
			Musc/skel	7				
			Hepatic	7				
			Renal	7				
			Endocr	7				
			Bd Wt		7	(decreased body weight gain)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
146	Rat (Wistar)	27 mo (F)	Resp	30			Kroes et al. 1974 As(+5) lead arsenate	
			Cardio	30				
			Gastro	30				
			Hemato	7	30	(slight anemia)		
			Musc/skel	30				
			Hepatic	7		30 (enlarged bile duct with extensive dilation and inflammation)		
			Renal	30				
			Endocr	30				
			Bd Wt	7	30	(decreased body weight gain)		
147	Rat (Long- Evans)	3 yr (W)	Resp	0.6			Schroeder et al. 1968 As(+3)	
			Cardio	0.6				
			Hepatic	0.6				
			Renal	0.6				
			Dermal	0.6				
			Bd Wt	0.6				

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
148	Mouse (NS)	48 wk (W)	Hepatic	11.1			Liu et al. 2000 As(+3)	
			Renal		5.6	(histological alterations of the kidney)		
			Bd Wt	11.1				
149	Mouse (NS)	48 wk (W)	Hepatic	18.5			Liu et al. 2000 As (+5)	
			Renal		18.5	(increased relative kidney weight)		
			Bd Wt	18.5				
150	Mouse (BALB/c)	15 mo (W)	Hepatic		0.7 M	(increased liver weight, altered liver histopathology, decreased hepatic enzymes in serum)	Santra et al. 2000 (NS)	
			Bd Wt		0.7 M	(13-17% decreased body weight)		
151	Mouse (CD)	2 yr (W)	Bd Wt		1	(decreased body weight gain after the first 6 months of the study)	Schroeder and Balassa 1967 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
152	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+3)	
			Cardio	2.4				
			Gastro	1		2.4 (bleeding in the gut)		
			Hemato	1	2.4 (slight to moderate anemia)			
			Hepatic	1	2.4 (hemosiderin deposits in hepatic macrophages)			
			Renal	2.4				
			Bd Wt	1		2.4 (44-61% weight loss)		
153	Dog (Beagle)	2 yr (F)	Resp	2.4			Byron et al. 1967 As(+5)	
			Cardio	2.4				
			Gastro	2.4				
			Hemato	1	2.4 (mild anemia)			
			Hepatic	1	2.4 (pigmentation in hepatic macrophages)			
			Renal	2.4				
			Bd Wt	1		2.4 (marked decreased weight gain)		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Neurological								
154	Human	>5 yr (W)		0.006 ^C M 0.007 F			EPA 1981b NS	
155	Human	3-7 yr (W)				0.11 F (wrist weakness)	Foy et al. 1992 NS	
156	Human	1-20 yr (W)			0.06 (tingling of hands and feet)		Guha Mazumder et al. 1988 NS	
157	Human	10 yr (W)		0.0046			Harrington et al. 1978 NS	
158	Human	NS (W)		0.0014		0.04 (functional denervation)	Hindmarsh et al. 1977 NS	
159	Human	NS (W)		0.004	0.005 (fatigue, headache, dizziness, insomnia, nightmare, numbness)		Lianfang and Jianzhong 1994 NS	
160	Human	28 mo (IN)				0.06 F (paresthesia)	Silver and Wainman 1952 As(+3)	
161	Human	55 yr (IN)			0.03 M (absent ankle jerk reflex and vibration sense in legs)		Szuler et al. 1979 As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
162	Human	NS (W)			0.0017	(decreased performance in neurobehavioral tests)	Tsai et al. 2003 (NS)	
163	Human	lifetime continuous (W)			0.005	(decreased performance in neurobehavioral tests)	Wasserman et al. 2004 (NS)	
164	Human	lifetime		0.0008	0.003	(decreased score in Performance domain of an intelligence scale)	Wasserman et al. 2007 (NS)	
Reproductive								
165	Human	NS (W)				0.008 F (increased frequencies for spontaneous abortion, stillbirth, and preterm birth rates)	Ahmad et al. 2001 (NS)	98% of the exposed group drank water containing 0.1 mg As/L or more.
166	Human	lifetime (W)				0.006 F (increased incidence of spontaneous abortion)	Milton et al. 2005 (NS)	
167	Human	lifetime (W)				0.02 F (increased risk of stilbirth)	von Ehrenstein et al. 2006 (NS)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Developmental								
168	Human	continuous (W)			0.002 (reduced birth weight)		Hopenhayn et al. 2003a (NS)	
169	Human	>1 yr 1 x/d (W)				0.03 (increased SMR for malignant and non-malignant lung disease)	Smith et al. 2006 (NS)	
170	Human	lifetime (W)		0.008			von Ehrenstein et al. 2006 (NS)	NOAEL is for no increase in risk of neonatal mortality or overall infant mortality.
Cancer								
171	Human	NS (W)				0.022 (CEL: skin cancer)	Cebrian et al. 1983 As(+5)	
172	Human	NS (W)				0.064 (CEL: bladder, lung and liver cancers)	Chen et al. 1986 NS	
173	Human	NS (W)				0.064 (CEL: malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b NS	
174	Human	NS (W)				0.003 (CEL: bladder cancer)	Chiou et al. 2001 (NS)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
175	Human	2 wk- 12 yr (IN)				3.67 (CEL: bladder cancer risk)	Cuzick et al.1992 As(+3)	
176	Human	NS (W)				0.0011 (CEL: lung cancer)	Ferreccio et al. 1998 NS	
177	Human	NS (W)				0.0017 (CEL: lung cancers)	Ferreccio et al. 2000 (NS)	
178	Human	NS (W)				0.018 (CEL: lung cancer mortality)	Guo 2004 (NS)	
179	Human	NS (W)				0.018 (CEL: bladder cancer)	Guo and Tseng 2000 (NS)	
180	Human	NS (W)				0.052 (CEL: increased incidence of transitional cell carcinomas of the bladder, kidney, ureters, and all urethral cancer)	Guo et al. 1997 NS	
181	Human	NS (W)				0.0049 ^C M (CEL: squamous cell carcinoma of the skin)	Guo et al. 2001b (NS)	
						0.0094 F		

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
182	Human	>1 yr (W)				0.0075 (CEL: basal or squamous skin carcinoma)	Hauptert et al. 1996 NS	
183	Human	16 yr (avg) (IN)				0.04 M (CEL: basal cell and squamous cell carcinomas of the skin, small cell and squamous cell carcinoma of the lung)	Luchtrath 1983 As(+5)	
184	Human	60 yr (W)				0.038 (CEL: intraepidermal carcinoma)	Tseng 1977 NS	
185	Human	>45 yr (W)				0.014 (CEL: squamous cell carcinoma of the skin)	Tseng et al. 1968 NS	
186	Human	~5 yr (W)				0.033 (CEL: lung, urinary tract cancer)	Tsuda et al. 1995a As(+3)	

Table 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
187	Human	12 yr (W)				0.015 ^c M (CEL: squamous cell carcinoma of the skin)	Zaldivar 1974 NS	
						0.018 F (CEL: squamous cell carcinoma of the skin)		
188	Human	22-34 yr (W)				0.014 M (CEL: basal cell and squamous cell carcinomas of the skin, hemangioendothelioma of the liver)	Zaldivar et al. 1981 NS	

a The number corresponds to entries in Figure 3-3.

b Used to derive provisional acute oral minimal risk level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 10 (for extrapolation from a LOAEL to a NOAEL).

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

d Used to derive chronic oral minimal risk level (MRL) of 0.0003 mg/kg/day; dose divided by an uncertainty factor of 3 (for human variability).

avg = average; ALAD = delta-aminolevulinic acid dehydratase; ALAS = delta-aminolevulinic acid synthetase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; GI = gastrointestinal; (GW) = gavage in water; gen = generation; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; Hb = hemoglobin; Hct = hematocrit; Hemato = hematological; hr = hour(s); (IN) = ingestion; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; pmd = pre-mating day; pnd = post-natal day; Resp = respiratory; SMR = standardized mortality ratio; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral
Acute (≤ 14 days)

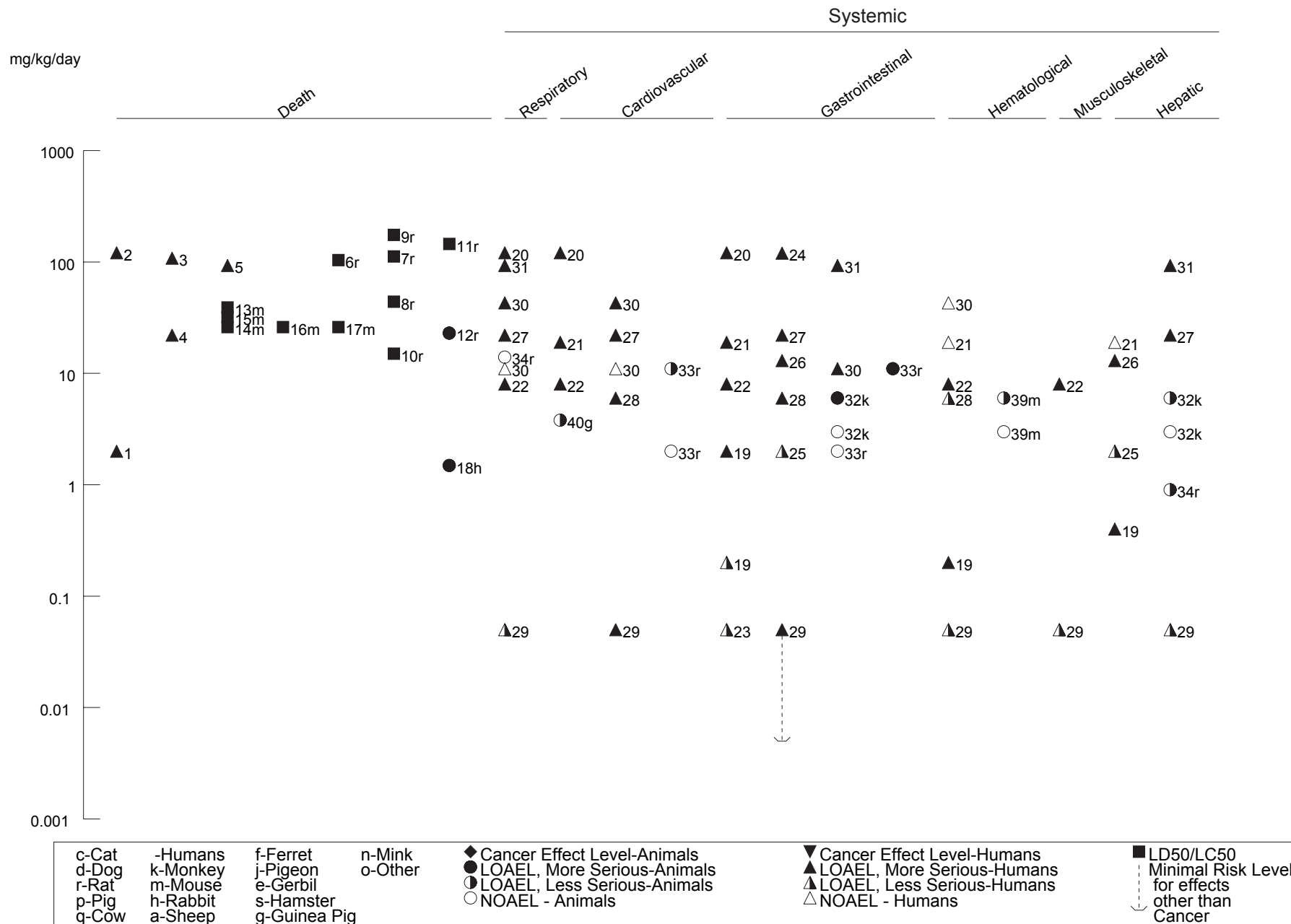


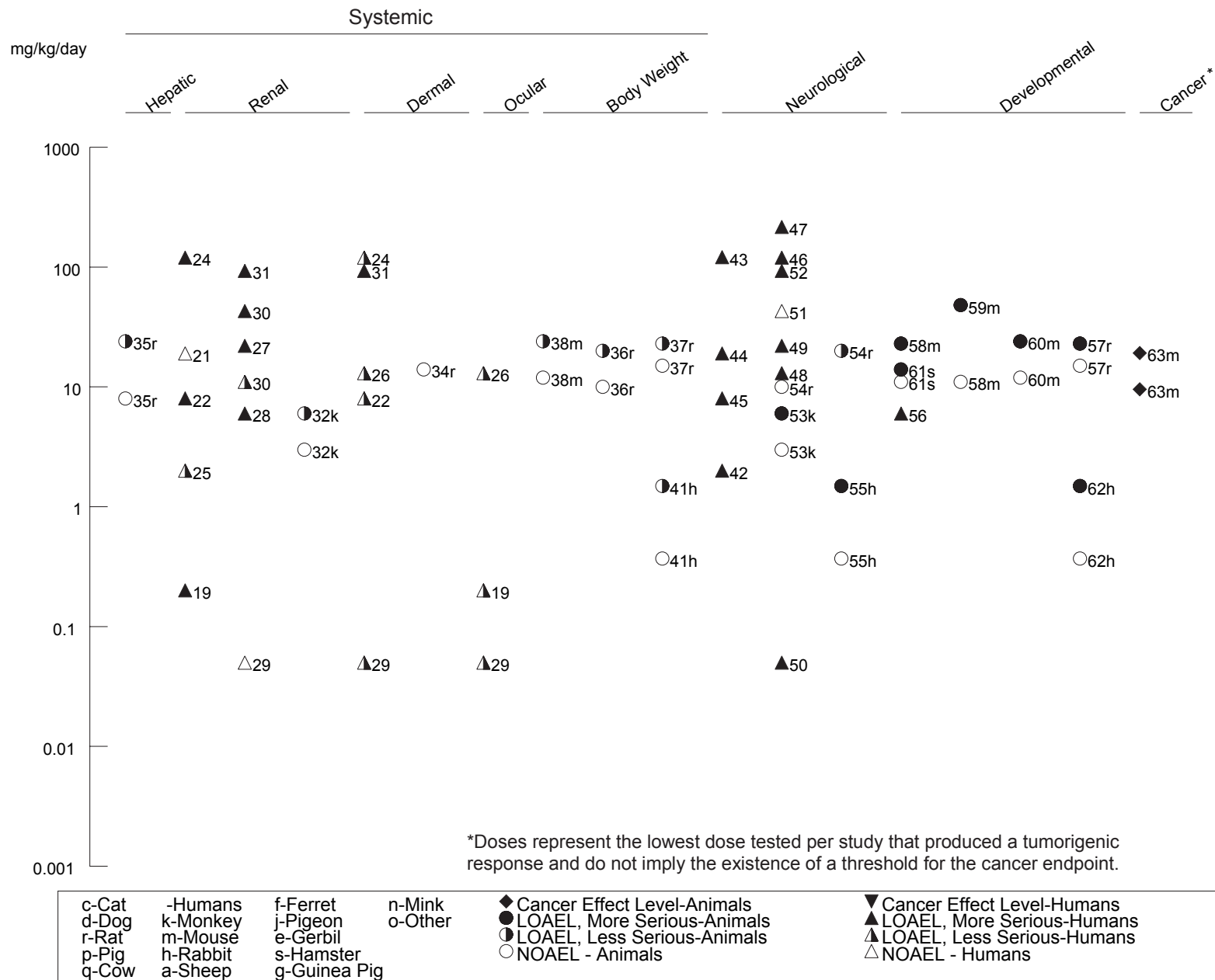
Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)Acute (≤ 14 days)

Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)

Intermediate (15-364 days)

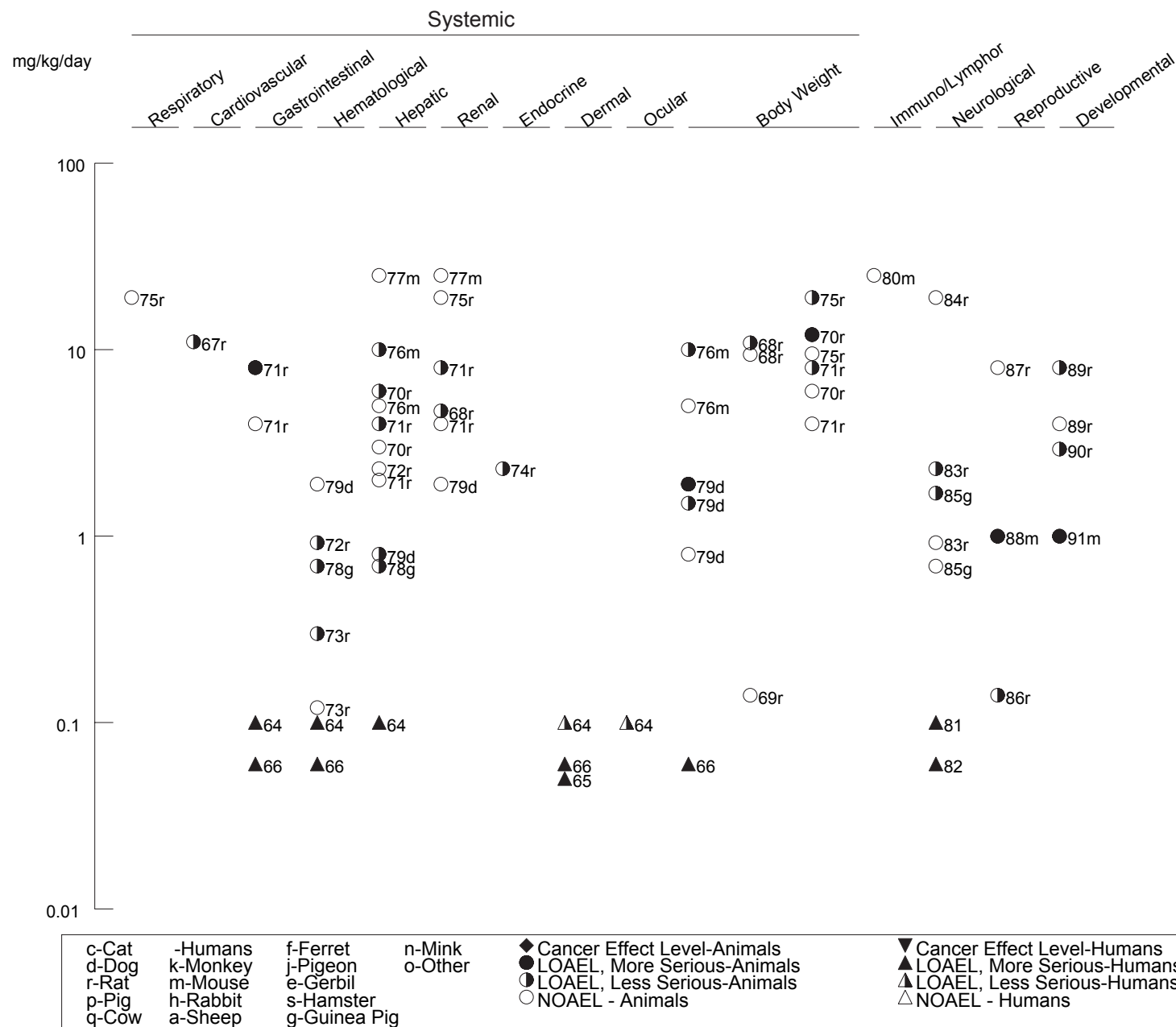


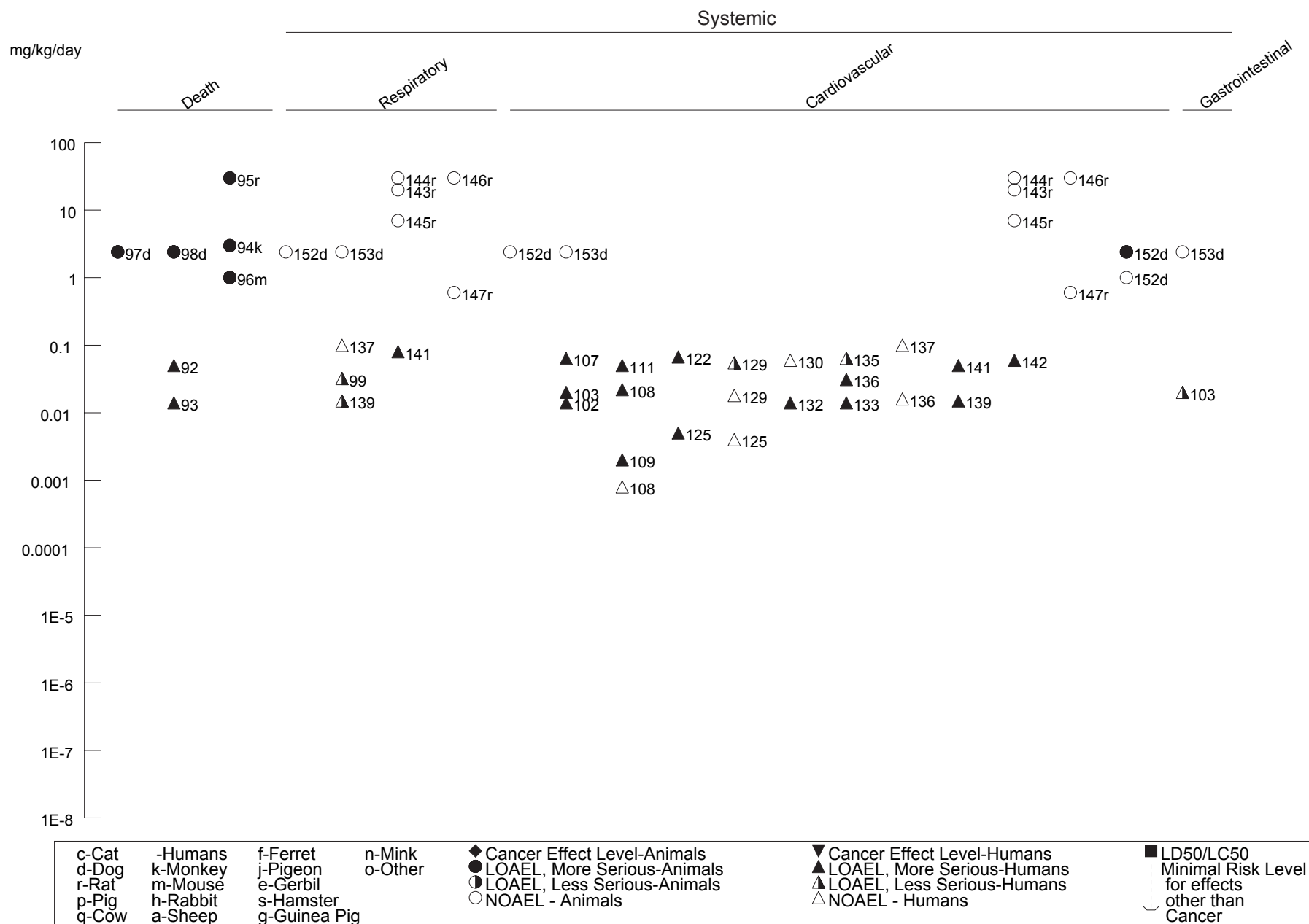
Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)Chronic (≥ 365 days)

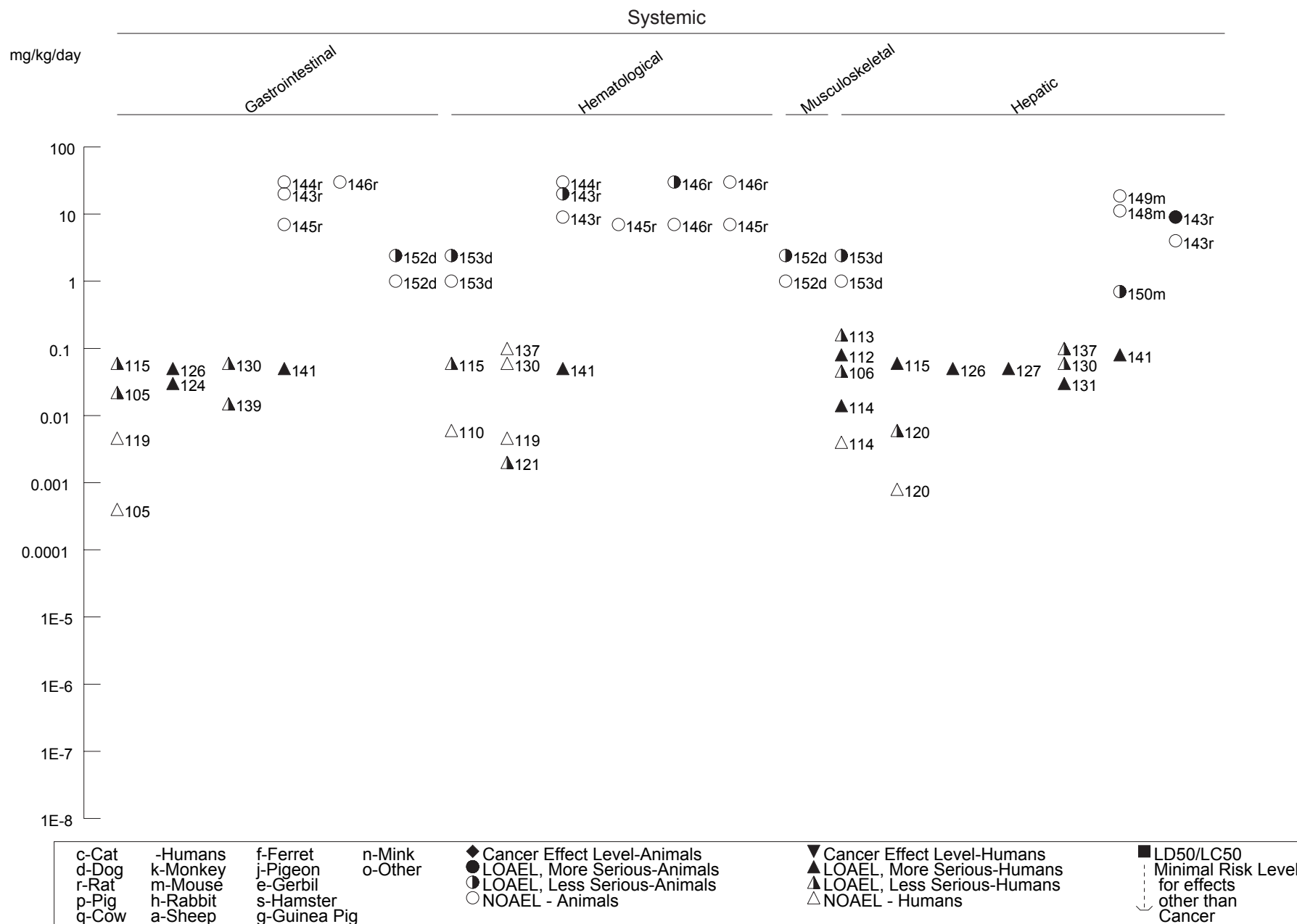
Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)Chronic (≥ 365 days)

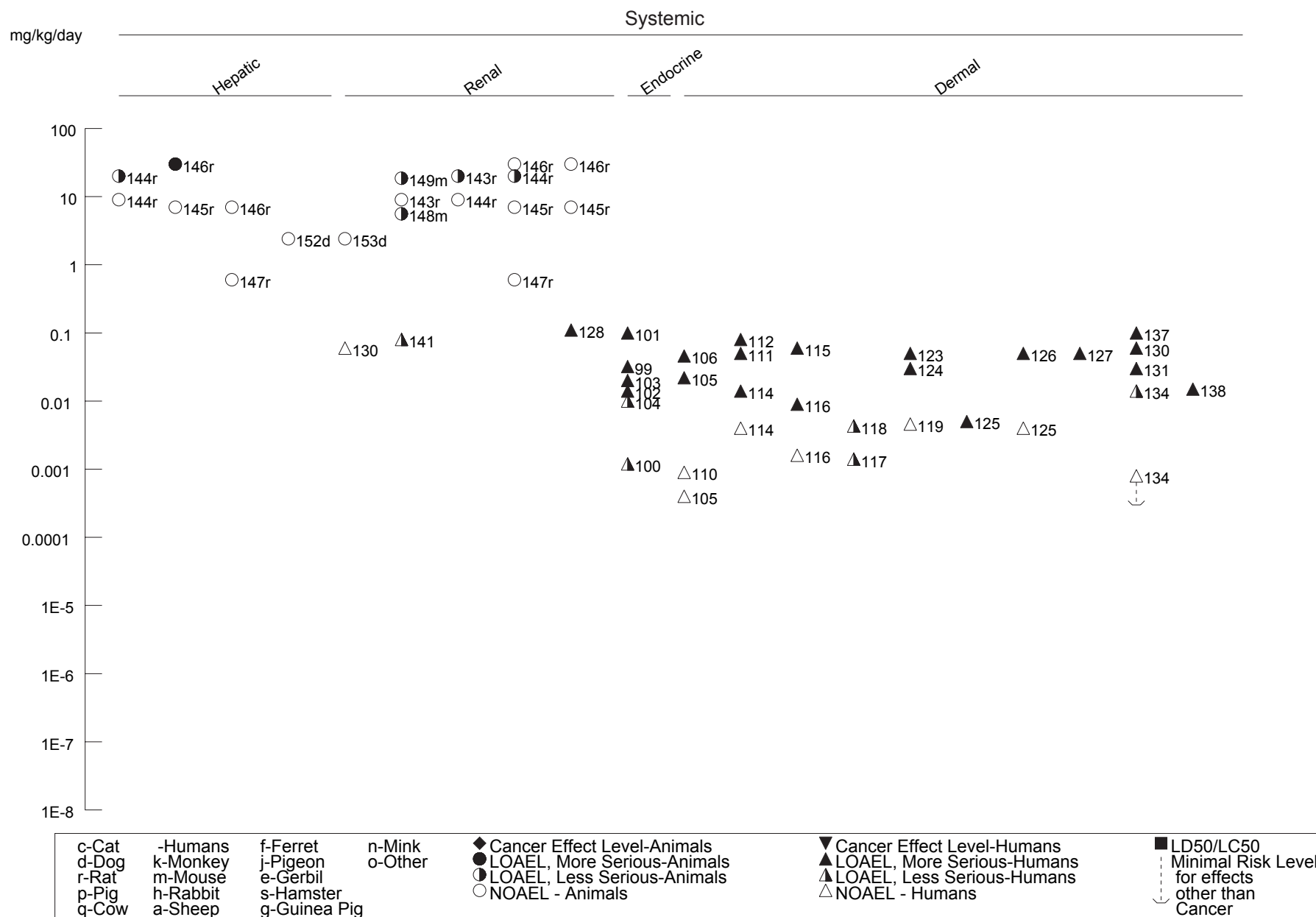
Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)Chronic (≥ 365 days)

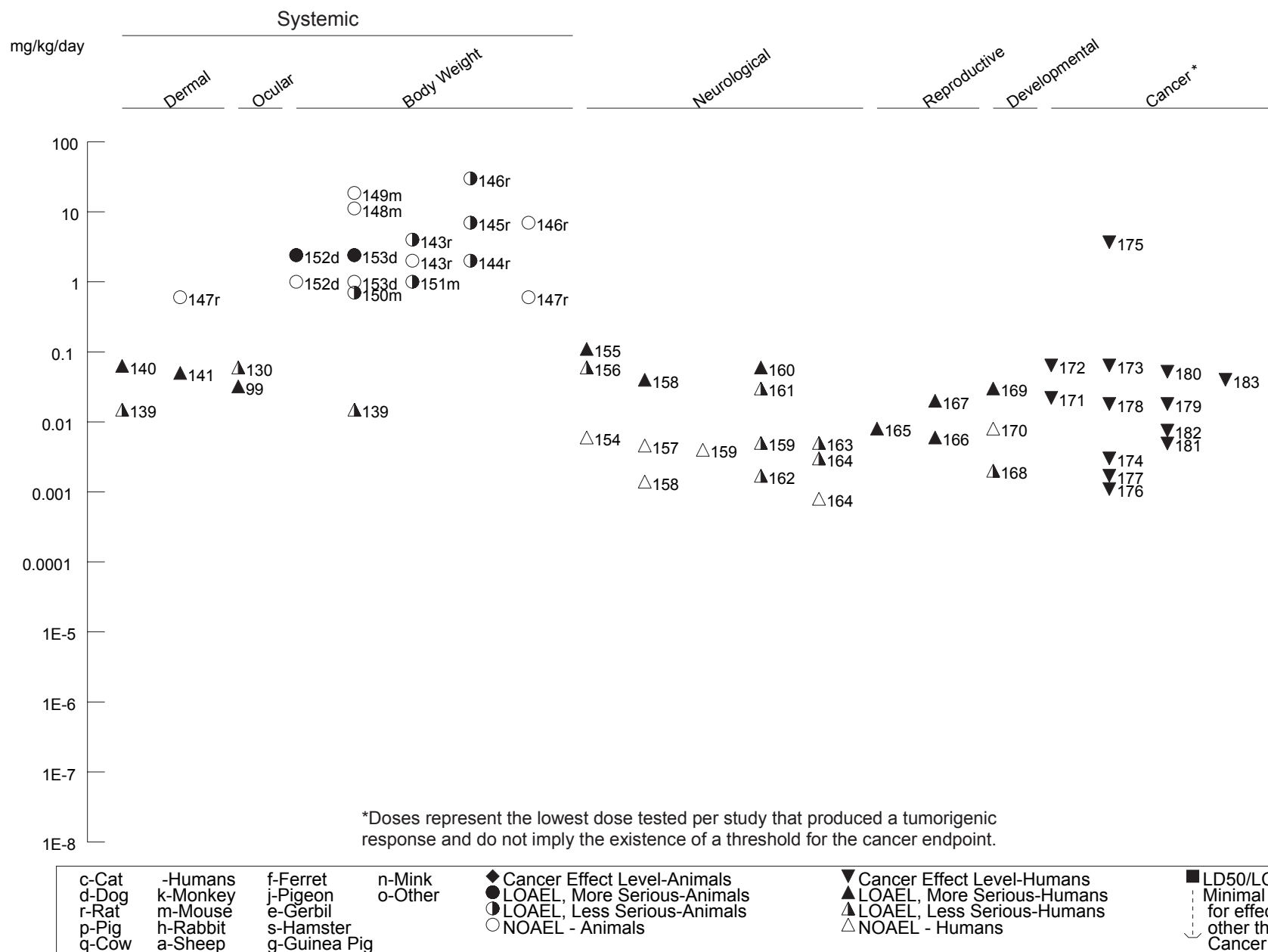
Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)Chronic (≥ 365 days)

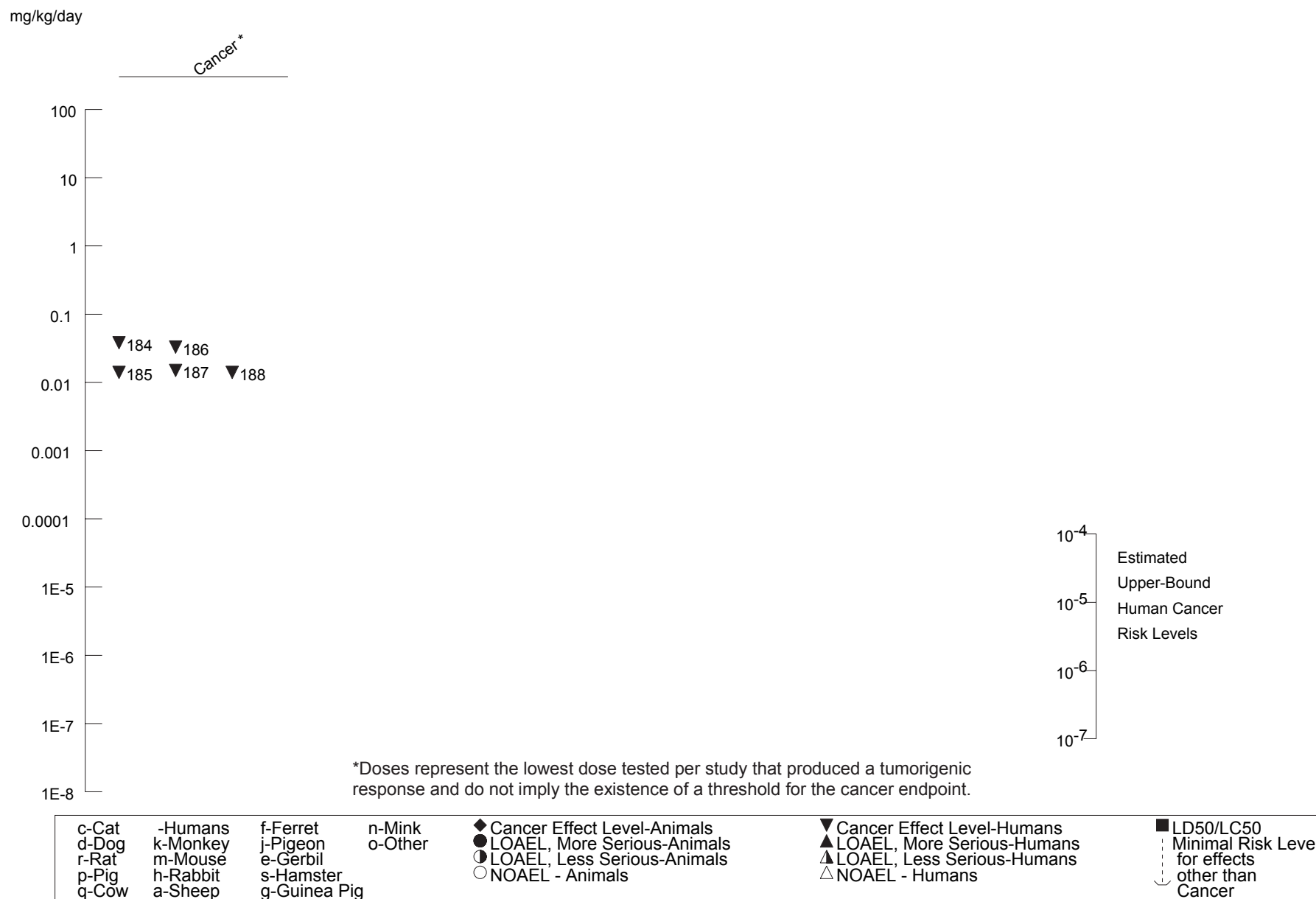
Figure 3-3 Levels of Significant Exposure to Inorganic Arsenic - Oral (*Continued*)Chronic (≥ 365 days)

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Sprague-Dawley)	once (GW)				3184 M (LD50) ^b 2449 F (LD50)	Gur and Nyska 1990 MSMA	
2	Mouse (ddY)	once (GW)				1800 M (LD50)	Kaise et al. 1989 MMA	
3	Rabbit (New Zealand)	once (GW)				102 M (LD50)	Jaghabir et al. 1988 MSMA	
Systemic								
4	Rat (Sprague-Dawley)	once (GW)	Gastro		2030 (mucoid feces and diarrhea)		Gur and Nyska 1990 MSMA	
			Bd Wt	2030				
5	Rat (Sprague-Dawley)	Gd 6-15 (GW)	Bd Wt	10 F	100 F (17% decrease in maternal body weight gain)	500 F (40% decrease in maternal body weight gain)	Irvine et al. 2006 MMA	
6	Mouse (ddY)	once (GW)	Resp			1800 M (respiratory arrest)	Kaise et al. 1989 MMA	
			Gastro		2200 M (diarrhea, slight congestion of the small intestine)			

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
7	Rabbit (New Zealand)	Gd 7-19 (GW)	Gastro	7 F	12 F (loose feces/diarrhea in 7/14 pregnant rabbits)		Irvine et al. 2006 MMA	
			Bd Wt	7 F		12 F (67% decrease in maternal body weight gain)		
8	Rabbit (New Zealand)	once (GW)	Gastro		60 M (diarrhea)		Jaghabir et al. 1988 MSMA	
Developmental								
9	Rat (Sprague-Dawley)	Gd 6-15 (GW)		100	500	(decreased fetal weight and increased fetal incidence of incomplete ossification of thoracic vertebrae)	Irvine et al. 2006 MMA	
10	Rabbit (New Zealand)	Gd 7-19 (GW)		7	12	(supernumerary thoracic ribs and eight lumbar vertebrae)	Irvine et al. 2006 MMA	
INTERMEDIATE EXPOSURE								
Death								
11	Rat (Fischer- 344)	52 wk (F)				106.9 M (increased mortality)	Arnold et al. 2003 MMA	

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic								
12	Rat (Fischer- 344) (F)	52 wk (F)	Gastro	3.5 ^C M	30.2 M (diarrhea)		Arnold et al. 2003 MMA	
			Bd Wt	30.2 M	106.9 M (14% decrease in body weight)			
13	Rat (Sprague-Dawley)	146-171 d pre-mating, mating, gestation, and lactation (F)	Bd Wt	76			Schroeder 1994 MMA	
14	Dog (Beagle)	52 wk (C)	Gastro		2 M (diarrhea)		Waner and Nyska 1988 MMA	
			Bd Wt	2 F	8 F (decrease in body weight)			
Reproductive								
15	Rat (Sprague-Dawley)	146-171 d pre-mating, mating, gestation, and lactation (F)		22	76 (decreased pregnancy rate and male fertility index in F0 and F1)		Schroeder 1994 MMA	
16	Mouse (Swiss)	19 d 3 d/wk (GW)			119 M (reduced fertility)		Prukop and Savage 1986 MSMA	

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Developmental								
17	Rat (Sprague-Dawley)	146-171 d pre-mating, mating, gestation, and lactation (F)		22	76	(decreased pup survival F1 and F2)	Schroeder 1994 MMA	
CHRONIC EXPOSURE								
Death								
18	Rat (Fischer- 344) (F)	104 wk				72.4 M (increased mortality)	Arnold et al. 2003 MMA	

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic								
19	Rat (Fischer- 344)	104 wk (F)	Gastro	3 M	25.7 M (diarrhea)	72.4 M (necrosis, ulceration, perforation in large intestine)	Arnold et al. 2003 MMA	
			Hemato	72.4 M				
			Musc/skel	72.4 M				
			Hepatic	72.4 M				
			Renal	3.9 F	33.9 F (increased absolute kidney weight and progressive glomerulonephropathy)			
			Endocr	3.9 F	33.9 F (hypertrophy of thyroid follicular epithelium, decreased absolute thyroid weight)			
			Dermal	72.4 M				
			Ocular	72.4 M				
			Bd Wt	3 M	25.7 M (15% decrease in body weight)	33.9 F (30% decrease in body weight)		

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
20	Rat (Fischer- 344)	104 wk (W)	Hemato	8.4 M			Shen et al. 2003 MMA	
			Hepatic	2.1 M	8.4 M (increased GST-P-positive foci)			
			Renal		2.1 M (hyperplasia of the bladder)			
			Bd Wt	8.4 M				
21	Mouse (B6C3F1)	104 wk (F)	Cardio	67.1 M			Arnold et al. 2003 MMA	
			Gastro	24.9 M	67.1 M (loose and mucoid feces, metaplasia of the cecum and colon)			
			Musc/skel	67.1 M				
			Hepatic	67.1 M				
			Renal	1.2 ^d M	6 M (increased incidence of progressive glomerulonephropathy)			
			Dermal	67.1 M				
			Ocular	67.1 M				
			Bd Wt	24.9 M	67.1 M (17% decrease in body weight)			

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
22	Dog (Beagle)	52 wk (C)	Resp	35			Waner and Nyska 1988 MMA	
			Gastro		2 M (diarrhea)			
			Hemato	35				
			Hepatic	35				
			Renal		8 (increased urine specific gravity; increased kidney weight)			
			Ocular	35				
			Bd Wt	2 F		8 F (42% decrease in body weight)		
Neurological								
23	Dog (Beagle)	52 wk (C)		35			Waner and Nyska 1988 MMA	
Reproductive								
24	Dog (Beagle)	52 wk (C)		35 M	35 F (decrease in estrus)		Waner and Nyska 1988 MMA	Histological examination of reproductive tissues
				8 F				

Table 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Cancer								
25	Rat (Fischer- 344) (W)	104 wk		8.4 M			Shen et al. 2003 MMA	

a The number corresponds to entries in Figure 3-4.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c The intermediate-duration oral MRL of 0.1 mg MMA/kg/day was calculated using a benchmark dose analysis. The BMDL10 of 12.38 mg MMA/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability)

d The chronic-duration oral MRL of 0.01 mg MMA/kg/day was calculated using a benchmark dose analysis. The BMDL10 of 1.09 mg MMA/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability)

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day; GST-P = glutathione S-transferase placental form; Hemato = hematological; IN = ingestion; LD50 = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsonic acid; MSMA = monosodium methane arsonate; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral

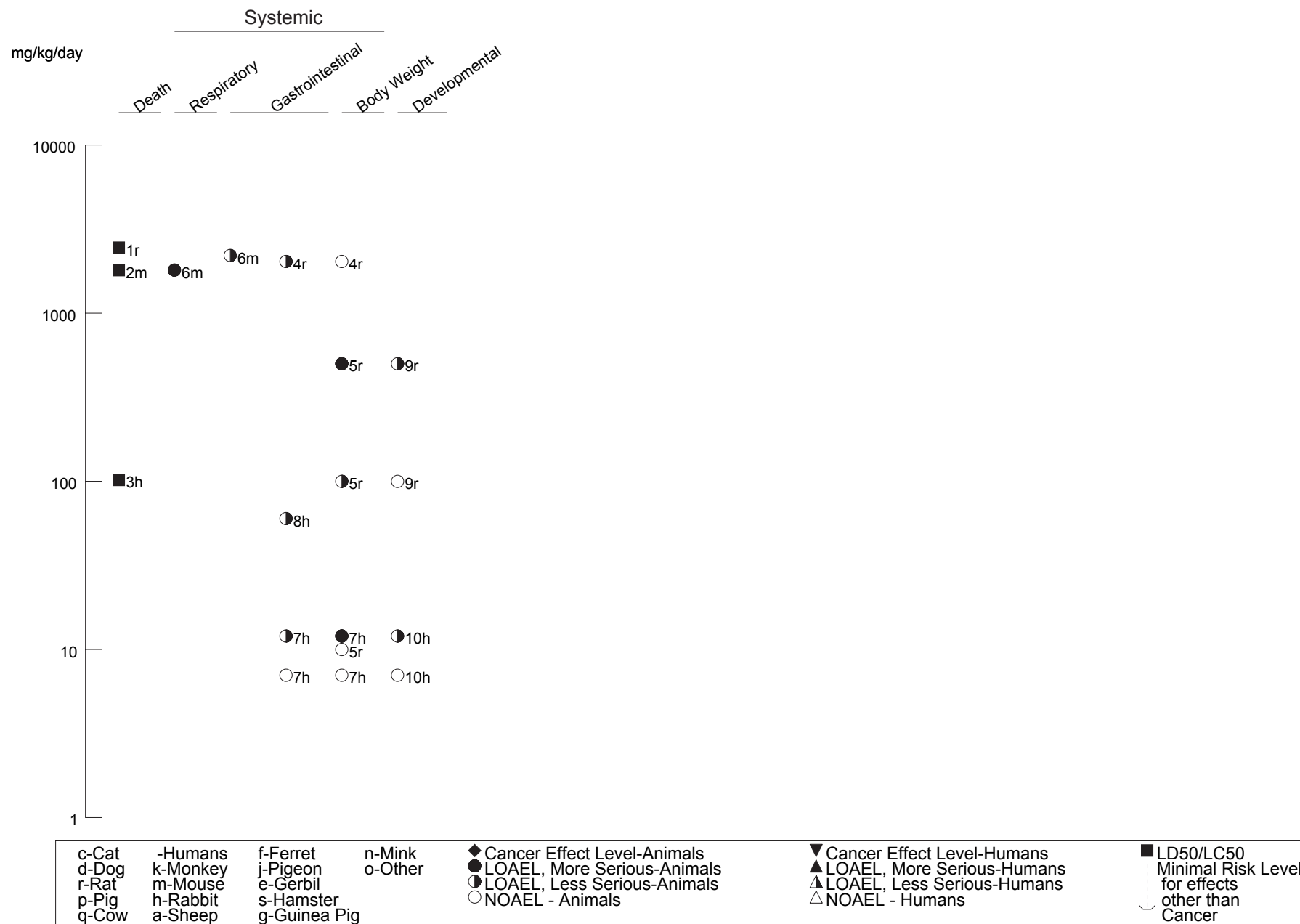
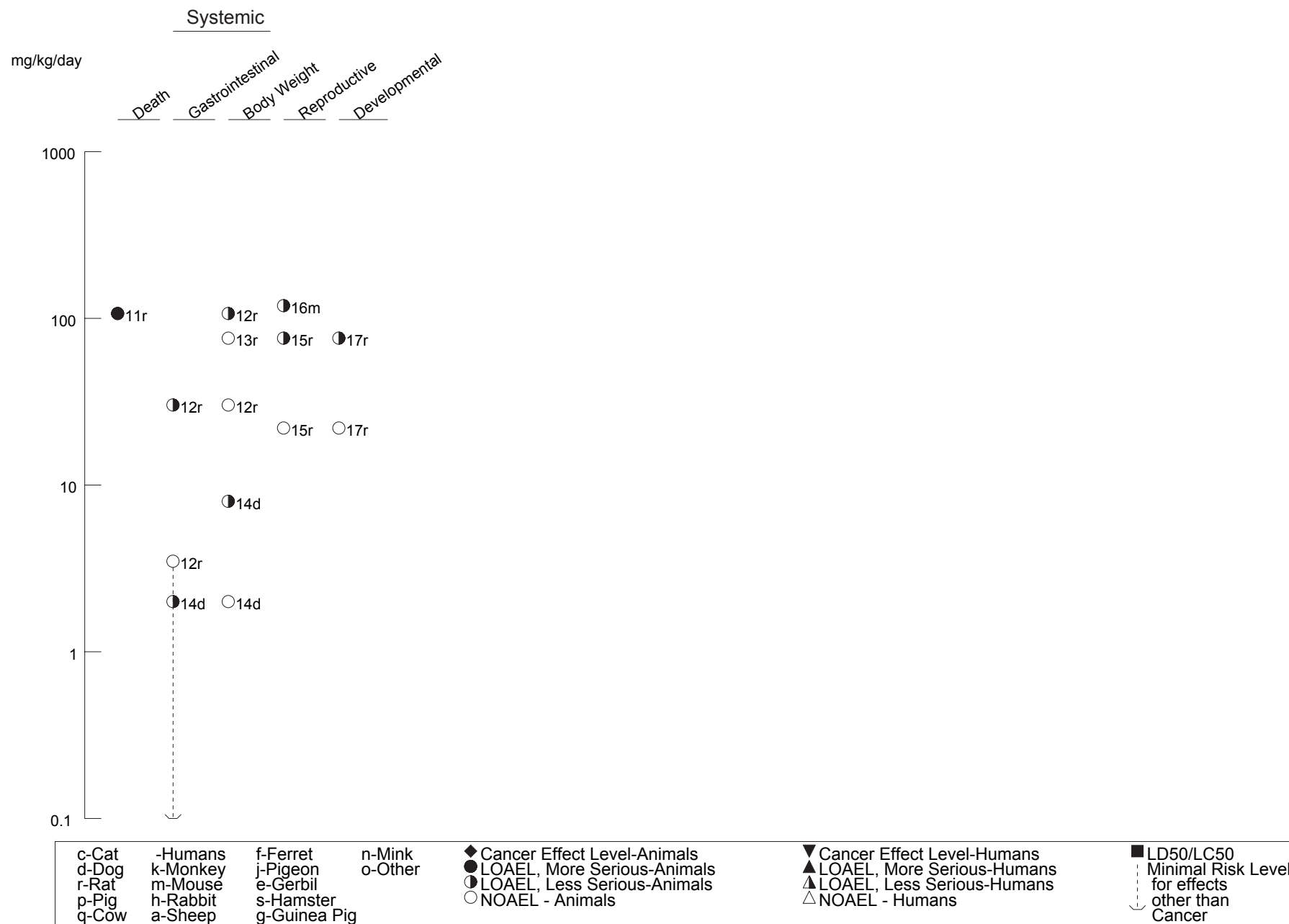
Acute (≤ 14 days)

Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (*Continued*)

Intermediate (15-364 days)



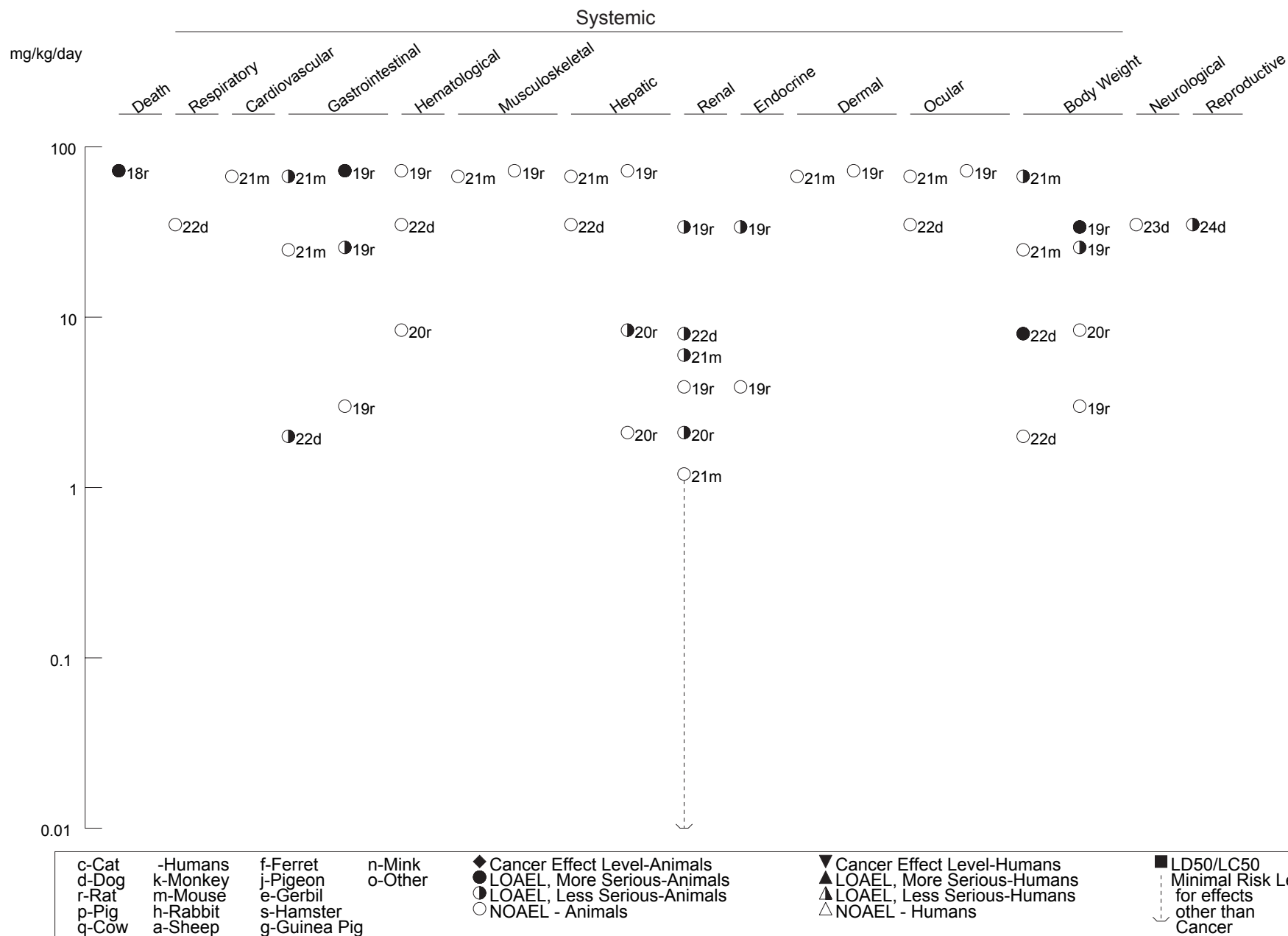
Chronic (≥ 365 days)

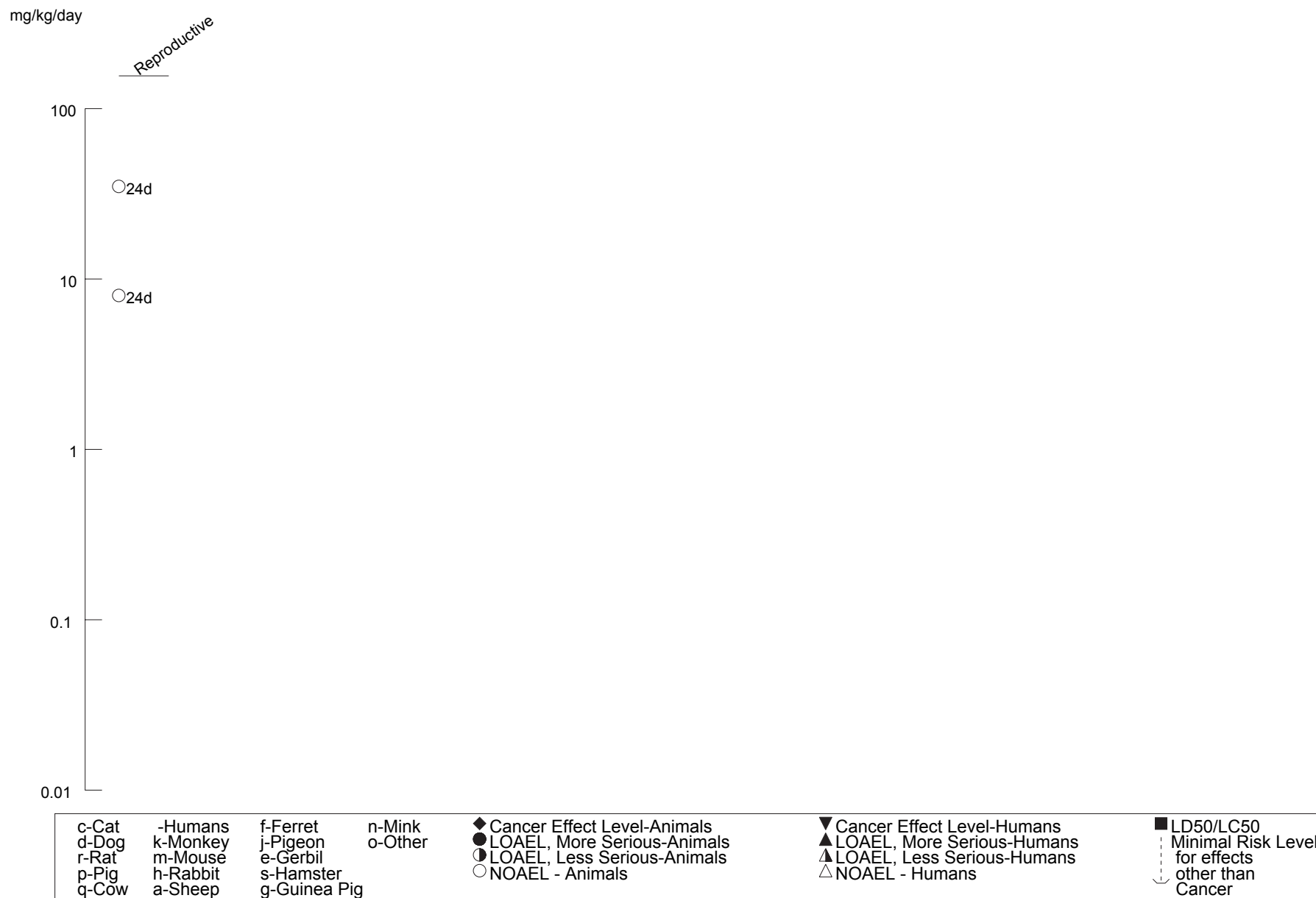
Figure 3-4 Levels of Significant Exposure to Monomethylarsonic Acid - Oral (*Continued*)Chronic (≥ 365 days)

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Fischer- 344) (F)	13 wk				475 M (100% mortality during first 2 weeks of study)	Crown et al. 1987 DMA	
2	Rat (CD)	10 d Gd 7-16 1 x/d (GW)				60 F (67% mortality)	Rogers et al. 1981 DMA	
3	Mouse (ddY)	once (GW)				1200 M (LD50)	Kaise et al. 1989 DMA	
4	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GW)				600 F (59% mortality)	Rogers et al. 1981 DMA	
Systemic								
5	Rat (Fischer- 344) (F)	2 wk	Renal		11 F (altered bladder cell surface characteristics)		Cohen et al. 2001 DMA	
			Bd Wt	11 F				
6	Rat (Fischer- 344) (F)	13 wk	Gastro		475 M (diarrhea and congestion and hemorrhagic contents in gastrointestinal tract in rats dying during first 2 weeks)		Crown et al. 1987 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
7	Rat (Sprague- Dawley)	Gd 6-15 (GW)	Bd Wt	12 F	36 F (decreased maternal body weight gain)		Irvine et al. 2006 DMA	
8	Rat (CD)	10 d Gd 7-16 1 x/d (GW)	Bd Wt			40 F (27% decreased maternal weight gain)	Rogers et al. 1981 DMA	
9	Mouse (B6C3F1)	24 hr 1 or 2 x (GW)	Resp		720 F (decreased lung ODC)		Ahmad et al. 1999a DMA	
			Hepatic		720 F (decreased liver GSH, GSSG, CYP-450 and ODC; increased serum ALT)			
10	Mouse (ddY)	once (GW)	Resp			900 M (respiratory arrest)	Kaise et al. 1989 DMA	
			Gastro		1757 M (diarrhea, slight congestion of the intestine)			
11	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GW)	Bd Wt			200 F (26% decreased maternal weight gain)	Rogers et al. 1981 DMA	
12	Dog (Beagle)	52 wk (C)	Gastro	6.5	16 (vomiting and diarrhea)		Zomber et al. 1989 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
13	Rabbit (New Zealand)	Gd 7-19 (GW)	Gastro	12 F	48 F (fluid gastrointestinal tract contents)		Irvine et al. 2006 DMA	
			Bd Wt	12 F		48 F (maternal weight loss)		
Neurological								
14	Mouse (ddY)	once (GW)				1757 M (increased startle reflex; ataxia)	Kaise et al. 1989 DMA	
Developmental								
15	Rat (Sprague-Dawley)	GD6-15 (GW)			40 F (decreased fetal body weight)		Chernoff et al. 1990 DMA	
16	Rat (Sprague-Dawley)	Gd 6-15 (GW)		12	36 (decreases in number of live fetuses and fetal weight; increases in fetuses with diaphragmatic hernia; delayed ossification)		Irvine et al. 2006 DMA	
17	Rat (CD)	10 d Gd 7-16 1 x/d (GW)		15		30 (malformed palates in 15%)	Rogers et al. 1981 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
18	Mouse (CD-1)	Gd 8 (GW)				1600 F (fetal deaths, decreased fetal weight, delayed ossification, skeletal malformations)	Kavlock et al. 1985 DMA	
19	Mouse (CD-1)	10 d Gd 7-16 1 x/d (GW)		200		400 (18% decrease in fetal weight, delayed ossification, cleft palate in 12/28; irregular palatine rugae in 4.8%)	Rogers et al. 1981 DMA	
20	Rabbit (New Zealand)	Gd 7-19 (GW)		12			Irvine et al. 2006 DMA	
INTERMEDIATE EXPOSURE								
Death								
21	Rat (Fischer- 344)	13 wk (F)				190 M (100% mortality during first 4 weeks of study)	Crown et al. 1987 DMA	
22	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)				57 (50% survival in males; 20% survival in females)	Murai et al. 1993 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
23	Rat (Fischer- 344)	8 wk (W)				17 M (10/10 died)	Wanibuchi et al. 1996 DMA	
Systemic								
24	Rat (Fischer- 344)	10 or 20 wk (F)	Renal	1 F	10 M (necrosis in bladder epithelium)		Arnold et al. 1999 DMA	
					^b 5 F (increased kidney weight, calcification at corticomedullary junction; increased bladder weight and increased BrdU labelling in bladder epithelium)			
			Bd Wt	10				
25	Rat (Fischer- 344)	10 wk (F)	Renal		11 F (increased bladder and kidney weights, hyperplasia and necrosis of bladder epithelium)		Cohen et al. 2001 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
26	Rat (Fischer- 344)	13 wk (F)	Resp	43.2 M			Crown et al. 1987 DMA	
			Cardio	43.2 M				
			Gastro	43.2 M	190 M (diarrhea and congestion and hemorrhagic contents in gastrointestinal tissues)			
			Hemato	0.44 F	4.5 F (decreased hemoglobin and erythrocyte levels)			
			Hepatic	23.5 M				
			Renal	0.4 M	4 M (increased urine volume and decreased specific gravity)			
			Endocr	0.4 M	4 M (hypertrophy of thyroid follicle epithelium)			
			Bd Wt	43.2 M				
27	Rat (Fischer- 344)	4 wk 5 d/wk 1 x/d (G)	Renal			57 (papillary necrosis and hyperplasia; cortical degeneration and necrosis)	Murai et al. 1993 DMA	
			Bd Wt		57 (decreased body weight)			

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
28	Rat (Sprague- Dawley)	10 wk pre-mating, gestation and lactation periods (F)	Resp	16.5			Rubin et al. 1989 DMA	
			Cardio	16.5				
			Hemato	0.34 M	2.3 M (decreased mean corpuscular hemoglobin concentration)			
			Hepatic	16.5				
			Renal	16.5				
			Endocr	2.3 F	16.5 F (hypertrophy of thyroid follicle epithelium)			
			Bd Wt	16.5				
29	Rat (Sprague- Dawley)	42 d (F)	Hemato	3.7 M			Siewicki 1981 DMA	
			Hepatic	3.7 M				
			Renal	3.7 M				
			Bd Wt	3.7 M				

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
30	Dog (Beagle)	6 d/wk 52 wk (C)	Gastro	6.5	16	(vomiting and diarrhea)	Zomber et al. 1989 DMA	
			Hemato	16 M	40 M	(decreased erythrocyte and increased leukocyte levels)		
Reproductive								
31	Rat (Sprague- Dawley)	10 wk pre-mating, gestation and lactation periods (F)		16.5			Rubin et al. 1989 DMA	
Cancer								
32	Mouse A/J	50 wk ad lib (W)				10.4 M (CEL: lung tumors)	Hayashi et al. 1998 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
CHRONIC EXPOSURE								
Systemic								
33	Rat (Fischer- 344)	daily 2 yr (F)	Resp	7.8			Arnold et al. 2006 DMA	
			Cardio	7.8				
			Gastro	7.8				
			Hemato	7.8				
			Musc/skel	7.8				
			Hepatic	7.8				
			Renal	0.77 M	3.1 M (nephrocalcinosis)			
				0.77 F	3.1 F (urothelial vacular degeneration and hyperplasia of urothelial cells in urinary bladder)			
			Endocr	3.1	7.8 (hypertrophy of thyroid follicle epithelium)			
			Dermal	7.8				
Ocular	7.8							
Bd Wt	7.8							
34	Rat (Fischer- 344)	104 wk (W)	Renal	0.75 M	3.4 M (nodular or papillary hyperplasia in urinary bladder)		Wei et al. 1999, 2002 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
35	Mouse (B6C3F1)	daily 2 yr (F)	Resp	94			Arnold et al. 2006 DMA	
			Cardio	94				
			Gastro	94				
			Hemato	94 F	94 F (decreased lymphocytes and increased monocytes)			
			Musc/skel	94				
			Hepatic	94				
			Renal	1.3 ^c F	37 M (progressive glomerulonephropathy)			
					7.8 ^b F (vacuolization of superficial cells of urothelium in urinary bladder)			
			Dermal	94				
			Ocular	94				
			Bd Wt	94				

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
36	Dog (Beagle)	6 d/wk 52 wk (C)	Resp	40			Zomber et al. 1989 DMA	
			Cardio	40				
			Gastro	6.5	16	(vomiting and diarrhea)		
			Hepatic	40				
			Renal	40				
Reproductive								
37	Rat (Fischer- 344)	daily 2 yr (F)		7.8			Arnold et al. 2006 DMA	Histological examination of reproductive tissues
38	Mouse (B6C3F1)	daily 2 yr (F)		94			Arnold et al. 2006 DMA	Histological examination of reproductive tissues
Cancer								
39	Rat (Fischer- 344)	daily 2 yr (F)				7.8 (CEL: urothelial cell papillomas and carcinomas in urinary bladder)	Arnold et al. 2006 DMA	
40	Rat (Fischer- 344)	104 wk (W)				3.4 M (CEL: urinary bladder tumors)	Wei et al. 1999, 2002 DMA	

Table 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
41	Mouse knockout	continuous 18 mo (W)				11.8 M (CEL)	Salim et al. 2003 DMA	

a The number corresponds to entries in Figure 3-5.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-5. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c The chronic-duration oral MRL of 0.02 mg DMA/kg/day was calculated using a benchmark dose analysis. The BMDL10 of 1.80 mg DMA/kg/day was divided by an uncertainty factor of 100 (10 to account for extrapolation from animals to humans and 10 for human variability)

ad lib = ad libitum; ALT = alanine aminotransferase; Bd Wt = body weight; BrdU = bromodeoxyuridine; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CYP = cytochrome p; d= day(s); DMA = dimethylarsinic acid; Endocr = endocrine; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; GSH = reduced glutathione; GSSG = oxidized glutathione; (GW) = gavage in water; Hemato = hematological; hr = hour(s); LD50 = lethal dose, 50% kill; ODC = ornithine decarboxylase; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral
Acute (≤ 14 days)

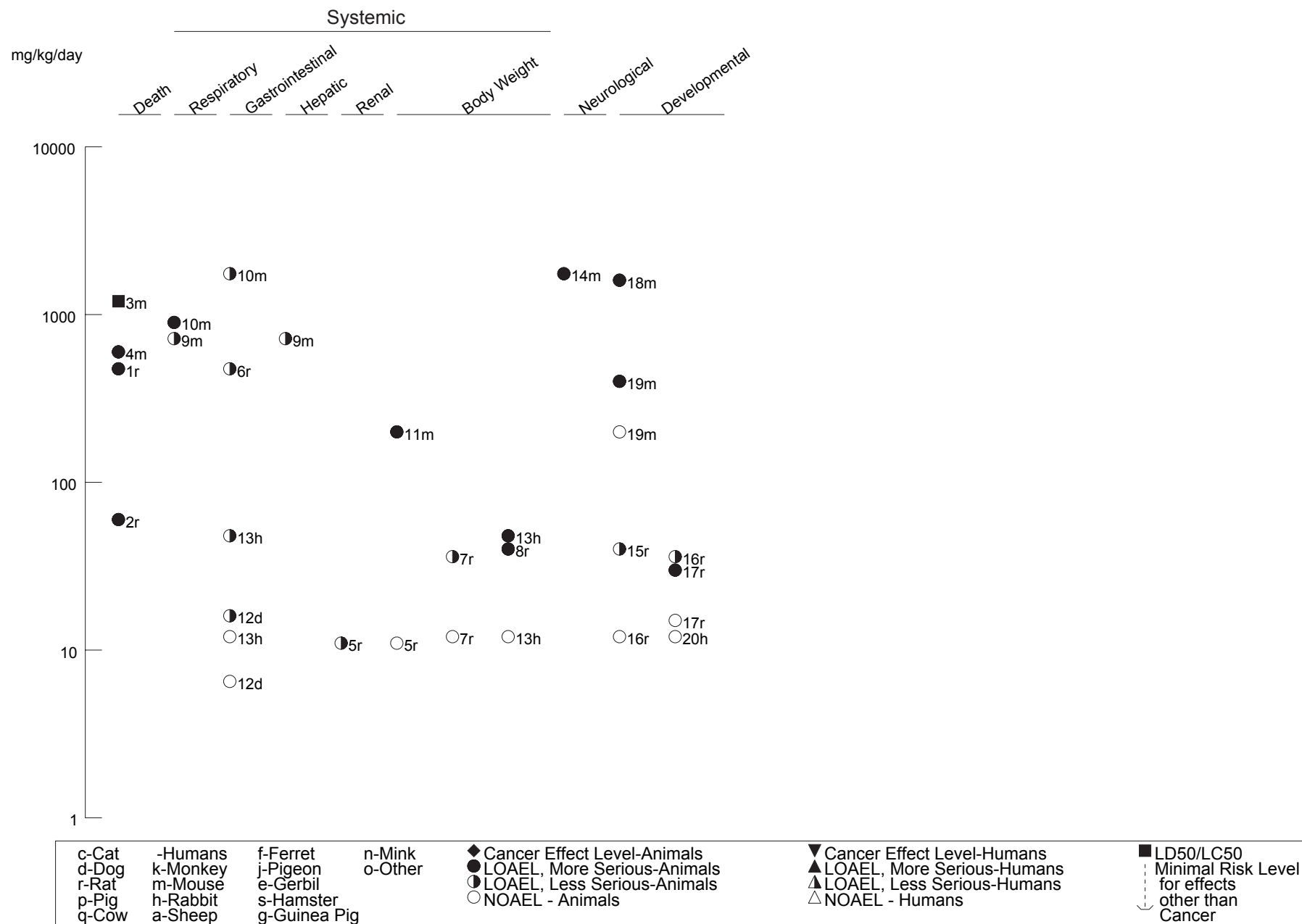


Figure 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (*Continued*)

Intermediate (15-364 days)

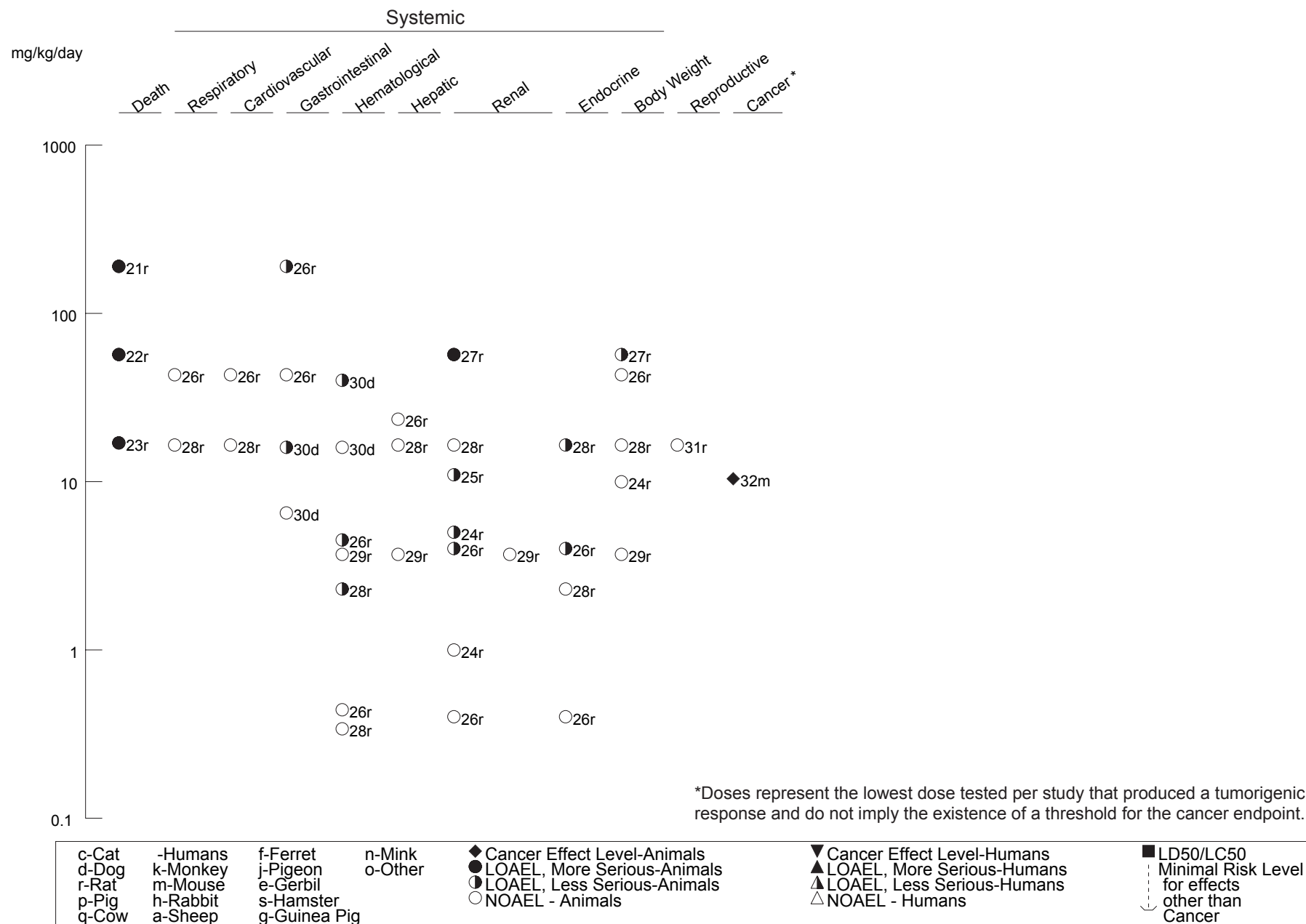


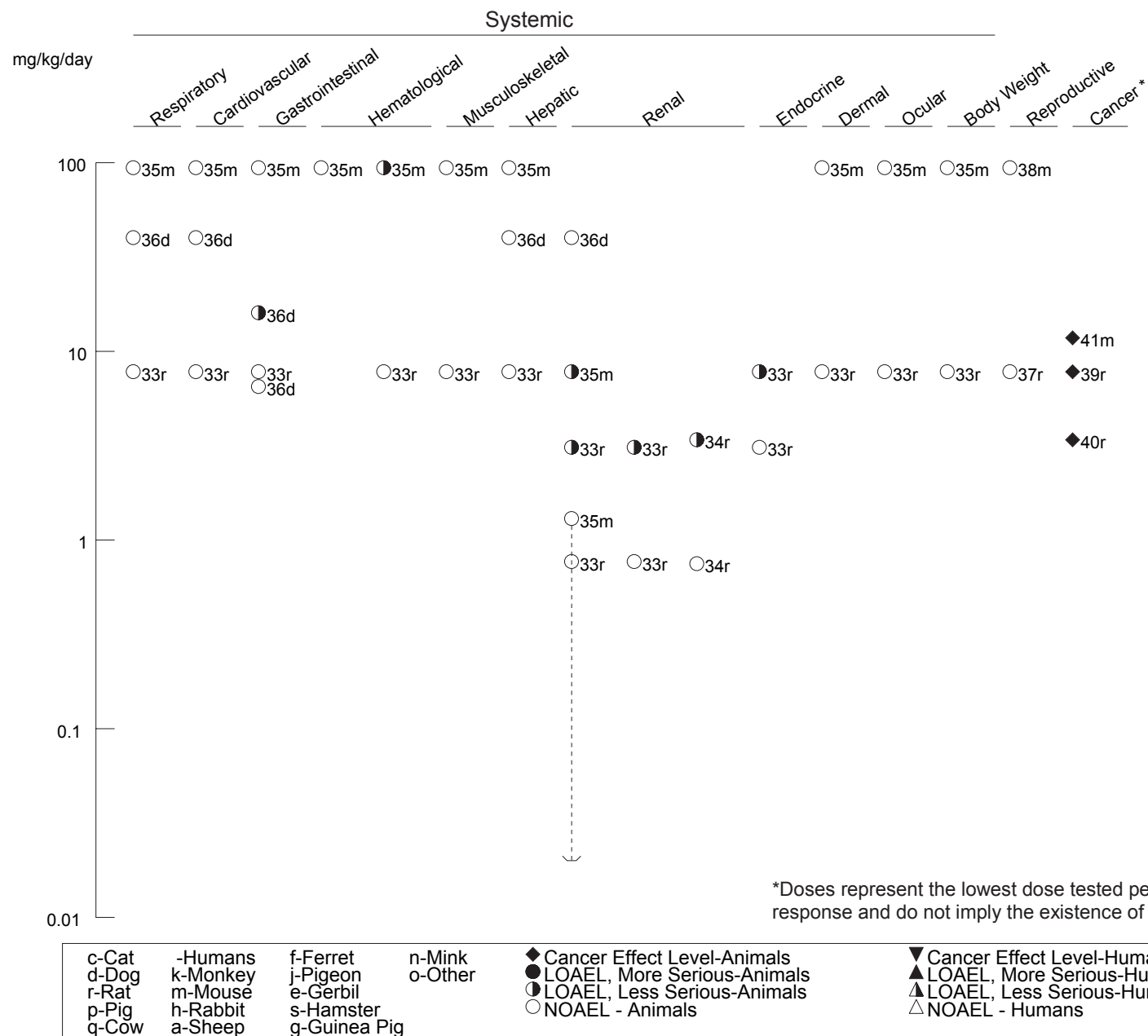
Figure 3-5 Levels of Significant Exposure to Dimethylarsinic Acid - Oral (*Continued*)Chronic (≥ 365 days)

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Holtzman)	once (GW)				155 (LD50)	Kerr et al. 1963 ROX	
2	Rat (Fischer- 344)	once (GO)				150 M (5/5 died) ^b 81 F (LD50)	NTP 1989b ROX	
3	Rat (Fischer- 344)	14 d (F)				^b 128 M (3/5 died) 144 F (5/5 died)	NTP 1989b ROX	
4	Mouse (B6C3F1)	once (GO)				300 M (5/5 died) ^b 244 F (LD50)	NTP 1989b ROX	
5	Mouse (B6C3F1)	14 d (F)				168 F (5/5 died)	NTP 1989b ROX	
Systemic								
6	Rat (Fischer- 344)	14 d (F)	Bd Wt	16 M	32 M (22% reduced body weight)		NTP 1989b ROX	
7	Mouse (B6C3F1)	14 d (F)	Bd Wt	84		168 (34% decrease in body weight)	NTP 1989b ROX	
Neurological								
8	Rat (Fischer- 344)	14 d (F)		16 M	32 M (slight inactivity)		NTP 1989b ROX	

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
9	Mouse (B6C3F1)	14 d (F)		20	42 (slight inactivity; ruffled fur)		NTP 1989b ROX	
10	Pig (Landrace)	30 d ad lib (F)				6.3 (muscle tremors and clonic convulsions)	Rice et al. 1985; Kennedy et al. 1986 ROX	
INTERMEDIATE EXPOSURE								
Death								
11	Rat (Holtzman)	13 wk (F)				20 (10/12 died)	Kerr et al. 1963 ROX	
12	Rat (Fischer- 344)	13 wk ad lib (F)				64 M (3/10 died)	NTP 1989b ROX	
13	Mouse (B6C3F1)	13 wk ad lib (F)				136 (6/10 males and 8/10 females died)	NTP 1989b ROX	

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Systemic								
14	Rat (Fischer- 344)	31 or 90 d ad lib (F)	Hemato	32 M			NTP 1989b ROX	
			Hepatic	9 F	36 F (decreased absolute and relative liver weight)			
			Renal	8 M	32 M (increased kidney weight; minimal tubular degeneration)			
			Bd Wt	8 M		32 M (27% decrease in body weight)		

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
15	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	64 M			NTP 1989b ROX	
			Cardio	64 M				
			Gastro	64 M				
			Musc/skel	64 M				
			Hepatic	4 M	8 M (increased relative liver weight)			
			Renal	16 M	32 M (interstitial inflammation, focal regenerative hyperplasia of tubular cell epithelium and mineralization)			
			Endocr	64 M				
			Dermal	64 M				
			Bd Wt	8 M	16 M (14% decreased body weight)	32 M (26% decreased body weight)		

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
16	Mouse (B6C3F1)	13 wk ad lib (F)	Cardio	136			NTP 1989b ROX	
			Gastro	136				
			Musc/skel	136				
			Hepatic	136				
			Renal	136				
			Endocr	136				
			Dermal	136				
			Bd Wt		136	(18% decreased body weight in males; 11% decreased body weight in females)		
17	Mouse (B6C3F1)	29 or 91 d ad lib (F)	Hemato	68			NTP 1989b ROX	
			Hepatic	68				
			Renal	68				
Neurological								
18	Rat (Fischer- 344)	13 wk ad lib (F)		32 M		64 M (trembling, ataxia, hyperexcitability, slight inactivity, ruffled fur)	NTP 1989b ROX	

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
19	Pig	28 d (F)				10 (muscle tremors)	Edmonds and Baker 1986 ROX	
20	Pig (Landrace)	30 d ad lib (F)				6.3 (paraplegia, myelin degeneration in spinal cord, peripheral nerves, optic nerve)	Rice et al. 1985; Kennedy et al. 1986 ROX	
CHRONIC EXPOSURE								
Systemic								
21	Rat (Fischer- 344)	103 wk ad lib (F)	Resp	4			NTP 1989b ROX	
			Cardio	4				
			Gastro	4				
			Musc/skel	4				
			Hepatic	4				
			Renal	4				
			Endocr	4				
			Dermal	4				
			Ocular	4				
			Bd Wt	4				
22	Mouse (Fischer- 344)	103 wk ad lib (F)	Resp	43 M			NTP 1989b ROX	
			Cardio	43 M				
			Gastro	43 M				
			Musc/skel	43 M				
			Hepatic	43 M				

Table 3-6 Levels of Significant Exposure to Roxarsone - Oral

(continued)

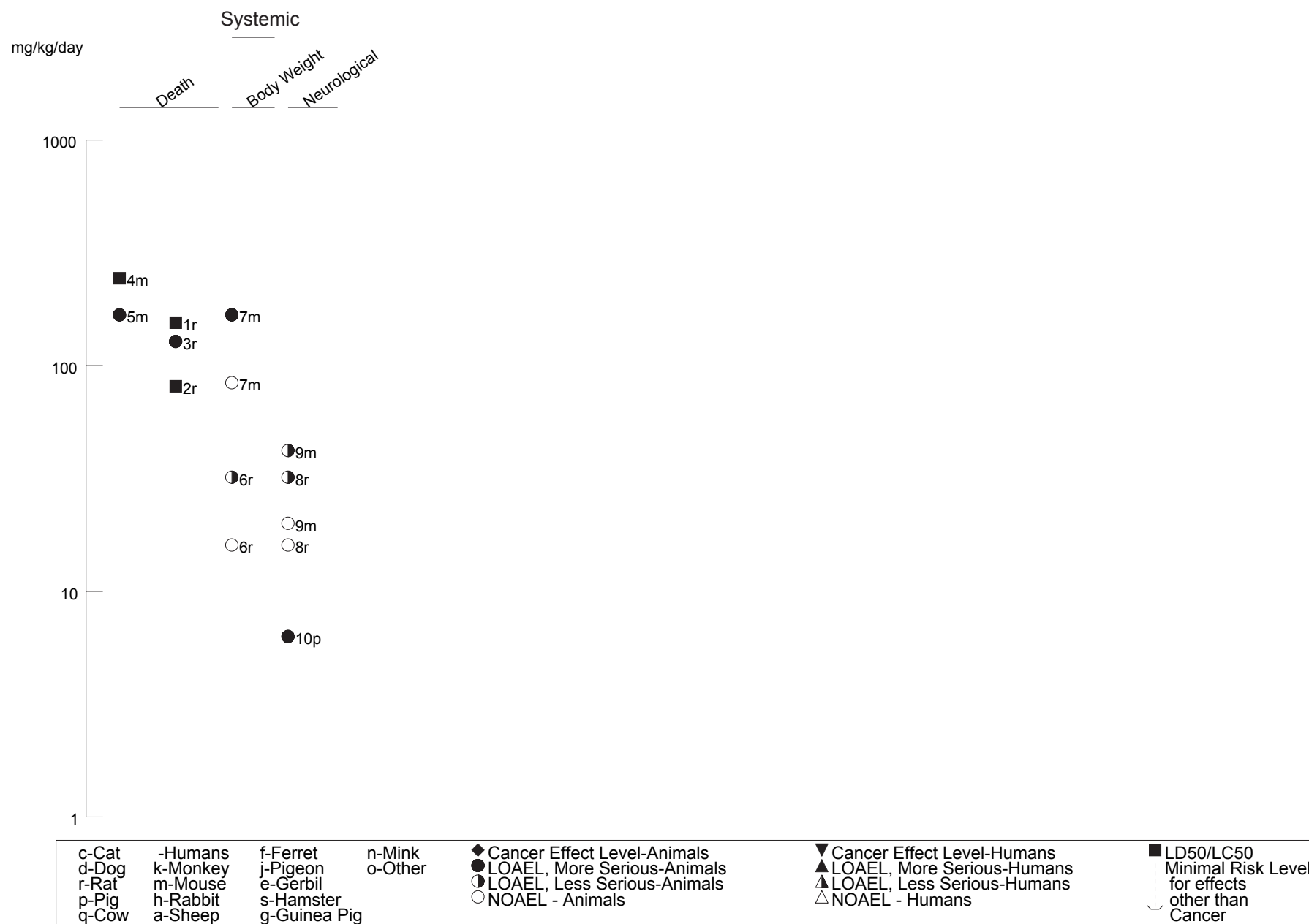
Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
			Renal	43 M				
			Endocr	43 M				
			Dermal	43 M				
			Ocular	43 M				
			Bd Wt	43 F				

^a The number corresponds to entries in Figure 3-6.

^b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-6. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; LC50 = lethal concentration, 50% kill, LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; occup = occupational; Resp = respiratory; wk = week(s)

Figure 3-6 Levels of Significant Exposure to Roxarsone - Oral
Acute (≤ 14 days)



Intermediate (15-364 days)

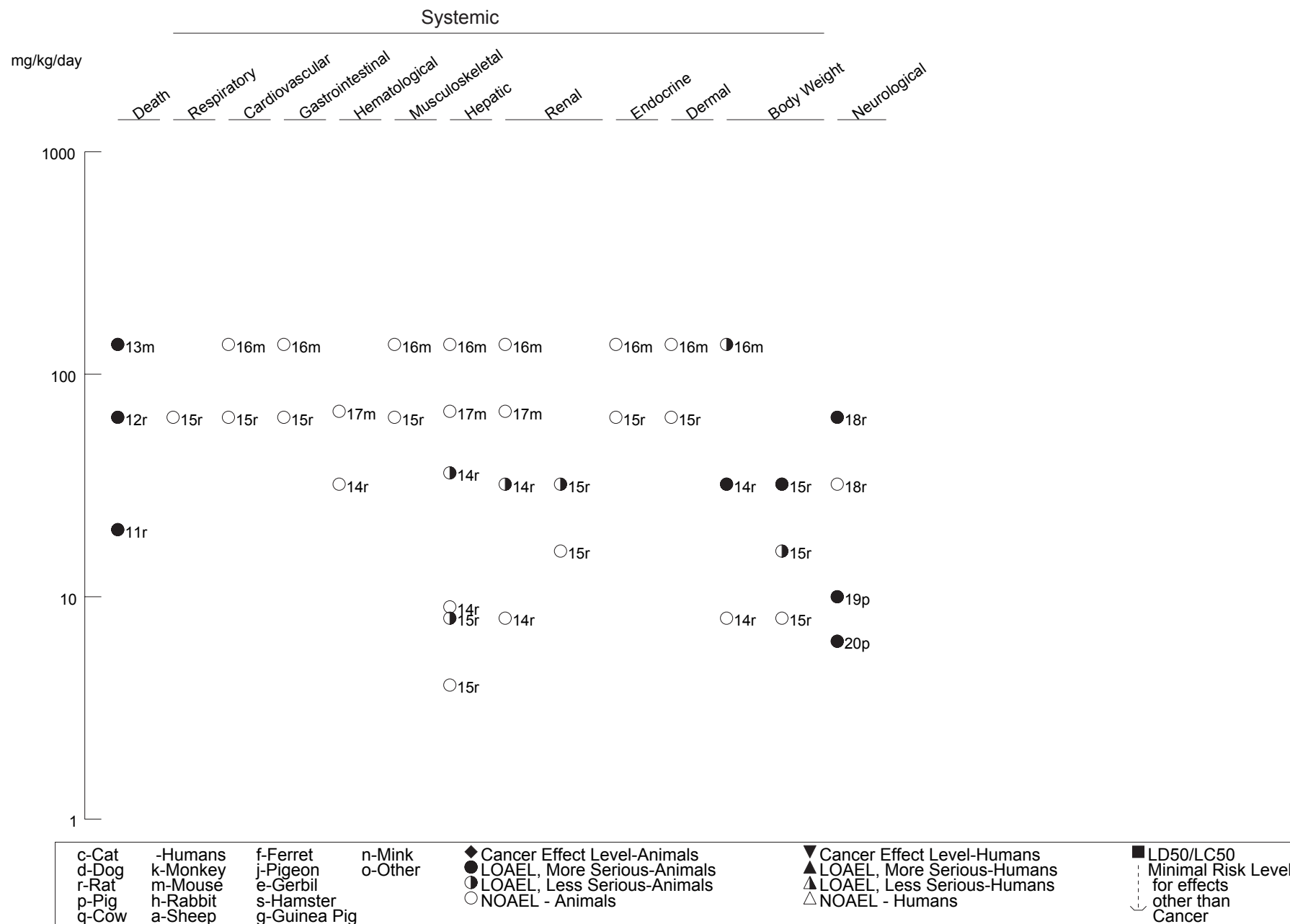
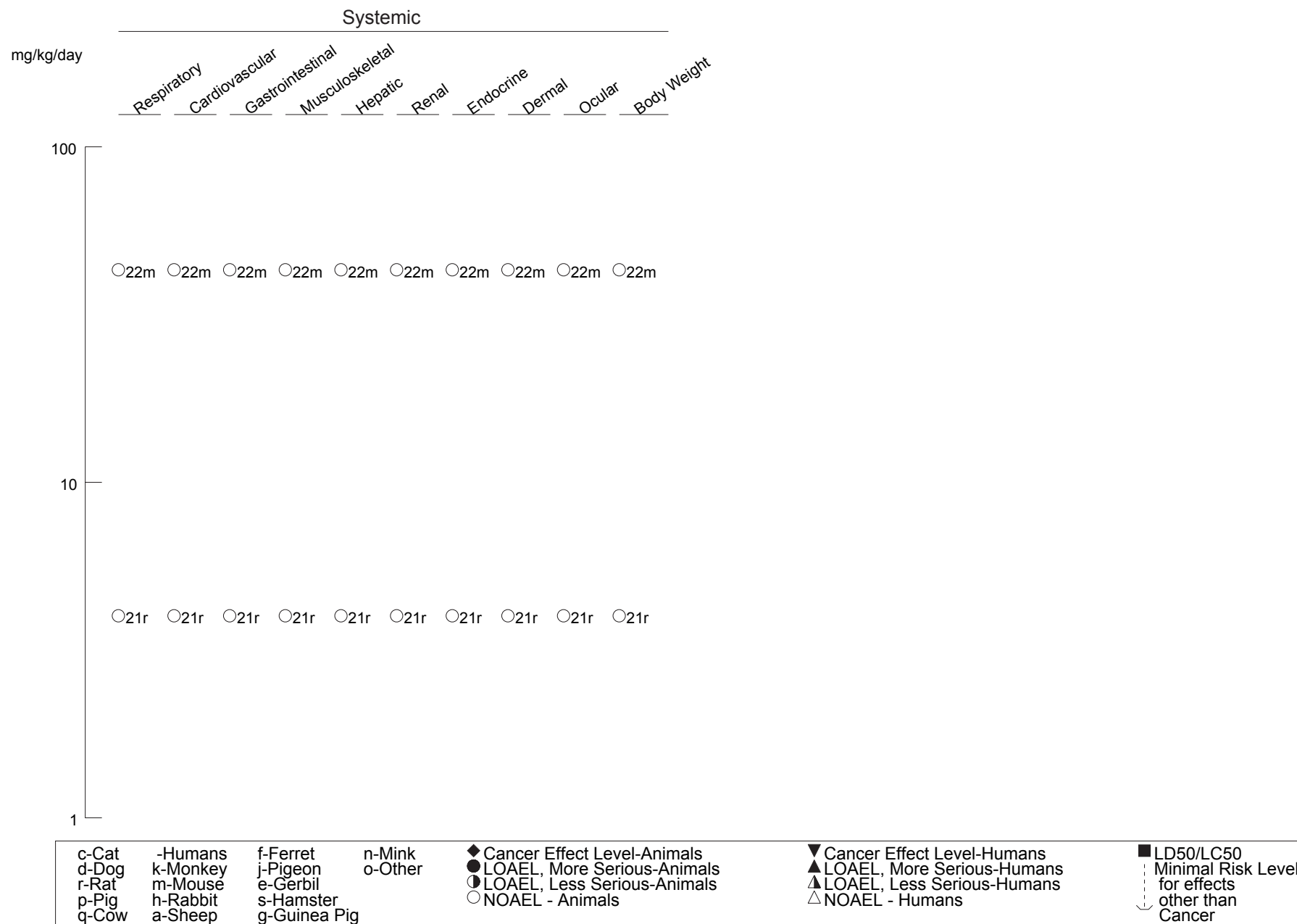


Figure 3-6 Levels of Significant Exposure to Roxarsone - Oral (*Continued*)Chronic (≥ 365 days)

3. HEALTH EFFECTS

Available LD₅₀ values for arsenate and arsenite in rats and mice range from 15 to 175 mg As/kg (Dieke and Richter 1946; Gaines 1960; Harrison et al. 1958; Kaise et al. 1985). The variability can be attributed to differences based on species, strain, specific route of exposure (feed vs. gavage), specific compound tested, and testing laboratory. Most deaths occurred within 1 day of exposure, but details regarding cause of death were not generally reported. Seven of 25 pregnant rats given a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation died soon after dosing, while no deaths occurred at doses of 4–15 mg As/kg (Stump et al. 1999). Data on lethality from repeated exposure studies in animals are relatively sparse. Seven of 20 pregnant rabbits died from repeated gavage doses of 1.5 mg As/kg/day as arsenic acid during gestation, while none died at 0.1–0.4 mg As/kg/day (Nemec et al. 1998). Chronic studies observed treatment-related mortality in monkeys exposed to 3 mg As/kg/day as arsenate (Heywood and Sortwell 1979), dogs exposed to 2.4 mg As/kg/day as arsenite or arsenate (Byron et al. 1967), mice exposed to 1 mg As/kg/day as arsenite (Schroeder and Balassa 1967), and rats exposed to 30 mg As/kg/day as lead arsenate (Kroes et al. 1974).

Reliable LOAEL and LD₅₀ values for lethality from oral exposure to inorganic arsenicals in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Organic Arsenicals. No studies were located regarding death in humans after oral exposure to organic arsenicals, but the acute lethality of MMA, DMA, and roxarsone have been investigated in several animal studies. The LD₅₀ values for MMA (including MSMA), DMA, and roxarsone are 102–3,184 mg/kg MMA or MSMA (Gur and Nyska 1990; Jaghabir et al. 1988; Kaise et al. 1989), 1,200 mg DMA/kg/day (Kaise et al. 1989), and 14.2–69.5 mg DMA/kg/day (Kerr et al. 1963; NTP 1989b), respectively. The cause of death was not investigated in any of these studies. Intermediate-duration exposure to MMA, DMA, or roxarsone resulted in increased mortality in laboratory animals exposed to 106.9 mg MMA/kg/day (Arnold et al. 2003), 17–190 mg DMA/kg/day (Crown et al. 1987; Murai et al. 1993; Wanibuchi et al. 1996) or 20–64 mg/kg/day roxarsone (Edmonds and Baker 1986; Kerr et al. 1963; NTP 1989b), respectively. Increased mortality was also observed in rats chronically exposed to 72.4 mg MMA/kg/day (Arnold et al. 2003).

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects from oral exposure in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3. Similar data for

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oral exposure to MMA, DMA, and roxarsone are shown in Tables 3-4, 3-5, and 3-6, and shown in Figures 3-4, 3-5, and 3-6, respectively.

Respiratory Effects.

Inorganic Arsenicals. Serious respiratory effects, including respiratory distress, hemorrhagic bronchitis, and pulmonary edema, have been reported in some cases of acute oral arsenic poisoning at doses of 8 mg As/kg and above (e.g., Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Moore et al. 1994b; Quatrehomme et al. 1992). These effects may be secondary to injury to the pulmonary vasculature (see Cardiovascular Effects, below). In addition, bronchitis and sequelae (bronchiectasis, bronchopneumonia) have been observed in patients and at autopsy in some chronic poisoning cases (Guha Mazumder et al. 2005; Milton and Rahman 2002; Rosenberg 1974; Tsai et al. 1999; Zaldívar 1974; Zaldívar and Guillier 1977). Bronchopneumonia secondary to arsenic-induced bronchitis was considered to be the cause of death in one young child who died after several years of exposure to an average dose of 0.08 mg As/kg/day (Zaldívar and Guillier 1977). Decrements in lung function, measured as decreased FEV₁, FVC, and FEF₂₅₋₇₅ have also been reported in subjects exposed to 0.1–0.5 mg As/L in the drinking water and exhibiting skin lesions (von Ehrenstein et al. 2005). In general, however, respiratory effects have not been widely associated with repeated oral ingestion of low arsenic doses. Nevertheless, a few studies have reported minor respiratory symptoms, such as cough, sputum, rhinorrhea, and sore throat, in people with repeated oral exposure to 0.03–0.05 mg As/kg/day (Ahmad et al. 1997; Mizuta et al. 1956).

There are few data regarding respiratory effects in animals following acute oral exposure to inorganic arsenic. An infant Rhesus monkey that died after 7 days of oral exposure to a complex arsenate salt at a dose of 3 mg As/kg/day exhibited bronchopneumonia with extensive pulmonary hemorrhage, edema, and necrosis (Heywood and Sortwell 1979). Two other monkeys in this treatment group survived a 1-year exposure period and had no gross or microscopic pulmonary lesions at sacrifice. Increased relative lung weights were seen in rats exposed to 6.66 mg As/kg/day as sodium arsenite 5 days/week for 12 weeks (Schulz et al. 2002). Chronic oral studies in dogs and rats treated with arsenate or arsenite failed to find respiratory lesions (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968).

One study utilizing gallium arsenide included limited investigation of respiratory function. Respiration rate was significantly decreased in rats following ingestion of a single dose of gallium arsenide at 1,040 mg As/kg, but was unaffected at a dose of 520 mg As/kg (Flora et al. 1997a). Respiration rate was measured 1, 7, and 15 days after dosing, but the decrease was most noticeable after 15 days.

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Organic Arsenicals. No respiratory effects were noted after acute human ingestion of 1,714 mg MSMA/kg (Shum et al. 1995). Mice exhibited respiratory arrest after a single oral dose of 1,800 mg MMA/kg (Kaise et al. 1989) or 900 mg DMA/kg (Kaise et al. 1989) and lung ornithine decarboxylase activity was reduced after ingestion of one or two doses of 720 mg DMA/kg (Ahmad et al. 1999a). Localized lung hemorrhage was observed in dogs after a single oral dose of 14.2 mg/kg roxarsone in a capsule (Kerr et al. 1963). No respiratory effects were seen after intermediate or chronic exposure of rats, mice, or dogs exposed to 35 mg MMA/kg/day (Waner and Nyska 1988), 7.8–94 mg DMA/kg/day (Arnold et al. 2006; Crown et al. 1987; Rubin et al. 1989; Zomber et al. 1989), or 4–136 mg/kg/day roxarsone (NTP 1989b).

Cardiovascular Effects.

Inorganic Arsenicals. A number of studies in humans indicate that arsenic ingestion may lead to serious effects on the cardiovascular system. Characteristic effects on the heart from both acute and long-term exposure include altered myocardial depolarization (prolonged QT interval, nonspecific ST segment changes) and cardiac arrhythmias (Cullen et al. 1995; Glazener et al. 1968; Goldsmith and From 1986; Heyman et al. 1956; Little et al. 1990; Mizuta et al. 1956; Moore et al. 1994b; Mumford et al. 2007). A significant dose-related increase in the prevalence of cardiac electrophysiologic abnormalities was observed in residents of Inner Mongolia, China; the incidences of QT prolongation were observed in 3.9, 11.1, and 20.6% of the residents with drinking water levels of <21, 110–300, and 430–690 µg/L, respectively (Mumford et al. 2007). Hypertrophy of the ventricular wall was observed at autopsy after acute exposure to 93 mg of arsenic (Quatrehomme et al. 1992). Long-term, low-level exposures may also lead to damage to the vascular system. The most dramatic example of this is "Blackfoot Disease," a condition that is endemic in an area of Taiwan where average drinking water levels of arsenic range from 0.17 to 0.80 ppm (Tseng 1977), corresponding to doses of about 0.014–0.065 mg As/kg/day (IRIS 2007). The disease is characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene (Chen et al. 1988b; Ch'i and Blackwell 1968; Tseng 1977, 1989; Tseng et al. 1968, 1995, 1996). Several researchers have presented evidence that other factors besides arsenic (e.g., other water contaminants, dietary deficits) may play a role in the etiology of this disease (Ko 1986; Lu et al. 1990; Yu et al. 1984). While this may be true, the clear association between the occurrence of Blackfoot Disease and the intake of elevated arsenic levels indicates that arsenic is at least a contributing factor. The results of a recent study suggested that individuals with a lower capacity to methylate

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inorganic arsenic to DMA have a higher risk of developing peripheral vascular disease in the Blackfoot Disease-hyperendemic area in Taiwan (Tseng et al. 2005).

Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular and microvascular diseases (Chiou et al. 1997; Wang et al. 2002, 2003) and ischemic heart disease (Chang et al. 2004; Chen et al. 1996; Hsueh et al. 1998b; Tsai et al. 1999; Tseng et al. 2003). Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, hypertension, defined as a systolic blood pressure of ≥ 140 mm Hg in combination with a diastolic blood pressure of ≥ 90 mm Hg, was associated with estimated lifetime doses of approximately 0.055 mg As/kg/day (0.25 mg/L in water) in a study of people in Bangladesh (Rahman et al. 1999); no significant association was found with estimated doses of 0.018 mg As/kg/day (0.75 mg/L in water). Wang et al. (2003) found an increased incidence of microvascular and macrovascular disease among subjects in Taiwan living in an arseniasis-endemic area in which the water of artesian wells had arsenic concentrations >0.35 mg/L (estimated doses of >0.03 mg As/kg/day). An additional study of Taiwanese subjects reported a significant increase in incidence of hypertension associated with concentrations of arsenic in the water >0.7 mg/L (estimated doses of >0.06 mg As/kg/day) (Chen et al. 1995). Studies in Chile indicate that ingestion of 0.6–0.8 ppm arsenic in drinking water (corresponding to doses of 0.02–0.06 mg As/kg/day, depending on age) increases the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgoño and Greiber 1972; Zaldívar 1974, 1977; Zaldívar and Guillier 1977). Autopsy of five children from this region who died of apparent arsenic toxicity showed a marked thickening of small and medium sized arteries in tissues throughout the body, especially the heart (Rosenberg 1974). In addition, cardiac failure, arterial hypotension, myocardial necrosis, and thrombosis have been observed in children who died from chronic arsenic ingestion (Zaldívar 1974), as well as adults chronically exposed to arsenic (Dueñas et al. 1998). Likewise, thickening and vascular occlusion of blood vessels were noted in German vintners exposed to arsenical pesticides in wine and in adults who drank arsenic-contaminated drinking water (Roth 1957; Zaldívar and Guillier 1977). A survey of Wisconsin residents using private wells for their drinking water found that residents exposed for at least 20 years to water concentrations of >10 $\mu\text{g As/L}$ had increased incidences of cardiac bypass surgery, high blood pressure, and circulatory problems as compared with residents exposed to lower arsenic concentrations (Zierold et al. 2004). Similarly, Lewis et al. (1999) reported increased mortality from hypertensive heart disease in both men and women among a cohort exposed to arsenic in their drinking water in Utah, as compared with the general population of Utah. Limitations in the study included lack of evaluation of smoking as a confounder and of other dietary sources of arsenic, and the lack of a dose-response for hypertensive heart disease. Another ecological study (Engel and Smith 1994) found significant increases in deaths from

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arteriosclerosis, aortic aneurysm, and all other diseases of the arteries, arterioles, and capillaries among U.S. residents with arsenic drinking waters of $>20 \mu\text{g/L}$; the increase in deaths from congenital anomalies of the heart and other anomalies of the circulatory system also observed in this subpopulation limits the interpretation of the findings.

Similar alterations in vascular reactivity have been noted in rats given repeated oral doses of arsenic trioxide (11 mg As/kg/day) for several weeks (Bekemeier and Hirschelmann 1989), although no histological effects could be detected in the hearts of rats or dogs exposed to up to 30 mg As/kg/day as arsenate or arsenite for 2 years (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Acute exposure of rats to gallium arsenide at a dose of 1,040 mg As/kg resulted in an increase in blood pressure and heart rate, while 520 mg As/kg had no effect (Flora et al. 1997a). Guinea pigs exposed to arsenic trioxide for 1 day (0, 7.6, 22.7, or 37.9 mg As/kg) or 8 days (0 or 3.8 mg As/kg/day) showed prolongation of the cardiac QT interval and action potential duration (Chiang et al. 2002).

Organic Arsenicals. No adverse cardiovascular effects were noted after acute human ingestion of 1,714 mg MSMA/kg (Shum et al. 1995). However, sinus tachycardia was noted after acute ingestion of 73 mg DMA/kg (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). No cardiovascular effects were seen after intermediate or chronic exposure of laboratory animals to 35–67.1 mg MMA/kg/day (Arnold et al. 2003; Waner and Nyska 1988), 7.8–94 mg DMA/kg/day (Arnold et al. 2006; Crown et al. 1987; Rubin et al. 1989; Zomber et al. 1989), or 4–136 mg/kg/day roxarsone (NTP 1989b).

Gastrointestinal Effects.

Inorganic Arsenicals. Clinical signs of gastrointestinal irritation, including nausea, vomiting, diarrhea, and abdominal pain, are observed in essentially all cases of short-term high-dose exposures to inorganic arsenic (e.g., Armstrong et al. 1984; Bartolome et al. 1999; Campbell and Alvarez 1989; Chakraborti et al. 2003a; Cullen et al. 1995; Fincher and Koerker 1987; Goebel et al. 1990; Kingston et al. 1993; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994b; Muzi et al. 2001; Uede and Furukawa 2003; Vantroyen et al. 2004). Similar signs are also frequently observed in groups or individuals with longer-term, lower-dose exposures (e.g., Borgoño and Greiber 1972; Cebrián et al. 1983; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a; Hauptert et al. 1996; Holland 1904; Huang et al. 1985; Mizuta et al. 1956; Nagai et al. 1956; Silver and Wainman 1952; Wagner et al. 1979; Zaldivar 1974), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases.

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Gastrointestinal irritation symptoms form the basis (in part) for the acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 3-3. More severe symptoms (hematemesis, hemoperitoneum, gastrointestinal hemorrhage, and necrosis) have been reported in some cases with acute exposure to 8 mg As/kg or more (Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), and also in some people with long-term ingestion of 0.03–0.05 mg As/kg/day as a medicinal preparation (Lander et al. 1975; Morris et al. 1974).

Clinical signs of gastrointestinal irritation were observed in monkeys and rats given repeated oral doses of arsenic (6 and 11 mg As/kg/day, respectively) for 2 weeks (Bekemeier and Hirschelmann 1989; Heywood and Sortwell 1979). Hemorrhagic gastrointestinal lesions have also been reported in animal studies. A monkey that died after repeated oral treatment with 6 mg As/kg/day for approximately 1 month was found to have acute inflammation and hemorrhage of the small intestine upon necropsy (Heywood and Sortwell 1979). This lesion was not found in other monkeys that died in this study, or in the survivors. Two pregnant mice that died after repeated gavage treatment with 24 mg As/kg/day as arsenic acid had hemorrhagic lesions in the stomach (Nemec et al. 1998). Gross gastrointestinal lesions (stomach adhesions, eroded luminal epithelium in the stomach) were seen frequently in rats treated by gavage with 8 mg As/kg/day as arsenic trioxide starting before mating and continuing through the end of gestation (Holson et al. 2000). The lesions were not found in rats treated with 4 mg As/kg/day in this study. No histological evidence of gastrointestinal injury was detected in rats exposed to arsenate or arsenite in the feed for 2 years at doses up to 30 mg As/kg/day, but dogs fed a diet containing 2.4 mg As/kg/day as arsenite for 2 years had some bleeding in the gut (Byron et al. 1967; Kroes et al. 1974).

Organic Arsenicals. Vomiting was noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Ingestion of 78 mg DMA/kg (as dimethyl arsenic acid and dimethyl arsenate) induced vomiting, abdominal pain, hyperactive bowel, and diarrhea (Lee et al. 1995).

The gastrointestinal tract appears to be the critical target of toxicity following oral exposure to MMA. Diarrhea/loose feces has been reported in mice and rabbits following a single gavage dose of 2,200 mg MMA/kg or 60 mg MSMA/kg, respectively (Jaghabir et al. 1988; Kaise et al. 1989), pregnant rabbits administered 12 mg MMA/kg/day via gavage (Irvine et al. 2006), rats exposed to 30.2 mg MMA/kg/day in the diet during the first year of a 2-year study (Arnold et al. 2003), dogs administered 2 mg MMA/kg/day via capsule for 52 weeks (Waner and Nyska 1988), rats fed diets containing 25.7 mg MMA/kg/day for 2 years (Arnold et al. 2003), and mice exposed to 67.1 mg MMA/kg/day in the diet for

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2 years (Arnold et al. 2003). However, the increased incidence of diarrhea is not always accompanied by macroscopic or histological alterations in the gastrointestinal tissues. For example, in the 2-year rat study (Arnold et al. 2003; incidence data reported in Crown et al. 1990), an increased incidence of diarrhea was observed at 25.7 mg MMA/kg/day; macroscopic or histological alterations were observed in some animals, but the incidence was similar to controls. At the next highest dose level (72.4 mg MMA/kg/day), thickened wall and edema and hemorrhagic, necrotic, ulcerated, or perforated mucosa were observed in the large intestine and significant increases in the incidence of squamous metaplasia of the epithelial columnar absorptive cells were found in the cecum, colon, and rectum. Squamous metaplasia was also observed in the cecum and colon of mice chronically exposed to 67.1 mg MMA/kg/day (Arnold et al. 2003; incidence data reported in Gur et al. 1991).

There are some reports of gastrointestinal effects in rats and dogs exposed to DMA; however, the LOAELs for these effects are higher than the LOAELs for MMA and most rodent studies do not report effects at nonlethal doses. Diarrhea with congestion and hemorrhagic gastrointestinal contents were observed in rats exposed to a lethal dose of 190 mg DMA/kg/day in the diet for 4 weeks (Crown et al. 1987) and diarrhea and vomiting were reported in dogs administered 16 mg DMA/kg/day via capsule 6 days/week (Zomber et al. 1989). No gastrointestinal effects were observed in rats or mice chronically exposed to 7.8 or 94 mg DMA/kg/day, respectively (Arnold et al. 2006).

Vomiting and gastrointestinal hemorrhage were observed in dogs after a single capsulized dose of 50 mg/kg roxarsone (Kerr et al. 1963), although slightly higher doses administered for 13 weeks to rats and mice had no effect (NTP 1989b). No gastrointestinal effects were seen after chronic exposure of rats (4 mg/kg/day) or mice (43 mg/kg/day) to roxarsone (NTP 1989b).

Hematological Effects.

Inorganic Arsenicals. Anemia and leukopenia are common effects of arsenic poisoning in humans, and have been reported following acute (Armstrong et al. 1984; Goldsmith and From 1986; Mizuta et al. 1956; Muzi et al. 2001; Westhoff et al. 1975), intermediate (Franzblau and Lilis 1989; Heyman et al. 1956; Nagai et al. 1956; Wagner et al. 1979), and chronic oral exposures (Chakraborti et al. 2003a; Glazener et al. 1968; Guha Mazumder et al. 1988; Hopenhayn et al. 2006; Kyle and Pease 1965; Tay and Seah 1975) at doses of 0.002 mg As/kg/day or more. These effects may be due to both a direct cytotoxic or hemolytic effect on the blood cells (Armstrong et al. 1984; Fincher and Koerker 1987; Goldsmith and From 1986; Kyle and Pease 1965; Lerman et al. 1980) and a suppression of erythropoiesis (Kyle and

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Pease 1965; Lerman et al. 1980). However, hematological effects are not observed in all cases of arsenic exposure (EPA 1981b; Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952) or even all acute poisoning cases (Cullen et al. 1995; Moore et al. 1994b).

In an acute animal study, Tice et al. (1997) found that there was a decrease in polychromatic erythrocytes in the bone marrow of mice treated with 6 mg As/kg/day for 1 or 4 days. There was no effect at 3 mg As/kg/day. Long-term studies found mild anemia in dogs fed arsenite or arsenate for 2 years at 2.4 mg As/kg/day, but no hematological effect in dogs fed 1 mg As/kg/day for 2 years or 1.9 mg As/kg/day for 26 weeks (Byron et al. 1967; Neiger and Osweiler 1989). Chronic rat studies found little or no evidence of anemia at doses up to 30 mg As/kg/day, even with co-exposure to lead (Byron et al. 1967; Kroes et al. 1974). No hematological effects were found in monkeys exposed to arsenic doses of 3–6 mg As/kg/day for 1 year (Heywood and Sortwell 1979).

Rats exposed to arsenate for 6 weeks had decreased activities of several enzymes involved in heme synthesis, but data were not provided on whether this resulted in anemia (Woods and Fowler 1977, 1978). Exposure of rats to ≥ 5 ppm of arsenic (0.30 mg As/kg/day as sodium arsenite) in the drinking water for 4 weeks resulted in increased platelet aggregation, while 10 or 25 ppm (0.60 or 1.5 mg As/kg/day) was associated with increased P-selectin-positive cells and decreased occlusion time (Lee et al. 2002), representing a change in platelet function. Similarly, exposure of rats or guinea pigs to 10 or 25 ppm of arsenic as arsenite (approximate doses of 0, 0.92, or 2.3 mg As/kg/day for rats and 0, 0.69, or 1.7 mg As/kg/day for guinea pigs) in the drinking water for 16 weeks (Kannan et al. 2001) resulted in decreases in erythrocyte and leukocyte numbers (rats and guinea pigs), increased blood mean corpuscular volume and corpuscular hemoglobin mass (guinea pigs only), and decreased mean corpuscular hemoglobin concentration (rats only). Gallium arsenide also disrupts heme synthesis in rats, although the evidence suggests that this effect is due primarily to the gallium moiety (Flora et al. 1997a).

Organic Arsenicals. No adverse hematological effects were noted in a man who ingested 78 mg/kg as dimethyl arsenic acid and dimethyl arsenate (Lee et al. 1995). No hematological effects were observed in rats exposed to 8.4 or 72.4 mg MMA/kg/day for 2 years (Arnold et al. 2003; Shen et al. 2003) or dogs administered 35 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988); additionally, no alterations in total or differential leukocyte levels were observed in mice exposed to 67.1 mg MMA/kg/day for 2 years (Arnold et al. 2003). Although some studies have reported hematological alterations following oral exposure to DMA, this is not a consistent finding. Observed alterations include decreased mean corpuscular hemoglobin concentration in rats exposed to 2.3 mg DMA/kg/day for 10 weeks (Rubin et al.

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1989), decreased hemoglobin and erythrocyte levels in rats exposed to 4.5 mg DMA/kg/day for 13 weeks (Crown et al. 1987), decreased erythrocyte levels and increased leukocyte levels in dogs administered capsules containing 40 mg DMA/kg/day for 52 weeks (Zomber et al. 1989), and decreased lymphocyte and increased monocyte levels were observed in mice chronically exposed to 94 mg DMA/kg/day (Arnold et al. 2006). No hematological alterations have been observed in rats exposed to 7.8 mg DMA/kg/day for 2 years (Arnold et al. 2006). Similarly, no hematological effects were observed in rats (Kerr et al. 1963; NTP 1989b), mice (NTP 1989b), or dogs (Prier et al. 1963) exposed to 20–32, 68, or 5 mg/kg/day roxarsone, respectively, for intermediate or chronic durations

Musculoskeletal Effects.

Inorganic Arsenicals. No studies were located regarding musculoskeletal effects in humans or animals after oral exposure to inorganic arsenicals.

Organic Arsenicals. No studies were located regarding musculoskeletal effects in humans after oral exposure to organic arsenicals. No musculoskeletal effects were seen after intermediate or chronic exposure of rats and mice to MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), or roxarsone (NTP 1989b).

Hepatic Effects.

Inorganic Arsenicals. A number of studies in humans exposed to inorganic arsenic by the oral route have noted signs or symptoms of hepatic injury. Clinical examination often reveals that the liver is swollen and tender (Chakraborty and Saha 1987; Franklin et al. 1950; Guha Mazumder et al. 1988, 1998a; Liu et al. 2002; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953; Zaldivar 1974), and analysis of blood sometimes shows elevated levels of hepatic enzymes (Armstrong et al. 1984; Franzblau and Lilis 1989; Guha Mazumder 2005; Hernández-Zavala et al. 1998). These effects are most often observed after repeated exposure to doses of 0.01–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953), although doses as low as 0.006 mg As/kg/day have been reported to have an effect following chronic exposure (Hernández-Zavala et al. 1998). Hepatic effects have also been reported in acute bolus poisoning cases at doses of 2 mg As/kg/day or more (Hantson et al. 1996; Kamijo et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Vantroyen et al. 2004), although acute exposure to 19 mg As/kg did not cause hepatic effects in an infant (Cullen et al. 1995).

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Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (Guha Mazumder 2005; Guha Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and bleeding from esophageal varices (Szuler et al. 1979); cirrhosis has also been reported at an increased frequency in arsenic-exposed individuals (Tsai et al. 1999). Several researchers consider that these hepatic effects are secondary to damage to the hepatic blood vessels (Morris et al. 1974; Rosenberg 1974), but this is not directly established.

Acute exposure of monkeys to 6 mg As/kg/day resulted in vacuolization of the hepatocytes (Heywood and Sortwell 1979). Studies in dogs or mice have not detected clinically significant hepatic injury following exposure to either arsenite or arsenate (Byron et al. 1967; Fowler and Woods 1979; Kerkvliet et al. 1980; Neiger and Osweiler 1989; Schroeder and Balassa 1967), although enlargement of the common bile duct was noted in rats fed either arsenate or arsenite in the diet for 2 years (Byron et al. 1967; Kroes et al. 1974) and lipid vacuolation and fibrosis were seen in the livers of rats exposed to 12 mg As/kg/day as arsenate in the drinking water for 6 weeks (Fowler et al. 1977). Similarly, fatty changes and inflammatory cell infiltration were seen in the livers of both normal and metallothionein-null mice exposed to 5.6 mg arsenic/kg/day in the drinking water for 48 weeks (Liu et al. 2000). Increases in liver zinc and copper concentrations were noted in rats receiving a single oral dose of 10 mg As/kg as sodium arsenite (Flora and Tripathi 1998) and hepatic levels of malondialdehyde were increased and glutathione levels were decreased in livers of rats receiving 200 mg As/kg as GaAs (Flora et al. 1998). An increase in indices of peroxidation was reported in rats dosed with approximately 0.02 mg As/kg/day for 60 days from drinking water containing 2.5 mg sodium arsenite/L (Bashir et al. 2006); absolute liver weight was also increased at this dose level. Elevated levels of serum aspartate aminotransferase (AST) were observed in rats administered a single oral dose of 100 mg As/kg as GaAs (Flora et al. 1998). Exposure of guinea pigs to 0.69 or 1.7 mg As/kg/day in the drinking water for 16 weeks, but not in rats exposed to 0.92 or 2.3 mg As/kg/day, resulted in increases in delta-aminolevulinic acid synthetase (ALAS) levels (Kannan et al. 2001). Exposure of BALB/C mice to 0.7 mg arsenic/kg/day in the drinking water for 15 months resulted in increased liver weights, changes in liver enzymes (glutathione S-transferase, glutathione reductase, catalase, glucose-6-phosphate dehydrogenase, glutathione peroxidase), fatty liver, and fibrosis (Santra et al. 2000).

Organic Arsenicals. No adverse hepatic effects were noted after ingestion of 1,714 mg/kg MSMA or 78 mg DMA/kg (as dimethyl arsenic acid and dimethyl arsenate) in a suicide attempt (Lee et al. 1995; Shum et al. 1995). No other studies of the hepatic effects of organic arsenicals in humans were located.

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Histological examination of livers from rabbits given repeated oral doses of MMA showed diffuse inflammation and hepatocellular degeneration (Jaghabir et al. 1989), but the lesions were not severe. Male rats exposed to a time-weighted average (TWA) dose of 72.4 mg MMA/kg/day for 104 weeks showed a decrease in absolute liver weight, while females exposed to 98.5 mg MMA/kg/day showed histiocytic proliferation of the liver (Arnold et al. 2003); however, these effects were probably due to a decrease in body weight and secondary complications of perforation and ulceration of the gastrointestinal effect, respectively. Shen et al. (2003) reported increases in and the number of GST-P-positive foci in the livers of rats exposed to average concentrations of 8.4 mg MMA/kg/day in the diet for 104 weeks. No effects were observed in rats exposed to DMA (Siewicki 1981), but mice exposed to one or two oral doses of 720 mg DMA/kg had decreased liver glutathione and cytochrome P-450 content and serum ornithine decarboxylase activity (Ahmad et al. 1999a). Generalized icterus was reported in dogs after acute exposure to roxarsone (Kerr et al. 1963). Some small fluctuations in liver weight have been noted in rats and mice after intermediate oral exposure to roxarsone, but the toxicological significance of this is not clear and is not observed after chronic exposure of rats and mice to lower doses (NTP 1989b).

Renal Effects.

Inorganic Arsenicals. Most case studies of acute and chronic arsenic toxicity do not report clinical signs of significant renal injury, even when other systems are severely impaired (e.g., Cullen et al. 1995; Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987; Mizuta et al. 1956; Silver and Wainman 1952). In some cases, elevated serum levels of creatinine or bilirubin have been noted (Armstrong et al. 1984; Levin-Scherz et al. 1987; Moore et al. 1994b), and mild proteinuria may occur (Armstrong et al. 1984; Glazener et al. 1968; Tay and Seah 1975). Acute renal failure in some bolus poisoning episodes (e.g., Fincher and Koerker 1987; Goebel et al. 1990; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994b) is probably a result of fluid imbalances or vascular injury (Rosenberg 1974; Zaldívar 1974). Glomerular congestion has been observed after an acute exposure to high doses (Quatrehomme et al. 1992).

Studies in animals also indicate that the kidney is not a major target organ for inorganic arsenic (Byron et al. 1967; Schroeder and Balassa 1967; Woods and Southern 1989), although some effects have been reported at high exposure levels. Mild histological changes in the renal tubules of monkeys exposed to arsenate for 2 weeks were noted by Heywood and Sortwell (1979), and some mild alterations in renal mitochondria in rats exposed to arsenate for 6 weeks were noted by Brown et al. (1976). Mild proteinuria

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(Flora et al. 1998) and an increase in kidney zinc concentration (Flora and Tripathi 1998) have also been noted in rats exposed orally to a single dose of 100 mg As/kg as GaAs or 10 mg As/kg as sodium arsenite, respectively. These data suggest that the kidney is relatively less sensitive to arsenic than most other organ systems, and renal effects are unlikely to be of concern except secondary to fluid imbalances or cardiovascular injury.

Organic Arsenicals. No adverse renal effects were noted after ingestion of 1,714 mg MSMA/kg in a suicide attempt (Shum et al. 1995). Animal studies have reported renal and urinary bladder effects following oral exposure to organic arsenicals; the available data suggest that the urinary system is a more sensitive target for DMA, than for MMA or roxarsone. A decrease in urine volume was observed in rabbits following a single gavage dose of 30 mg MSMA/kg/day (Jaghabir et al. 1988) and a decrease in urine volume (35 mg MMA/kg/day) and an increase in urine specific gravity (8 mg MMA/kg/day) were observed in dogs administered MMA via capsule for 52 weeks (Waner and Nyska 1988). However, these effects may be indicative of dehydration due to diarrhea rather than a direct effect on the kidney. In a 2-year study in rats (Arnold et al. 2003), an increase in the severity of progressive glomerulonephropathy was observed in females at 33.9 mg MMA/kg/day. Hydronephrosis, pyelonephritis, cystitis, and decreases in urine volume and pH were also observed 72.4 mg MMA/kg/day; however, the investigators noted that these lesions probably resulted from urinary tract obstruction, which was secondary to peritonitis caused by gastrointestinal tract ulcerations. An increased incidence of progressive glomerulonephropathy was also observed in male mice exposed to ≥ 6.0 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003; incidence data reported in Gur et al. 1991); the investigators (Gur et al. 1991) noted that the kidney lesions were consistent with the normal spectrum of spontaneous lesions and that there were no differences in character or severity of the lesions between the different groups.

Exposure to DMA has resulted in kidney effects in rats and mice exposed to at least 3.1 or 37 mg DMA/kg/day, respectively; no renal effects were observed in dogs exposed to doses as high as 40 mg As/kg/day for 52 weeks (Zomber et al. 1989). In rats, the renal damage is characterized by increased urine volume and pH, decreased urine osmolarity and electrolyte (sodium, potassium, chlorine) levels, increased urinary calcium levels, and increased organ weight, nephrocalcinosis, and necrosis in the renal papillae and/or cortex; an increase in water consumption is also typically observed. The LOAELs for these effects are 5–57 mg DMA/kg/day in intermediate-duration studies (Arnold et al. 1999; Crown et al. 1987; Murai et al. 1993) and 3.1 mg DMA/kg/day in a chronic-duration study (Arnold et al. 2006). Another study did not find renal effects in rats exposed to 16.5 mg DMA/kg/day (Rubin et al. 1989). This study involved exposure to Sprague-Dawley rats compared to Fischer 344 rats used in the studies with

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positive results; it is not known if this reflects a difference in strain sensitivity. In mice, progressive glomerulonephropathy was observed at 37 mg DMA/kg/day and nephrocalcinosis was observed at 94 mg DMA/kg/day (Arnold et al. 2006).

Increased kidney weights and minimal tubular epithelial cell degeneration, tubular casts, and focal mineralization were observed in rats exposed to 32 mg/kg/day roxarsone for 13 weeks (NTP 1989b). No adverse effects were observed in rats at doses as high as 20 mg/kg/day (Kerr et al. 1963; NTP 1989b) for 13 weeks or 10 mg/kg/day for 2 years (NTP 1989b; Prier et al. 1963). No adverse renal effects have been observed in mice exposed to roxarsone doses as high as 136 mg/kg/day (NTP 1989b) or 43 mg/kg/day (NTP 1989b; Prier et al. 1963) for intermediate or chronic durations, respectively, or in dogs exposed to 5 mg/kg/day for a chronic duration (Prier et al. 1963).

Damage to the urinary bladder has been observed in several studies in which rats were exposed to DMA. The observed effects include altered bladder cell surface characteristics in rats exposed to 11 mg DMA/kg/day in the diet for 2 weeks (Cohen et al. 2001), increased bladder weight and regenerative proliferation (measured as an increase in BrdU labeling) in bladder epithelium at 5 mg DMA/kg/day for 10 weeks (Arnold et al. 1999), necrosis of bladder epithelium at 10 mg DMA/kg/day for 10 weeks (Arnold et al. 1999), nodular or papillar hyperplasia at 3.4 mg DMA/kg/day for 2 years (Wei et al. 2002), and urothelial vacuolar degeneration and hyperplasia of urothelial cells at 3.1 mg DMA/kg/day for 2 years (Arnold et al. 2006). Vacuolization of the urothelium in the urinary bladder have also been observed in mice exposed to 7.8 mg DMA/kg/day in the diet for 2 years (Arnold et al. 2006). Inconsistent results were found for MMA. Hyperplasia was observed in the bladders of rats exposed to 1 mg As/kg/day as MMA in drinking water for 2 years (Shen et al. 2003), but bladder effects were not observed in another 2-year study (Arnold et al. 2003) in which rats were exposed to doses as high as 34.8 mg As/kg/day as MMA in the diet. No urinary bladder effects were found in rats and mice exposed to 64 or 136 mg/kg/day roxarsone for 13 weeks (NTP 1989b) or 4 or 43 mg/kg/day roxarsone for 2 years (NTP 1989b).

Endocrine Effects.

Inorganic Arsenicals. Very little has been written about the effects of oral exposure to arsenic on endocrine glands. In a report of the autopsies of five children who died in Chile after chronic exposure to arsenic in the drinking water, arterial thickening in the pancreas was noted (Rosenberg 1974). An association has been demonstrated between exposure to arsenic in drinking water and an increased

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incidence of diabetes mellitus (Lai et al. 1994; Rahman et al. 1998; Tsai et al. 1999; Tseng et al. 2000; Wang et al. 2003), although dose-response relationships are not available.

Exposure of rats to 2.3 mg As/kg/day as arsenic trioxide for 30 days resulted in reductions in the number of islet cells in the pancreas, as well as significant reductions in pancreatic superoxide dismutase (SOD) and catalase enzyme levels and increases in the production of nitric oxide and malondialdehyde (Mukherjee et al. 2004).

Organic Arsenicals. No studies of effects of organic arsenic compounds on endocrine glands in humans were found. Hypertrophy of thyroid epithelium was observed in rats exposed to 33.9 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003), 4.0 mg DMA/kg/day in the diet for 13 weeks (Crown et al. 1987), 16.5 mg DMA/kg/day in the diet for at least 10 weeks (Rubin et al. 1989), and 7.8 mg DMA/kg/day in the diet for 2 years (Arnold et al. 2006). No other biologically significant effects were observed in other endocrine tissues following exposure to MMA or DMA. No adverse effects were seen in the adrenal or pituitary glands, thyroid, or pancreas after intermediate or chronic exposure of rats (20–64 or 4 mg/kg/day, respectively) and mice (136 or 43 mg/kg/day, respectively) to roxarsone (NTP 1989b).

Dermal Effects.

Inorganic Arsenicals. One of the most common and characteristic effects of arsenic ingestion is a pattern of skin changes that include generalized hyperkeratosis and formation of hyperkeratotic warts or corns on the palms and soles, along with areas of hyperpigmentation interspersed with small areas of hypopigmentation on the face, neck, and back. These and other dermal effects have been noted in a large majority of human studies involving repeated oral exposure (e.g., Ahmad et al. 1997, 1999b; Ahsan et al. 2000; Bickley and Papa 1989; Borgoño and Greiber 1972; Borgoño et al. 1980; Cebrián et al. 1983; Chakraborti et al. 2003a, 2003b; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a, 1998b, 1998c; Guo et al. 2001a; Hauptert et al. 1996; Huang et al. 1985; Lander et al. 1975; Liu et al. 2002; Lühtrath 1983; Milton et al. 2004; Mizuta et al. 1956; Morris et al. 1974; Nagai et al. 1956; Piontek et al. 1989; Rosenberg 1974; Saha and Poddar 1986; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Tseng et al. 1968; Wade and Frazer 1953; Wagner et al. 1979; Wong et al. 1998a, 1998b; Zaldívar 1974, 1977). In cases of low-level chronic exposure (usually from water), these skin lesions appear to be the most sensitive indication of effect, so this end point is considered to be the most appropriate basis for establishing a chronic oral MRL. This is supported by the finding that other effects (hepatic injury, vascular disease, neurological

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effects) also appear to have similar thresholds. As shown in Table 3-3 and Figure 3-3, numerous studies in humans have reported dermal effects at chronic dose levels generally ranging from about 0.01 to 0.1 mg As/kg/day (Ahmad et al. 1997; Bickley and Papa 1989; Borgoño and Greiber 1972; Borgoño et al. 1980; Cebrián et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Guha Mazumder et al. 1988; Huang et al. 1985; Lücktrath 1983; Piontek et al. 1989; Silver and Wainman 1952; Tseng et al. 1968; Zaldívar 1974, 1977). However, in a study with detailed exposure assessment, all confirmed cases of skin lesions ingested water containing >100 µg/L arsenic (approximately 0.0037 mg As/kg/day) and the lowest known peak arsenic concentration ingested by a case was 0.115 µg/L (approximately 0.0043 mg As/kg/day) (Haque et al. 2003). Another large study reported increased incidence of skin lesions associated with estimated doses of 0.0012 mg As/kg/day (0.023 mg As/L drinking water) (Ahsan et al. 2006). Several epidemiological studies of moderately sized populations (20–200 people) exposed to arsenic through drinking water have detected no dermal or other effects at average chronic doses of 0.0004–0.01 mg As/kg/day (Cebrián et al. 1983; EPA 1981b; Guha Mazumder et al. 1988; Harrington et al. 1978; Valentine et al. 1985), and one very large study detected no effects in any person at an average total daily intake (from water plus food) of 0.0008 mg As/kg/day (Tseng et al. 1968). This value has been used to calculate a chronic oral MRL for inorganic arsenic of 0.0003 mg/kg/day, as described in footnote c in Table 3-3.

Another prominent dermal effect associated with chronic ingestion of inorganic arsenic is skin cancer. As discussed in greater detail in Section 3.2.2.7 (below), some of these skin cancers may evolve from the hyperkeratotic corns or warts, while the areas of altered pigmentation are not considered to be precancerous (EPA 1988d).

Dermal lesions similar to those observed in humans have not been noted in oral exposure studies in monkeys (Heywood and Sortwell 1979), dogs (Byron et al. 1967), or rodents (Schroeder et al. 1968). However, a hyperplastic response to oral arsenic exposure was reported in arsenic-exposed mice (Rossman et al. 2004).

Organic Arsenicals. No studies were located regarding dermal effects in humans after oral exposure to organic arsenicals. No gross or histological skin alterations were observed in rats or mice following intermediate- or chronic-duration exposure to MMA (Arnold et al. 2003; as reported in Crown et al. 1990; Gur et al. 1991), DMA (Arnold et al. 2006; as reported in Gur et al. 1989a, 1989b), or roxarsone (NTP 1989b)

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Ocular Effects.

Inorganic Arsenicals. Periorbital swelling was reported in people drinking contaminated well water at an approximate dose of 0.2 mg As/kg for 1 week (Armstrong et al. 1984). Facial edema, generally involving the eyelids, was a prominent feature of arsenic poisoning among 220 cases associated with an episode of arsenic contamination of soy sauce in Japan (Mizuta et al. 1956). Exposure was to an estimated dose of 0.05 mg/kg/day and lasted for up to 2–3 weeks. The edema developed soon after the initial exposure and then subsided. This effect forms the basis (in part) for the acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 3-3. Nemec et al. (1998) noted the appearance of dried red material around the eyes of mice receiving daily oral doses of 24 mg As/kg as arsenic acid for 10 days during gestation.

Organic Arsenicals. No studies were located regarding ocular effects in humans or animals after oral exposure to organic arsenicals. No gross or histological alterations in the eye were observed in rats or mice following intermediate- or chronic-duration exposure to MMA (Arnold et al. 2003; as reported in Crown et al. 1990; Gur et al. 1991), DMA (Arnold et al. 2006; as reported in Gur et al. 1989a, 1989b), or roxarsone (NTP 1989b).

Body Weight Effects.

Inorganic Arsenicals. A 41-year old woman exposed to arsenic in the drinking water for 4 months at an approximate dose of 0.06 mg As/kg/day reported losing 40 pounds (18 kg) of body weight before seeking treatment (Wagner et al. 1979). Weight loss was also among the effects observed in a series of 475 chronic arsenism patients hospitalized in Antofagasto, Chile after receiving approximate doses of 0.02 mg As/kg/day in the drinking water for an unspecified number of years (Zaldívar 1974).

Reductions in body weight gain are commonly seen in animal studies of ingested arsenic. In pregnant rats, body weight gain was reduced by gavage treatment with 23 mg As/kg/day as arsenic trioxide on day 9 of gestation (NOAEL=15 mg As/kg/day, Stump et al. 1999), and by repeated gavage treatment with 8 mg As/kg/day as arsenic trioxide from 2 weeks prior to mating through gestation (NOAEL=4 mg As/kg/day, Holson et al. 2000). Exposure of rats by gavage to 26.6 mg As/kg/day as sodium arsenite, but not 13.3 mg As/kg/day or lower, 5 days/week for 4 weeks resulted in a significant decrease in body weight (Schulz et al. 2002). In 6-week rat studies, body weight gain was decreased at 11–12 mg As/kg/day, but not at 6–9 mg As/kg/day (Brown et al. 1976; Fowler et al. 1977). In a 12-week oral

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gavage study, rats dosed with 1.5 mg/kg/day sodium arsenite had a median final body weight 18% lower than controls Dhar et al. (2005). A 60-day rat study with sodium arsenite in the drinking water reported a 13% reduction in final body weight in rats dosed with approximately 0.02 mg As/kg/day (Bashir et al. 2006). In chronic rat studies of arsenate and arsenite, body growth decreases were found at doses as low as 2 mg As/kg/day in feeding studies (Byron et al. 1967; Kroes et al. 1974), while rats exposed to lower levels of sodium arsenite in the drinking water (0.6 mg As/kg/day) throughout their lifetimes grew normally (Schroeder et al. 1968). Rats given a single oral dose of 100 mg As/kg as GaAs exhibited a 15% reduction in body weight compared to controls 7 days after exposure (Flora et al. 1998). Body weight gain was decreased in mice at 24 mg As/kg/day in a gestation exposure study (Nemec et al. 1998), 10 mg As/kg/day in a 6-week study (Fowler and Woods 1979), and 1 mg As/kg/day in a 2-year study (Schroeder and Balassa 1967). Growth was unaffected in mice that received 12 mg As/kg/day in the gestation exposure study (Nemec et al. 1998), 5 mg As/kg/day in the 6-week study (Fowler and Woods 1979), or 0.7–0.8 mg As/kg/day in 1–3 month arsenate drinking water studies (Healy et al. 1998). Dogs chronically treated with 2.4 mg As/kg/day as sodium arsenite lost 44–61% of their starting body weight and died, while lower doses had no effect on growth (Byron et al. 1967). Weight depression was also reported in dogs chronically treated with 2.4 mg As/kg/day as sodium arsenate (Byron et al. 1967). Feed consumption and body weight gain were significantly reduced in a dose-related manner in dogs fed 1.5 or 1.9 mg As/kg/day as sodium arsenite in the diet (Neiger and Osweiler 1989). Dogs in the high-dose group lost 25% of their body weight over the 17-week study period. Pair-fed controls lost weight at the same rate as high-dose dogs, showing that the effect on body weight was due to reduced feed consumption, rather than a direct effect of arsenic.

Organic Arsenicals. No studies were located regarding body weight effects in humans after oral exposure to organic arsenicals. In animal studies of organic arsenicals, decreases in body weight gain were observed in rats and mice after acute, intermediate, and chronic duration exposure to MMA (Arnold et al. 2003; Waner and Nyska 1988), DMA (Murai et al. 1993), and roxarsone (NTP 1989b); decreases in body weight gain have also been reported in pregnant rats and rabbits exposed to MMA (Irvine et al. 2006) or DMA (Irvine et al. 2006; Rogers et al. 1981). For MMA, the decreases in body weight gain were observed following intermediate-duration exposure of rats and dogs to 106.9 or 8 mg MMA/kg/day (Arnold et al. 2003; Waner and Nyska 1988), respectively, and following chronic-duration exposure of rats, mice, and dogs to 25.7, 67.1, or 8 mg MMA/kg/day, respectively (Arnold et al. 2003; Waner and Nyska 1988). The decreases in body weight gain occurred at doses that were associated with diarrhea and histological alterations in the gastrointestinal tract (Arnold et al. 2003; Waner and Nyska 1988). One DMA study in nonpregnant animals reported decreases in body weight gain in rats administered 57 mg

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DMA/kg/day via gavage 5 days/week for 4 weeks (Murai et al. 1993); other DMA studies have not reported decreases in body weight gain in rats following exposure to 11 mg DMA/kg/day for acute durations (Cohen et al. 2001), 3.7–60 mg DMA/kg/day for intermediate durations (Arnold et al. 1999; Crown et al. 1987; Rubin et al. 1989; Siewicki 1981; Wanibuchi et al. 1996; Yamamoto et al. 1995), or 0.77 mg DMA/kg/day for chronic durations (Arnold et al. 2006). No alterations in body weight gain were observed in mice exposed to 94 mg DMA/kg/day for 2 years (Arnold et al. 2006). The lowest doses of roxarsone to produce a decrease in growth were 32 and 16 mg/kg/day in rats following acute- or intermediate-duration exposure, respectively, and 168 and 136 mg/kg/day in mice following acute or intermediate exposure (NTP 1989b); at the highest dose tested in chronic studies, no significant alterations in body weight gain were observed in rats at 4 mg/kg/day or in mice at 43 mg/kg/day (NTP 1989b).

3.2.2.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to inorganic arsenicals. No evidence of immunosuppression was detected in mice exposed to arsenate at levels up to 100 ppm (20 mg As/kg/day) in drinking water (Kerkvliet et al. 1980). This NOAEL is shown in Table 3-3 and Figure 3-3. Gallium arsenide at doses of 52–260 mg As/kg/day produced significant, dose-related decreases in relative spleen weight, spleen cellularity, humoral immune response (antibody forming cell response to sheep RBC), and delayed type hypersensitivity in rats (Flora et al. 1998). However, it is not clear to what extent these effects are due to the arsenic moiety.

Organic Arsenicals. No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to organic arsenicals. No histological alterations were observed in immunological or lymphoreticular tissues following intermediate-duration exposure of rats to 43.2 mg DMA/kg/day in the diet (Crown et al. 1987) or rats and mice to 18.23 or 38.7 mg As/kg/day as roxarsone, respectively (NTP 1989b) or following chronic-duration exposure of rats and mice to 72.4 or 67.1 mg MMA/kg/day (Arnold et al. 2003), 7.8 or 94 mg DMA/kg/day (Arnold et al. 2006), or 4 or 43 mg/kg/day roxarsone (NTP 1989b). No studies examined immune function following oral exposure to organic arsenicals.

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3.2.2.4 Neurological Effects

Inorganic Arsenicals. A large number of epidemiological studies and case reports indicate that ingestion of inorganic arsenic can cause injury to the nervous system. Acute, high-dose exposures (2 mg As/kg/day or above) often lead to encephalopathy, with signs and symptoms such as headache, lethargy, mental confusion, hallucination, seizures, and coma (Armstrong et al. 1984; Bartolome et al. 1999; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Quatrehomme et al. 1992; Uede and Furukawa 2003; Vantroyen et al. 2004). Repeated exposures to lower levels (0.03–0.1 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Chakraborti et al. 2003a, 2003b; Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Lewis et al. 1999; Mizuta et al. 1956; Muzi et al. 2001; Silver and Wainman 1952; Szuler et al. 1979; Wagner et al. 1979). This neuropathy usually begins as numbness in the hands and feet, but later may develop into a painful "pins and needles" sensation. Both sensory and motor nerves are affected, and muscle weakness often develops, sometimes leading to wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). Diminished sensitivity to stimulation and abnormal patellar reflexes have also been reported (Mizuta et al. 1956). Histological examination of nerves from affected individuals reveals a dying-back axonopathy with demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). Some recovery may occur following cessation of exposure, but this is a slow process and recovery is usually incomplete (Fincher and Koerker 1987; Le Quesne and McLeod 1977; Murphy et al. 1981). Peripheral neuropathy is also sometimes seen following acute high-dose exposures, with or without the previously described encephalopathy (Armstrong et al. 1984; Baker et al. 2005; Fincher and Koerker 1987; Goebel et al. 1990; Hantson et al. 1996; Kamijo et al. 1998). Neurological effects were not generally found in populations chronically exposed to doses of 0.006 mg As/kg/day or less (EPA 1981b; Harrington et al. 1978; Hindmarsh et al. 1977), although fatigue, headache, dizziness, insomnia, nightmare, and numbness of the extremities were among the symptoms reported at 0.005, but not 0.004 mg As/kg/day in a study of 31,141 inhabitants of 77 villages in Xinjiang, China (Lianfang and Jianzhong 1994), and depression was reported in some Wisconsin residents exposed to 2–10 µg As/L in the drinking water for 20 years or longer (Zierold et al. 2004).

There is emerging evidence suggesting that exposure to arsenic may be associated with intellectual deficits in children. For example, Wasserman et al. (2004) conducted a cross-sectional evaluation of intellectual function in 201 children 10 years of age whose parents were part of a larger cohort in Bangladesh. Intellectual function was measured using tests drawn from the Wechsler Intelligence Scale for Children; results were assessed by summing related items into Verbal, Performance, and Full-Scale

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raw scores. The mean arsenic concentration in the water was 0.118 mg/L. The children were divided into four exposure groups, representing <5.5, 5.6–50, 50–176, or 177–790 µg As/L drinking water. After adjustment for confounding factors, a dose-related inverse effect of arsenic exposure was seen on both Performance and Full-Scale subset scores; for both end points, exposure to ≥ 50 µg/L resulted in statistically significant differences ($p < 0.05$) relative to the lowest exposure group (<5.5 µg/L). In a later report, the same group of investigators examined 301 6-year-old children from the same area (Wasserman et al. 2007). In this case, the children were categorized into the following quartiles based on water arsenic concentration: 0.1–20.9, 21–77.9, 78–184.9, and 185–864 µg/L. After adjustment for water Mn, blood lead, and sociodemographic features known to contribute to intellectual function, water arsenic was significantly negatively associated with both Performance and Processing speed raw scores. Analyses of the dose-response showed that compared to the first quartile, those in the second and third categories had significantly lower Performance raw scores ($p < 0.03$ and $p = 0.05$, respectively). Those in the fourth category had marginally significantly lower Full-Scale and Processing Speed raw scores. It should be mentioned, however, that in general, arsenic in the water explained <1% of the variance in test scores. Water arsenic made no contribution to IQ outcomes. A study of 351 children age 5–15 years from West Bengal, India, found significant associations between urinary arsenic concentrations and reductions in scores of tests of vocabulary, object assembly, and picture completion; the magnitude of the reductions varied between 12 and 21% (von Ehrenstein et al. 2007). In this cohort, the average lifetime peak arsenic concentration in well water was 0.147 mg/L. However, no clear pattern was found for increasing categories of peak arsenic water concentrations since birth and children's scores in the various neurobehavioral tests conducted. Furthermore, using peak arsenic as a continuous variable in the regression models also did not support an adverse effect on the tests results. Exposure to arsenic *in utero* also did not suggest an association with the tests scores. Von Ehrestein et al. (2007) concluded that the study provided little evidence for an effect of long-term arsenic concentrations in drinking water and that the lack of findings with past exposures via drinking water may be due to incomplete assessment of past exposure, particularly exposure originating from food. Wasserman's results are consistent with those of ecological studies in children in Taiwan (Tsai et al. 2003) and in China (Wang et al. 2007). In the former, adolescents exposed to low (0.0017–0.0018 mg As/kg/day; $n=20$) levels of inorganic arsenic in the drinking water showed decreased performance in the switching attention task, while children in the high exposure group (0.0034–0.0042 mg As/kg/day; $n=29$) showed decreased performance in both the switching attention task and in tests of pattern memory, relative to unexposed controls ($n=60$). In the study in China (age 8–12 years), 87 children whose mean arsenic concentration in the drinking water was 0.190 mg/L had a mean IQ score of 95 compared with 101 for children ($n=253$) with 0.142 mg/L arsenic in the water and 105 for control children ($n=196$) with 0.002 mg/L arsenic in the drinking water (Wang et

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al. 2007). The differences in IQ scores between the two exposure groups and the control group were statistically significant.

Neurological effects have also been observed in animal studies. Rodriguez et al. (2001) evaluated neurobehavioral changes in male Sprague-Dawley rats exposed to 0, 5, 10, or 20 mg As/kg/day as sodium arsenite by gavage for 2 or 4 weeks; significant effects were seen in spontaneous locomotor activity and the food pellet manipulation test in the high-dose animals, while no effects were seen in the low- or mid-dose rats. Decreased performance in open field tests were also seen in rats exposed to 26.6 mg As/kg/day, but not to 13.3 mg/kg/day or less, as sodium arsenite for 4 weeks (Schulz et al. 2002); curiously, the behavioral changes were no longer present at 8 and 12 weeks of exposure, which may suggest an adaptive response. Heywood and Sortwell (1979) reported salivation and uncontrolled head shaking in two monkeys given several doses of 6 mg As/kg/day as arsenate, while no such effects were noted in monkeys given 3 mg As/kg/day for 2 weeks. Nemec et al. (1998) observed ataxia and prostration in pregnant female rabbits treated with 1.5 mg As/kg/day repeatedly during gestation, but not in rabbits treated with 0.4 mg As/kg/day. Some changes in levels of neurotransmitters (dopamine, norepinephrine, and 5-hydroxytryptamine) were seen in rats exposed to 2.3 mg As/kg/day as sodium arsenite and guinea pigs exposed to 1.7 mg As/kg/day as sodium arsenite in the drinking water for 16 weeks (Kannan et al. 2001) or in rats exposed to 0.14 mg As/kg/day as sodium arsenite by gavage for 28 days (Chattopadhyay et al. 2001), but the functional significance of these changes is not clear.

The highest NOAEL values and all reliable LOAEL values for neurological effects from inorganic arsenic in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

Organic Arsenicals. Numbness and tingling of the fingertips, toes, and circumoral region were reported by a woman exposed to an unspecified amount of organic arsenic in bird's nest soup. Discontinuation of exposure resulted in the disappearance of symptoms (Luong and Nguyen 1999). Decreased absolute brain weights were seen in male rats exposed to 25.7 mg MMA/kg/day and female rats exposed to ≥ 33.9 mg MMA/kg/day, but decreased body weight also occurred at these exposure levels, and relative brain weights were increased in the males at 25.7 mg MMA/kg/day and the females at ≥ 33.9 mg MMA/kg/day in this study (Arnold et al. 2003). No neurological clinical signs or brain lesions were observed following chronic exposure of rats to 72.4 mg MMA/kg/day or mice to 67.1 mg MMA/kg/day (Arnold et al. 2003). Decreased spontaneous motility, increased startle response, and ataxia were observed in mice receiving a single gavage dose of 1,757 mg DMA/kg/day (Kaise et al. 1989); no other evidence (clinical signs or histological alterations) were observed in chronic studies of DMA in which

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rats and mice were exposed to 7.8 or 94 mg DMA/kg/day, respectively (Arnold et al. 2006). Two studies in pigs indicate that repeated oral doses of roxarsone (6.3–20 mg/kg/day for 1 month) can cause significant neurotoxicity (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). The main signs were time-dependent degenerations of myelin and axons (Kennedy et al. 1986; Rice et al. 1985). Evidence of neurological effects (hyperexcitability, ataxia, trembling) was noted in some rat and mouse studies (Kerr et al. 1963; NTP 1989b). Reliable NOAELs and LOAELs are presented in Tables 3-4, 3-5, and 3-6, and Figures 3-4, 3-5, and 3-6.

3.2.2.5 Reproductive Effects

Inorganic Arsenicals. Exposure to arsenic in drinking water has been associated with adverse reproductive outcomes in some studies. For example, a study of 96 women in Bangladesh who had been drinking water containing ≥ 0.10 mg As/L (approximately 0.008 mg As/kg/day) for 5–10 years reported a significant increase in spontaneous abortions ($p=0.008$), stillbirth ($p=0.046$), and preterm birth ($p=0.018$) compared to a nonexposed group (Ahmad et al. 2001). Similar results were reported by Milton et al. (2005) who found a significant association between concentrations of arsenic in the water >0.05 mg/L (approximately 0.006 mg As/kg/day) and spontaneous abortion (odds ratio [OR]=2.5; 95% CI=1.5–4.3) in a study of 533 women, also from Bangladesh. A study of 202 women from West Bengal, India, reported that exposure to arsenic concentrations of arsenic ≥ 0.2 mg/L in drinking water (approximately 0.02 mg As/kg/day) during pregnancy were associated with a 6-fold increased risk of stillbirth (OR=6.1; 95% CI=1.54–24.0) after adjustment for confounders (von Ehrenstein et al. 2006). No association was found between arsenic exposure and risk of spontaneous abortion (OR=1.01; 95% CI=0.73–10.8). An earlier study of 286 women in the United States also found no significant association between arsenic in the drinking water (0.0016 mg/L; approximately 0.00005 mg As/kg/day) and spontaneous abortion (OR=1.7; 95% CI=0.7–4.2) (Aschengrau et al. 1989).

Lugo et al. (1969) reported a case of a 17-year-old mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at week 30 of pregnancy. Twenty-four hours after ingestion of approximately 30 mL of arsenic trioxide (0.39 mg As/kg), she was admitted for treatment of acute renal failure. She went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated and she died at 11 hours of age.

Reproductive performance was not affected in female rats that received gavage doses of 8 mg As/kg/day (as As₂O₃) from 14 days prior to mating through gestation day 19 (Holson et al. 2000). Reproductive

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indices that were evaluated included the precoital interval (time to mating), mating index (percentage of rats mated), and fertility index (percentage of matings resulting in pregnancy). In a 3-generation study in mice given sodium arsenite in drinking water at an average dose of 1 mg As/kg/day, there was a significant increase in the incidence of small litters and a trend toward a decreased number of pups per litter in all three generations of the treated group (Schroeder and Mitchener 1971). This finding is consistent with the results of developmental toxicity studies reported in Section 3.2.2.6. Female rats exposed to 0.24 mg As/kg/day (as arsenite) for 28 days showed changes in several reproductive system end points, including decreases in wet weights of the ovary and uterus, inhibition of steroidogenic enzymes, decreased ovarian and uterine peroxidase activities, and decreased estradiol levels relative to controls (Chattopadhyay et al. 2001). NOAEL and LOAEL values from these studies are shown in Table 3-3 and Figure 3-3.

Organic Arsenicals. No studies were located regarding reproductive effects in humans after oral exposure to organic arsenicals. No histological alterations in male or female reproductive tissues were observed in laboratory animals following exposure to MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), or roxarsone (NTP 1989b) and no alterations in sperm parameters were observed in male rats exposed to 76 mg MMA/kg/day for at least 14 weeks (Schroeder 1994). However, some functional alterations have been reported in animals exposed to MMA or DMA. A decrease in estrus was observed in dogs exposed to 35 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988); decreases in body weight gain (terminal body weight was 59% lower than controls) were also observed at this dose level and the effect may have been secondary to systemic toxicity. Decreases in pregnancy rate and male fertility index were observed in F₀ and F₁ rats exposed to 76 mg MMA/kg/day for 14 weeks prior to mating and during the mating, gestation, and lactation periods (Schroeder 1994). In the F₀ animals, the pregnancy rate and male fertility index were not statistically different from controls; however, the values were below historical controls and the investigators considered the effect to be treatment-related. In the F₁ animals, the male fertility index was statistically different from controls but the pregnancy rate was not; both parameters were within the range found in historical controls, but the investigators considered the effect to be treatment-related due to the consistency of the findings in the F₀ and F₁ animals. Impaired fertility, as evidenced by a decreased number of litters, was observed in male mice dosed with MSMA (119 mg/kg/day) during a 19-day mating period with unexposed females (Prukop and Savage 1986); the poor reporting of the study protocol and results precludes drawing conclusions from this study. An increase in the number of does with aborted fetuses was observed in rabbits exposed to 48 mg DMA/kg/day as DMA (Irvine et al. 2006); severe maternal toxicity (weight loss, reduced food intake, and

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diarrhea) was also observed at this dose level. No reproductive effects were observed in a 2-generation rat study in which rats were exposed to 16.5 mg DMA/kg/day (Rubin et al. 1989).

3.2.2.6 Developmental Effects

Inorganic Arsenicals. Whether ingestion of inorganic arsenic may cause developmental effects in humans has not been extensively investigated. Lugo et al. (1969) reported a case of a mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at 30 weeks of gestation. Twenty-four hours after ingestion, she went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated with frequent episodes of apnea and bradycardia; subsequent venous blood gas determinations documented hypoxia, hypercapnea, and acidosis. The infant died at 11 hours of age. Autopsy performed 8 hours after death showed organ immaturity, generalized petechial hemorrhages, and hyaline membrane disease. Severe intra-alveolar pulmonary hemorrhage was remarkable. High arsenic levels were found in the infant's liver, kidney, and brain, demonstrating easy passage of inorganic arsenic across the placenta. The authors considered most of the findings in the neonate to be attributable to immaturity, but suggested that arsenic may have played a role in the severe intra-alveolar hemorrhaging that contributed to death.

Chronic exposure of women to arsenic in the drinking water has been associated with infants with low birth weights in Taiwan (Yang et al. 2003) and Chile (Hopenhayn et al. 2003a). Similar associations have been made between late fetal mortality, neonatal mortality, and postneonatal mortality and exposure to high levels of arsenic in the drinking water (up to 0.86 mg/L during over a decade), based on comparisons between subjects in low- and high-arsenic areas of Chile (Hopenhayn-Rich et al. 2000). More recently, von Ehrenstein et al. (2006) reported no significant association between exposure to concentrations of ≥ 0.1 mg/L arsenic in drinking water (approximately 0.008 mg As/kg/day) ($n=117$; 29 women were exposed to ≥ 0.5 mg/L) and increased risk for neonatal death or infant mortality during the first year of life in a study of a population in West Bengal, India. The same group of investigators reported significantly increased SMRs for lung cancer and bronchiectasis among subjects in a city in Chile who had probable exposure *in utero* (maternal exposure) or during childhood to high levels of arsenic (near 0.9 mg/L) in the drinking water (Smith et al. 2006). For those exposed in early childhood, the SMR for lung cancer was 7.0 (95% CI=5.4–8.9, $p<0.001$) and for bronchiectasis 12.4 (95% CI=3.3–31.7, $p<0.001$). For those born during the high-exposure period, the corresponding SMRs were 6.1 (95% CI=3.5–9.9, $p<0.001$) and 46.2 (95% CI=21.1–87.7, $p<0.001$). The mortality data analyzed were for the age range 30–49 years.

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No overall association between arsenic in drinking water and congenital heart defects was detected in a case-control study in Boston (Zierler et al. 1988), although an association with one specific lesion (coarctation of the aorta) was noted (OR=3.4, 95% CI=1.3–8.9). A study of 184 women with neural tube defects in the offspring living in a Texas county bordering Mexico found that exposure to levels of arsenic in the drinking water >0.010 mg/L (range or upper limit not specified) did not significantly increase the risk for neural tube defects (OR=2.0, 95% CI=0.1–3.1) (Brender et al. 2006).

Studies in animals, however, suggest that ingested inorganic arsenic may produce developmental effects at high doses that also produce overt maternal toxicity. Rats treated with a single gavage dose of 23 mg As/kg as arsenic trioxide on day 9 of gestation had a significant increase in postimplantation loss and a decrease in viable fetuses per litter, while those treated with 15 mg As/kg showed no effects (Stump et al. 1999). Rats treated by daily gavage with 8 mg As/kg/day starting 14 days before mating and continuing through gestation had significantly reduced fetal body weights and significantly increased incidences of several skeletal variations (unossified sternebrae #5 or #6, slight or moderate sternebrae malalignment, 7th cervical ribs) that the researchers considered to be consequences of developmental growth retardation (Holson et al. 2000). No developmental effects were found at 4 mg As/kg/day in this study. Exposure of rats to 2.93–4.20 mg As/kg/day throughout gestation and for 4 months postnatally resulted in alterations in neurobehavioral parameters in the offspring, including increased spontaneous locomotor activity and number of errors in a delayed alternation task; maternal behavior was not affected (Rodriguez et al. 2002). Studies in mice found increased fetal mortality, decreased fetal body weight, a low incidence of gross malformations (primarily exencephaly), and an increase in skeletal malformations in mice given single gavage doses of 23–48 mg As/kg during gestation (Baxley et al. 1981; Hood et al. 1978), with no effects at 11 mg As/kg. Similarly, in mice treated with 24 mg As/kg/day as arsenic acid on days 6–15 of gestation, there was a significant increase in the number of resorptions per litter (42% vs. 4% in controls) and significant decreases in the number of live pups per litter (6.6 vs. 12.3 in controls) and mean fetal weight (1.0 g vs. 1.3 g in controls), while no developmental effects were found at 12 mg As/kg/day (Nemec et al. 1998). Hamsters treated with a single gavage dose of 14 mg As/kg during gestation also had increased fetal mortality and decreased fetal body weight (Hood and Harrison 1982), with no effect at 11 mg As/kg. However, the most sensitive species was the rabbit, which had increased resorptions and decreased viable fetuses per litter at 1.5 mg As/kg/day and a developmental NOAEL of 0.4 mg As/kg/day, following repeated gavage dosing with arsenic acid during gestation (Nemec et al. 1998). In each of these studies (except Hood et al. 1978, which failed to report maternal effects), overt maternal toxicity, including death in some cases, was found at the same or lower doses as the developmental

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effects (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Nemec et al. 1998; Stump et al. 1999).

It is noteworthy that the effect in the 3-generation reproduction study in mice by Schroeder and Mitchener (1971), decreased pups per litter (all generations), is consistent with the findings of many of these shorter-term studies (Baxley et al. 1981; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). The dose in this long-term study was 1 mg As/kg/day; in a 2-year study by these researchers, this dose produced effects such as decreased body weight gain and increased mortality (Schroeder and Balassa 1967).

A series of studies presented evidence that inorganic arsenic may be a transplacental carcinogen in animals. Waalkes et al. (2003, 2004a, 2004b, 2004c) exposed timed-pregnant AJ mice to 0, 42.5, or 85 ppm of sodium arsenite in the drinking water from gestation day 8 through 18 and observed the offspring for 90 weeks following birth; the study authors estimated daily doses at 9.55 and 19.3 mg As/kg/day. A dose-related increase was reported in the incidence of hepatocellular carcinomas and adrenal tumors in the male offspring from both treatment levels, while male offspring from high-dose animals showed an increase in total number of tumors. In female offspring, an increase in uterine hyperplasia was seen in the offspring of both treated groups while the offspring of high-dose animals showed increased incidence of lung carcinomas. For both exposed groups, regardless of gender, the offspring showed a significant increase in the number of malignant tumors (Waalkes et al. 2003). More recent studies from the same group of investigators have suggested that aberrant estrogen signaling, potentially through inappropriate estrogen receptor- α (ER- α), may play a role in arsenic-induced liver tumors in male offspring (Waalkes et al. 2006a) and in arsenic-induced uterine and bladder carcinoma in female offspring (Waalkes et al. 2006b). The latter was based on the observation of over-expression of ER- α and *pS2*, an estrogen-regulated gene, in the respective tissues.

These studies (shown in Table 3-3 and Figure 3-3) indicate that the fetus may be affected by ingested arsenic.

Organic Arsenicals. No studies were located regarding developmental effects in humans after oral exposure to organic arsenicals. The developmental toxicity of organic arsenicals has been investigated in rats and rabbits for MMA and in rats, mice, and rabbits for DMA. Decreased fetal weights and an increased incidence of fetuses with incomplete ossification of thoracic vertebrae were observed in the offspring of rats administered via gavage 500 mg MMA/kg/day on gestational days 6–15; no

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developmental effects were observed at 100 mg MMA/kg/day (Irvine et al. 2006). Decreases in maternal body weight gain were observed at 100 and 500 mg MMA/kg/day. A decrease in pup survival was observed in F₁ and F₂ offspring of rats exposed to 76 mg MMA/kg/day (Schroeder 1994); although pup survival was not statistically different from controls, the investigators considered the effect to be biologically significant because survival in the MMA pups was outside the lower range of survival in historical controls. Increases in the number of fetuses with supernumerary thoracic ribs and eight lumbar vertebrae were observed in the offspring of rabbits administered to 12 mg MMA/kg/day on gestational days 7–19 (Irvine et al. 2006); the investigators noted that these effects were probably secondary to maternal stress.

No developmental effects were observed in the offspring of rats administered via gavage 15 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981). At 30 mg DMA/kg/day, there was an increase in the percentage of fetuses with irregular palatine rugae; no maternal effects were observed at this dose level (Rogers et al. 1981). The investigators noted that the functional significance of aberrant rugae in rats is not known. Doses of ≥ 36 mg DMA/kg/day resulted in decreases in fetal weights and delays in ossification (Chernoff et al. 1990; Irvine et al. 2006; Rogers et al. 1981); decreases in maternal body weight gain were often observed at the same dose levels. Irvine et al. (2006) also reported an increase in the occurrence of diaphragmatic hernia in the offspring of rats exposed to 36 mg DMA/kg/day as DMA on gestational days 6–15. Mice appear to be less sensitive than rats to the developmental toxicity of DMA. No developmental effects were observed in the offspring of mice administered 200 mg DMA/kg/day on gestational days 7–16 (Rogers et al. 1981); at higher doses, decreases in fetal body weight, delays in ossification, and cleft palate were observed (Kavlock et al. 1985; Rogers et al. 1981). In rabbits, a NOAEL of 12 mg DMA/kg/day was identified (Irvine et al. 2006); at 48 mg DMA/kg/day, there were increased maternal deaths and abortions.

3.2.2.7 Cancer

Inorganic Arsenicals. There is convincing evidence from a large number of epidemiological studies and case reports that ingestion of inorganic arsenic increases the risk of developing skin cancer (Alain et al. 1993; Beane Freeman et al. 2004; Bickley and Papa 1989; Cebrián et al. 1983; Chen et al. 2003; Guo et al. 2001a; Hauptert et al. 1996; Hsueh et al. 1995; Lewis et al. 1999; Lühtrath 1983; Mitra et al. 2004; Morris et al. 1974; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; Tsai et al. 1998a, 1999; Tseng 1977; Tseng et al. 1968; Zaldivar 1974; Zaldivar et al. 1981). Lesions commonly observed are multiple squamous cell carcinomas, some of which appear to develop from the

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hyperkeratotic warts or corns described in Section 3.2.2.2. In addition, multiple basal cell carcinomas may occur, typically arising from cells not associated with hyperkeratinization. In most cases, skin cancer develops only after prolonged exposure, but one study has reported skin cancer in people exposed for <1 year (Reymann et al. 1978). Although both types of skin cancer can be removed surgically, they may develop into painful lesions that may be fatal if left untreated (Shannon and Strayer 1989).

A number of studies that identify CELs in exposed humans are summarized in Table 3-3 and shown in Figure 3-3. The EPA reviewed the studies that provided dose-response data on the risk of skin cancer (EPA 1988d) and concluded that the most useful study for the purposes of quantitative risk assessment was the ecologic epidemiology study by Tseng et al. (1968). In this study, the incidence of skin cancer was measured as a function of exposure level in over 40,000 people residing in 37 villages in Taiwan, and compared to a control group of over 7,500 people. Beyond the very large sample size, other strengths of this study include excellent case ascertainment (physical examination), inclusion of both males and females, and lifetime exposure duration. Weaknesses and uncertainties include poor nutritional status of the exposed populations, their genetic susceptibility, their exposure to inorganic arsenic from nonwater sources, and the applicability of extrapolating data from Taiwanese to the U.S. population because of different background rates of cancer, possibly genetically determined, and differences in diet other than arsenic (e.g., low protein and fat and high carbohydrate) (EPA 1988d). Because of a lack of information on the amount of individual exposure, subjects were classified into three exposure groups (i.e., high, medium, and low). Based upon pooled data for skin cancer incidence and average well concentrations for each village in the Tseng et al. (1968) study, the EPA calculated a unit risk (the upper-bound excess cancer risk from lifetime exposure to water containing 1 $\mu\text{g As/L}$) of 5×10^{-5} (IRIS 2007). The average daily doses (expressed as mg As/kg/day) that correspond to excess cancer risks of 1×10^{-4} – 1×10^{-7} are shown in Figure 3-3.

The use of a cancer risk estimate derived from the Tseng et al. (1968) study for a U.S. population has been the source of intense debate. Some have argued and have provided data in support of the view that there is persuasive evidence that inorganic arsenic is a cause of human cancer at several sites (i.e., Smith et al. 1992, 1995, 2002). On the other hand, a number of concerns have been raised regarding the strength, or lack of strength, of the database, including: the adequacy of the model used by EPA and the accuracy and reliability of the exposure data (Brown et al. 1997a, 1997b); a number of host and environmental factors among the Taiwanese not applicable elsewhere (Carlson-Lynch et al. 1994); a possible threshold for arsenic carcinogenicity and nonlinearities in the dose-response curve (Abernathy et al. 1996; Slayton et al. 1996); differences in health and nutrition between Taiwan and the United States

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that might increase cancer risk in Taiwan (Beck et al. 1995); the possibility that lower doses of arsenic may be beneficial role in some physiological processes (EPA 1988d; FNB/IOM 2001; NRC 1999, 2001); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997). Many of these factors were recognized by EPA (1988d). A report by NRC (2001) suggested that the risks calculated based on increases in incidence of lung and bladder cancers may be greater than those calculated by the EPA based on incidences of skin cancer.

Several early epidemiological studies performed in the United States did not report an increased frequency of skin cancer in small populations consuming water containing arsenic at levels of around 0.1–0.2 ppm (EPA 1981b; Goldsmith et al. 1972; Harrington et al. 1978; Morton et al. 1976). These early data suggested that arsenic-associated skin cancer is not a common problem in this country, but these studies lacked sufficient statistical power to detect small increases in skin cancer incidence that might have occurred at these low doses (EPA 1983g). Later studies in exposed U.S. populations from Utah (Lewis et al. 1999) and Iowa (Beane Freeman et al. 2004) have suggested that arsenic-exposed individuals within the United States may have increased incidence or risk of mortality from some skin cancers, melanoma in particular; however, exposure data from these studies are generally insufficient for dose-response analysis. Another study found a suggestion of an arsenic-induced effect on the development of skin cancer, but the association did not achieve statistical significance (Karagas et al. 2001). Therefore, the risk of arsenic-induced skin cancers in U.S. populations, while it may appear to be less than in some other evaluated populations, may be the reflection that, in most studies, exposures were lower.

In addition to the risk of skin cancer, there is mounting evidence that ingestion of arsenic may increase the risks of internal cancers as well. Many case studies have noted the occurrence of internal tumors of the liver and other tissues in patients with arsenic-induced skin cancer (Falk et al. 1981b; Kasper et al. 1984; Koh et al. 1989; Lander et al. 1975; Regelson et al. 1968; Sommers and McManus 1953; Tay and Seah 1975; Zaldívar et al. 1981). These studies are supported by large-scale epidemiological studies, where associations and/or dose response trends have been detected for tumors of the bladder, kidney, liver, lung, and prostate (Chen and Wang 1990; Chen et al. 1985, 1986, 1988a, 1988b, 1992; Chiou et al. 1995; Cuzick et al. 1992; Ferreccio et al. 1998; Guo et al. 1997; Hopenhayn-Rich et al. 1998; Kurttio et al. 1999; Lewis et al. 1999; Moore et al. 2002; Rivara et al. 1997; Smith et al. 1998; Tsuda et al. 1995a; Wu et al. 1989). The EPA has not yet calculated a unit risk value or slope factor for arsenic-induced internal tumors.

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There is increasingly convincing evidence that long-term exposure to arsenic can result in the development of bladder cancer (Bates et al. 2004; Chen et al. 1992, 2003; Chiou et al. 1995, 2001; Cuzick et al. 1992; Guo et al. 2001b; Karagas et al. 2004; Lamm et al. 2004; Michaud et al. 2004; Steinmaus et al. 2003), with transitional cell cancers being the most prevalent. Chiou et al. (1995) reported a dose-response relationship between long-term arsenic exposure from drinking artesian well water and the incidence of lung cancer, bladder cancer, and cancers of all sites combined (after adjustment for age, sex, and cigarette smoking) in four townships in Taiwan exposed to inorganic arsenic in drinking water (0–1.14 mg/L). In a later followup study of the same cohort, the increase in bladder cancer was found to be statistically significant only in subjects exposed for 40 years or longer (Chiou et al. 2001). Cuzick et al. (1992) evaluated a cohort treated with Fowler's solution (potassium arsenite) in Lancashire, England, during the period 1945–1969 and followed through 1991; the cohort of 478 patients showed a significant excess of bladder cancer, but no excess for other causes of death. Of a subcohort of 142 patients examined for signs of arsenicism around 1970 (Cuzick et al. 1992), all 11 subsequent cancer deaths occurred in those with signs of arsenicism ($p=0.0009$). Hopenhayn-Rich et al. (1996a) investigated bladder cancer mortality for the years 1986–1991 in the 26 counties of Cordoba, Argentina, and reported that bladder cancer SMRs were consistently higher in counties with documented arsenic exposure; a later case-control study by the same authors (Bates et al. 2004) did not report statistically significant increases in bladder cancers resulting from arsenic exposure, except in individuals exposed for 50 years or longer. Guo et al. (2001a) reported significantly increased rate differences for bladder cancer in men and women in Taiwan exposed to 0.64 mg arsenic/L in the drinking water, but not at lower exposure levels. The arsenic-induced bladder tumors do not appear to be histologically different than similar bladder tumor types of nonarsenic origin (Chow et al. 1997), although they tended to be more pronounced. In contrast, Michaud et al. (2004) reported no correlation between arsenic levels in toenails and the incidence of bladder cancers in Finnish workers. Among evaluated U.S. cohorts, there has generally been no association between arsenic exposure (~60–100 $\mu\text{g As/L}$) and the incidence of mortality from bladder cancers (Lamm et al. 2004; Steinmaus et al. 2003), although it is possible that smoking may render individuals more susceptible to arsenic-induced bladder tumors (Karagas et al. 2004; Steinmaus et al. 2003).

Studies have also suggested that chronic oral exposure to arsenic may result in the development of respiratory tumors and increased incidence of lung cancer (Ferreccio et al. 2000; Guo 2004; Nakadaira et al. 2002; Smith et al. 1998; Viren and Silvers 1999). A study of arsenic-exposed individuals in northern Chile reported significantly increased odds ratios for lung cancer among subjects with $\geq 30 \mu\text{g As/L}$ of drinking water (Ferreccio et al. 2000), although when adjusted for socioeconomic status, smoking, and

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other factors, the increase was only significant at 60 $\mu\text{g As/L}$ or greater. Guo (2004) reported significantly increased rates differences (RD) for lung cancer for Taiwanese men and women exposed to 0.64 mg As/L or greater, with those subjects >50 years of age being particularly at risk. Nakadaira et al. (2002) suggested that even comparatively short exposure durations (≤ 5 years) may be sufficient for the development of arsenic-induced lung cancer.

Studies in U.S. populations exposed to arsenic in drinking water (EPA 1981b; Lamm et al. 2004; Lewis et al. 1999; Morton et al. 1976; Steinmaus et al. 2003; Valentine et al. 1992) have not yielded the cancer incidences and health effects noted in Taiwan, Mexico, and Chile. Whether this difference is due to a smaller population of subjects compared to Taiwan, to overall lower doses in exposed U.S. populations, or to differences in nutritional or socioeconomic conditions has not been resolved. It should be noted that exposed populations in Mexico and Chile are also smaller than those in Taiwan.

Most studies of animals exposed to arsenate or arsenite by the oral route have not detected any clear evidence for an increased incidence of skin cancer or other cancers (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Arsenic has sometimes been called a “paradoxical” human carcinogen because of this lack of animal data (Jager and Ostrosky-Wegman 1997). The basis for the lack of tumorigenicity in animals is not known, but could be related to species-specific differences in arsenic distribution, and induction of cell proliferation (Byrd et al. 1996) (see Section 3.5). As discussed in Section 3.5 below, the carcinogenic effects of arsenic may partially result from its function as a cocarcinogen, which would not manifest in most animal carcinogenicity studies.

One mouse study using transgenic mice (which carry the v-Ha-ras oncogene) administered 48 mg As/kg/day as sodium arsenite in drinking water for 4 weeks followed by dermal application of 12-O-tetradecanoylphorbol-13-acetate (TPA) to shaved back skin twice a day for 2 weeks showed an increase in the incidence of skin papillomas when compared to transgenic mice receiving only TPA treatment, only arsenic, or to wild-type mice receiving both TPA and arsenic (Germolec et al. 1998); arsenic treatment alone did not result in increased papilloma incidence. Increases in mRNA transcripts for the growth factors transforming growth factor- α (TGF- α) and granulocyte/ macrophage-colony stimulating factor (GM-CSF) were detected in the epidermis of the arsenic-treated mice.

A few studies in mice have noted that arsenic ingestion may actually decrease the incidence of some tumor types. For example, arsenic exposure caused decreased incidence of urethane-induced pulmonary tumors (Blakley 1987), spontaneous mammary tumors (Schrauzer and Ishmael 1974; Schrauzer et al.

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1976), and tumors resulting from injection of mouse sarcoma cells (Kerkvliet et al. 1980). However, arsenic also increased the growth rate of the tumors that did occur, resulting in a net decrease in survival time in tumor-bearing animals (Kerkvliet et al. 1980; Schrauzer and Ishmael 1974). These observations suggest that arsenic may affect different types of neoplastic cells differently, perhaps acting mainly as a tumor promoter (Schrauzer and Ishmael 1974; Shirachi et al. 1983), although some studies have suggested that arsenic's actions are not consistent with tumor promotion (Baroni et al. 1963; Boutwell 1963).

There is evidence suggesting that inorganic arsenic can induce cancer in the offspring from mice exposed to arsenic during gestation (transplacental carcinogen) (Waalkes et al. 2003, 2004a, 2004b, 2004c, 2006a, 2006b). These studies are summarized in Section 3.2.2.6, Developmental Effects.

Organic Arsenicals. No studies were located regarding cancer in humans after oral exposure to organic arsenicals. Two lifetime carcinogenicity studies with MMA did not find significant increases in tumors in rats exposed to 72.4 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003) or 8.4 mg MMA/kg/day in drinking water for 2 years (Shen et al. 2003). No significant increases in neoplastic lesions were observed in mice exposed to 67.1 mg MMA/kg/day in the diet for 2 years (Arnold et al. 2003).

In contrast, significant increases in the incidence of urinary bladder tumors have been observed in rats exposed for 2 years to 7.8 mg DMA/kg/day in the diet (Arnold et al. 2006) or 3.4 mg DMA/kg/day in drinking water (Wei et al. 1999, 2002). The incidence of bladder tumors was similar to controls in the rats exposed to 0.77 mg DMA/kg/day (Arnold et al. 2006) or 0.75 mg DMA/kg/day (Wei et al. 1999, 2002). Neither study reported significant increases in the incidence of neoplastic lesions in other tissues. Arnold et al. (2006) did not find increases in the incidence of neoplastic lesions in mice exposed to doses as high as 94 mg DMA/kg/day in the diet for 2 years. Hayashi et al. (1998) reported that exposure of A/J mice (a strain susceptible to lung tumorigenesis) to 10.4 mg DMA/kg/day (but not 1.3 or 5.2 mg DMA/kg/day) in drinking water for 50 weeks resulted in an increased incidence of papillary adenomas and/or adenocarcinomas and an increased number of lung tumors per mouse.

The incidence of basophilic foci (believed to be a precancerous lesion) in the liver of rats initiated with diethylnitrosamine was increased by subsequent 6-month drinking water exposure to 11 mg DMA/kg/day, suggesting that this compound could act as a cancer promoter (Johansen et al. 1984). Additional evidence for the possible role of DMA as a promoter comes from Yamamoto et al. (1995), who reported that 15 or 60 mg DMA/kg/day in the drinking water for 24 weeks significantly enhanced the tumor induction in the

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urinary bladder, kidney, liver, and thyroid gland in male F344 rats treated with a series of initiators. Wanibuchi et al. (1996) reported that treatment of F344 rats for 32 weeks with up to 14.3 mg DMA/kg/day DMA in the drinking water did not result in increased incidences of urinary bladder papillomas or carcinomas, but that incidence of these tumors was elevated if the animals were first pretreated with an initiating compound (BBN). A later study by Li et al. (1998) reported that NBR rats (which do not synthesize $\alpha_2\mu$ -globulin) exposed to an initiator for 4 weeks followed by DMA for 32 weeks, similar to the Wanibuchi et al. (1996) study, showed a statistically significant increase in simple hyperplasia and papillary or nodular hyperplasia of the bladder. A study by Salim et al. (2003) suggested that DMA primarily exerts its carcinogenic effects on spontaneous tumor development.

No increases in tumor incidence were observed in rats, mice, or dogs exposed to 10, 13, or 5 mg/kg/day roxarsone, respectively, in the diet for 2 years (Prior et al. 1963). Similarly, no evidence of carcinogenicity was observed in female rats or male or female mice exposed to 4 or 43 mg/kg/day as roxarsone in the diet for 2 years (NTP 1989b). However, a slight increase in pancreatic tumors was noted in male rats exposed to 4 mg/kg/day (NTP 1989b); this was considered to constitute equivocal evidence of carcinogenicity.

3.2.3 Dermal Exposure

Adverse effects from dermal exposure to inorganic or organic arsenicals have not been extensively investigated. Table 3-7 summarizes studies in animals and humans that provide quantitative data on dermal exposure-effect relationships for inorganic arsenicals. No quantitative data on dermal exposure to organic arsenicals were located. Available quantitative and qualitative data are discussed in greater detail below.

3.2.3.1 Death

Inorganic Arsenicals. No studies were located regarding death in humans after dermal exposure to inorganic arsenicals. In rats, no deaths resulted from dermal exposure to arsenate or arsenite at doses up to 1,000 mg As/kg (Gaines 1960). These data indicate that dermal exposure to inorganic arsenic compounds is very unlikely to result in death.

Organic Arsenicals. No studies were located regarding death in humans after dermal exposure to organic arsenicals. No deaths were observed in rabbits receiving daily dermal applications of 540 mg As/kg as

Table 3-7 Levels of Significant Exposure to Inorganic Arsenic - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
ACUTE EXPOSURE							
Immuno/ Lymphoret							
Gn Pig (Hartley)	once		580 mg/L			Wahlberg and Boman 1986 As(+3)	
Gn Pig (Hartley)	once		4000 mg/L			Wahlberg and Boman 1986 As(+5)	
INTERMEDIATE EXPOSURE							
Systemic							
Mouse (Rockland)	30 wk 11 x/wk	Dermal		6 F mg/kg/day	(gross hyperplasia, ulceration)	Boutwell 1963 As(+3)	

F = female; Gn pig = guinea pig; Immuno/Lymphoret = immunological/lymphoreticular; wk = week(s); x = time(s)

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MMA 5 days/week for 21 days (Margitich and Ackerman 1991b) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991a).

3.2.3.2 Systemic Effects

No studies were located that have associated respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans or animals with dermal exposure to inorganic arsenicals.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to organic arsenicals. No histological effects were observed in the respiratory tracts of rabbits following dermal application of 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to organic arsenicals. No histological effects were observed in the hearts of rabbits following dermal application of 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to organic arsenicals. No treatment-related hematological alterations were observed in rabbits receiving dermal applications of 1,000 mg MMA/kg/day (Margitich and Ackerman 1991a) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991b).

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to organic arsenicals. No significant alterations in blood clinical chemistry, liver weights, or histopathology were observed in rabbits dermally exposed to 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to organic arsenicals. No significant alterations in urinalysis, kidney weights, or histopathology were observed in rabbits following dermal exposure to 1,000 mg MMA/kg/day (Margitich and Ackerman 1991a) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991b).

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Endocrine Effects. No studies were located regarding endocrine effects in humans after dermal exposure to organic arsenicals. No alterations in adrenal gland weight or histopathology of the adrenal glands, pancreas, pituitary gland, thyroid gland, and parathyroid gland were observed in rabbits following dermal application of 1,000 mg/kg/day MMA or DMA 5 days/week for 21 days (Margitich and Ackerman 1991a, 1991b).

Dermal Effects.

Inorganic Arsenicals. Several studies of humans exposed to arsenic dusts in the workplace have reported that inorganic arsenic (usually arsenic trioxide) can cause contact dermatitis (Holmqvist 1951; Pinto and McGill 1953). Typical responses included erythema and swelling, with papules and vesicles in more severe cases (Holmqvist 1951). The dermal contact rates that cause these effects in humans have not been quantified, but a similar direct irritation of the skin has been noted in mice exposed to 4 mg As/kg/day as potassium arsenite for 30 weeks (Boutwell 1963). In contrast, no significant dermal irritation was noted in guinea pigs exposed to aqueous solutions containing 4,000 mg As/L as arsenate or 580 mg As/L as arsenite (Wahlberg and Boman 1986). These studies indicate that direct contact may be of concern at high exposure levels, but do not suggest that lower levels are likely to cause significant irritation.

Studies on possible dermal sensitization by inorganic arsenicals are discussed in Section 3.2.3.3 below.

Organic Arsenicals. Contact dermatitis was reported in workers involved in the application of an organic arsenical herbicide, which is a mixture of DMA and its sodium salt (Peoples et al. 1979).

Application of an unspecified amount of MMA to the skin of rabbits was reported to result in mild dermal irritation in a Draize test (Jaghabir et al. 1988). No dermal irritation was reported in rabbits repeatedly exposed to 1,000 mg MMA/kg/day (Margitich and Ackerman 1991a) or 1,000 mg DMA/kg/day 5 days/week for 21 days (Margitich and Ackerman 1991b).

Ocular Effects. No studies were located regarding ocular effects in humans or animals after dermal exposure to organic arsenicals.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to organic arsenicals. No significant alterations in body weight gain were observed in rabbits

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following a 5 day/week exposure to 1,000 mg/kg/day MMA or DMA for 21 days (Margitich and Ackerman 1991a, 1991b).

3.2.3.3 Immunological and Lymphoreticular Effects

Inorganic Arsenicals. Examination of workers exposed to arsenic trioxide dusts in a copper smelter led Holmqvist (1951) to suspect that repeated dermal contact could lead to dermal sensitization. In support of this, Holmqvist (1951) found a positive patch test in 80% of the exposed workers compared to 30% in a control population. These data do suggest that workers may be sensitized to arsenic, but the high response rate in controls seems unusual. A much lower response rate (0.5%) was noted in another patch test study of dermal sensitization (Wahlberg and Boman 1986), and the few positive responses seemed to be due to a cross-reactivity with nickel. Mohamed (1998) evaluated 11 male workers at a tin smelting factory where arsenic trioxide levels ranged from 5.2 to 14.4 mg/m³. The workers experienced symptoms of generalized itch, dry and hyperpigmented skin, folliculitis, and superficial ulcerations. The authors concluded that arsenic-containing dust collected on the sweat on the workers' skin, causing contact dermatitis. Studies in guinea pigs did not yield evidence of a sensitization reaction to inorganic arsenic (Wahlberg and Boman 1986).

Organic Arsenicals. Support for sensitization to DMA is provided in a case report of a 26-year-old woman who was occupationally exposed to DMA and experienced eczema on her face (Bourrain et al. 1998). Patch testing confirmed an allergic reaction to DMA, and avoidance of DMA resulted in disappearance of the symptoms. No studies were located regarding immunological or lymphoreticular effects in animals after dermal exposure to organic arsenicals.

No studies were located that have associated any of the following effects in humans or animals with dermal exposure to inorganic or organic arsenicals:

3.2.3.4 Neurological Effects**3.2.3.5 Reproductive Effects****3.2.3.6 Developmental Effects****3.2.3.7 Cancer**

Inorganic Arsenicals. No studies were found that have associated cancer in humans with dermal exposure to arsenic. Application of arsenic acid to the skin of mice pretreated with dimethylbenz-

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anthracene did not result in any skin tumors (Kurokawa et al. 1989), suggesting that arsenic does not act as a promoter in this test system.

Organic Arsenicals. No studies were located regarding cancer in humans or animals after dermal exposure to organic arsenicals.

3.3 GENOTOXICITY

Inorganic Arsenicals. There have been a large number of studies of the genotoxic effects of arsenic. Tables 3-8 and 3-9 summarize a number of reports on the *in vitro* and *in vivo* genotoxicity of inorganic arsenicals, respectively. In general, *in vitro* studies in prokaryotic organisms have been negative for gene mutations (Lantzsch and Gebel 1997; Löfroth and Ames 1978; Nishioka 1975; Rossman et al. 1980; Ulitzur and Barak 1988). Studies in human fibroblasts, lymphocytes, and leukocytes, mouse lymphoma cells, Chinese hamster ovary cells, and Syrian hamster embryo cells demonstrate that *in vitro* arsenic exposure can induce chromosomal aberrations and sister chromatid exchange (see Table 3-8 for citations). *In vitro* studies in human, mouse, and hamster cells have also been positive for DNA damage and repair and enhancement or inhibition of DNA synthesis.

Studies of humans have detected a higher-than-average incidence of chromosomal aberrations in peripheral lymphocytes, both after inhalation exposure (Beckman et al. 1977; Nordenson et al. 1978) and oral exposure (Burgdorf et al. 1977; Nordenson et al. 1979). These studies must be interpreted with caution, since in most cases, there were only a small number of subjects and a number of other chemical exposures were possible (EPA 1984a). Human and animal data are available indicating that inhaled inorganic arsenic is clastogenic. Workers exposed to unspecified concentrations of arsenic trioxide at the Ronnskar copper smelter in Sweden were found to have a significant increase in the frequency of chromosomal aberrations in peripheral lymphocytes (Beckman et al. 1977; Nordenson et al. 1978). This result is supported by an animal study that found increased chromosomal aberrations in the livers of fetuses from pregnant mice exposed to 22, but not 2.2 or 0.20, mg As/m³ as arsenic trioxide on days 9–12 of gestation (Nagymajtényi et al. 1985). Workers in the arsenic-based glass making industry in southern India had a significantly increased frequency of micronuclei in buccal cells and increased DNA damage in leukocytes compared to a control group (Vuyyuri et al. 2006). Exposure levels were not available, but the concentration of arsenic in the blood from workers was approximately 5 times higher than in the reference group.

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Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
As ⁺³	<i>Escherichia coli</i>	Reverse mutation	No data	+	Nishioka 1975
As ⁺³	<i>E. coli</i> PQ37	Gene mutation	No data	–	Lantzsch and Gebel 1997
As ⁺³	<i>E. coli</i> (six strains)	Reverse mutation	No data	–	Rossman et al. 1980
As ⁺³	<i>Salmonella typhimurium</i>	Gene mutation	No data	–	Löfroth and Ames 1978
As ⁺³	<i>Photobacterium fischeri</i>	Gene mutation	No data	–	Ulitzur and Barak 1988
As ⁺⁵	<i>S. typhimurium</i>	Gene mutation	No data	–	Löfroth and Ames 1978
As ⁺⁵	<i>P. fischeri</i>	Gene mutation	No data	+	Ulitzur and Barak 1988
Eukaryotic organisms:					
Fungi:					
As ⁺³ , As ⁺⁵	<i>Saccharomyces cerevisiae</i>	Gene mutation	No data	–	Singh 1983
Mammalian cells:					
As ⁺³	Human fibroblasts	DNA repair inhibition	No data	+	Okui and Fujiwara 1986
As ⁺³	Human fibroblasts	DNA repair and mutant frequencies	+	+	Wiencke et al. 1997
As ⁺³	Human fibroblasts	DNA repair inhibition	+	+	Hartwig et al. 1997
As ⁺³	Human fibroblasts (MRC5CV1)	DNA migration	No data	+	Hartmann and Speit 1996
As ⁺³	Human fibroblasts (HFW cells)	Cytotoxicity	No data	+	Lee and Ho 1994
As ⁺³	Human skin fibroblasts (HFW)	Chromosome endoreduplication	No data	+	Huang et al. 1995
As ⁺³	Human skin fibroblasts	Chromosomal aberrations	No data	+	Yih et al. 1997
As ⁺³	Human fetal lung fibroblasts	DNA strand breaks	No data	+	Dong and Luo 1993
As ⁺³	Human fetal lung fibroblasts (2BS cells)	DNA damage and repair	No data	+	Dong and Luo 1994
As ⁺³ , As ⁺⁵	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
As ⁺³	Diploid human fibroblasts	Morphological transformation	No data	+	Landolph 1994

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Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As ⁺³	Human leukocytes	Chromosomal aberration	No data	+	Nakamuro and Sayato 1981
As ⁺³	Human lymphocytes	DNA protein cross-links	—	—	Costa et al. 1997
As ⁺³ , As ⁺⁵	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993a
As ⁺³ , As ⁺⁵	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993b
As ⁺³ , As ⁺⁵	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1994
As ⁺³	Human lymphocytes	Hyperdiploidy and chromosomal breakage	No data	(+)	Rupa et al. 1997
As ⁺³	Human lymphocytes	Hyperdiploid nuclei	No data	+	Ramirez et al. 1997
As ⁺³	Human lymphocytes	Chromosomal aberration	No data	+	Beckman and Nordenson 1986
As ⁺³	Human lymphocytes	Chromosomal aberrations and sister chromatid exchange	No data	+	Nordenson et al. 1981
As ⁺³	Human lymphocytes	Chromosomal aberration	No data	+	Sweins 1983
As ⁺³	Human lymphocytes	Chromosomal aberrations	No data	+	Yager and Wiencke 1993
As ⁺³	Human lymphocytes	Chromosomal aberrations	No data	+	Vega et al. 1995
As ⁺³	Human lymphocytes	Chromosomal aberrations	No data	+	Wan et al. 1982
As ⁺³	Human lymphocytes	Chromosomal aberrations and sister chromatic exchange	No data	+	Wiencke and Yager 1992
As ⁺³	Human lymphocytes	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As ⁺³	Human lymphocytes	Sister chromatid exchange	No data	+	Gebel et al. 1997
As ⁺⁵	Human lymphocytes	Sister chromatid exchange	No data	—	Gebel et al. 1997
As ⁺³	Human lymphocytes	Sister chromatid exchange	No data	+	Hartmann and Speit 1994
As ⁺³	Human lymphocytes	Sister chromatid exchange	No data	+	Jha et al. 1992
As ⁺³	Human lymphocytes	Sister chromatid exchange	No data	+	Rasmussen and Menzel 1997

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Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As ⁺³ , As ⁺⁵	Human T-cell lymphoma-derived cell line (Molt-3)	PARP activity inhibition	No data	+	Yager and Wiencke 1997
As ⁺³	Human cervix carcinoma HeLa and cisplatin-resistant HeLa/CPR variant cells	DNA repair modification	+	+	Chao 1996
As ⁺³	Human cervix carcinoma cells (HeLa)	DNA damage recognition	No data	-	Hartwig et al. 1998
As ⁺³	Human osteosarcoma cells (HOS)	DNA repair	No data	+	Hu et al. 1998
As ⁺³	Human osteosarcoma cells (HOS)	Cell transformation	No data	+	Mure et al. 2003
As ⁺³	Human-hamster hybrid A ₁ cells	DNA adducts	No data	+	Kessel et al. 2002
As ⁺³	Mouse lymphoma cells	Enhanced viral forward mutation	No data	(+)	Oberly et al. 1982
As ⁺³ , As ⁺⁵	Mouse lymphoma cells [L5178Y/TK ⁺ / (-3.7.2C)]	Chromosomal mutations	No data	+	Moore et al. 1997a
As ⁺³	Mouse lymphoma cells [L5178Y tk ⁺ / (3.7.sc)]	Mutagenicity	No data	+	Oberly et al. 1996
As ⁺³ , As ⁺⁵	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Moore et al. 1994a
As ⁺³	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Sofuni et al. 1996
As ⁺³	Mouse 3T6 cells	Gene amplification	No data	+	Lee et al. 1988
As ⁺³	Mouse embryo fibroblasts (C3H/10T/2 Cl8)	Morphological transformation	No data	+	Landolph 1994
As ⁺³	Chinese hamster V79 cells	Gene mutation	No data	—	Li and Rossman 1991
As ⁺³	Chinese hamster V79 cells	Gene mutation	No data	—	Rossman et al. 1980
As ⁺³	Chinese hamster V79 cells	DNA damage, DNA-protein cross-linking, micronucleus induction	No data	+	Gebel et al. 1998a
As ⁺³	Chinese hamster V79 cells	DNA repair and mutant frequencies	No data	+	Li and Rossman 1991
As ⁺³	Chinese hamster V79 cells	Intrachromosomal homologous recombination	No data	+	Helleday et al. 2000
As ⁺³	Chinese hamster ovary cells (CHO-AL)	Gene mutation	No data	+	Hei et al. 1998
As ⁺³	Chinese hamster ovary cells (CHO-AS52)	Mutagenicity	No data	+	Meng and Hsie 1996

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Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As ⁺³	Chinese hamster ovary cells	Gene mutation	No data	+	Yang et al. 1992
As ⁺³	Chinese hamster ovary cells	DNA repair inhibition	No data	+	Lee-Chen et al. 1993
As ⁺³	Chinese hamster ovary cells	DNA repair inhibition	No data	—	Lee-Chen et al. 1992
As ⁺³	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	+	+	Lee-Chen et al. 1994
As ⁺³	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	No data	+	Lynn et al. 1997
As ⁺³	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Jan et al. 1986
As ⁺³	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Lee et al. 1986
As ⁺³	Chinese hamster ovary cells	Chromosomal aberrations	+	+	Huang et al. 1992
As ⁺³	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations	No data	+	Huang et al. 1993
As ⁺³ , As ⁺⁵	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations and sister chromatid exchange	No data	+	Kochhar et al. 1996
As ⁺³	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	+	+	Lin and Tseng 1992
As ⁺³	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	No data	+	Wan et al. 1982
As ⁺³	Chinese hamster ovary cells	Sister chromatid exchange and micronucleus induction	No data	+	Fan et al. 1996
As ⁺³	Chinese hamster ovary cells	Cell-killing and micronucleus induction	No data	+	Wang and Huang 1994
As ⁺³	Chinese hamster ovary cells	Micronuclei	No data	+	Liu and Huang 1997
As ⁺³	Chinese hamster ovary cells	Micronuclei formation	No data	+	Yee-Chien and Haimei 1996
As ⁺³	Chinese hamster ovary cells	Micronuclei induction	No data	+	Wang et al. 1997
As ⁺³	Chinese hamster ovary cells	Cytotoxicity	No data	—	Lee and Ho 1994
As ⁺³	Syrian hamster embryo cells	Gene mutation	No data	—	Lee et al. 1985

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Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As ⁺³	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As ⁺³	Syrian hamster embryo cells	Chromosomal aberration	No data	+	Lee et al. 1985
As ⁺³	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As ⁺³	Syrian hamster embryo cells	Micronuclei induction	No data	—	Gibson et al. 1997
As ⁺³	Syrian hamster embryo cells	Micronuclei induction	No data	—	Gibson et al. 1997
As ⁺³	Syrian hamster embryo cells	Morphological transformation	No data	+	Kerckaert et al. 1996
As ⁺³	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As ⁺³	Syrian hamster embryo cells	Morphological transformation	No data	+	Casto et al. 1979
As ⁺⁵	Human fibroblasts	DNA repair inhibition	No data	—	Okui and Fujiwara 1986
As ⁺⁵	Human leukocytes	Chromosomal aberrations	No data	(+)	Nakamuro and Sayato 1981
As ⁺⁵	Human lymphocytes	Chromosomal aberrations	No data	—	Nordenson et al. 1981
As ⁺⁵	Human lymphocytes	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As ⁺⁵	Human lymphocytes	Sister chromatid exchange	No data	—	Rasmussen and Menzel 1997
As ⁺⁵	Human peripheral lymphocytes	Sister chromatid exchange	No data	+	Zanzoni and Jung 1980
As ⁺⁵	Human keratinocyte line SCC-9 cells	Keratinocyte programming and transcriptional activity	No data	+	Kachinskas et al. 1997
As ⁺⁵	Mouse lymphoma cells	Gene mutation	No data	—	Amacher and Paillet 1980
As ⁺⁵	Mouse lymphoma cells	Gene mutation	No data	—	Amacher and Paillet 1980
As ⁺⁵	Chinese hamster ovary cells	Chromosomal aberrations	No data	+	Wan et al. 1982
As ⁺⁵	Syrian hamster embryo cells	Gene mutation	No data	—	Lee et al. 1985
As ⁺⁵	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981

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Table 3-8. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As ⁺⁵	Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Lee et al. 1985
As ⁺⁵	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As ⁺⁵	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As ⁺⁵	Syrian hamster embryo cells	Morphological transformation	No data	+	DiPaolo and Casto 1979

(+) = weakly positive or marginal result; – = negative result; + = positive result; DNA = deoxyribonucleic acid

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Table 3-9. Genotoxicity of Inorganic Arsenic *In Vivo*

Valence	Exposure route	Species (test system)	End point	Results	Reference
Nonmammalian					
As ⁺³ As ⁺⁵	Injection	<i>Drosophila melanogaster</i>	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As ⁺³ As ⁺⁵	Larval feeding	<i>D. melanogaster</i>	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As ⁺⁵	Larvae	<i>D. melanogaster</i>	Mitotic recombinations	+	de la Rosa et al. 1994
Mammalian					
As ⁺³	Inhalation	Human (lymphocytes)	Chromosomal aberrations	—	Beckman et al. 1977
As ⁺³	Inhalation	Human (lymphocytes)	Chromosomal aberrations	+	Nordenson et al. 1978
As ⁺³	Oral	Human (lymphocytes)	Chromosomal aberrations	—	Burgdorf et al. 1977
No data	Oral	Human (lymphocytes)	Chromosomal aberrations	—	Vig et al. 1984
No data	Oral	Human (skin)	DNA adducts	+	Matsui et al. 1999
As ⁺³	Oral	Human (lymphocytes)	Sister chromatid exchange	—	Burgdorf et al. 1977
As ⁺³	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Hsu et al. 1997
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Lerda 1994
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Liou et al. 1999
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Mahata et al. 2003
As ⁺³	Oral	Human (lymphocytes)	Sister chromatid exchange	—	Nordenson et al. 1978
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	—	Vig et al. 1984
No data	Oral	Human skin carcinoma	Mutation and overexpression of p53	+	Hsu et al. 1999
As ⁺³	Oral	Exfoliated human epithelial cells	Micronuclei	+	Moore et al. 1996
As ⁺³	Oral	Exfoliated human epithelial cells	Micronuclei	+	Tian et al. 2001
No data	Oral	Human (bladder cells)	Micronuclei	+	Moore et al. 1995
No data	Oral	Human (lymphocytes)	Micronuclei	+	Martinez et al. 2004
No data	Oral	Human (lymphocytes)	Micronuclei	+	Basu et al. 2004
No data	Oral	Human (oral mucosa cells)	Micronuclei	+	Basu et al. 2004

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Table 3-9. Genotoxicity of Inorganic Arsenic *In Vivo*

Valence	Exposure route	Species (test system)	End point	Results	Reference
No data	Oral	Human (urothelial cells)	Micronuclei	+	Basu et al. 2004
As ⁺⁵	Oral	Rat (bone marrow cells)	Chromosomal aberrations	+	Datta et al. 1986
As ⁺³	Inhalation	Mouse (fetal liver)	Chromosomal aberrations	(+)	Nagymajtényi et al. 1985
As ⁺³	Oral	Mouse (bone marrow cells)	Chromosomal aberrations	+	Das et al. 1993
As ⁺³	Oral	Mouse (bone marrow cells)	Chromosomal aberrations	+	Poddar et al. 2000
As ⁺³	Oral	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1987
As ⁺³	Oral	Mouse (spermatogonia)	Chromosomal aberrations	–	Poma et al. 1987
As ⁺³	Oral	Mouse (leukocytes)	Chromosomal breaks	+	McDorman et al. 2002
As ⁺³	Intraperitoneal	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1981
As ⁺³	Intraperitoneal	Mouse (bone marrow cells)	Micronuclei	+	DeKnudt et al. 1986
As ⁺³	Intraperitoneal	Mouse (spermatogonia)	Spermatogonia	–	Poma et al. 1981
As ⁺³	Intraperitoneal	Mouse (spermatogonia)	Sperm morphology	–	DeKnudt et al. 1986
As ⁺³	Intraperitoneal	Mouse (spermatogenesis)	Dominant lethal mutations	–	DeKnudt et al. 1986

(+) = weakly positive or marginal result; – = negative result; + = positive result; DNA = deoxyribonucleic acid

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Investigations of genotoxic effects of ingested arsenic have yielded mixed results possibly due to the different types of cells examined and the different exposure levels experienced by the populations studied. A study of p53 mutations in arsenic-related skin cancers from patients in Taiwan exposed to arsenic from drinking water found a high rate of p53 mutations and different types of p53 mutations compared with those seen in UV-induced skin cancers (Hsu et al. 1999); similar results have been found in mice (Salim et al. 2003). In humans exposed to Fowler's solution (potassium arsenite, usually taken at a dose of about 0.3 mg As/kg/day [Holland 1904]), increased sister chromatid exchanges, but no increase in chromosomal aberrations, was reported in one study (Burgdorf et al. 1977), while just the converse (increased aberrations but no increase in sister chromatid exchange) was reported in another (Nordenson et al. 1979). Moore et al. (1997a) reported an exposure-dependent increase in the occurrence of micronucleated cells in epithelial cells from the bladder in a male population in northern Chile chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15 µg As/L, respectively), and noted that chromosome breakage was the major cause of micronucleus (MN) formation. Similar results were reported by Martínez et al. (2004) who evaluated micronuclei formation in peripheral lymphocytes from people in northern Chile exposed to up to 0.75 mg As/L in their drinking water. In contrast, Martínez et al. (2005) did not find a significant increase in micronuclei in buccal cells from subjects from the same area relative to a low exposure group. Vig et al. (1984) found no significant differences in the frequency of chromosomal aberrations or sister chromatid exchanges between two populations in Nevada with differing levels of arsenic in their drinking water (mean concentrations of 5 and 109 µg/L). In animal studies, an increased incidence of chromosomal abnormalities was detected in rats given oral doses of sodium arsenate (4 mg As/kg/day) for 2–3 weeks (Datta et al. 1986), but no consistent increase in chromosomal aberrations was detected in bone marrow cells or spermatogonia from mice given sodium arsenite (about 50 mg As/kg/day) for up to 8 weeks (Poma et al. 1987). These studies suggest that ingested arsenic may cause chromosomal effects, but these data are too limited to draw a firm conclusion.

Organic Arsenicals. The genotoxicity of the organic arsenicals has been investigated in a number of studies (see Table 3-10). Several tests indicate that DMA and roxarsone may be able to cause chromosome aberrations, mutations, and deoxyribonucleic acid (DNA) strand breaks; *in vitro* studies with MMA did not find significant increases in the occurrence of chromosome aberrations, forward or reverse mutations, unscheduled DNA synthesis (Chun and Killeen 1989a, 1989b, 1989c, 1989d). An increased number of DNA strand breaks were detected in lung and other tissues of mice and rats given oral doses of ~1,500 mg/kg DMA (Okada and Yamanaka 1994; Yamanaka et al. 1989a); this effect appeared to be related to the formation of some active oxygen species. These breaks were largely repaired within 24 hours, so the relevance with respect to health risk is uncertain.

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Table 3-10. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms (<i>in vitro</i>):					
MMA	<i>Salmonella typhimurium</i>	Gene mutation	–	–	Chun and Killeen 1989c
DMA	<i>Escherichia coli</i>	Gene mutation	No data	+	Yamanaka et al. 1989b
Roxarsone	<i>S. typhimurium</i>	Gene mutation	–	–	NTP 1989b
Eukaryotic organisms (<i>in vitro</i>):					
MMA	Chinese hamster ovary cells	Chromosome aberrations	–	–	Chun and Killeen 1989a
MMA	Mouse lymphoma cells (L5178Y/TK ^{+/+})	Forward mutation	–	–	Chun and Killeen 1989b
MMA	Rat hepatocytes	Unscheduled DNA synthesis	No data	–	Chun and Killeen 1989d
DMA	Human peripheral lymphocytes	Mitogenesis inhibited	No data	–	Endo et al. 1992
DMA	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
DMA	Human alveolar (L-132) cells	Lung-specific DNA damage	No data	+	Kato et al. 1994
DMA	Human alveolar type II (L-132) cells	DNA single-strand breaks	+	+	Kawaguchi et al. 1996
DMA	Human diploid L-132 epithelial cells	DNA single-strand breaks	No data	+	Rin et al. 1995
DMA	Human alveolar type II (L-132) cells	DNA strand breaks	No data	+	Tezuka et al. 1993
DMA	Human embryonic cell line of type II alveolar epithelial cells (L-132)	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1993
DMA	Human alveolar epithelial (L-132) cells	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1995
DMA	Human pulmonary epithelial (L-132) cells	DNA single-strand breaks	No data	+	Yamanaka et al. 1997
DMA	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
DMA	Mouse lymphoma cells (L5178Y/TK ^{+/+} -3.7.2C)	Chromosomal mutations	No data	+	Moore et al. 1997a
DMA	Chinese hamster lung and diploid cells (V79)	Mitotic arrest and tetraploid formation	No data	+	Endo et al. 1992

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Table 3-10. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
DMA	Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Ueda et al. 1997
DMA	Chinese hamster lung and diploid cells (V79)	Chromosomal aberrations	No data	+	Kitamura et al. 2002
DMA	Chinese hamster lung and diploid cells (V79)	Chromosomal aberrations	+	+	Kuroda et al. 2004
DMA	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
MMA	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
MMA	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
Roxarsone	<i>Drosophila melanogaster</i>	Sex linked recessive	No data	–	NTP 1989b
Roxarsone	Rat hepatocyte	DNA double-strand breaks	No data	+	Storer et al. 1996
Roxarsone	A31-1-13 clone of BALB/c-3T3 cells	Transformation response and mutagenicity	No data	–	Matthews et al. 1993
Roxarsone	Mouse lymphoma (L5178Y) cells	Trifluorothymidine resistance	No data	+	NTP 1989b
Eukaryotic organisms (<i>in vivo</i>):					
DMA	Rat (oral exposure)	DNA single-strand breaks in lung	No data	+	Yamanaka and Okada 1994
DMA	Mouse (oral exposure)	DNA strand breaks in tissues	No data	+	Yamanaka et al. 1989b
DMA	Mouse (oral exposure)	DNA single-strand breaks in lung	No data	+	Yamanaka et al. 1993
DMA	Mouse (oral exposure)	DNA single-strand breaks in lung	No data	–	Yamanaka et al. 1989a
DMA	Mouse (oral exposure)	DNA adduct formation	No data	+	Yamanaka et al. 2001
DMA	Mouse (injection)	Aneuploidy in bone marrow cells	No data	+	Kashiwada et al. 1998

– = negative result; + = positive result; DMA = dimethylarsinic acid; DNA = deoxyribonucleic acid; MMA = monomethylarsonic acid

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3.4 TOXICOKINETICS

There is an extensive database on the toxicokinetics of inorganic arsenic. Most studies have been performed in animals, but there are a number of studies in humans as well. These studies reveal the following main points:

- Both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Absorption by the dermal route has not been well characterized, but is low compared to the other routes. Inorganic arsenic in soil is absorbed to a lesser extent than solutions of arsenic salts.
- The rate of absorption of arsenic in highly insoluble forms (e.g., arsenic sulfide, lead arsenate) is much lower than that of more soluble forms via both oral and inhalation routes.
- Once absorbed, arsenites are oxidized to arsenates and methylated. This process may then be repeated to result in dimethylated arsenic metabolites.
- Distribution of arsenic in the rat is quite different from other animal species, suggesting that the rat is probably not an appropriate toxicokinetic model for distribution, metabolism, or excretion of arsenic by humans.
- The As(+3) form undergoes enzymic methylation primarily in the liver to form MMA and DMA. The rate and relative proportion of methylation production varies among species. The rate of methylation varies considerably among tissues.
- Most arsenic is promptly excreted in the urine as a mixture of As(+3), As(+5), MMA, and DMA; DMA is usually the primary form in the urine. Smaller amounts are excreted in feces. Some arsenic may remain bound to tissues, depending inversely on the rate and extent of methylation.

Less information is available for the organic arsenicals. It appears that both MMA and DMA are well absorbed, but are rapidly excreted in the urine and feces. MMA may be methylated to DMA, but neither MMA nor DMA are demethylated to yield inorganic arsenic.

A review of the evidence that supports these conclusions is presented below.

3.4.1 Absorption**3.4.1.1 Inhalation Exposure**

Inorganic Arsenicals. Since arsenic exists in air as particulate matter, absorption across the lung involves two processes: deposition of the particles onto the lung surface, and absorption of arsenic from the deposited material. In lung cancer patients exposed to arsenic in cigarette smoke, deposition was

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estimated to be about 40% and absorption was 75–85% (Holland et al. 1959). Thus, overall absorption (expressed as a percentage of inhaled arsenic) was about 30–34%. In workers exposed to arsenic trioxide dusts in smelters, the amount of arsenic excreted in the urine (the main route of excretion; see Section 3.4.4) was about 40–60% of the estimated inhaled dose (Pinto et al. 1976; Vahter et al. 1986). Absorption of arsenic trioxide dusts and fumes (assessed by measurement of urinary metabolites) correlated with time weighted average arsenic air concentrations from personal breathing zone air samplers (Offergelt et al. 1992). Correlations were best immediately after a shift and just before the start of the next shift. Although the percent deposition was not measured in these cases, it seems likely that nearly all of the deposited arsenic was absorbed. This conclusion is supported by intratracheal instillation studies in rats and hamsters, where clearance of oxy compounds of arsenic (sodium arsenite, sodium arsenate, arsenic trioxide) from the lung was rapid and nearly complete (60–90% within 1 day) (Marafante and Vahter 1987; Rhoads and Sanders 1985). In contrast, arsenic sulfide and lead arsenate were cleared more slowly (Marafante and Vahter 1987), indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form. There are no data to suggest that absorption of inhaled arsenic in children differs from that in adults.

Organic Arsenicals. No studies were located regarding absorption of organic arsenicals in humans or animals after inhalation exposure. However, DMA instilled in the lungs of rats was absorbed very rapidly (half-time of 2.2 minutes) and nearly completely (at least 92%) (Stevens et al. 1977). This indicates that organic arsenicals are likely to be well absorbed by the inhalation route.

3.4.1.2 Oral Exposure

Inorganic Arsenicals. Several studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from a study that evaluated the 6-day elimination of arsenic in healthy humans who were given water from a high-arsenic sampling site (arsenic species not specified) and that reported approximately 95% absorption (Zheng et al. 2002). A similar absorption efficiency can be estimated from measurements of fecal excretion in humans given oral doses of arsenite, where <5% was recovered in the feces (Bettley and O'Shea 1975). This indicates absorption was at least 95%. These results are supported by studies in which urinary excretion in humans was found to account for 55–87% of daily oral intakes of arsenate or arsenite (Buchet et al. 1981b; Crecelius 1977; Kumana et al. 2002; Mappes 1977; Tam et al. 1979b). In contrast, ingestion of arsenic triselenide (As_2Se_3) did not lead to a measurable increase in urinary excretion (Mappes 1977), indicating that

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gastrointestinal absorption may be much lower if highly insoluble forms of arsenic are ingested. There are no data to suggest that absorption of arsenic from the gut in children differs from that in adults.

These observations in humans are supported by a number of studies in animals. Fecal excretion of arsenates and arsenites ranged from 2 to 10% in monkeys and mice, with 70% or more appearing in urine (Charbonneau et al. 1978; Roberts et al. 2002; Vahter 1981; Vahter and Norin 1980). Oral absorption of [^{73}As] labeled sodium arsenate in mice was unaffected by dose (0.0005–5 mg/kg) as reflected in percentage of dose excreted in feces over 48 hours (Hughes et al. 1994). Absorption ranged from 82 to 89% at all doses. Gonzalez et al. (1995) found that the percentage of arsenate that was absorbed in rats decreased as the dose increased from 6 to 480 μg , suggesting saturable, zero-order absorption of arsenate in this species. Hamsters appear to absorb somewhat less than humans, monkeys, and mice, since fecal excretion usually ranges from 10 to 40% (Marafante and Vahter 1987; Marafante et al. 1987a; Yamauchi and Yamamura 1985). Rabbits also appear to absorb less arsenate than humans, monkeys, or mice after oral exposure (Freeman et al. 1993). After a gavage dose of 1.95 mg/kg sodium arsenate, 45% of the arsenate was recovered in feces in males and 52% in females. As in humans, when highly insoluble arsenic compounds are administered (arsenic trisulfide, lead arsenate), gastrointestinal absorption is reduced 20–30% (Marafante and Vahter 1987).

Bioavailability of arsenic was measured in rabbits ingesting doses of smelting soils that contained arsenic primarily in the form of sulfides (Freeman et al. 1993). Bioavailability was assessed by comparing the amounts of arsenic that was excreted after ingestion of the soil to that excreted after an intravenous dose of sodium arsenate. The bioavailability of the arsenic in the ingested soil was $24\pm 3.2\%$ and that of sodium arsenate in the gavage dose was $50\pm 5.7\%$. Approximately 80% of the arsenic from ingested soil was eliminated in the feces compared with 50% of the soluble oral dose and 10% of the injected dose. In another study, rabbits dosed with sodium arsenite (0.8 mg As/kg) had 5 times greater blood arsenic concentrations than rabbits dosed with arsenic-containing soil (2.8 mg As/kg), suggesting a lower bioavailability of the arsenic in soil (Davis et al. 1992).

Studies of the bioavailability of arsenic suggest that absorption of arsenic in ingested dust or soil is likely to be considerably less than absorption of arsenic from ingested salts (Davis et al. 1992, 1996; EPA 1997g; Freeman et al. 1993, 1995; Pascoe et al. 1994; Roberts et al. 2002, 2007; Rodriguez et al. 1999). Oral absorption of arsenic in a group of three female *Cynomolgus* monkeys from a soluble salt, soil, and household dust was compared with absorption of an intravenous dose of sodium arsenate (Freeman et al. 1995). Mean absolute percentage bioavailability based on urine arsenic excretion was reported at

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67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The arsenic in the dust and soil was approximately 3.5–5-fold (based on levels in the urine) and 8–9-fold (based on levels in the blood) less bioavailable than arsenic in solution. Two other studies in monkeys reported relative bioavailability of arsenic in soil from a number of locations (electrical substation, wood preserving sites, pesticide sites, cattle-dip sites, volcanic soil, and mining sites) ranged from 5 to 31% (Roberts et al. 2002, 2007). A study in beagle dogs fed with soil containing As₂O₅ or treated with intravenous soluble arsenic found that compared to injection the bioavailability of arsenic from ingested soil was 8.3±2.0% (Groen et al. 1993). The bioavailability of arsenic in soil has been studied in juvenile swine that received daily oral doses of soil or sodium arsenate (in food or by gavage) for 15 days (EPA 1997g). The soils were obtained from various mining and smelting sites and contained, in addition to arsenic at concentrations of 100–300 µg/g, lead at concentrations of 3,000–14,000 µg/g. The arsenic doses ranged from 1 to 65.4 µg/kg/day. The fraction of the arsenic dose excreted in urine was measured on days 7 and 14 and the relative bioavailability of the soil-borne arsenic was estimated as the ratio of urinary excretion fractions, soil arsenic:sodium arsenate. The mean relative bioavailability of soil-borne arsenic ranged from 0 to 98% in soils from seven different sites (mean±SD, 45%±32). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from 7 to 51% (mean±SD, 35%±27). Rodriguez et al. (1999) used a similar approach to estimate the relative bioavailability of arsenic in mine and smelter wastes (soils and solid materials) in juvenile swine. Samples included iron slag deposits and calcine deposits and had arsenic concentrations that ranged from 330 to 17,500 µg/g. Relative bioavailability (waste:sodium arsenate) ranged from 3 to 43% for 13 samples (mean, 21%) and was higher in iron slag wastes (mean, 25%) than in calcine wastes (mean, 13%).

Bioavailability of arsenic from soil is reduced by low solubility and inaccessibility due to the presence of secondary reaction products or insoluble matrix components (Davis et al. 1992). This is supported by studies conducted with *in vitro* simulations of the gastric and/or intestinal fluids (Hamel et al. 1998; Pouschat and Zagury 2006; Rodriguez et al. 1999; Ruby et al. 1996, 1999; Williams et al. 1998). When soils containing arsenic are incubated in simulated gastrointestinal fluids, only a fraction of the arsenic becomes soluble. Estimates of the soluble, or bioaccessible, arsenic fraction have ranged from 3 to 50% for various soils and mining and smelter waste materials (Pouschat and Zagury 2006; Rodriguez et al. 1999; Ruby et al. 1996); these estimates are similar to *in vivo* estimates of the relative bioavailability of arsenic in these same materials (Ruby et al. 1999).

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Organic Arsenicals. Based on urinary excretion studies in volunteers, it appears that both MMA and DMA are well absorbed (at least 75–85%) across the gastrointestinal tract (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in animals, where at least 75% absorption has been observed for DMA (Marafante et al. 1987b; Stevens et al. 1977; Vahter et al. 1984; Yamauchi and Yamamura 1984) and MMA (Hughes et al. 2005; Yamauchi et al. 1988). In mice, the relative bioavailability of MMA appears to be dose-dependent; 81% was absorbed following a single gavage dose of 0.4 mg MMA/kg/day compared to 60% following administration of 4 mg MMA/kg/day (Hughes et al. 2005).

3.4.1.3 Dermal Exposure

Inorganic Arsenicals. No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Percutaneous absorption of [^{73}As] as arsenic acid (H_3AsO_4) alone and mixed with soil has been measured in skin from cadavers (Wester et al. 1993). Labeled arsenic was applied to skin in diffusion cells and transit through the skin into receptor fluid measured. After 24 hours, 0.93% of the dose passed through the skin and 0.98% remained in the skin after washing. Absorption was lower with [^{73}As] mixed with soil: 0.43% passed through the skin over 24 hours and 0.33% remained in the skin after washing.

Dermal absorption of arsenic has been measured in Rhesus monkeys (Lowney et al. 2005; Wester et al. 1993). After 24 hours, 6.4% of [^{73}As] as arsenic acid was absorbed systemically, as was 4.5% of [^{73}As] mixed with soil (Wester et al. 1993). Similarly, 2.8% of soluble arsenic in water was detected in the urine 24 hours after exposure (Lowney et al. 2005). However, arsenic from soil was poorly absorbed; 0.12% was detected in the urine after 24 hours. Differences between the Wester et al. (1993) and Lowney et al. (2005) studies in terms of uptake from soil may be due to the differences in forms of arsenic in the soil. In the Wester et al. (1993) study, soil was mixed with radiolabelled arsenic acid in water; Lowney et al. (2005) used soil samples from a pesticide manufacturing facility that historically manufactured arsenical pesticides (the arsenic was primarily in the iron oxide and iron silicate mineral phases). Lowney et al. (2005) also measured urinary levels of arsenic following dermal application of CCA residues and found that the levels did not increase from background. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solutions of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver, and spleen over the next 5 days (Dutkiewicz 1977). The rate of uptake was estimated to be 1–33 $\mu\text{g}/\text{cm}^2/\text{hour}$. These findings suggest that dermal exposure leads initially to arsenic binding to skin, and that the bound arsenic may slowly be taken up into the blood, even after exposure ends.

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Organic Arsenicals. No studies were located on absorption of organic arsenicals in humans or animals after dermal exposure.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Inorganic Arsenicals. No studies were located on the distribution of arsenic in humans or animals after inhalation exposure, but intratracheal administration of arsenic trioxide to rats resulted in distribution of arsenic to the liver, kidney, skeleton, gastrointestinal tract, and other tissues (Rhoads and Sanders 1985). This is consistent with data from oral and parenteral studies (below), which indicate that absorbed arsenic is distributed throughout the body.

Organic Arsenicals. No studies were located regarding the distribution of organic arsenicals in humans or animals after inhalation exposure. However, DMA administered to rats by the intratracheal route was distributed throughout the body (Stevens et al. 1977), suggesting that inhalation of organic arsenicals would also lead to widespread distribution.

3.4.2.2 Oral Exposure

Inorganic Arsenicals. Analysis of tissues taken at autopsy from people who were exposed to background levels of arsenic in food and water revealed that arsenic is present in all tissues of the body (Liebscher and Smith 1968). Most tissues had about the same concentration level (0.05–0.15 ppm), while levels in hair (0.65 ppm) and nails (0.36 ppm) were somewhat higher. This indicates that there is little tendency for arsenic to accumulate preferentially in any internal organs. However, exposure levels may not have been high enough to cause elevated levels in tissues. Arsenic exposure may have been low enough that the methylation process in the body resulted in limited accumulation in internal organs. Tissue analysis of organs taken from an individual following death from ingestion of 8 g of arsenic trioxide (about 3 g of arsenic) showed a much higher concentration of arsenic in liver (147 µg/g) than in kidney (27 µg/g) or muscle, heart, spleen, pancreas, lungs, or cerebellum (11–12 µg/g) (Benramdane et al. 1999a). Small amounts were also found in other parts of the brain (8 µg/g), skin (3 µg/g), and hemolyzed blood (0.4 µg/g). Many studies have been performed where arsenic levels in hair and nails have been measured and correlations with exposure analyzed. Some of these studies are discussed in Section 3.8, Biomarkers of Exposure.

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Inorganic arsenic passes easily through the placenta. High levels of arsenic were found in the liver, kidney, and brain during autopsy of an infant prematurely born to a young mother who had ingested inorganic arsenic at week 30 of gestation (Lugo et al. 1969). Arsenic was detected in human breast milk at concentrations of 0.00013–0.00082 ppm in a World Health Organization study (Somogyi and Beck 1993). Arsenic concentrations were 0.0001–0.0044 ppm in human milk sampled from 88 mothers on the Faroe Islands whose diets were predominantly seafood (Grandjean et al. 1995). Exposures to arsenic from the seafood diet in this population was most likely to organic “fish arsenic.” In a population of Andean women exposed to high concentrations (about 200 ppb) of inorganic arsenic in drinking water, concentrations of arsenic in breast milk ranged from about 0.0008 to 0.008 ppm (Concha et al. 1998b).

Studies in mice and hamsters given oral doses of arsenate or arsenite have found elevated levels of arsenic in all tissues examined (Hughes et al. 2003; Vahter and Norin 1980; Yamauchi and Yamamura 1985), including the placenta and fetus of pregnant females (Hood et al. 1987, 1988). Inorganic arsenic crosses the placental barrier and selectively accumulates in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). In mice, radiolabel from orally administered 74-As was widely distributed to all tissues, with the highest levels in skin, kidney, and liver (Hughes et al. 2003). No obvious differences between As(+3) and As(+5) were found, although residual levels after 24 hours tended to be higher for As(+3) than As(+5) (Vahter and Norin 1980). However, *in vitro* studies have found that the cellular uptake of As(+3) was higher than that of As(+5) (Bertolero et al. 1987; Dopp et al. 2004); in mouse cells, the difference was 4-fold (Bertolero et al. 1987). In hamsters, increases in tissue levels were noted after oral treatment with As(+3) for most tissues (hair, kidney, liver, lung, skin, muscle), with the largest increases in liver and lung (Yamauchi and Yamamura 1985). Liver and kidney arsenic concentrations increased with dose in dogs fed arsenite in the diet for 6 months (Neiger and Osweiler 1992). A study examining the speciation of arsenic following a single dose exposure to sodium arsenate to mice (Kenyon et al. 2005) found that the levels of inorganic arsenic and DMA were similar in the blood, liver, and kidney; much lower levels of MMA were found in these tissues. The concentration of DMA in the lungs exceeded inorganic arsenic and the levels of inorganic arsenic and MMA were similar; the DMA concentration was about 6 times higher than that of inorganic arsenic.

Inorganic arsenic crosses the placental barrier and selectively accumulates in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). Following maternal exposure to arsenite or arsenate throughout gestation and lactation, inorganic arsenic and DMA were detected in the

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newborn mouse brains (Jin et al. 2006). The levels of inorganic arsenic in the brain were similar to those in the newborn livers; however, the levels of DMA in the brain were about twice as high as in the liver.

Organic Arsenicals. No studies were located on the distribution of organic arsenicals in humans following oral exposure. Studies in animals found MMA and DMA distributed to all tissues after acute oral doses (Hughes et al. 2005; Stevens et al. 1977; Vahter et al. 1984; Yamauchi and Yamamura 1984; Yamauchi et al. 1988). In mice, MMA is rapidly distributed throughout the body with peak tissue concentrations occurring between 0.25 and 4 hours after administration of a single gavage dose of 0.4 or 4 mg MMA/kg (Hughes et al. 2005). The peak levels of MMA in the bladder, kidneys, and lungs were higher than blood, with the highest levels occurring in the bladder. The terminal half-lives of MMA were 4.2–4.9 hours in the liver, lung, and blood, 9.0 hours in the urinary bladder, and 15.9 hours in the kidney in mice dosed with 0.4 mg MMA/kg; similar half-lives were measured in the 4.0 mg MMA/kg mice. Two hours after dosing, most of the methylated arsenic in the tissues was in the form of MMA. In rats exposed to 100 mg/kg DMA in the diet for 72 days, high levels of arsenic was detected in the blood (Lu et al. 2004a). The arsenic was primarily found in the erythrocyte; the concentration in the erythrocyte was 150 times higher than the arsenic concentration in the plasma.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of inorganic or organic arsenicals in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Inorganic Arsenicals. Studies in mice, rabbits, and monkeys injected intravenously with solutions of arsenite or arsenate confirm that arsenic is widely distributed throughout the body (Lindgren et al. 1982; Marafante and Vahter 1986; Vahter and Marafante 1983; Vahter et al. 1982). Shortly after exposure, the concentration of arsenic tends to be somewhat higher in liver, kidney, lung, and gastrointestinal epithelium (Hughes et al. 2000; Lindgren et al. 1982; Vahter and Marafante 1983; Vahter et al. 1982), but levels tend to equilibrate over time. Arsenate shows a tendency to deposit in skeletal tissue that is not shared by arsenite (Lindgren et al. 1982, 1984), presumably because arsenate is an analog of phosphate.

The distribution of arsenic in the rat is quite different from other animal species. Following intramuscular injection of carrier-free radio-arsenate in rats, most of the injected arsenic became bound to hemoglobin in red blood cells, and very little reached other tissues (Lanz et al. 1950). However, similar experiments

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in dogs, mice, guinea pigs, rabbits, and chicks found very little uptake of arsenic into the blood in these species (cats gave intermediate results).

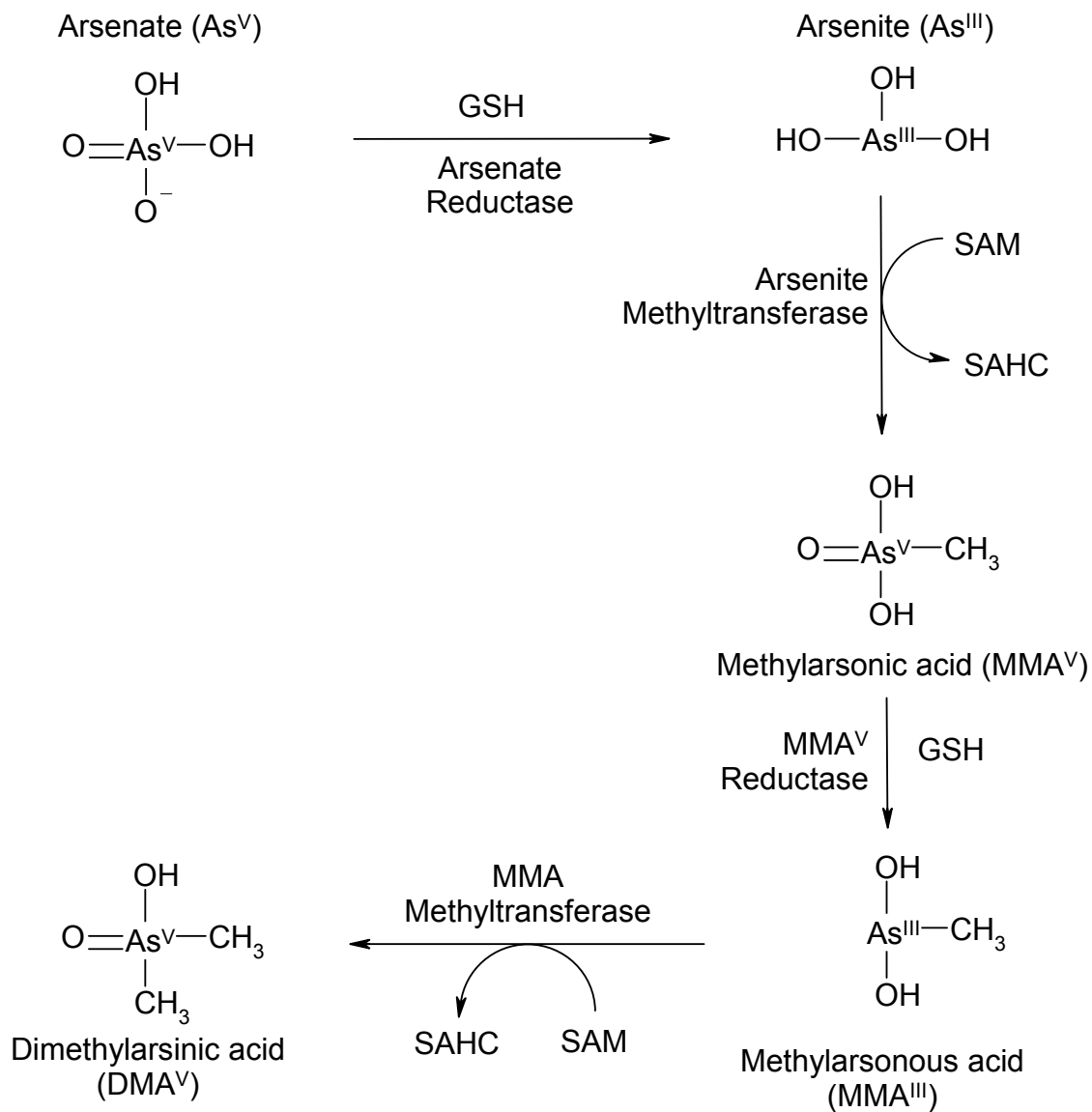
Organic Arsenicals. Following intravenous administration of DMA in mice, DMA is rapidly distributed throughout the body (Hughes et al. 2000). In the blood, the DMA was initially detected in the plasma, but fairly rapidly equilibrated between the plasma and erythrocytes. Blood, plasma, erythrocyte, liver, and kidney distribution and elimination of DMA did not differ in groups of mice administered 1.11 or 111 mg DMA/kg. However, a significant difference in DMA elimination from the lungs was observed; the elimination half-time increased from 91 minutes in the 1.11 mg DMA/kg group to 6,930 minutes in the 111 mg DMA/kg group.

3.4.3 Metabolism

Inorganic Arsenicals. The metabolism of inorganic arsenic has been extensively studied in humans and animals, and is diagrammed in Figure 3-7. Two basic processes are involved: (1) reduction/oxidation reactions that interconvert As(III) and As(V), and (2) methylation reactions, which convert arsenite to MMA and DMA. The resulting series of reactions results in the reduction of inorganic arsenate to arsenite (if necessary), methylation to MMA(V), reduction to MMA(III), and methylation to DMA(V). These processes appear to be similar whether exposure is by the inhalation, oral, or parenteral route. The human body has the ability to change inorganic arsenic to organic forms (i.e., by methylation) that are more readily excreted in urine. In addition, inorganic arsenic is also directly excreted in the urine. It is estimated that by means of these two processes, >75% of the absorbed arsenic dose is excreted in the urine (Marcus and Rispin 1988), although this may vary with the dose and exposure duration. This mechanism is thought to have an upper-dose limit which, when overwhelmed, results in a higher incidence of arsenic toxicity. This is supported by a case report of an individual who died 3 days after ingesting 8 g of arsenic trioxide (about 3 g of arsenic) (Benramdane et al. 1999a). Only 20% of the total arsenic in all tissues analyzed was methylated (14% MMA, 6% DMA), while 78% remained as arsenite and 2% as arsenate.

The majority of the evidence characterizing the metabolic pathways of arsenic is derived from analysis of urinary excretion products. Exposure of humans to either arsenates or arsenites results in increased levels of inorganic As(+3), inorganic As(+5), MMA, and DMA in urine (Aposhian et al. 2000a, 2000b; Buchet et al. 1981a, 1981b; Concha et al. 1998a, 1998b; Crecelius 1977; Kurttio et al. 1998; Lovell and Farmer

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Figure 3-7. Inorganic Arsenic Biotransformation Pathway

SAHC = S-adenosylhomocysteine; SAM = S-adenosylmethionine

Source: adapted from Aposhian et al. 2000b

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1985; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). Similar results are obtained from studies in mice (Vahter 1981; Vahter and Envall 1983), hamsters (Hirata et al. 1988; Marafante and Vahter 1987; Takahashi et al. 1988), and rabbits (Maiorino and Aposhian 1985; Marafante et al. 1985; Vahter and Marafante 1983). Historically, little distinction was made between MMA(V) and MMA(III) in the urine in most studies, and the assumption was that the majority of MMA in the urine was MMA(V); however, Aposhian et al. (2000a, 2000b) demonstrated that the methylated arsenic atom may be in either valance state.

The relative proportions of As(+3), As(+5), MMA, and DMA in urine can vary depending upon the chemical administered, time after exposure, route of exposure, dose level, and exposed species. In general, however, DMA is the principal metabolite following long-term exposure, with lower levels of inorganic arsenic [As(+3) and As(+5)] and MMA. In humans, the relative proportions are usually about 40–75% DMA, 20–25% inorganic arsenic, and 15–25% MMA (Buchet et al. 1981a; Hopenhayn et al. 2003b; Loffredo et al. 2003; Mandal et al. 2001; Smith et al. 1977; Tam et al. 1979b; Tokunaga et al. 2002; Vahter 1986). With relatively constant exposure levels, these metabolic proportions remain similar over time (Concha et al. 2002), and appear to be similar among family members (Chung et al. 2002). One study of groups of women and children in two villages in Argentina showed that children ingesting large amounts of arsenic in their drinking water (200 µg/L) excreted about 49% inorganic arsenic and 47% DMA (Concha et al. 1998b). This compared to 32% inorganic arsenic and 66% DMA for the women in the study. This may indicate that metabolism of arsenic in children is less efficient than in adults. The rabbit has a ratio of metabolites similar to human adults (Maiorino and Aposhian 1985), suggesting that this may be a good animal model for toxicokinetics in humans. Mice may also be a good human toxicokinetic model based on the similarity of arsenic metabolism and deposition (Vahter et al. 2002). In contrast, the guinea pig, marmoset, and tamarin monkey do not methylate inorganic arsenic (Healy et al. 1998; Vahter and Marafante 1985; Vahter et al. 1982; Zakharyan et al. 1996); thus, they may be poor models for humans.

Reduction of arsenate to arsenite can be mediated by glutathione (Menzel et al. 1994). Scott et al. (1993) showed that glutathione forms complexes with both arsenate and arsenite *in vitro*, and that glutathione is oxidized (and arsenate reduced) in the glutathione-arsenate reaction. Studies *in vitro* indicate that the substrate for methylation is As(+3), and that As(+5) is not methylated unless it is first reduced to As(+3) (Buchet and Lauwerys 1985, 1988; Lerman et al. 1983). The main site of methylation appears to be the liver, where the methylation process is mediated by enzymes that utilize S-adenosylmethionine as cosubstrate (Buchet and Lauwerys 1985, 1988). Under normal conditions, the availability of methyl

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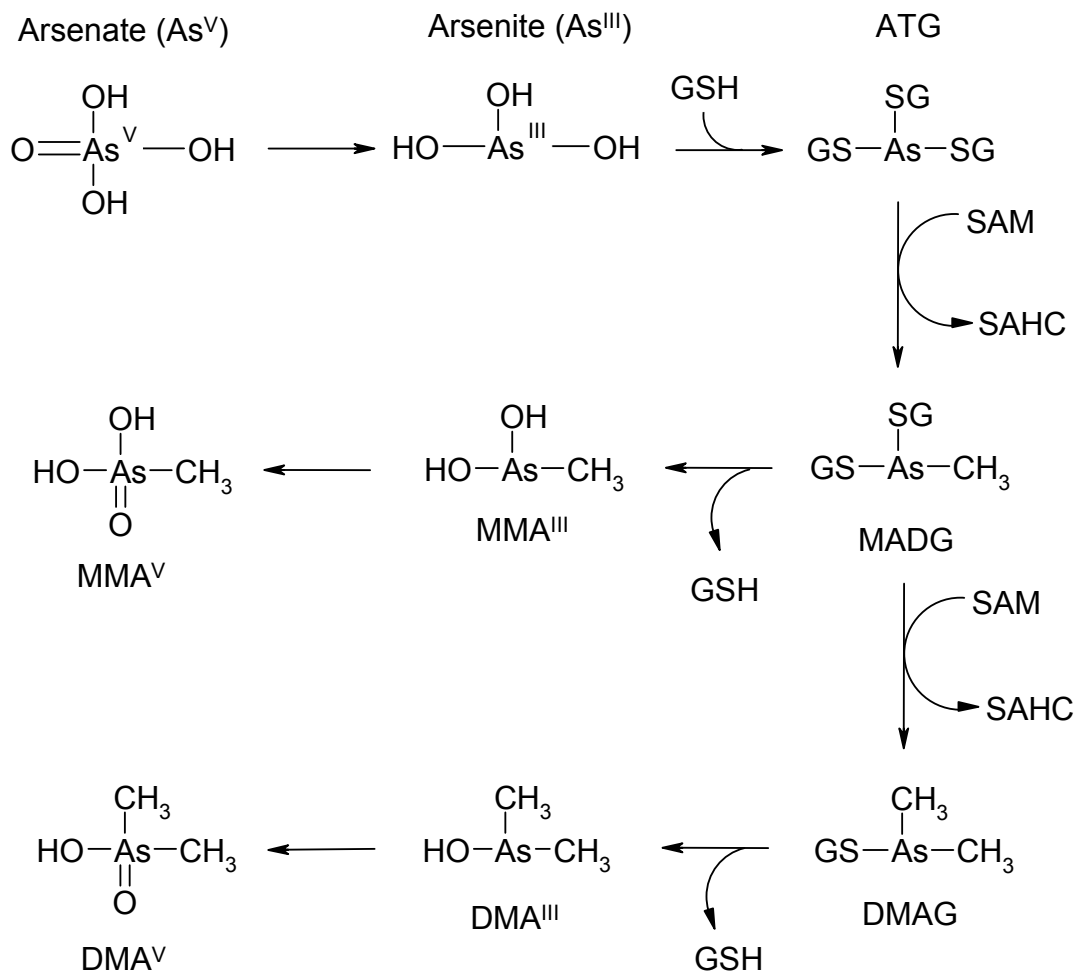
donors (e.g., methionine, choline, cysteine) does not appear to be rate limiting in methylating capacity, either in humans (Buchet et al. 1982) or in animals (Buchet and Lauwerys 1987; Buchet et al. 1981a). However, severe dietary restriction of methyl donor intake can result in significant decreases in methylating capacity (Buchet and Lauwerys 1987; Vahter and Marafante 1987).

Arsenic methyltransferase and MMA methyltransferase activities have been purified to homogeneity from cytosol of rabbit liver (Zakharyan et al. 1995), Rhesus monkey liver (Zakharyan et al. 1996), and rat liver (Thomas et al. 2004). It appears that a single protein catalyzes both activities. This activity transfers a methyl group from S-adenosylmethionine to As(+3) yielding MMA, which is then further methylated to DMA. Reduced glutathione is probably a co-factor *in vivo*, but other thiols can substitute *in vitro* (L-cysteine, dithiothreitol). The substrate saturation concentration for rabbit arsenite methyltransferase is 50 μM , for MMA methyltransferase it is 1,000 μM . The purified activity is specific for arsenite and MMA; selenite, selenate, selenide, and catechols do not serve as substrates. Thomas et al. (2004) reported cloning the gene for an S-adenosylmethionine-dependent methyltransferase from rat liver cytosol that catalyzes the conversion of arsenic to methylated and dimethylated species. It bears a high similarity to translations of *cyt19* genes in both the mouse and the human; both this gene and protein are now termed arsenic (+3 oxidation state) methyltransferase (AS3MT).

Studies in mice indicate that exposure to arsenic does not induce arsenic methylation activity (Healy et al. 1998). Mice receiving up to 0.87 mg As/kg/day as sodium arsenate in drinking water for 91 days had the same arsenic methylating activity as unexposed controls. Specific activities were highest in testis (1.45 U/mg) followed by kidney (0.70 U/mg), liver (0.40 U/mg), and lung (0.20 U/mg). None were affected by arsenic exposure.

An alternative biotransformation pathway (Figure 3-8) has recently been proposed for arsenic (Hayakawa et al. 2005) based on the nonenzymatic formation of glutathione complexes with arsenite resulting in the formation of arsenic triglutathione. The arsenic triglutathione is subsequently methylated by AS3MT to form monomethyl arsenic glutathione. At low glutathione levels (1 mM), the monomethyl arsenic glutathione is hydrolyzed to form MMA(III). At high glutathione levels (5 mM), the monomethyl arsenic glutathione is methylated to dimethylarsinic glutathione by AS3MT. Dimethylarsinic glutathione is quickly hydrolyzed to form DMA(III) (Hayakawa et al. 2005; Thomas et al. 2007). In the classical inorganic arsenic biotransformation pathway (Figure 3-7), MMA(V) is converted to the more toxic MMA(III); in contrast, in the alternative pathway, MMA(III) is converted to the less toxic MMA(V).

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Figure 3-8. Alternative Inorganic Arsenic Biotransformation Pathway

ATG = arsenic triglutathione; DMAG = dimethylarsinic glutathione; GSH = glutathione; MADG = monomethyl arsenic glutathione; SAHC = S-adenosylhomocysteine; SAM = S-adenosylmethionine

Source: Hayakawa et al. 2005; Thomas et al. 2007

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Since methylation tends to result in lower tissue retention of inorganic arsenic (Marafante and Vahter 1984, 1986; Marafante et al. 1985; Vahter and Marafante 1987), the methylation process is usually viewed as a detoxification mechanism. However, several studies showing an elevated toxicity of MMA(III) relative even to As(III) in cultured human liver cells (Petrick et al. 2000, 2001) have called this assumption into question. Because methylation is an enzymic process, an important issue is the dose of arsenic that saturates the methylation capacity of an organism, resulting in a possible increased level of the more toxic As(III) in tissues, or whether or not such a dose exists. Limited data from studies in humans suggest that methylation may begin to become limiting at doses of about 0.2–1 mg/day (0.003–0.015 mg/kg/day) (Buchet et al. 1981b; Marcus and Rispin 1988). However, these observations are relatively uncertain since they are based on data from only a few subjects, and the pattern of urinary excretion products in humans who ingested high (near lethal) oral doses or were exposed to elevated levels in the workplace is not much different from that in the general population (Lovell and Farmer 1985; Vahter 1986). Furthermore, the nutrient intakes reported by Engel and Receveur (1993) were sufficient to accommodate the body stores of methyl groups needed for arsenic biomethylation. At the highest arsenic level reported in the endemic area, the biomethylation process required only a few percent of the total daily methyl intake (Mushak and Crocetti 1995). Thus, the dose rate at which methylation capacity becomes saturated cannot be precisely defined with current data.

Organic Arsenicals. With the exception of arsenosugars, which may undergo extensive metabolism, organic arsenicals appear to undergo little metabolism. Humans who ingested a dose of MMA converted a small amount (about 13%) to DMA (Buchet et al. 1981a). Similarly, in mice and hamsters, DMA and MMA are primarily excreted unchanged in the urine (Hughes et al. 2005; Marafante et al. 1987b; Vahter et al. 1984). In mice, a small percentage of MMA is methylated to DMA and some is further methylated to trimethylarsine oxide (TMAO) (Hughes et al. 2005). In contrast, administration of MMA(III) to mice resulted in the excretion of mostly DMA(V) and smaller amounts of MMA(V), MMA(III), and DMA(III) (Hughes et al. 2005). As with MMA, only a small percentage (<10%) of the DMA is methylated to TMAO (Hughes et al. 2005; Marafante et al. 1987b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

MMA and DMA are more extensively methylated in rats compared to other animal species. After 1 week of exposure to 100 mg As/kg/day as MMA in drinking water, rats excreted 50.6% of the total arsenic in urine as MMA, 19.0% as DMA, 6.9% as TMAO, and 0.4% as tetramethylarsonium (Yoshida et al. 1998). In contrast, mice exposed to a single dose of 40 mg As/kg as MMA excreted 89.6% of the dose as MMA, 6.2% as DMA, and 1.9% as TMAO (Hughes et al. 2005). Similarly, 24 hours after administration of a

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single oral dose of 50 mg As/kg as MMA in hamsters, 26.9% was excreted in urine as MMA, 1.43% as DMA, and 0.07% as trimethylarsenic compound (Yamauchi et al. 1988). As with MMA, oral exposure of mice and hamsters to DMA results in most of the dose being excreted in the urine in the form of DMA (or DMA complex) (Marafante et al. 1987b); in rats, the levels of DMA and TMAO are about equal (Yoshida et al. 1998).

The available data suggest that the methylarsenates are not demethylated to inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 1977; Yamauchi and Yamamura 1984; Yoshida et al. 2001).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Inorganic Arsenicals. As noted previously (see Section 3.4.1.1), urinary excretion of arsenic appears to account for 30–60% of the inhaled dose (Holland et al. 1959; Pinto et al. 1976; Vahter et al. 1986). Since the deposition fraction usually ranges from about 30 to 60% for most respirable particles (EPA 1989b), this suggests that nearly all arsenic that is deposited in the lung is excreted in the urine. The time course of excretion in humans exposed by inhalation has not been thoroughly investigated, but urinary arsenic levels in workers in a smelter rose within hours after they came to work on Monday and then fell over the weekend (Vahter et al. 1986). This implies that excretion is fairly rapid, and this is supported by intratracheal studies in rats (Rhoads and Sanders 1985) and hamsters (Marafante and Vahter 1987), where whole-body clearance of administered arsenate or arsenite occurred with a half-time of 1 day or less. However, the study in rats (Rhoads and Sanders 1985) found that the clearance of arsenic trioxide was biphasic, with 95% cleared with a half-time of 29 minutes and the remaining arsenic cleared with a half-time of 75 days. For sodium arsenate and sodium arsenite, <0.1% of the dose was retained in the lung 3 days after exposure of hamsters; 1.3% of the arsenic trisulfide dose was retained after 3 days (Marafante and Vahter 1987). The Marafante and Vahter (1987) study suggested that lung clearance was influenced by compound solubility. The primary forms of arsenic found in the urine of inhalation-exposed humans are DMA and MMA, with inorganic arsenic comprising <25% of the total urinary arsenic (Apostoli et al. 1999).

Organic Arsenicals. No studies were located regarding the excretion of organic arsenicals by humans or animals after inhalation exposure. However, rats that were given a single intratracheal dose of DMA

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excreted about 60% in the urine and about 8% in the feces within 24 hours (Stevens et al. 1977). This indicates that organic arsenicals are likely to be promptly excreted after inhalation exposure.

3.4.4.2 Oral Exposure

Inorganic Arsenicals. Direct measurements of arsenic excretion in humans who ingested known amounts of arsenite or arsenate indicate that very little is excreted in the feces (Bettley and O'Shea 1975), and that 45–85% is excreted in urine within 1–3 days (Apostoli et al. 1999; Buchet et al. 1981a; Crecelius 1977; Mappes 1977; Tam et al. 1979b). At low exposure levels, urinary arsenic levels generally increase linearly with increasing arsenic intake (Calderon et al. 1999). During lactation, a very small percent of ingested arsenic may also be excreted in the breast milk (Concha et al. 1998a). A similar pattern of urinary and fecal excretion is observed in hamsters (Marafante and Vahter 1987; Yamauchi and Yamamura 1985) and mice (Vahter and Norin 1980); this pattern is typically modeled as a biphasic process (e.g., Hughes et al. 2003). Generally, whole body clearance is fairly rapid, with half-times of 40–60 hours in humans (Buchet et al. 1981b; Mappes 1977). Clearance is even more rapid in mice and hamsters, with 90% removed in 2 days (Hughes et al. 2003; Marafante and Vahter 1987; Vahter 1981; Vahter and Norin 1980).

A study in pregnant women exposed to elevated levels of inorganic arsenic in drinking water found that most of the ingested arsenic was excreted in the urine as DMA (79–85%), with smaller amounts excreted as inorganic arsenic (8–16%) or MMA (5–6%) (Christian et al. 2006). Similarly, in mice, arsenate is primarily excreted in the urine as DMA, with lesser amounts of inorganic arsenic and MMA (Kenyon et al. 2005). Following a single oral dose of 10 $\mu\text{mol/kg}$ sodium arsenate, 78.4% was excreted as DMA, 20.2% as inorganic arsenic, and 1.45% as MMA; at a 10-fold higher dose, the ratio of DMA to inorganic arsenic decreased (57.7% DMA, 39.8% inorganic arsenic, and 2.59% MMA).

Arsenic is also excreted in the bile via the formation of two arsenic-glutathione complexes (arsenic triglutathione and methylarsenic diglutathione) (Kala et al. 2000). In rats administered 5.0 mg/kg sodium arsenite, equal amounts of arsenic triglutathione and methylarsenic diglutathione were found in the bile 18–20 minutes after exposure. At a lower arsenic dose (0.5 mg/kg), only methylarsenic diglutathione was found. As discussed in Section 3.4.4.4, biliary excretion of arsenic has also been detected in mice, hamsters, guinea pigs, and rabbits following parenteral exposure (Csanaky and Gregus 2002).

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Organic Arsenicals. Studies in humans indicate that ingested MMA and DMA are excreted mainly in the urine (75–85%), and this occurs mostly within 1 day (Buchet et al. 1981a; Marafante et al. 1987b). This is supported by studies in rats, mice, and hamsters, although in animals, excretion is more evenly distributed between urine and feces (Hughes et al. 2005; Marafante et al. 1987b; Stevens et al. 1977; Yamauchi and Yamamura 1984; Yamauchi et al. 1988). In mice administered 40 mg As/kg as DMA, 56.4% was excreted in the urine as DMA, 7.7% as a DMA complex, and 3.5% as TMAO during a 48-hour period after dosing; in the feces, 24.3% was DMA and 4.9% as DMA complex (Marafante et al. 1987b). In hamsters, 38.7% was DMA, 11.2% as DMA complex, and 6.4% as TMAO in the urine; in the feces, 37.3% as DMA and 4.9% as DMA complex. As with DMA, most MMA is excreted in the urine and feces as parent compound. In the urine of mice administered 0.4 mg As/kg as MMA, 98.2% of the urinary arsenicals was in the form of MMA(V) and 1.8% as MMA(III) (Hughes et al. 2005); at a 10-fold higher dose, 89.6% was excreted as MMA(V), 1.2% as MMA(III), 6.2% as DMA(V), 1.1% as DMA(III), and 1.9% as TMAO. As discussed previously, exposure of rats to MMA or DMA results in the excretion of a higher percentage of metabolites. After 1 week exposure to MMA, 50.6% of the dose was excreted as MMA, 19.0% as DMA, and 6.9% of TMAO (Yoshida et al. 1998). A 1-week exposure to DMA, 44.9% was excreted as DMA in the urine and 40.0% as TMAO (Yoshida et al. 1998). A longer-term exposure to DMA (>7 months) resulted in a higher percentage of the amount of parent compound excreted; 56–65% as DMA and 23–35% as TMAO (Li et al. 1998; Wanibuchi et al. 1996; Yoshida et al. 1998).

In mice and hamsters, DMA and MMA are rapidly cleared from the body (Hughes et al. 2005; Marafante et al. 1987b; Vahter et al. 1984). In mice, 85% of the initial oral dose of DMA was eliminated from the body with a half-life of 2.5 hours (Vahter et al. 1984). In contrast to the mouse data, 45% of the initial DMA dose to rats was eliminated with a half-time of 13 hours and the remaining 55% had an elimination half-time of 50 days (Vahter et al. 1984).

3.4.4.3 Dermal Exposure

Inorganic Arsenicals. No studies were located regarding excretion of inorganic arsenicals in humans or animals following dermal exposure. In rats, arsenic absorbed through the tail was excreted approximately equally in urine and feces, similar to the excretion pattern following oral exposure (Dutkiewicz 1977).

Organic Arsenicals. No studies were located regarding excretion of organic arsenicals in humans or animals following dermal exposure.

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3.4.4.4 Other Routes of Exposure

Inorganic Arsenicals. Excretion of arsenate and arsenite following parenteral exposure of animals is similar to that seen following oral exposure. In rabbits and mice, urinary excretion within 8 hours usually accounts for about 50–80% of the dose (Maehashi and Murata 1986; Maiorino and Aposhian 1985; Vahter and Marafante 1983). Somewhat lower levels (30–40%) are excreted in the urine of marmoset monkeys (Vahter and Marafante 1985; Vahter et al. 1982), probably because of the absence of methylation in this species. Whole-body clearance studies in mice indicate that arsenate is over 65% removed within 24 hours, while arsenite is about 86% removed at 24 hours (Lindgren et al. 1982). A relatively small proportion of an injected dose of arsenic V (10% for rats, 4% for mice, and <2% for hamsters, guinea pigs, and rabbits) was found to be excreted into the bile within the first 2 hours postinjection (Csanaky and Gregus 2002). Following arsenic III injection, a much greater percentage (92% for guinea pigs and 75% for rats) of the arsenic was found in the bile in the first 2 hours after administration (Csanaky and Gregus 2002). Similarly, approximately 40% of an intravenous dose of sodium arsenite was excreted into the bile of rats, most of it occurring during the first hour after exposure (Kala et al. 2000). Kala et al. (2000) determined that the biliary transport of arsenic was dependent on the formation of arsenic-glutathione complexes, which were transported out of hepatocytes by multidrug resistance associated protein 2 (MRP2/cMOAT); most of the arsenic in bile was in the form of arsenic triglutathione or methylarsenic diglutathione.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewett and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and

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Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

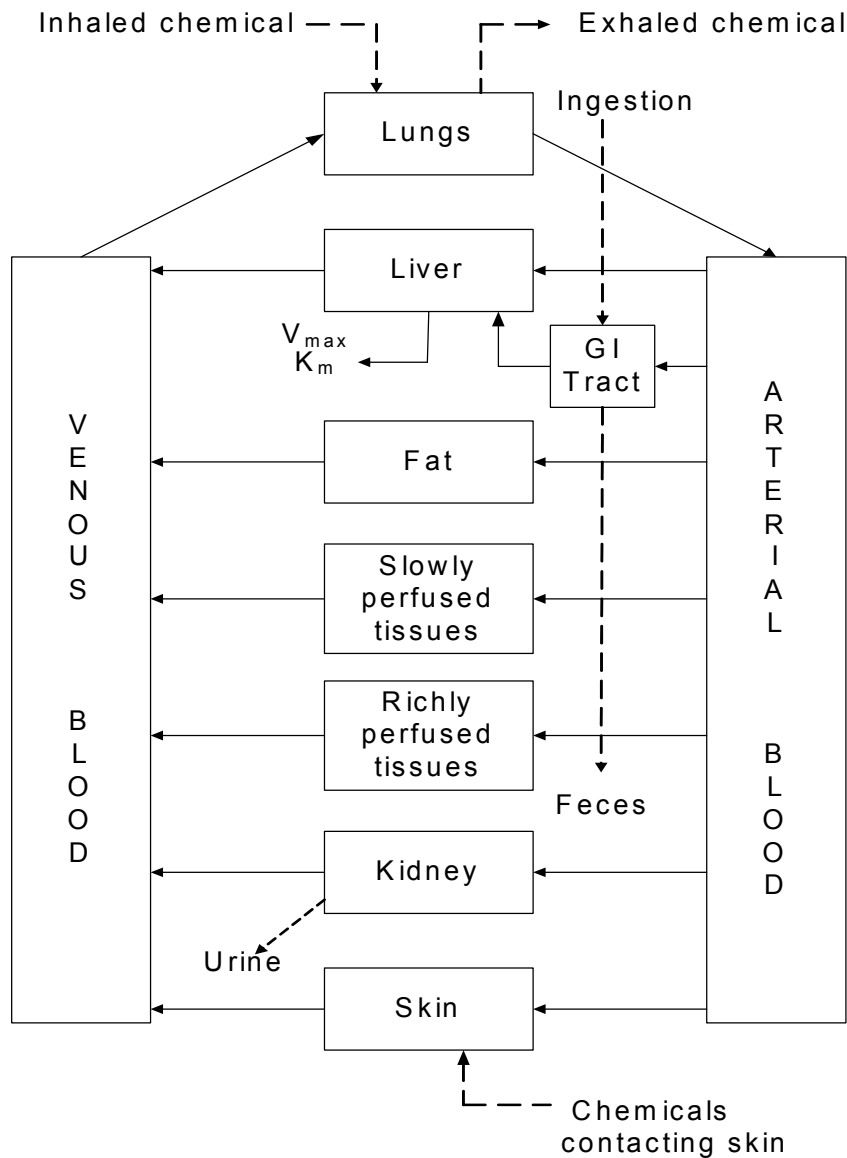
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-9 shows a conceptualized representation of a PBPK model.

If PBPK models for arsenic exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

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Figure 3-9. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

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Several PBPK models have been developed for inorganic arsenic; the Mann, Yu, and Menzel models are discussed below. A joint research effort between the Chemical Industry Institute of Toxicology (CIIT) Centers for Health Research, EPA, ENVIRON International, and the Electric Power Research Institute (EPRI) is underway to develop a biologically based dose response model of carcinogenicity. Part of this effort involves refining the existing PBPK models (Clewell et al. 2007).

3.4.5.1 Summary of PBPK Models

The Mann model (Gentry et al. 2004; Mann et al. 1996a, 1996b), Yu model (Yu 1998a, 1998b; Yu 1999a, 1999b), and Menzel model (Menzel et al. 1994) are the PBPK models for arsenic currently available. The Mann model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral and inhalation exposure in mice, hamsters, rabbits, and humans. The Yu model simulates the absorption, distribution, metabolism, elimination, and excretion of As(+3), As(+5), MMA, and DMA after oral exposure to inorganic arsenic in mice, rats, or humans. The Menzel model is a preliminary model that predicts internal organ burden of arsenic during specific oral exposures, simulating the metabolism, distribution to organs and binding to organs in mice, rats, and humans.

3.4.5.2 Arsenic PBPK Model Comparison

The Mann model is a well-derived model, consisting of multiple compartments and metabolic processes, and modeling four chemical forms of arsenic (two organic and two inorganic), which has been validated using experimental data. The Yu model has more compartments than the Mann model, also models metabolism and fate of four forms of arsenic, and has likewise been validated using experimental data. The Menzel model is still preliminary and has not been validated.

3.4.5.3 Discussion of Models**The Mann Model**

Risk assessment. The Mann model was not used for risk assessment.

Description of the model. The Mann model was initially developed to simulate oral, intratracheal, and intravenous exposure to arsenic in rabbits and hamsters (Mann et al. 1996a). In a companion paper, the model was expanded to include inhalation exposure and extrapolated and applied to humans (Mann et al. 1996b). A subsequent paper further expanded the model to include mice (Gentry et al. 2004).

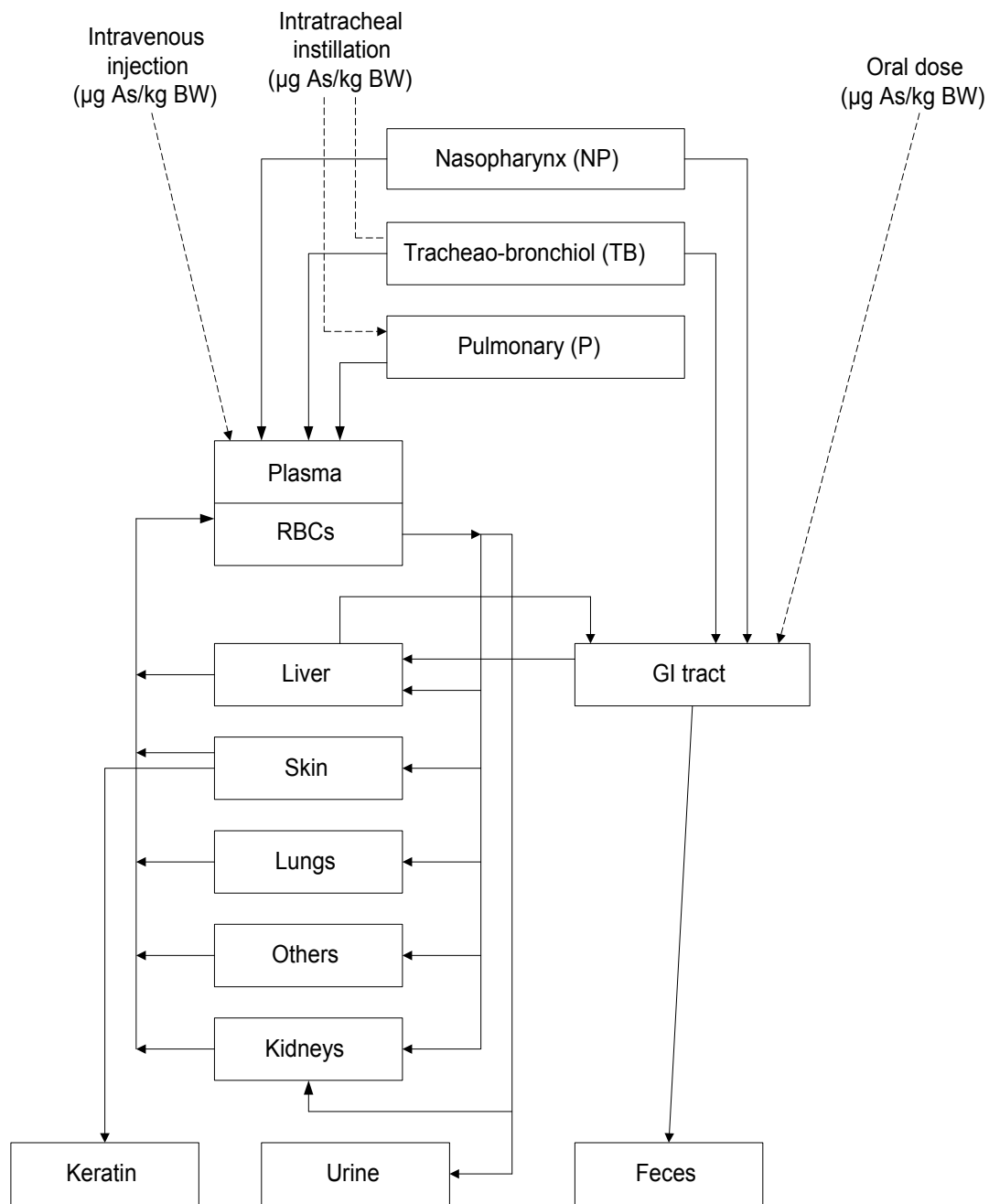
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The model consists of six tissue compartments: blood, liver, kidneys, lungs, skin, and other tissues. The blood compartment is divided into plasma and red blood cell subcompartments, considered to be at equilibrium. Three routes of exposure are considered in the model. Oral exposure is considered to enter the liver from the gastrointestinal tract via first-order kinetics. Intratracheal exposure results in deposition into the pulmonary and tracheo-bronchial regions of the respiratory tract. Uptake into blood from the pulmonary region is considered to be via first order kinetics into plasma, uptake from the tracheo-bronchial region is by both transfer into plasma and transport into the gastrointestinal tract. Intravenous injection results in a single bolus dose into the plasma compartment.

Metabolism in the model consists of oxidation/reduction and two methylation reactions. The oxidation/reduction of inorganic arsenic was modeled as a first order process in the plasma, with reduction also included in the kidneys. Methylation of As(+3) was modeled as a two-step process occurring in the liver according to Michaelis-Menton kinetics.

Most physiological parameters were derived by scaling to body weight. In cases where parameters were not available (absorption rates, tissue affinity, biotransformation), estimates were obtained by fitting. This was done by duplicating the initial conditions of published experiments in the model, varying the unknown parameters and comparing the results of the simulation to the reported results. Tissue affinity constants were estimated using reported arsenic levels in tissues at various times after exposure. Metabolic rate constants and absorption rate constants were estimated using data for excretion of arsenic metabolites in urine and feces. Figure 3-10 shows the animal model and Tables 3-11, 3-12, 3-13, and 3-14 provide the parameters used in the animal model. The human model is similar to the animal models with adjustments for body weight and absorption and metabolic rates. A naso-pharynx compartment is included in the human model, which was not present in the animal models. Penetration and deposition in the respiratory tract are based on the log-normal particle size distribution of the aerosol. Metabolic and absorption rate constants were fitted using experimental data on urinary excretion of arsenic following a single oral dose of As(+3) (Buchet et al. 1981a) or As(+5) (Tam et al. 1979b) in volunteers. The lung absorption rate constant was obtained by fitting the total urinary excretion of arsenic as predicted with the model to experimental data obtained from occupational exposure to arsenic trioxide (Offergelt et al. 1992). Figure 3-11 shows the human model, and Tables 3-15 and 3-16 provide the data and constants used in the human model.

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Figure 3-10. Parameters Used in the Mann PBPK Model for Animals

Source: Mann et al. 1996b

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Table 3-11. Parameters Used in the Mann PBPK Model for Animals

Physiological parameter	Rabbit (body weight=3.5 kg)	Hamster (body weight=0.100 kg)
Blood volume (mL)	253	7.0
Organ weight (g)		
Liver	121	4.8
Kidneys	25	1.2
Lungs	31	1.0
Skin	420	17.1
Organ volume (mL)		
Others	2,386	62.0
Lumen volume (mL)		
Stomach	15	0.5
Small intestine	20	0.6
Blood flow (mL/minute)		
Cardiac output	556	38.3
Liver, hepatic	25	1.2
Liver, splanchnic	98	6.0
Kidneys	100	7.0
Lungs	13	0.7
Skin	38	2.6
Others	282	20.8
Clearance (mL/minute)		
Glomerular Filtration Rate	10	0.6
Small intestine length (cm)	180	56.0
Total capillary surface area (cm ²)	93,835	2,681.0

PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

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Table 3-12. Tissue Affinity Constants (K_{ij}) Obtained for the Mann PBPK Model for Animals by Fitting for Rabbits and Hamsters

Tissue (<i>i</i>)	K_{ij} (unitless)			
	As(V)	As(III)	MMA	DMA
Liver	1	200	10	1
Kidneys	40	20	100	5
Lungs	1	1	1	20
Skin	1	60	50	1
Others	10	40	1	1

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

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Table 3-13. Metabolic Rate Constants for the Mann PBPK Model for Animals Obtained by Fitting for Rabbits and Hamsters

Oxidation/reduction	First order	Rabbit	Hamster
Reduction	(1/hour)	3,000.00	100.00
Oxidation	(1/hour)	6,000.00	400.00
Kidney reduction	(1/hour)	30.00	1.00
Methylation	Michaelis–Menten		
1st step	K_{MMA} ($\mu\text{mol/mL}$)	0.05	0.12
	$V_{MAX_{MMA}}$ ($\mu\text{mol/mL-hour}$)	4.00	0.12
2nd step	K_{DMA} ($\mu\text{mol/mL}$)	0.90	0.08
	$V_{MAX_{DMA}}$ ($\mu\text{mol/mL-hour}$)	1.50	0.12

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

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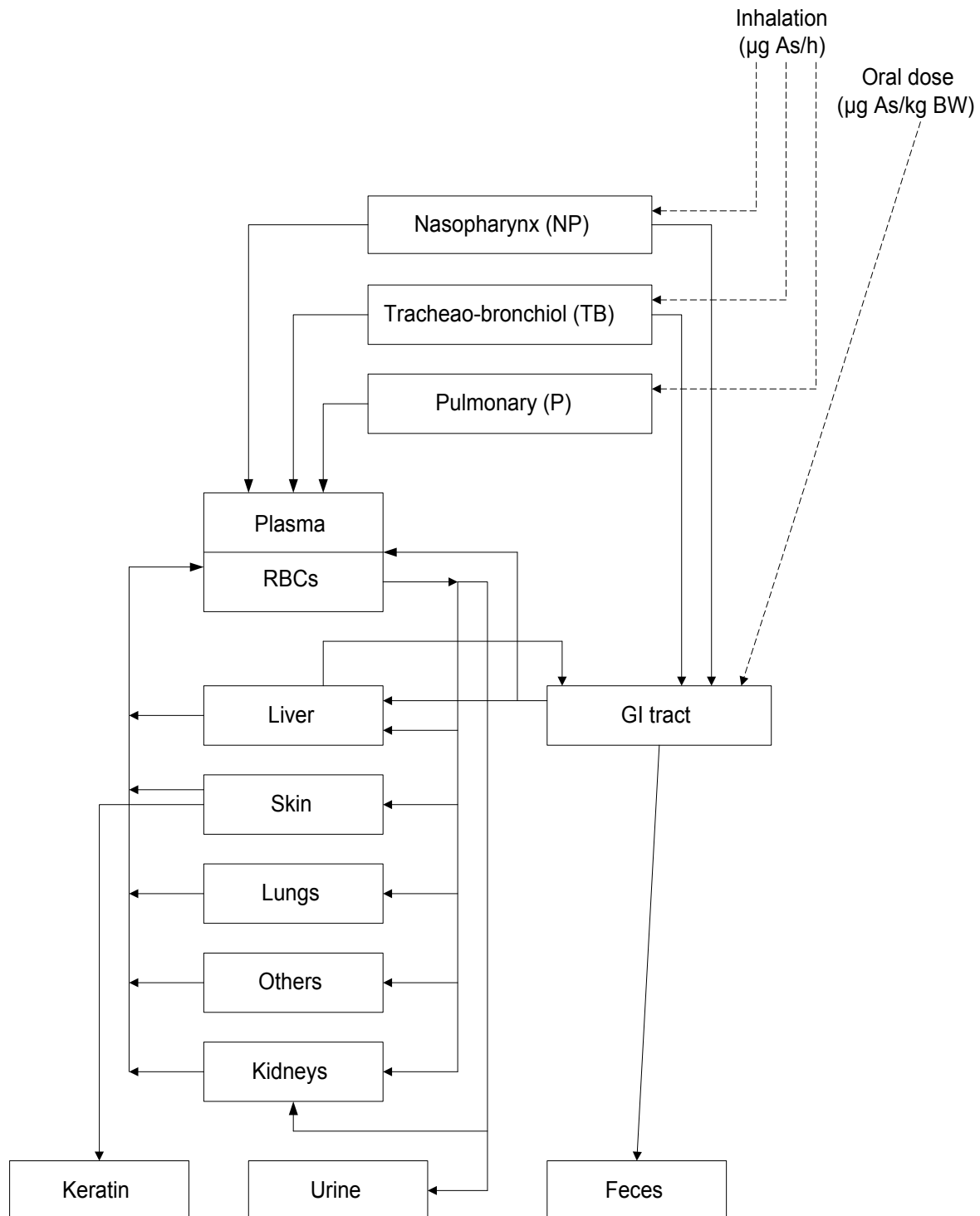
Table 3-14. Fitted Gastrointestinal Tract and Lung Absorption Half-time for the Hamster for the Mann PBPK Model

Arsenic compound	Absorption, half-time (hour)	
	Gastrointestinal tract	Lung
As(V)		
Na ₃ (AsO ₄)	0.08	12
Pb ₃ (AsO ₄)	0.39	690
As ₂ O ₅	0.28	—
As(III)		
NaAsO ₂	0.08	12
As ₂ S ₃	0.48	12
As ₂ O ₃	0.02	—
DMA	0.09	—

DMA = dimethylarsinic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996a

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Figure 3-11. Parameters Used in the Mann PBPK Model for Humans

Source: Mann et al. 1996b

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Table 3-15. Physiological Data Used in the Mann PBPK Model for Humans

Physiological parameter	Organ	Units	Human (body weight=70 kg)
Blood volume		mL	5,222
Organ weight	Liver	g	1,856
	Kidneys	g	314
	Lungs	g	584
	Skin	g	6,225
	Others	g	55,277
Lumen volume	Stomach	mL	274
	Small intestine	mL	393
Blood flow	Cardiac output	L/minute	5.29
	Liver, hepatic	L/minute	0.32
	Liver, splanchnic	L/minute	1.02
	Kidneys	L/minute	0.95
	Lungs	L/minute	0.16
	Skin	L/minute	0.35
	Others	L/minute	2.49
Creatinine			
Male		g/day	1.7
Female		g/day	1.0
Clearance			
Glomerular filtration rate		mL/minute	156
Small intestine length		cm	481
Nasopharynx area		cm ²	177
Tracheobronchial area		cm ²	5,036
Pulmonary area		cm ²	712,471
Total capillary surface area		cm ²	1,877x10 ⁶

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996b

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Table 3-16. Tissue Affinity Constants (K_{ij}) Obtained by Fitting the Mann PBPK Animal Model for Use with Humans

Tissue (i)	K_{ij} (unitless)			
	As(V)	As(III)	MMA	DMA
Liver	1	200	10	1
Kidneys	40	20	100	5
Lungs	1	1	1	20
Skin	1	60	50	1
Red blood cells	0.2	1.5	0.2	0.2
Others	10	40	1	1

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; PBPK = physiologically based pharmacokinetic

Source: Mann et al. 1996b

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Validation of the model. The model was generally successful in describing the disposition of an intravenous dose of sodium arsenate in rabbits over a 24-hour period (Marafante et al. 1985). Discrepancies included a 6–7-fold overestimation of levels in skin at 24 hours and underestimation of As(+5) in plasma in the hour following injection. A statistical assessment of how well the model fit the empirical data was not presented. In hamsters, the model was also generally predictive of oral and intratracheal exposures (Marafante and Vahter 1987). Generally, predictions were better for the exposures to As(+5) than for those to As(+3).

The human model was validated using data from studies of repeated oral intake of sodium arsenite in volunteers (Buchet et al. 1981b), occupational exposure to arsenic trioxide and elemental arsenic (Vahter et al. 1986), and community exposure to As(+5) via drinking water (Harrington et al. 1978; Valentine et al. 1979). Simulations were generally in good agreement with the experimental data.

The predictions of tissue distribution, metabolism, and elimination of arsenic compounds from the mouse model were compared with experimental data, and showed generally good agreement. The model tended to overpredict the concentration of organic arsenicals in the lungs, and to a lesser extent in the kidneys and liver, while for inorganic arsenic, the model overpredicted the levels of arsenic (V) present in the urine of acutely-exposed mice.

Target tissues. Levels in skin were not well predicted by this model in animals. Results for the lung were not presented, except for the mouse model, which tended to overpredict lung levels. The human model was only used to predict urinary metabolites.

Species extrapolation. Species extrapolation was not attempted in this model. However, tissue affinities derived for the rabbit and hamster models were used in the human model.

Interroute extrapolation. Interroute extrapolation was not attempted in this model.

The Menzel Model

Risk assessment. The Menzel model was not used for risk assessment.

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Description of the model. The Menzel model was developed to simulate oral exposure to arsenic from drinking water and food. Inhalation of arsenic in the particulate phase or as arsine gas is not considered. The chemical species in drinking water is assumed to be As(+5).

The model consists of two sets of compartments: those in which the pools of arsenic are not influenced by blood perfusion, and those in which blood perfusion does determine arsenic burden. The former set of compartments includes the gut, feces, hair, bladder, and urine. The latter set of compartments included lung, liver, fat, skin, kidney, and other tissues. Oral exposure is considered to enter the liver from the gastrointestinal tract.

The model followed that of Andersen and coworkers (Andersen et al. 1987; Ramsey and Andersen 1984). Data from mice were used to test predictions of absorption. Excretion is considered to be rapid and complete into the urine, with no reabsorption from the kidney. Fecal arsenic content accounts for unabsorbed arsenic excreted in the bile, and complex arsenic species from food. Metabolism includes reduction by glutathione and methylation. Arsenic accumulation in the skin, hair and nails was included by assuming that arsenic binds irreversibly to protein sulfide groups in hair and nails.

Validation of the model. The model was preliminary and has not been validated.

Target tissues. Target tissues have not yet been modeled.

Species extrapolation. Species extrapolation was not attempted in this model.

Interoute extrapolation. Interoute extrapolation was not attempted in this model.

The Yu Model

Risk assessment. The Yu model was not used for risk assessment.

Description of the model. The Yu model was developed to simulate oral exposure to arsenic in mice and rats (Yu 1998a, 1998b), and was later adapted for oral exposures in humans (Yu 1999a, 1999b). Inhalation of arsenic in the particulate phase or as arsine gas is not considered. As(+3), As(+5), MMA, and DMA were all considered in the model, though the movements of MMA and DMA were not considered.

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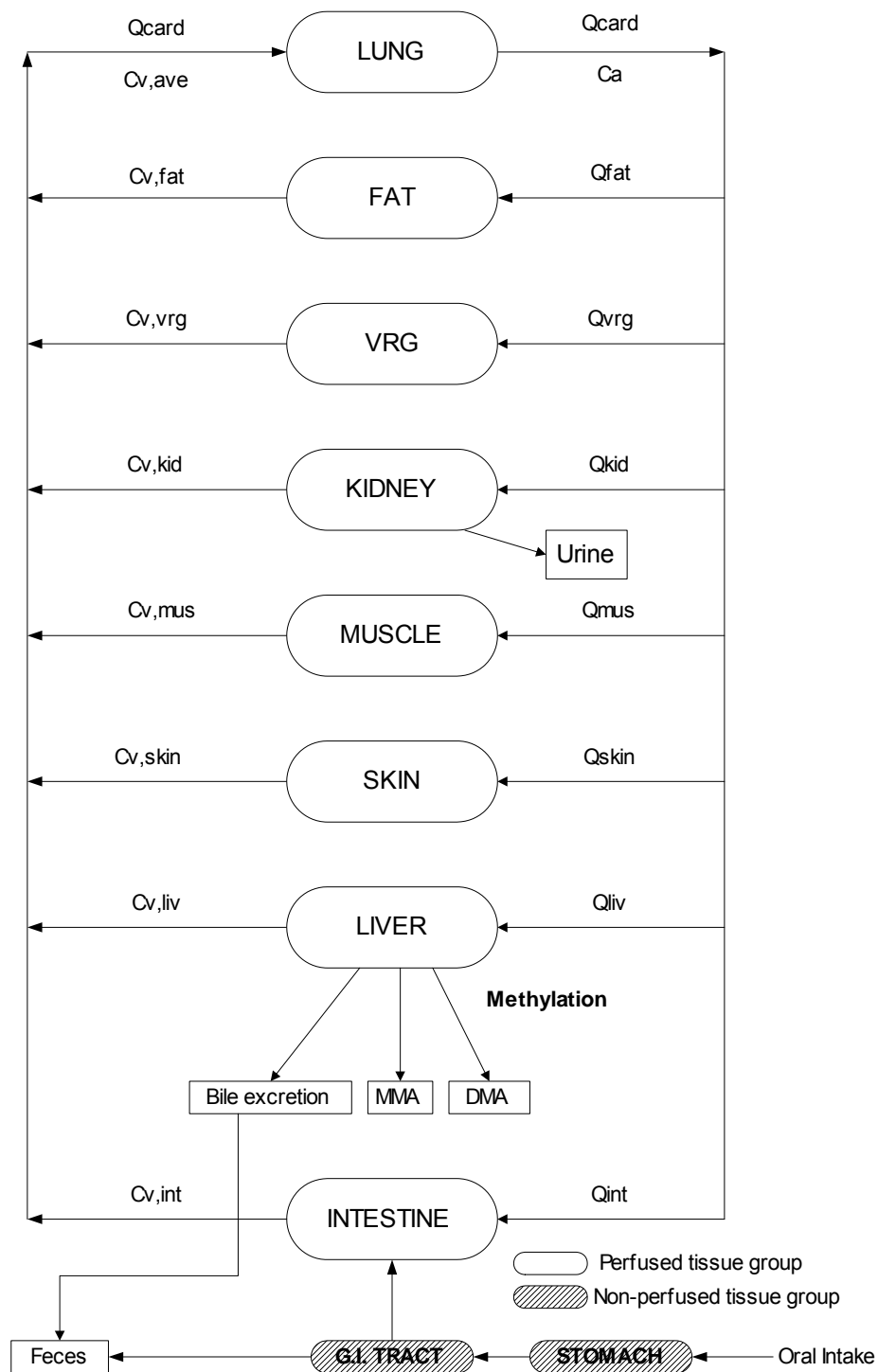
The model consists of eight tissue compartments: intestine, skin, muscle, fat, kidney, liver, lung, and vessel-rich group (VRG, e.g., brain); in the human model, the VRG and kidney compartments were combined. Only oral exposure was considered. Absorption is based on absorption to the stomach, which then passes the arsenic to the gastrointestinal tract. From the gastrointestinal tract, arsenic is either transferred to the blood or excreted in the feces.

The physiological parameters for the model were obtained from published values in the literature. Tissue/blood partition coefficients were based on the postmortem blood and tissue concentrations from a fatal human poisoning case study (Saady et al. 1989). Tissue volumes and blood flow rates were based on published values from a number of sources (EPA 1988e; Reitz et al. 1990). Absorption and excretion rate constants were based on experimental observations of blood concentrations and urinary and fecal excretion following oral administration of inorganic arsenic (Odanaka et al. 1980; Pomroy et al. 1980). Metabolic rate constants for the methylation and dimethylation of inorganic arsenic were also based on experimental observations (Buchet et al. 1981a; Crecelius 1977). Figure 3-12 shows the model and Table 3-17 provides the parameters used for each species.

Validation of the model. The model was generally successful at predicting the urinary excretion 48 hours after administration of 5 mg/kg inorganic arsenic in both rats and mice. After 48 hours, the observed/predicted ratios associated with excreted doses ranged from 0.78 to 1.11 for the mouse and from 0.85 to 0.93 for the rat. However, the model overpredicted the amount of inorganic arsenic found in the feces of mice at 24 and 48 hours, and overpredicted the amount of DMA formed by exposed mice at 48 hours. In rats, the model overestimated the urinary and fecal excretion of inorganic arsenic at 24 hours postexposure, though at 48 hours, measured values all fell within the predicted ranges. The human model was also generally successful at predicting the urinary excretion of arsenic compounds following oral exposure, based on results of controlled human exposure studies (Buchet et al. 1981a; Vahter 1983). In general, however, the model underpredicts excretion at early time points and overpredicts at later time points, with 24 hours being the time at which its predictive capabilities agreed most strongly with available data.

The ability of the model to predict tissue burdens was not compared to actual data for any species.

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Figure 3-12. Parameters Used in the Yu PBPK Model for Animals

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Table 3-17. Parameters Used in the Yu PBPK Model

	Mouse	Rat	Human
Partition coefficients			(As ^{III} /As ^V /MMA/DMA)
Intestine	6.0	6.0	2.8/2.8/1.2/1.4
Skin	5.0	5.0	2.5/2.5/1.25/1.25
VRG	6.0	6.0	Combined with kidney
Muscle	5.0	10.0	2.6/2.6/1.8/2.8
Fat	—	0.5	0.3/0.3/0.3/0.3
Kidney	8.5	7.5	4.15/4.15/1.8/2.075
Liver	10.0	10.0	5.5/5.3/2.35/2.65
Lung	4.0	4.0	4.15/4.15/1.8/2.075
Blood flow rate (mL/hour)			
Intestine	100	528	1,810
Skin	7.68	37.8	130
VRG	157	960	N/A
Muscle	153	1,260	25,850
Fat	—	253.2	6,467
Kidney	255	255	45,240
Liver	255	1,260	32,320
Lung	N/R	N/R	129,000
Tissue volume (mL)			
Intestine	1.94	6.9	558
Skin	1.83	15.4	606
VRG	0.81	23.0	N/A
Muscle	19.9	162	6,989
Fat	—	14.5	2,328
Kidney	0.484	1.63	248
Liver	1.67	5.82	422
Lung	0.124	1.0	400
Metabolism constants			
V _{max} (MMA) (μmol/hour)	0.45	0.15	11.25
V _{max} (DMA) (μmol/hour)	0.375	0.06	22.25
K _m (MMA) (μmol/hour)	1.0	0.2	0.01
K _m (DMA) (μmol/hour)	0.2	0.2	0.01

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Table 3-17. Parameters Used in the Yu PBPK Model

	Mouse	Rat	Human
First-order rate constants			(As ^{III} /As ^V /MMA/DMA)
K _{SI} (hour ⁻¹)	0.3	0.3	-/1.2/-/-
K _{AI} (hour ⁻¹)	1.5	3.6	-/1.2/-/-
K _{fecal} (hour ⁻¹)	0.33	0.048	-/0.0012/0.0/0.0
K _{urinary} (hour ⁻¹)	1.32	0.9	0.05/0.075/0.07/0.04
K _{biliary} (hour ⁻¹)	0.33	0.3	-/0.018/-/-

DMA = dimethylarsinic acid; MMA = monomethylarsonic acid; N/A = not applicable; N/R = not reported

Source: Yu 1998a, 1998b, 1999a, 1999b

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Target tissues. Model predictions of tissue burdens were not compared to actual data. The model accurately predicted, with a few exceptions, the urinary and fecal excretion of inorganic arsenic and its metabolites in rats, mice, and humans.

Species extrapolation. Species extrapolation beyond rats and mice was not attempted using this model. The human model has not been compared to, or linked with, either of the rodent models.

Interroute extrapolation. Interroute extrapolation was not attempted using this model.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Arsenic absorption depends on its chemical form. In humans, As(+3), As(+5), MMA, and DMA are orally absorbed $\geq 75\%$. Arsenic is also easily absorbed via inhalation. Absorption appears to be by passive diffusion in humans and mice, although there is evidence (Gonzalez et al. 1995) for a saturable carrier-mediated cellular transport process for arsenate in rats (for review, see Rosen 2002). Dermal absorption appears to be much less than by the oral or inhalation routes. Bioavailability of arsenic from soil appears to be lower via the oral route than it is for sodium salts of arsenic. Arsenic in soil may form water insoluble compounds (e.g., sulfides), which are poorly absorbed.

Arsenic and its metabolites distribute to all organs in the body; preferential distribution has not been observed in human tissues at autopsy or in experiments with animal species other than rat (in which arsenic is concentrated in red blood cells). Since the liver is a major site for the methylation of inorganic arsenic, a “first-pass” effect is possible after gastrointestinal absorption; however, this has not been investigated in animal models.

Arsenic and its metabolites are largely excreted via the renal route. This excretion mechanism is not likely to be saturated within the dose range expected from human exposure. Excretion can also occur via feces after oral exposure; a minor excretion pathway is nails and hair. The methylation of inorganic arsenic is the major metabolism pathway. The proportion of metabolites recovered in urine (As(+3), As(+5), MMA, DMA) are roughly consistent in humans regardless of the exposure scenario. However, interindividual variation is great enough that it cannot be determined if capacity limitation may occur in some individuals.

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The manifestation of arsenic toxicity depends on dose and duration of exposure. Single oral doses in the range of 2 mg As/kg and higher have caused death in humans. Doses as low as 0.05 mg As/kg/day over longer periods (weeks to months) have caused gastrointestinal, hematological, hepatic, dermal, and neurological effects. These effects appear to be a result of direct cytotoxicity. Long-term exposure (years) to drinking water at levels as low as 0.001 mg As/kg/day have been associated with skin diseases and skin, bladder, kidney, and liver cancer. Long-term inhalation exposure to arsenic has also been associated with lung cancer at air levels as low as 0.05–0.07 mg/m³. It is not clear at this time why long-term toxicity is different between the oral and inhalation routes, given that arsenic is easily absorbed into the systemic circulation by both routes.

Studies in mice and rats have shown that arsenic compounds induce metallothionein, a metal-binding protein thought to detoxify cadmium and other heavy metals, *in vivo* (Albores et al. 1992; Hochadel and Waalkes 1997; Kreppel et al. 1993; Maitani et al. 1987a). The potency of arsenic compounds in inducing metallothionein parallels their toxicity (i.e., As(+3) > As(+5) > MMA > DMA). For cadmium, it is thought that metallothionein binds the metal, making it biologically inactive. For arsenic, however, only a small percentage of the administered arsenic is actually bound to metallothionein (Albores et al. 1992; Kreppel et al. 1994; Maitani et al. 1987a). *In vitro* studies have shown that affinity of arsenic for metallothionein is much lower than that of cadmium or zinc (Waalkes et al. 1984). It has been proposed that metallothionein might protect against arsenic toxicity by acting as an antioxidant against oxidative injury produced by arsenic (NRC 1999).

3.5.2 Mechanisms of Toxicity

Mechanisms of arsenic-induced toxicity and carcinogenicity have not been clearly identified. However, recent efforts to elucidate mechanisms of arsenic toxicity and carcinogenicity have resulted in numerous *in vitro* and *in vivo* reports. Whereas these mechanistic studies typically employed relatively high arsenic exposure levels, some of the most recent studies were performed using more environmentally-relevant exposure levels. Due to the extremely large amount of mechanistic data for arsenic, it is not feasible to include all pertinent primary studies that address issues concerning proposed mechanisms of arsenic toxicity and carcinogenicity. Therefore, the following discussion of mechanisms of arsenic toxicity represents a summary of information from several recent review articles (Chen et al. 2004, 2005; Florea et al. 2005; Hughes 2002; Kitchin 2001; Lantz and Hays 2006; Navas-Acien et al. 2005; Rossman 2003; Roy and Saha 2002; Thomas et al. 2007; Vahter 2002).

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It is becoming increasingly evident that the toxicity and carcinogenicity of arsenic is likely to be closely associated with metabolic processes. Absorbed pentavalent arsenic (AsV) is rapidly reduced to trivalent arsenic (AsIII) at least partially in the blood. Much of the formed AsIII is distributed to tissues and taken up by cells (particularly hepatocytes). Many cell types appear to accumulate AsIII more rapidly than AsV. Because AsIII (as arsenite) is known to be more highly toxic than AsV (as arsenate), the reduction step may be considered bioactivation rather than detoxification. Glutathione appears to play a role in the reduction of AsV to AsIII, which is required prior to methylation. Methylation of arsenic ultimately forms relatively less toxic MMA and DMA; this process is accomplished by alternating between the reduction of AsV to AsIII and the addition of a methyl group; S-adenosylmethionine is considered to be the source of the methyl group. Both MMA and DMA are less reactive with tissue constituents than inorganic arsenic and both are readily excreted in the urine. The methylation process appears to include multiple intermediates, some of which are more reactive than inorganic arsenic. For example, reactive trivalent metabolites, MMAIII and DMAIII, have been detected in the urine of human subjects chronically exposed to arsenic in drinking water, and *in vitro* studies have demonstrated MMAIII to be more toxic than arsenite or arsenate to human hepatocytes, epidermal keratinocytes, and bronchial epithelial cells. Additional *in vitro* studies have demonstrated genotoxic and DNA damaging properties of both MMAIII and DMAIII.

AsV (as arsenate) has been demonstrated to: (1) replace phosphate in glucose-6-phosphate and 6-phosphogluconate *in vitro*, (2) replace phosphate in the sodium pump and the anion exchange transport system of human red blood cells, (3) diminish the *in vitro* formation of adenosine-*t'*-triphosphate (ATP) by replacing phosphate in enzymatic reactions, and (4) deplete ATP in some cellular systems, but not in human erythrocytes. However, it is becoming more apparent that the major source of arsenic toxicity and carcinogenicity is related to its reduction to arsenite.

AsIII (as arsenite) is known to react with thiol-containing molecules such as glutathione and cysteine *in vitro*. Methylated trivalent arsenics such as MMAIII are potent inhibitors of glutathione reductase and thioredoxin reductase. It has been suggested that binding of arsenite and methylated trivalent arsenicals to critical thiol groups could lead to the inhibition of essential biochemical reactions, alteration of cellular redox status, and eventual cytotoxicity. Binding of MMAIII and DMAIII to protein has also been demonstrated *in vitro*. Arsenite inhibits pyruvate dehydrogenase (PDH), a complex that oxidizes pyruvate to acetyl-CoA, a precursor to intermediates of the citric acid cycle that provides reducing equivalents to the electron transport system for ATP production. This property may explain the depletion of carbohydrates in arsenite-treated rats.

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Evidence that arsenic may induce alterations in nitric oxide metabolism and endothelial function includes findings that persons exposed to high levels of arsenic in drinking water had decreased serum and urine concentrations of nitric oxide metabolites, which was reversed upon intervention with drinking water containing lower levels of arsenic. Urinary arsenic levels have been inversely associated with nitric oxide production in activated monocytes. Arsenite concentrations of 1–25 μM inhibited endothelial nitric oxide synthase activity and resulting decreased cell growth in human endothelial cells, although lower concentrations up-regulated the expression of constitutive nitric oxide synthase 3, which might serve as an explanation for observed arsenic-induced cell growth and angiogenesis.

Although epidemiological studies demonstrate the carcinogenicity of arsenic in humans, early animal cancer bioassays failed to demonstrate a carcinogenic effect following lifetime exposure to inorganic arsenic. However, more recent focus has resulted in the development of animal models that exhibit carcinogenic activity in skin, urinary bladder, liver, and lung, tissues implicated in arsenic-induced cancer in humans. This concordance in target sites among animal models and humans indicates that common mechanisms of action may be applicable to humans and laboratory animals.

Several modes of action have been proposed to explain, at least in part, the carcinogenicity of arsenic. It is likely that multiple mechanisms are involved, some of which may relate to noncancer effects as well.

Oxidative Stress. Mechanistic studies of arsenic toxicity have suggested a role of the generation of reactive oxygen species in the toxicity of inorganic arsenic. Results of both *in vivo* and *in vitro* studies of arsenic-exposed humans and animals suggest the possible involvement of increased lipid peroxidation, superoxide production, hydroxyl radical formation, blood nonprotein sulfhydryls, and/or oxidant-induced DNA damage. Reduction of cellular oxidant defense by treatment with glutathione-depleting agents results in an increased sensitivity of cells to arsenic toxicity. Support for mechanisms of toxicity that involves arsenic-induced oxidative stress includes findings that inhaled arsenic can predispose the lung to oxidative damage, chronic low-dose arsenic alters genes and proteins that are associated with oxidative stress and inflammation, and major transcriptional regulators of altered genes are redox sensitive.

Genotoxicity. Collectively, *in vitro* and *in vivo* genotoxicity assays have demonstrated that arsenics cause single strand breaks, formation of apurinic/apyrimidinic sites, DNA base and oxidative base damage, DNA-protein crosslinks, chromosomal aberrations, aneuploidy, sister chromatid exchanges, and micronuclei. Chromosomal aberrations, characterized by chromatid gaps, breaks and fragmentation,

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endoreduplication, and chromosomal breaks, are dose-dependent and arsenite is more potent than arsenate. Both MMAIII and DMAIII are directly genotoxic and are many times more potent than arsenite at inducing DNA damage. Inorganic arsenic can potentiate the mutagenicity observed with other chemicals, although arsenic itself does not appear to induce point mutations. Arsenic-induced genotoxicity may involve oxidants or free radical species.

Altered Growth Factors→Cell Proliferation→Promotion of Carcinogenesis. Increased concentrations of growth factors can lead to cell proliferation and eventual promotion of carcinogenesis. Arsenic-induced cell death can also lead to compensatory cell regeneration and carcinogenesis. Altered growth factors, cell proliferation, and promotion of carcinogenesis have all been demonstrated in one or more systems exposed to arsenics. Altered growth factors and mitogenesis were noted in human keratinocytes. Cell death was observed in human hepatocytes and rat bladder epithelium. Cell proliferation was demonstrated in human keratinocytes and intact human skin and rodent bladder cells. Promotion of carcinogenesis was noted in rat bladder, kidney, liver, and thyroid, and mouse skin and lung.

Additional Mechanisms of Toxicity Data. Inorganic arsenic exposure has been shown to modify the expression of a variety of genes related to cell growth and defense, including the tumor suppressor gene p53, as well as to alter the binding of nuclear transcription factors. Carcinogenic effects of arsenic may result from a cocarcinogenic effect. Whereas arsenic exposure alone did not elicit skin tumors in mice, co-exposure to arsenic and ultraviolet light resulted in skin tumors that were greater in number and larger in size than those produced by ultraviolet light alone. Arsenate and arsenite enhanced the amplification of a gene that codes for the enzyme dihydrofolate reductase, arsenate being more potent than arsenite. Furthermore, inhibition of DNA repair has been demonstrated in arsenic-treated cells.

3.5.3 Animal-to-Human Extrapolations

The usefulness of animal models for toxicity studies with arsenic is significantly limited by two major factors. First and most importantly, no animal model exists for the health effect of greatest concern for human exposure: carcinogenicity in skin and other organs after oral exposure. Second, the pattern of metabolism in humans (significant excretion of the methylated forms of arsenic) is unlike that of most other mammalian species (the mouse and rabbit may be exceptions). The ratios of inorganic to organic arsenic excreted also vary between species. The rat sequesters arsenic in its erythrocytes and is not a suitable model for human toxicity.

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3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997h). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There is little evidence to suggest that arsenic functions as an endocrine disruptor. An association has been demonstrated between exposure to arsenic in drinking water and increased incidence of diabetes mellitus (Rahman et al. 1998; Tsai et al. 1999; Tseng et al. 2000; Wang et al. 2003), although dose-response relationships are not available and the mechanism of action for this response has not been characterized. Studies by Waalkes and coworkers (Waalkes et al. 2006a, 2006b) have suggested that in

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mice, arsenic may interact with estrogens to enhance production of female urogenital cancers and male hepatocellular cancer following exposure to arsenic *in utero*. The mechanism by which this might happen has not been elucidated. No other relevant data were located in humans or animals. Data on general effects of arsenic compounds on the endocrine system are presented in Sections 3.2.1.2 and 3.2.2.2 above.

In vitro studies provide suggestive evidence that arsenic may act as an endocrine disruptor. Studies by Bodwell et al. (2004, 2006) and Davey et al. (2007) demonstrate that arsenic can alter gene regulation of steroid hormone receptors for glucocorticoids, mineralocorticoids, progesterone, and estrogen.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek

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1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Arsenic has been recognized as a human toxicant for many centuries, and the symptoms of acute poisoning are well known. Children who are exposed to high levels of arsenic exhibit symptoms similar to those seen in adults, including respiratory, cardiovascular, dermal, and neurological effects, and vomiting if the arsenic is ingested (Borgoño et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Muzi et al. 2001; Rosenberg 1974; Zaldívar 1974; Zaldívar and Guillier 1977). Arterial thickening of the pancreas was observed in five children who died in Chile after chronic exposure to arsenic (Rosenberg 1974). Foy et al. (1992) described systemic effects of chronic arsenic exposure in children in a village near a tin and tungsten mining operation in Thailand. The arsenic concentration in water samples from 35 shallow wells averaged 0.82 mg As/L (range, 0.02–2.7 mg As/L). Piped water (available in some homes) had a concentration of 0.07 mg As/L. A survey of skin manifestations of arsenic poisonings was conducted in the autumn of 1987. The case reports of four children were presented. All of the children had hyperkeratosis and hyperpigmentation of the extremities, including tibia, palms, and soles. In addition, one child had developed weakness 3 years previously and had anorexia and a chronic cough for 1 year. She had been held back twice in school as a slow learner. On examination, she had a runny nose and

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weakness of her wrist joints. The liver was about 4 finger-breadths below the right costal margin with a sharp but tender edge. Blood arsenic levels ranged from 0.087 to 0.46 $\mu\text{g/mL}$ and the arsenic level in hair ranged from 14.4 to 20 $\mu\text{g/g}$. The authors concluded that the finding of typical skin manifestations of chronic arsenic poisoning suggests that it may take a considerably shorter period of time to develop these manifestations than previously thought. However, it is not known what effect co-exposure to tin and tungsten might have had on skin manifestations in these children. Exposure to high arsenic levels during gestation and/or during early childhood also was associated with significant increases in SMRs for lung cancer and bronchiectasis during adulthood in a study of residents in a city in Chile with high arsenic levels in the drinking water (near 0.9 mg/L) during several years (Smith et al. 2006).

As previously mentioned in Sections 3.2.1.4 and 3.2.2.4, exposure of children to arsenic also has been associated with neurological deficits in children. Studies by Wasserman et al. (2004, 2007) of 6- and 10-year-old children from Bangladesh reported small but significant decreases in some tests of cognitive function associated with levels of arsenic in the water ≥ 0.05 mg/L. A study of pre-school age children in West Bengal, India, reported an association between current urinary arsenic concentrations, but not long-term water arsenic, and small decrements in intellectual tests (von Ehrenstein et al. 2007). Similar results were reported in a study of children in Taiwan (Tsai et al. 2003) and in China (Wang et al. 2007). Neurological effects have also been associated with elevated levels of arsenic in the air. For example, Bencko et al. (1977) reported that children of approximately 10 years of age living near a power plant burning coal of high arsenic content showed significant hearing losses (increased threshold) compared to a control group of children living outside the polluted area (Bencko et al. 1977). Also, in a study of Mexican children, Calderón et al. (2001) reported that children living near a smelter complex had poor performance on tests evaluating verbal IQ than children who lived farther from the smelter. Thus, the limited data available suggest that exposure of children to inorganic arsenic may result in detrimental effects on neurobehavioral parameters.

Wulff et al. (1996) conducted a retrospective study of a cohort of children born between 1961 and 1990 in the municipality of Skelleftea, Sweden, where a smelter released arsenic and other pollutants including lead, copper, cadmium, and sulfur dioxide. Childhood cancer incidences among children born in the vicinity of the smelter (i.e., within 20 km) and distant from the smelter (>20 km) were compared with expected incidences based on Swedish national statistics. There appeared to be an increased risk of childhood cancer (all types combined) among children born in the vicinity of the smelter (SIR=195, 95% CI=88–300, based on 13 cases observed and 6.7 expected), but the increase was not statistically significant, and in any event, the role of arsenic in any finding from this study is confounded by the

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presence of other metals. The number of cases (n=42) was very close to the expected number (n=41.8) among children born distant from the smelter. Similar results were reported in a study by Moore et al. (2002), which did not find increased incidence ratios for all childhood cancers or for childhood leukemias in children from an area of Nevada with high arsenic exposures.

Inorganic arsenic has been characterized as a developmental toxicant. It is known to cross the placental barrier and selectively accumulate in the neuroepithelium of the developing animal embryo (Hanlon and Ferm 1977; Lindgren et al. 1984). Studies in animals have also revealed that various fetal malformations occur after embryonic exposure to arsenic *in vitro*; neural tube defects are the predominant and consistent malformation in these studies (Chaineau et al. 1990; Mirkes and Cornel 1992; Morrissey and Mottet 1983; Mottet and Ferm 1983; Tabacova et al. 1996; Willhite and Ferm 1984; Wlodarczyk et al. 1996). *In vivo* studies have shown that high doses of ingested arsenic can produce developmental effects (fetal mortality, skeletal defects), but generally only at maternally toxic doses (Baxley et al. 1981; Holson et al. 1999, 2000; Hood and Harrison 1982; Hood et al. 1978; Nemec et al. 1998; Stump et al. 1999). A series of studies showed an increased incidence of tumors in the offspring of mice exposed to arsenic from gestational day 8 through day 18 (Waalkes et al. 2003, 2004a, 2004b, 2004c, 2006a, 2006b) (see Section 3.2.2.6 for further details). In humans, acute prenatal exposure to high doses of inorganic arsenic can result in miscarriage and early neonatal death (Bolliger et al. 1992; Lugo et al. 1969). Although several studies have reported marginal associations between prolonged low-dose human arsenic exposure and adverse reproductive outcomes, including spontaneous abortion, stillbirth, developmental impairment, and congenital malformation (Ahmad et al. 2001; Aschengrau et al. 1989; Chakraborti et al. 2003c; Hopenhayn-Rich et al. 2000; Nordström et al. 1978a, 1979b; Yang et al. 2003; Zierler et al. 1988), none of these studies have provided convincing evidence for such effects or information concerning possible dose-response relationships.

There is no evidence for differences in absorption of arsenic in children and adults. Ingestion of arsenic in dirt may be an important route of exposure for young children. A study that used a synthetic gastric juice designed to mimic gastric conditions in a 2-year-old child found that absorption of arsenic from contaminated soil was likely to be up to 5 times lower than the total concentration of arsenic in the soil (Williams et al. 1998). As previously mentioned, arsenic crosses the placenta and preferentially accumulates in the embryonic neuroepithelium. In addition, arsenic is known to be present in breast milk at low concentrations. Arsenic concentrations were low in human milk sampled from 88 mothers in the Faroe Islands (0.0001–0.0044 ppm), where the diet is predominantly seafood (exposures were primarily to “fish arsenic” [Grandjean et al. 1995]), in a population of Andean women (0.0008–0.008 ppm) exposed

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to high concentrations of inorganic arsenic in drinking water (Concha et al. 1998b), and in a World Health Organization survey (0.00013–0.00082 ppm) (Somogyi and Beck 1993). There is no information in the literature describing storage of arsenic in maternal tissues. There is some evidence that metabolism of arsenic in children is less efficient than in adults. Children in two villages in Argentina ingesting large amounts of arsenic in their drinking water (200 µg/L) excreted about 49% inorganic arsenic and 47% DMA, compared to 32% inorganic arsenic and 66% DMA for the women in the study (Concha et al. 1998b). No PBPK models specifically targeted at fetuses, infants, or children, or pregnant or lactating women were found in the literature. There are no biomarkers that have been specifically identified for children exposed to arsenic. In addition, no unique interactions of arsenic with other chemicals have been identified in children.

The mechanism of toxic action of arsenic in the mammalian cell may involve inhibition of proliferation of cells (Dong and Luo 1993; Jha et al. 1992; Petres et al. 1977). In addition, high-dose arsenic impairs assembly and disassembly of microtubules, thus interfering with mitotic spindle formation and embryonal cell division (Léonard and Lauwerys 1980; Li and Chou 1992; Mottet and Ferm 1983). Arsenic compounds also cause chromosomal aberrations (Jha et al. 1992; Léonard and Lauwerys 1980), which may disrupt cell cycling. The direct toxic effects of high levels of arsenic in the developing embryo result not from a difference in the mechanism of toxicity during development, but rather from the existence of a unique target tissue, the neuroepithelium. The process of neurulation involves cell shape changes, cytokinesis, and cell adhesion, which are dependent upon cytoskeletal elements that are functionally affected by arsenic (Dallaire and Béliveau 1992; Edelman 1992; Gunn et al. 1992; Li and Chou 1992; Moriss-Kay et al. 1994; Schoenwolf and Smith 1990; Taubeneck et al. 1994). However, since arsenic is known to affect vasculature, and since altered placental and/or embryonal vasculature has been suggested as a mechanism leading to neural tube defects, the embryo may be sensitive to this manifestation of arsenic toxicity.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic

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substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to arsenic are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by arsenic are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Arsenic

Arsenic levels in blood, urine, hair, and nails have all been investigated and used as biological indicators of exposure to arsenic. Since arsenic is cleared from blood within a few hours (Tam et al. 1979b; Vahter 1983), measurements of blood arsenic reflect exposures only within the very recent past. Typical values in nonexposed individuals are <1 µg/L (Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al.

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1979). Consumption of medicines containing arsenic is associated with blood values of 100–250 µg/L, while blood levels in acutely toxic and fatal cases may be 1,000 µg/L or higher (Driesback 1980).

However, blood levels do not appear to be reliable indicators of chronic exposure to low levels of arsenic. For example, there was no correlation between the level of arsenic in blood of residents and the level of arsenic in drinking water in several U.S. communities where water levels ranged from about 6 to 125 µg/L (Valentine et al. 1979, 1981). Consequently, measurement of blood arsenic is not generally considered to be a reliable means of monitoring human populations for arsenic exposure.

As discussed in Section 3.4.4, most arsenic that is absorbed from the lungs or the gastrointestinal tract is excreted in the urine, mainly within 1–2 days. For this reason, measurement of urinary arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure, and this approach has proved useful in identifying above-average exposures in populations living near industrial point sources of arsenic (e.g., Milham and Strong 1974; Polissar et al. 1990). By the inhalation route, several researchers have found that there is a good quantitative correlation between the concentration of arsenic in workplace air (C_{air} , µg/m³) and the concentration in the urine (C_{urine} , µg/L) of exposed workers. For example, Pinto et al. (1976) found a linear relationship for exposures ranging up to 150 µg/m³, given by the following equation:

$$C_{\text{air}} = 0.3 C_{\text{urine}}$$

Enterline et al. (1987a) reinvestigated this relationship over a wider range of exposures (up to 3,500 µg/m³), and found that the curve tended to be concave upward, as given by the following equation:

$$C_{\text{air}} = 0.0064 (C_{\text{urine}})^{1.94}$$

This indicates that at higher exposure levels, a higher fraction of the dose is excreted in urine, although the toxicokinetic basis for this is not certain. Numerous studies have used above-average urinary levels (i.e., higher than about 100 µg/L) as evidence of recent arsenic ingestion (e.g., Borgoño et al. 1980; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goldsmith and From 1986; Kyle and Pease 1965; Valentine et al. 1981). Calderon et al. (1999) found a quantitative correlation between the log of the mean total urinary arsenic concentration/creatinine (TAs/c, µg/mg) of people living in areas with arsenic-contaminated drinking water sources and the log of the inorganic arsenic concentration in the drinking water (InAs, µg/L). The equation for the regression line is:

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$$TAs/c=10^{-2.57} \times (InAs)^{0.63}$$

where -2.57 and 0.63 are the intercept and slope, respectively, for the regression of the log10-transformed data. Mixed model regression analysis showed that the log of estimated arsenic intake from drinking water ($\mu\text{g}/\text{day}$) is also a good predictor of TAs/c excretion (Calderon et al. 1999).

There is some indication that speciation of urinary arsenic may indicate the extent of past cumulative exposure to arsenic. Hsueh et al. (1998a) reported higher levels of DMA and MMA in the urine of individuals with higher cumulative past exposure to inorganic arsenic. Speciated urinary arsenic is also a recommended biomarker for recent inorganic arsenic exposure. Walker and Griffin (1998) used the EPA Exposure Assessment Model and a number of site-specific data covering environmental and biological factors to predict total and speciated urinary arsenic concentrations for children living near high levels of arsenic-contaminated soil. There was reasonable agreement between the measured and predicted speciated urinary arsenic concentrations.

An important limitation to the use of total urinary arsenic as a biomarker of exposure is that arsenobetaine is excreted (unmetabolized) in urine after ingestion of certain seafoods (Brown et al. 1990; Kalman 1987; Tam et al. 1982). Since "fish arsenic" is essentially nontoxic, analytical methods based on total urinary arsenic content may overestimate exposures to arsenic species that are of health concern. As discussed in Section 7.1, there are adequate methods for distinguishing arsenobetaine from other forms of arsenic in urine (inorganic, MMA, DMA), although these are not convenient to use as a routine screening method.

Arsenic tends to accumulate in hair and nails, and measurement of arsenic levels in these tissues may be a useful indicator of past exposures. Normal levels in hair and nails are 1 ppm or less (Choucair and Ajax 1988; Franzblau and Lilis 1989). These values may increase from several-fold to over 100-fold following arsenic exposure (Agahian et al. 1990; Bencko 2005; Bencko et al. 1986; de Peyster and Silvers 1995; EPA 1977a, 1981b; Karagas et al. 1996; Milham and Strong 1974; Valentine et al. 1979; Yamauchi et al. 1989) and remain elevated for 6–12 months (Choucair and Ajax 1988). Minimum exposure levels that produce measurable increases in arsenic levels in hair and nails have not been precisely defined. For hair, ingestion of 50–120 ppb of arsenic in drinking water produced only a marginal effect, but a clear increase was noted at 393 ppb (Valentine et al. 1979). A study of children living in a region polluted with arsenic derived from a power plant burning coal with a high arsenic content found a significant correlation between arsenic levels in hair and distance from the source of emission (Bencko and Symon 1977).

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Inhalation exposure of workers to about $0.6 \mu\text{g}/\text{m}^3$ of arsenic in air significantly increased average levels in nails (Agahian et al. 1990), although there was wide variation between individuals.

Analysis of hair may yield misleading results due to the presence of arsenic adsorbed to the external surface, but this can be minimized by collecting samples from close to the scalp or from unexposed areas and by washing the hair before analysis (e.g., Paschal et al. 1989). Similarly, extensive washing of nails is required to remove exogenous contamination (Agahian et al. 1990). The relationship between consumption of food items and levels of arsenic in toenails has been evaluated by MacIntosh et al. (1997) using standard multivariate regression models. This approach does not appear to be highly reliable, but may be sufficient for exploring associations between diet and disease. Kurttio et al. (1998) used linear regression models to show that there is a good association between arsenic concentration in hair (mg/kg) and total arsenic concentration in urine ($\mu\text{g}/\text{L}$), arsenic concentration in drinking water ($\mu\text{g}/\text{L}$) or daily intake of arsenic ($\mu\text{g}/\text{day}$). A $10 \mu\text{g}/\text{L}$ increase in the drinking water concentration or a $10\text{--}20 \mu\text{g}/\text{day}$ increase in daily arsenic intake corresponded to a $0.1 \text{ mg}/\text{kg}$ increase in the arsenic concentration in hair. It is also important to note that the measurement of arsenic in hair and fingernails is a process not readily accessible to many clinical offices.

3.8.2 Biomarkers Used to Characterize Effects Caused by Arsenic

As discussed in Section 3.2, the characteristic pattern of skin changes caused by arsenic (hyperkeratinization, hyperpigmentation) is probably the most sensitive and diagnostic clinical indicator of chronic exposure to arsenic. However, no means has been developed for detecting these effects except by routine dermatological examination.

Peripheral neuropathy is another characteristic effect of arsenic exposure, and several researchers have investigated decreased nerve conduction velocity or amplitude as a biomarker for peripheral neuropathy. While effects can usually be detected in individuals with clinical signs of neuropathy (e.g., Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), effects are only marginal (EPA 1977a; Hindmarsh et al. 1977; Valentine et al. 1981) or undetectable (EPA 1981b; Kreiss et al. 1983) in exposed populations without obvious clinical signs of toxicity. This indicates that this approach is probably not sufficiently sensitive to detect neurological effects earlier than by standard neurological examination (Hindmarsh and McCurdy 1986). Also, decreases in nerve conduction velocity or amplitude are not specific for arsenic-induced neuropathy.

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Arsenic is known to affect the activity of a number of enzymes, and some of these may have potential as biomarkers of effect. Most promising is the spectrum of effects caused by arsenic on the group of enzymes responsible for heme synthesis and degradation, including inhibition of coproporphyrinogen oxidase and heme synthetase (Woods and Fowler 1978; Woods and Southern 1989) and activation of heme oxygenase (Sardana et al. 1981). Menzel et al. (1998) has examined the *in vitro* induction of human lymphocyte heme oxygenase 1(HO1) as a biomarker of arsenite exposure. Arsenite did induce *de novo* synthesis of HO1 in human lymphoblastoid cells, but it has not been determined if the same response is induced *in vivo*. It has been shown in animals that these arsenic-induced enzymic changes result in increased urinary levels of uroporphyrin, coproporphyrin, and bilirubin (Albores et al. 1989; Woods and Fowler 1978), and it has been shown that these effects can be detected in the urine of arsenic-exposed humans (García-Vargas and Hernández-Zavala 1996). Therefore, altered urinary levels of these heme-related compounds could serve as a biomarker of effect. However, it is known that numerous other toxic metals also have similar effects on heme metabolism (Albores et al. 1989; Sardana et al. 1981; Woods and Southern 1989), so it is likely that these effects would not be specific for arsenic.

For more information on biomarkers for renal and hepatic effects of chemicals, see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (Agency for Toxic Substances and Disease Registry 1990b) and for information on biomarkers for neurological effects, see OTA (1990).

3.9 INTERACTIONS WITH OTHER CHEMICALS

A number of researchers have found that arsenic compounds tend to reduce the effects of selenium (Hill 1975; Howell and Hill 1978; Kraus and Ganther 1989; Levander 1977; Miyazaki et al. 2003; Moxon et al. 1945; Schrauzer 1987; Schrauzer et al. 1978). Likewise, selenium can decrease the effects of arsenic, including clastogenicity (Beckman and Nordenson 1986; Biswas et al. 1999; Sweins 1983), delayed mutagenesis (Rossman and Uddin 2004), cocarcinogenesis (Uddin et al. 2005), cytotoxicity (Babich et al. 1989; Rössner et al. 1977; Styblo and Thomas 2001), and teratogenicity (Holmberg and Ferm 1969). The mechanism of this mutual inhibition of effects is not known, but may be related to the formation of a selenium-arsenic complex (seleno-bis [S-gluthionyl] arsinium ion; Gailer et al. 2002) that is excreted more rapidly than either arsenic or selenium alone (Cikrt et al. 1988; Hill 1975; Levander 1977; Levander and Baumann 1966) or due to selenium-induced changes in arsenic methylation (Styblo and Thomas 2001; Walton et al. 2003). There is little direct evidence that variations in selenium exposure in humans lead to significant increases or decreases in arsenic toxicity, although copper smelter workers who developed lung cancer had lower tissue levels of selenium than workers who did not develop lung tumors

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(Gerhardsson et al. 1985, 1988). This suggests that selenium deficiency could significantly increase the risk of lung cancer following inhalation exposure to arsenic, but it is difficult to distinguish cause from effect in such a study. However, there is evidence that administration of selenene can facilitate recovery from arsenic poisoning. In residents living in an area of Inner Mongolia with high levels of arsenic in drinking water, administration of 100–200 µg selenium/day in the form of selenium yeast and exposure to arsenic-free water for 14 months resulted in a greater improvement in clinical signs and symptoms, liver function, and EKG readings as compared to residents administered arsenic-free water only (Wuyi et al. 2001; Yang et al. 2002). An improvement in skin lesions was observed in 67 and 21% of the subjects in the selenium-supplemented and control groups (Yang et al. 2002). Additionally, the levels of arsenic in blood, hair, and urine were significantly lower after the 14-month period only in the selenium supplemented group.

The interaction between cigarette smoking, inhalation of arsenic, and the risk of lung cancer has not been extensively investigated. Smoking appeared to increase lung cancer risk synergistically (multiplicatively) in one study of smelter workers (Pershagen et al. 1981), although the data are not adequate to exclude a simple additive interaction (Thomas and Whittemore 1988). Cigarette smoking has been shown to increase the occurrence of lung cancer in people with high levels of arsenic in the drinking water (Chiou et al. 1995; Tsuda et al. 1995a). Suggestive evidence of a positive interaction between arsenic and benzo(a)pyrene has also been noted for induction of lung adenocarcinomas in hamsters (Pershagen et al. 1984).

Co-exposure to ethanol and arsenic may exacerbate the toxic effects of arsenic. Simultaneous exposure of rats to ethanol (10% in drinking water) and arsenic (dose not stated) for 6 weeks produced a significant increase in the concentration of arsenic in the kidney, a nonsignificant increase of arsenic in the liver and a significant increase in the concentration of glutathione in the liver, compared to rats treated with either ethanol or arsenic alone (Flora et al. 1997a, 1997b). Histological damage to the liver, but not the kidneys, was increased in rats treated with both ethanol and arsenic compared to those receiving only arsenic.

Studies of rats exposed to arsenic, lead, and cadmium, alone or in combination, have revealed mainly additive or subadditive effects on body weight, hematological parameters, and enzymes of heme synthesis (Mahaffey and Fowler 1977; Mahaffey et al. 1981). Similarly, studies of the tissue levels of arsenic in rats fed arsenic with or without lead or cadmium revealed only limited evidence of any toxicokinetic interactions (Mahaffey et al. 1981). Pretreatment of rats with a nontoxic dose of cadmium had no effect on the lethality of a high dose of arsenic and did not reduce arsenic-induced hepatotoxicity (Hochadel and

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Waalkes 1997). These data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to these metals. However, supplementation with zinc or chromium may be useful in reducing chronic arsenism. Arsenic has been shown to cause an increase in total plasma cholesterol; co-administration of chromium(III) counteracts this effect (Aguilar et al. 1997). Pretreatment of mice with zinc, at least 24 hours before injection with arsenic-73, reduced arsenic retention compared to controls that did not receive the zinc pretreatment or received it only a short time before the administration of arsenic (Kreppel et al. 1994). Zinc is an inducer of metallothionein, but this induction does not appear to be the mechanism that reduces arsenic toxicity because other inducers of metallothionein did not reduce arsenic toxicity and arsenic elimination was increased by the zinc pretreatment.

Since methylation of arsenic is a detoxification mechanism, it is possible that chemicals that interfere with the methylation process could increase toxicity. This is supported by studies in animals in which reagents that inhibit methylation enzymes (e.g., periodate-oxidized adenosine) caused an increase in tissue levels of inorganic arsenic (Marafante and Vahter 1986; Marafante et al. 1985). Similarly, cellular glutathione levels appear to play a role in the methylation process, and treatment with reagents (e.g., phorone) that decrease glutathione levels increases arsenic toxicity (Buchet and Lauwerys 1987). Inadequate dietary intake of methionine, choline, or protein may also exacerbate arsenic toxicity. Rabbits pretreated with diets low in choline, methionine, or protein showed a significant increase in tissue retention of arsenic and a significant decrease in the excretion of dimethylarsinic acid (Vahter and Marafante 1987). The increased retention of arsenic in rabbits fed these deficient diets is likely to be due to a reduction in arsenic methylation. Thus, the toxic effects of chronic arsenic ingestion may be increased in populations that are also subject to malnutrition.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to arsenic than will most persons exposed to the same level of arsenic in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of arsenic, or compromised function of organs affected by arsenic. Populations who are at greater risk due to their unusually high exposure to arsenic are discussed in Section 6.7, Populations with Potentially High Exposures.

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No studies were located that identified an unusual susceptibility of any human subpopulation to arsenic. Several studies have evaluated possible sex-related differences in arsenic toxicity and carcinogenesis (Aposhian et al. 2000a, 2000b; Calderon et al. 1999; Loffredo et al. 2003; Mandal et al. 2001; Watanabe et al. 2001), but have not consistently identified differences. However, since the degree of arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 3.4.3), it seems likely that some members of the population might be especially susceptible because of lower than normal methylating capacity. Studies of exposed humans in Taiwan suggested that subjects with lower secondary methylation indices have an increased risk of bladder cancer (Chen et al. 2003) and peripheral vascular disease (Tseng et al. 2005), particularly in subjects with high exposure levels. Reduced hepatic methylation could result from dietary deficiency of methyl donors such as choline or methionine (Buchet and Lauwerys 1987; Vahter and Marafante 1987), although this is unlikely to be a concern for most people in the United States. There is evidence that methylation capacity can vary greatly among individuals (e.g., Buchet et al. 1981a; Foà et al. 1984; Hopenhayn-Rich et al. 1996b; Tam et al. 1979b), but the basis of this variation and its impact on human susceptibility have not been fully established. There is some evidence that low dietary protein intake and possibly other nutritional deficiencies can decrease arsenic methylation (Steinmaus et al. 2005a). Recently, Heck et al. (2007) examined whether the capacity to methylate arsenic differs by nutrient intake in a cohort of 1,016 Bangladeshi adults exposed to arsenic in drinking water. The results showed that higher intakes of cysteine, methionine, calcium, protein, and vitamin B-12 were associated with lower percentages of inorganic arsenic and higher ratios of MMA to inorganic arsenic in urine. In addition, higher intakes of niacin and choline were associated with higher DMA/MMA ratios, after adjustment for sex, age, smoking, total urinary arsenic, and total energy intake. The issue of increased susceptibility to arsenic due to poor nutrition was discussed by NRC (2001), it was concluded that, with regard to skin effects, studies of cohorts from India, Bangladesh, and Taiwan suggest that nutrition plays an important role in arsenic toxicity. On the other hand, studies in other regions of the world (i.e., Chile) involving populations with much better nutrition argue against poor nutrition having a major impact on arsenic toxicity.

Various genetic polymorphisms also seem to play a role in arsenic-induced toxicity. For example, a study of 85 lung cancer patients and 108 healthy controls in northern Chile reported that there was a nonstatistically significant difference for the frequency of the GSTM1 null genotype between the healthy and lung cancer patients stratified by gender and smoking status. The same results were observed for the MspI CYP450 1A1 polymorphism (Adonis et al. 2005). Hsueh et al. (2005) examined the association of four polymorphisms: NAD(P)H oxidase, manganese superoxide dismutase (MnSOD), catalase, and endothelial nitric oxide synthase (eNOS) with arsenic related hypertension risk among 79 hypertensive

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cases and 213 controls in an arseniasis-hyperendemic area in Taiwan. The results showed that MnSOD polymorphism significantly increased the risk of hypertension regardless of exposure to arsenic. NAD(P)H oxidase and eNOS polymorphisms were significantly associated with increased risk of hypertension in subjects with higher cumulative arsenic exposure (≥ 10.5 mg/L x year), whereas catalase polymorphism was not associated with hypertension. The results also showed that the association between MnSOD, NAD(P)H oxidase, and eNOS polymorphisms and risk of hypertension were more pronounced in subjects with high triglyceride level. A study of a population of West Bengal, India, exposed to arsenic via drinking water reported that the frequencies of null genotype in GSTT1 were 13.52 and 12.92% in skin-symptomatic and skin-asymptomatic individuals, and GSTM1 null genotype were 13.90 and 22.47% in skin-symptomatic and skin-asymptomatic individuals, respectively (Ghosh et al. 2006). Compared to those with GSTM1 null genotype, subjects with GST1-positive (at least one allele) had significantly higher risk of arsenic-induced skin lesions. Recently, Steinmaus et al. (2007) investigated urinary arsenic methylation patterns and genetic polymorphisms in methylenetetrahydrofolate reductase (MTHFR) and GST in 170 subjects (139 males) from an arsenic-exposed region in Argentina. MTHFR is a key enzyme in the metabolism of folate and has been linked to arsenic metabolism and toxicity (NRC 1999). Steinmaus et al. (2007) found that subjects with the TT/AA variant of MTHFR 677/1298 (associated with lower MTHFR activity) excreted a significantly higher proportion on ingested arsenic as inorganic arsenic and a smaller proportion as DMA(V). The study also reported that women with null genotype of GSTM1 excreted a significantly higher proportion of arsenic as monomethylarsenate than women with the active genotype. The study also found no association between polymorphisms in GSTT1 and arsenic methylation.

There is a report that described severe arsenic-induced neuropathy that developed only in a 5,10-methylenetetrahydrofolate-reductase (MTHFR) deficient member of a family that had been exposed to arsenic (Brouwer et al. 1992). The authors suggest that the MTHFR deficiency in this girl might explain the fact that of all the family members exposed to arsenic, only she developed severe clinical signs of arsenic poisoning. Liver disease does not appear to decrease methylation capacity in humans, at least at low levels of arsenic exposure (Buchet et al. 1982; Geubel et al. 1988).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to arsenic. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to arsenic. When specific

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exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to arsenic:

Tintinalli JE, Ruiz E, Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4th ed. New York, NY: The McGraw-Hill Companies, Inc.

Goldfrank RL, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th ed. Stamford, CT: Appleton and Lange.

Ellenhorn MJ. 1997. Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning. Baltimore, MD: Williams & Wilkins.

3.11.1 Reducing Peak Absorption Following Exposure

No data were located regarding the reduction of absorption after inhalation exposure to arsenic.

There are a number of methods for reducing absorption of arsenic following oral exposure. In cases of acute high-dose exposure, the removal of arsenic from the gastrointestinal tract may be facilitated by gastric lavage, stomach intubation, induced emesis, or use of cathartics (saline, sorbitol) within a few hours after ingestion (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Kamijo et al. 1998; Stutz and Janusz 1988). However, the efficacy of several of these methods has been questioned by some authors, and in some cases, the treatments may be contraindicated. For example, vomiting and diarrhea often occur soon after ingesting arsenic, and therefore, use of an emetic or cathartic may not be necessary. Also, emesis should not be induced in obtunded, comatose, or convulsing patients (Campbell and Alvarez 1989; Ellenhorn and Barceloux 1988; EPA 1989e), and saline cathartics should be used with caution in patients with impaired renal function (Campbell and Alvarez 1989). Vantroyen et al. (2004) described a case of a massive arsenic trioxide overdose that was successfully treated by continuous gastric irrigation with sodium bicarbonate, forced diuresis, and administration of BAL and DMSA. Treatments of this sort are unlikely to be required following low-level exposures.

Another possible approach for reducing absorption following oral exposure is to administer substances that bind the arsenic in the gastrointestinal tract. For example, activated charcoal is sometimes used for this purpose (Campbell and Alvarez 1989; EPA 1989e; Stutz and Janusz 1988), although the effectiveness of this treatment is not well established. Because pentavalent arsenic is a phosphate analogue,

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administration of phosphate-binding substance such as aluminum hydroxide might possibly be useful, but this has not been investigated. Sulfhydryl compounds might be given to bind trivalent arsenic, but it seems unlikely that these would be effective under the acid conditions in the stomach, and it is not clear that such complexes would have reduced gastrointestinal absorption.

Following dermal or ocular exposure to arsenic, several measures can be taken to minimize absorption. All contaminated clothing should be removed, and contacted skin should be immediately washed with soap and water. Eyes that have come in contact with arsenic should be flushed with copious amounts of clean water (EPA 1989e; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Acute arsenic intoxication may require treatment with chelating agents such as dimercaprol (BAL) and D-penicillamine. Although body burden is not necessarily reduced, these chelators bind free arsenic and serve to reduce the body's pool of biologically active arsenic. Chelation therapy is most effective when instituted within a few hours after exposure, and efficacy decreases as time after exposure increases (Agency for Toxic Substances and Disease Registry 1990a; Kamijo et al. 1998; McFall et al. 1998; Peterson and Rumack 1977).

In general, chelating agents should be used with caution, since they may have serious side effects such as pain, fever, hypotension, and nephrotoxicity (Ellenhorn and Barceloux 1988). Some water-soluble and less toxic analogues of BAL such as dimercaptosuccinic acid (DMSA), dimercaptopropyl phthalamadic acid (DMPA), and dimercaptopropane sulfonic acid (DMPS) are currently under investigation and may prove to be promising treatments for arsenic poisoning (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Aposhian et al. 1997; Guha Mazumder 1996; Kreppel et al. 1995). However, a randomized placebo trial of 2,3-dimercaptosuccinic acid as a therapy for chronic arsenosis due to drinking contaminated water found no significant difference between patients treated with 2,3-dimercaptosuccinic acid and those treated with a placebo (Guha Mazumder et al. 1998a). N-acetylcysteine has been used in animals to chelate arsenic (Haddad and Winchester 1990), and a human case study reported N-acetylcysteine to be successful in treating a case of arsenic poisoning that was not responding well to BAL treatment (Martin et al. 1990). Vantroyen et al. (2004) described a case of a massive arsenic trioxide overdose that was successfully treated by continuous gastric irrigation with sodium bicarbonate, forced diuresis, and administration of BAL and DMSA.

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As discussed in Section 3.4.3, once arsenic has been absorbed into the blood stream, it undergoes methylation to yield MMA and DMA. These forms of arsenic are less toxic than inorganic arsenic and are cleared from the body by excretion in the urine. Therefore, if it were possible to enhance arsenic methylation, both body burden and toxicity of arsenic might be reduced. However, experimental evidence in animals and humans suggests that arsenic methylation is not enhanced to any significant degree by supplementation with methylation cofactors (Buchet and Lauwerys 1987; Buchet et al. 1982), presumably because it is enzyme level and not cofactor availability that is rate limiting in arsenic methylation.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

It is generally thought that trivalent arsenic exerts its toxic effects mainly by complexing with sulfhydryl groups in key enzymes within the body, thereby inhibiting critical functions such as gluconeogenesis and DNA repair (Aposhian and Aposhian 1989; Li and Rossman 1989). Therefore, administration of sulfhydryl-containing compounds soon after exposure could provide alternative target molecules for arsenic, and prevent inhibition of enzyme functions. In fact, many of the chelating agents discussed above (BAL, DMSA, DMPA, DMPS, N-acetylcysteine) contain sulfhydryl groups, and this may account for their efficacy.

The mechanism by which pentavalent arsenic acts is less certain. Since pentavalent arsenic is reduced in the body to the trivalent state, pentavalent arsenic may act in a similar manner as described above for trivalent arsenic. If this is the case, efforts to inhibit the reduction of pentavalent arsenic would decrease its toxicity. However, no methods are currently recognized for blocking this reduction. Pentavalent arsenic may also exert effects by acting as a phosphate analogue. As a phosphate analogue, pentavalent arsenic could potentially affect a number of biological processes, including ATP production, bone formation, and DNA synthesis. However, any effort to interfere in normal phosphate metabolism could produce serious side effects, and no method is known for selectively interfering with arsenate metabolism.

3.12 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the

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initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

3.12.1 Existing Information on Health Effects of Arsenic

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to inorganic and organic arsenic are summarized in Figures 3-13 and 3-14, respectively. The purpose of this figure is to illustrate the existing information concerning the health effects of arsenic. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 3-13, there is a substantial database on the toxicity of inorganic arsenicals, both in humans and in animals. The oral route has been most thoroughly investigated, and reports are available on most end points of concern following acute, intermediate, and chronic exposure. The inhalation route has also been studied extensively, mainly in humans, with special emphasis on lung cancer. A number of noncancer end points have also been studied following inhalation exposure, but information on these effects is less extensive. Limited information on the effects of dermal exposure is also available in both humans and animals, focusing mainly on direct irritancy and dermal sensitization reactions. The absence of studies on other effects of inorganic arsenic following dermal exposure is probably not a critical data need, since dermal uptake of inorganic arsenic appears to be sufficiently limited that other routes of exposure (oral or inhalation) would almost always be expected to be of greater concern.

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Figure 3-13. Existing Information on Health Effects of Inorganic Arsenic

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●		●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal		●	●	●	●	●				

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●		●	●		●	●	●
Oral	●	●	●	●	●	●	●	●	●	●
Dermal	●	●	●		●					●

Animal

● Existing Studies

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Figure 3-14. Existing Information on Health Effects of Organic Arsenic

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●		●		●				
Oral		●				●				
Dermal						●				

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●								
Oral	●	●	●	●	●	●	●	●	●	●
Dermal		●								

Animal

● Existing Studies

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As shown in Figure 3-14, very little information is available on the effects of organic arsenic compounds in humans, although there are a number of studies in animals. These studies mainly involve the oral route, since all of these compounds are nonvolatile solids, although a few acute inhalation studies have been performed. Limited information is available on acute dermal lethality and dermal irritancy of some organic arsenicals, but data are lacking on other effects of organic arsenicals following dermal exposure. As discussed previously, in evaluating the adequacy of the database on arsenic, it is important to keep in mind that most studies in animals indicate that they are quantitatively less sensitive to arsenic than humans. For this reason, data from animal studies should be used to draw inferences about effects in humans only with caution.

3.12.2 Identification of Data Needs

Acute-Duration Exposure.

Inorganic Arsenicals. There is only limited information on the effects of acute inhalation exposure to arsenic in humans, but the chief symptoms appear to be irritation of the respiratory and gastrointestinal tracts (Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Dunlap 1921; Ide and Bullough 1988; Morton and Caron 1989; Pinto and McGill 1953). Quantitative data are lacking, but effects generally appear to be mild even at high-exposure levels. On this basis, it seems that risks of acute effects are probably low for inhalation exposures in the environment or near waste sites. Research to obtain a quantitative acute inhalation NOAEL value that could be used to derive an acute inhalation MRL would, therefore, be useful but not critical. There are numerous case studies in humans on the acute oral toxicity of arsenic, and the main end points (gastrointestinal irritation, pancytopenia, hepatic injury, neuropathy) are well characterized (Armstrong et al. 1984; Fincher and Koerker 1987). An acute oral MRL of 0.005 mg As/kg/day was derived for inorganic arsenic based on a LOAEL for gastrointestinal symptoms and facial edema reported by Mizuta et al. (1956). Additional studies to define an acute oral NOAEL would be useful to reduce uncertainty in the MRL derivation. Acute dermal exposure is unlikely to cause serious systemic injury, but it can lead to contact dermatitis and skin sensitization (Holmqvist 1951; Pinto and McGill 1953). However, available data do not permit a quantitative estimate of the concentration of arsenic on the skin or in air, dust, soil, or water that causes these effects. Further research would be valuable to obtain a quantitative NOAEL for direct dermal effects, since humans may have dermal contact with contaminated soil or water near hazardous waste sites.

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Organic Arsenicals. Information on the acute toxicity of organic arsenicals in humans is limited to reports of gastrointestinal irritation in individuals ingesting pesticides containing organic arsenicals (Lee et al. 1995; Shum et al. 1995); these case reports provide limited dosing information. Acute lethality and systemic toxicity data exist for several compounds by inhalation, oral, and dermal exposure of animals. Inhalation data are limited to a lethality study of rats and mice exposed to MMA or DMA that reported respiratory and ocular irritation (Stevens et al. 1979). The oral acute studies consist of lethality studies for MMA (Gur and Nyska 1990; Jaghabir et al. 1988; Kaise et al. 1989), DMA (Kaise et al. 1989), and roxarsone (Kerr et al. 1963; NTP 1989b), systemic toxicity studies (or longer-term studies reporting effects within the first 2 weeks of exposure) for MMA (Irvine et al. 2006), DMA (Ahmad et al. 1999a; Chernoff et al. 1990; Cohen et al. 2001; Crown et al. 1987; Irvine et al. 2006; Kavlock et al. 1985; Rogers et al. 1981; Zomber et al. 1989), or roxarsone (NTP 1989b). For MMA, the available data suggest that the gastrointestinal tract may be the most sensitive target of toxicity; however, the study identifying the lowest LOAEL (Irvine et al. 2006) involved bolus administration and this is not an appropriate exposure route to estimate human risk for gastrointestinal effects following environmental exposure to MMA. The available animal studies for DMA have examined urinary bladder (Cohen et al. 2001) and developmental toxicity (Chernoff et al. 1990, Irvine et al. 2006; Kavlock et al. 1985; Rogers et al. 1981). For DMA, acute-duration studies in rats suggest that the urinary bladder is the most sensitive target of toxicity in rats (Cohen et al. 2001); however, there is evidence from longer-term studies that rats may be more sensitive than humans and other species for bladder effects. Thus, rat data were not considered as the basis of an acute-duration oral MRL for DMA. Other effects observed following acute exposure to DMA include developmental and maternal effects in mice (Kavlock et al. 1985; Rogers et al. 1981) and rabbits (Irvine et al. 2006) and diarrhea and vomiting in dogs receiving a bolus dose of DMA (Zomber et al. 1989). An acute-duration oral MRL was not derived for DMA because it is not known if systemic effects would occur at lower doses than the developmental effects. For roxarsone, the available data suggest that the most sensitive effect following acute oral exposure is neuropathy observed in pigs (Kennedy et al. 1986; Rice et al. 1985). At the only dose tested in this study, tremors, clonic convulsions, and equivocal evidence of myelin degeneration were observed; these were considered serious effects and not suitable for the derivation of an acute-duration oral MRL for roxarsone. Additional studies are needed for MMA, DMA, and roxarsone that examine a variety of end points in several species; studies for roxarsone should also include examination of neurological end points, which would be useful for identifying the critical targets of toxicity and establishing dose-response relationships.

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Intermediate-Duration Exposure.

Inorganic Arsenicals. Intermediate-duration inhalation exposure of humans to arsenic appears to result in respiratory tract irritation (occasionally including perforation of the nasal septum) and mild gastrointestinal tract irritation (Ide and Bullough 1988). Quantitative data are too limited (only one study, of one individual) to derive an intermediate-duration inhalation MRL. Further studies to define the NOAEL for intermediate-duration inhalation exposure of humans would be valuable, since humans could be exposed to arsenic-containing airborne dusts near smelters, chemical plants, or waste sites. Effects of intermediate-duration oral exposure are similar to those of acute oral exposure, but may also include development of vascular injury and a characteristic group of skin changes (Franzblau and Lilis 1989; Holland 1904; Wagner et al. 1979). Most studies indicate that these effects occur at doses of about 0.05 mg As/kg/day or higher, but the data do not provide a firm basis for identifying the intermediate-duration NOAEL. For this reason, no intermediate-duration oral MRL has been derived. Further studies to establish the NOAEL would be valuable, since humans could have intermediate-duration oral exposures to arsenic through ingestion of contaminated soil or water near smelters, chemical factories, or waste sites. Since dermal effects appear to be restricted to acute irritancy, intermediate-duration dermal studies are probably not essential.

Organic Arsenicals. No information was located on the intermediate-duration toxicity of organic arsenicals in humans. Several studies have examined the intermediate-duration oral toxicity of MMA; dietary exposure studies in rats and mice (Arnold et al. 2003) identify the gastrointestinal tract as the most sensitive target. Diarrhea and lesions in the cecum, colon, and rectum have been observed. The rat 13-week study (Arnold et al. 2003) was used as the basis of the MRL. Because rats appear to be more sensitive to the toxicity of DMA, rat studies were not considered for MRL derivation. The only non-rat study was a chronic-duration dog study reporting effects during the first 51 weeks of exposure (Zomber et al. 1989); these effects included diarrhea and vomiting. However, because DMA was administered via capsule, this study was not considered adequate for derivation of an MRL. Additional studies are needed for DMA to identify critical targets of toxicity and establish dose-response relationships in non-rat species. The available data for roxarsone suggest that neurotoxicity in pigs is the most sensitive end point. One of the two available neurotoxicity studies in pigs (Edmonds and Baker 1986) did not include sensitive tests of toxicity and was not considered for MRL derivation; the other study identified a serious LOAEL at the only dose tested and thus, was not suitable for MRL derivation. Several comprehensive studies examined the toxicity of roxarsone in rats and mice (NTP 1989b). Renal tubular damage in rats was the most sensitive end point (NTP 1989b); however, the LOAEL for this effect was 9 times higher

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than the dose associated with neurotoxicity in pigs. Additional studies are needed to establish a no effect level for neurotoxicity in pigs, which could be used to derive an intermediate duration MRL for roxarsone. Further studies on the intermediate-duration inhalation and dermal toxicity of these compounds would be valuable, especially in humans, since people may be exposed to organic arsenicals during their manufacture or use, or from materials deposited in waste sites.

Chronic-Duration Exposure and Cancer.

Inorganic Arsenicals. The target tissues of chronic-duration exposure of humans to inorganic arsenic are the same as for intermediate-duration exposure for both the oral and inhalation routes. Effects of dermal exposure appear to be restricted to direct irritation of exposed surfaces. Therefore, chronic-duration studies are probably not essential for the dermal route. Quantitative data from one study identify an inhalation exposure level of about 0.1 mg As/m³ as the LOAEL for skin changes (Perry et al. 1948), but because there are no additional supporting studies and a NOAEL is not clearly established, a chronic-duration inhalation MRL has not been derived. Additional studies in humans to define the chronic inhalation NOAEL for dermal or other effects would be valuable, since humans may be chronically exposed to arsenic dusts in air near smelters, chemical factories, or waste sites. Chronic oral exposure data from studies in humans indicate that the LOAEL for skin lesions and other effects is probably about 0.01–0.02 mg As/kg/day (10–20 µg As/kg/day), and that the NOAEL is probably between 0.0004 and 0.0009 mg As/kg/day (0.4–0.9 µg As/kg/day) (Cebrián et al. 1983; EPA 1981b; Hindmarsh et al. 1977; Tseng 1977; Tseng et al. 1968). The NOAEL of 0.0008 mg As/kg/day from the study by Tseng et al. (1968) is appropriate for derivation of a chronic-duration oral MRL, but an uncertainty factor of 3 was required to account for the fact that the population that constituted the no-effect group were relatively young (possibly decreasing the ability to detect dermal or other effects that increase in prevalence with age). Another issue that needs to be acknowledged, which is common to ecological studies and contributes to uncertainty, is the fact that individual doses were not available and were calculated from group mean arsenic concentrations in well water using estimated water intake parameters. For this reason, further epidemiological studies that do not rely on an ecological-based exposure assessment that would provide additional support for the threshold dose for arsenic in humans would be valuable.

There are numerous studies in humans that support the carcinogenic effects of inorganic arsenic from inhalation exposure (Enterline et al. 1987a, 1987b, 1995; Järup and Pershagen 1991; Järup et al. 1989; Lee-Feldstein 1986; Welch et al. 1982) and oral exposure (Chen et al. 1986, 1988b, 1992; Chiou et al. 1995; Ferreccio et al. 1996; Hsueh et al. 1995; Lander et al. 1975; Liu and Chen 1996; Lüchtrath 1983;

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Smith et al. 1992; Tseng 1977; Tseng et al. 1968; Yu et al. 1992; Zaldívar 1974; Zaldívar et al. 1981). Quantitative slope factors have been derived for both routes. There is a noticeable absence, however, of 2-year animal carcinogenicity studies for either the inhalation or oral route of exposure (Chan and Huff 1997). In light of the ongoing controversy over the reasons for the absence of a carcinogenic effect in animals, it seems prudent to firmly establish a negative effect in a 2-year study. The carcinogenic effects of chronic dermal exposure to inorganic arsenicals have not been studied, but dermal exposure is a relatively minor route of exposure, and these studies would not be a top priority.

The mechanism of arsenic carcinogenicity is not known, although the current view is that it functions mainly as a promoter or cocarcinogen. Further studies on the mechanism of arsenic toxicity would be particularly valuable to improve our ability to evaluate human cancer risks from inhalation or oral exposures that might occur near waste sites. Also, mechanistic studies could help in the evaluation of cancer risks from organic derivatives (see below).

Organic Arsenicals. There is very little information on the chronic toxicity of organic arsenicals in humans. One study of workers exposed to arsanilic acid did not identify any adverse effects, but no systematic, clinical, or toxicological examinations of exposed people were performed (Watrous and McCaughey 1945). Chronic toxicity studies are available for rats, mice, and dogs exposed to MMA (Arnold et al. 2003; Waner and Nyska 1988), DMA (Arnold et al. 2006; Zomber et al. 1989), and roxarsone (NTP 1989b; Prier et al. 1963). Chronic exposure to MMA results in diarrhea in rats, mice, and dogs (Arnold et al. 2003; Waner and Nyska 1988) and an increase in progressive nephropathy in rats and mice (Arnold et al. 2003). The increased incidence of progressive nephropathy was used as the basis of the chronic-duration oral MRL for MMA. For DMA, chronic exposure also resulted in an increased incidence of diarrhea and vomiting in dogs (Zomber et al. 1989) and an increased incidence of vacuolization in the urinary bladder and progressive nephropathy in mice (Arnold et al. 2006). The vacuolization in the urinary bladder was used as the basis of a chronic-duration oral MRL for DMA. The available data for chronic-exposure to roxarsone were considered inadequate for derivation of an MRL. The highest doses tested in the rat, mouse, and dog studies (NTP 1989b; Prier et al. 1963) were NOAELs. Intermediate-duration studies identify neurotoxicity in pigs as the most sensitive end point; this has not been adequately examined following chronic exposure and studies are needed.

No information was located on carcinogenic effects of organic arsenicals in humans. The carcinogenic potential of MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), and roxarsone (NTP 1989b) following oral exposure has been investigated in rats and mice. No evidence of carcinogenicity was observed

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following oral exposure to MMA (Arnold et al. 2003) and equivocal evidence of carcinogenicity was found in male rats, with no evidence of carcinogenicity in female rats or in male or female mice orally exposed to roxarsone (NTP 1989b). Oral exposure to DMA resulted in an increased incidence of urinary bladder tumors in rats and no evidence of carcinogenicity in mice (Arnold et al. 2006). However, there is concern that the rat is not a good model to assess the carcinogenic potential of DMA in humans due to species differences in the toxicokinetic properties of DMA. No information was located on the carcinogenicity of organic arsenicals following inhalation or dermal exposure. Studies of humans exposed in the workplace would provide valuable information on the carcinogenic potential of organic arsenicals, particularly DMA. Studies on cancer risk following inhalation and dermal exposure to organic arsenicals are would be useful since these are possible routes of exposure for humans.

Genotoxicity.

Inorganic Arsenicals. There are several studies that suggest that inorganic arsenic may cause genotoxicity (mainly chromosomal effects) in exposed humans (Burgdorf et al. 1977; Nordenson et al. 1978), and this is supported by numerous studies in animals (Datta et al. 1986; DeKnudt et al. 1986; Nagymajtényi et al. 1985) and cultured cells (Beckman and Nordenson 1986; Casto et al. 1979; DiPaolo and Casto 1979; Lee et al. 1985; Nakamuro and Sayato 1981; Nishioka 1975; Oberly et al. 1982; Okui and Fujiwara 1986; Sweins 1983; Ulitzur and Barak 1988; Zanzoni and Jung 1980). The mechanism of genotoxicity is not known, but may be due to the ability of arsenite to interfere with DNA repair (Li and Rossman 1989) or to alter apoptosis (Pi et al. 2005) or the ability of arsenate to act as a phosphate analog. Further studies to improve our understanding of the mechanism of genotoxicity would be valuable, since this could aid in the understanding of arsenic-induced cancer risk.

Organic Arsenicals. For organic arsenicals, *in vitro* genotoxicity studies are available for arsenobetaine (Eguchi et al. 1997; Oya-Ohta et al. 1996), MMA (Chun and Killeen 1989a, 1989b, 1989c, 1989d; Eguchi et al. 1997; Oya-Ohta et al. 1996), DMA (Eguchi et al. 1997; Endo et al. 1992; Kato et al. 1994; Kawaguchi et al. 1996; Kitamura et al. 2002; Kuroda et al. 2004; Moore et al. 1997a; Oya-Ohta et al. 1996; Rasmussen and Menzel 1997; Rin et al. 1995; Tezuka et al. 1993; Ueda et al. 1997; Yamanaka et al. 1989b, 1993, 1995, 1997), and roxarsone (Matthews et al. 1993; NTP 1989b; Storer et al. 1996) and *in vivo* studies are available for DMA (Kashiwada et al. 1998; Yamanaka and Okada 1994; Yamanaka et al. 1989a, 1989b, 1993, 2001). The results of these studies suggest that DMA and roxarsone are clastogenic and can cause DNA strand breaks. Additional *in vivo* studies are needed to evaluate the genotoxic potential of MMA and roxarsone.

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Reproductive Toxicity.

Inorganic Arsenicals. Several studies have examined reproductive function in populations living in Bangladesh or India exposed to high levels of arsenic in drinking water and found increases in spontaneous abortions/stillbirths or preterm births (Ahmad et al. 2001; von Ehrenstein et al. 2006); another study in U.S. women did not find an increase in adverse reproductive outcomes (Aschengrau et al. 1989). Available animal studies did not find evidence for reproductive effects following inhalation or oral exposure (Holson et al. 1999, 2000), except for a trend toward decreased pups per litter in mice in a 3-generation study (Schroeder and Mitchener 1971) that is consistent with embryoletality observed in developmental studies of inorganic arsenic. Studies on spermatogenesis and reproductive success in arsenic-exposed workers would be valuable in evaluating whether there are significant reproductive risks of arsenic in humans, and this could be further strengthened by studies including histopathological examination of reproductive tissues (which was not done in the existing studies) in animals.

Organic Arsenicals. No information was located on reproductive effects of organic arsenicals in humans and no inhalation or dermal exposure animal studies were located. Intermediate- and chronic-duration oral studies for MMA (Arnold et al. 2003), DMA (Arnold et al. 2006), and roxarsone (NTP 1989b) have not reported histological damage to reproductive tissues. Decreases in pregnancy rate and male fertility index were observed in a two-generation study in rats (Schroeder 1994) and a single generation study in mice (Prukop and Savage 1986) exposed to MMA; the poor reporting in the Prukop and Savage (1986) study limits its usefulness in assessing reproductive toxicity. However, in the two-generation study, the differences between control and exposed rats were not statistically different; the effect was considered biologically significant because effects observed in the exposed rats were outside the range found in historical controls. Another reproductive performance study to confirm these results would be useful. No reproductive effects were observed in a two generation study in rats exposed to DMA (Rubin et al. 1989).

Developmental Toxicity.

Inorganic Arsenicals. There are several epidemiological studies that suggest that inhalation (Ihrig et al. 1998; Nordström et al. 1978a, 1978b, 1979a, 1979b) or oral (Hopenhayn et al. 2003a; Yang et al. 2003) exposure to inorganic arsenic might increase the risk of low birth weight, congenital defects, or abortion in exposed women. These studies do not establish that arsenic was responsible, since all involved exposures to other chemicals or risk factors, but do suggest that additional studies on developmental

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parameters in humans exposed to arsenic would be valuable in determining whether this is an effect of concern. Other human studies have not found significant associations between arsenic levels in drinking water and increased neonatal deaths or infant mortality (von Ehrenstein et al. 2006) or the increase in congenital heart defects (Zierler et al. 1988) or neural tube defects (Brender et al. 2006). Studies in animals support the view that oral, inhalation, and parenteral exposure to inorganic arsenic can all increase the incidence of fetotoxicity and teratogenicity, although this appears to occur only at doses that are toxic or even lethal to the dams (Baxley et al. 1981; Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986; Holson et al. 1999, 2000; Hood and Bishop 1972; Hood and Harrison 1982; Hood et al. 1978; Mason et al. 1989; Nagymajtényi et al. 1985; Nemec et al. 1998; Stump et al. 1999; Willhite 1981). There are also some data to suggest that it may increase the risk of transplacental cancer in humans (Smith et al. 2006) and animals (Waalkes et al. 2003). Thus, additional studies in animals may be useful in defining the mechanisms of these developmental effects and in identifying the time of maximum susceptibility of the fetus, but such studies probably will not help identify a safe exposure level for humans.

Organic Arsenicals. No information was located regarding developmental effects in humans after oral or inhalation exposure to organic arsenicals. Animal studies conducted in rats (Chernoff et al. 1990; Irvine et al. 2006; Rogers et al. 1981), mice (Kavlock et al. 1985; Rogers et al. 1981), and rabbits (Irvine et al. 2006) have examined the developmental toxicity of organic arsenicals. Decreases in fetal body weights and delays in ossification were commonly reported at maternally toxic (decreases in body weight gain) doses of DMA (Irvine et al. 2006; Kavlock et al. 1985; Rogers et al. 1981). However, one study found increases in the percentage of fetuses with irregular palatine rugae at DMA doses not associated with maternal toxicity (Rogers et al. 1981). This effect has not been reported in other studies and additional developmental studies are needed to confirm the finding. In view of the apparent differences in susceptibility between animals and humans, it would be valuable to investigate whether there are any measurable effects on development in humans exposed to organic arsenicals in the workplace or the environment.

Immunotoxicity.

Inorganic Arsenicals. No studies were located on immunotoxic effects in humans after oral exposure to inorganic arsenic. One inhalation study in humans (Bencko et al. 1988), an inhalation study in animals (Aranyi et al. 1985), one oral study in animals (Kerkvliet et al. 1980), and one intratracheal instillation study in animals (Sikorski et al. 1989) suggest that arsenic causes little or no functional impairment of the

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immune system, but one inhalation study in animals found decreased pulmonary bactericidal activity and increased susceptibility to streptococcal infection in exposed mice (Aranyi et al. 1985). Additional studies (both in humans and animals) would be valuable to investigate this end point further. Dermal exposure of humans to high levels of arsenic dusts may cause dermal sensitization (Holmqvist 1951), but the dose and time dependence of this phenomenon are not known. Studies to determine whether dermal sensitization occurs in people with low level dermal exposures to arsenic in dust or soil, such as might occur for residents near an arsenic-containing waste site, would be valuable in assessing the significance of this effect to nonoccupationally exposed populations.

Organic Arsenicals. No information was located on the effect of organic arsenicals exposure in humans or animals on immune function. Since there are suggestions that inorganic arsenic may cause some changes in the immune system, studies on possible immune effects of the common organic arsenicals might be helpful.

Neurotoxicity.

Inorganic Arsenicals. There is convincing evidence from studies in humans that inorganic arsenic can cause serious neurological effects, both after inhalation (Beckett et al. 1986; Bencko et al. 1977; Blom et al. 1985; Buchancová et al. 1998; Calderón et al. 2001; Danan et al. 1984; Feldman et al. 1979; Gerr et al. 2000; Lagerkvist and Zetterlund 1994; Morton and Caron 1989) and oral exposure (Armstrong et al. 1984; Bartolome et al. 1999; Chakraborti et al. 2003a, 2003b; Civantos et al. 1995; Cullen et al. 1995; Danan et al. 1984; EPA 1977a; Feldman et al. 1979; Fincher and Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Lewis et al. 1999; Mizuta et al. 1956; Muzi et al. 2001; Quatrehomme et al. 1992; Silver and Wainman 1952; Szuler et al. 1979; Tsai et al. 2003; Uede and Furukawa 2003; Vantroyen et al. 2004; Wagner et al. 1979). This is based mainly on clinical observations and neurological examinations of exposed persons. Available studies provide a reasonable estimate of LOAEL and NOAEL values by the oral route, but similar data are lacking for the inhalation route. Further studies designed to identify the threshold for neurological effects in humans exposed by the inhalation route would be valuable, since humans may be exposed to arsenic dusts in air from smelters, chemical factories, or waste sites. Adult animals appear to be much less susceptible than humans to the neurological effects of inorganic arsenic, so studies in adult animals would probably not help in estimation of a safe exposure limit. However, in light of recent findings of possible associations between arsenic in drinking water and neurobehavioral alterations in children (Tsai et al. 2003; von Ehrenstein et

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al. 2007; Wang et al. 2007; Wasserman et al. 2004, 2007), studies in animals, in which confounding can be eliminated, may be warranted.

Organic Arsenicals. Information on neurological effects of organic arsenicals in humans is limited to an occupational study that did not find increases in the frequency of central or peripheral nervous system complaints (Watrous and McCaughey 1945) and a case report of a woman reporting numbness and tingling of the fingertips, toes, and circumoral region who was exposed to organic arsenic in soup (Luong and Nguyen 1999). Neurological effects have also been observed in some animal studies. Decreases spontaneous motility, ataxia, and increased startle response were observed in mice exposed to a single high dose of DMA (Kaise et al. 1989). Degeneration of myelin and axons were observed in several studies involving oral exposure of pigs to roxarsone (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). Hyperexcitability, ataxia, and trembling have also been observed in rats and mice orally exposed to roxarsone (Kerr et al. 1963; NTP 1989b). These findings suggest that more extensive investigations of the neurotoxic potential of roxarsone and other organic arsenicals would be valuable to determine the potential human health risk from these compounds, since humans could be exposed during the manufacture or use of these compounds, or near waste sites where they have been deposited.

Epidemiological and Human Dosimetry Studies. Numerous epidemiologic studies of humans exposed to inorganic arsenic by the oral and inhalation routes constitute the database on arsenic-related cancer and noncancer human health effects. As with virtually all epidemiologic investigations, these studies are limited by possible confounding from factors such as smoking, exposure to other chemicals, and differences in population characteristics (e.g., nutritional state, metabolism, and toxicokinetics) that inhibit extrapolation of study results to a wider population. Moreover, many of these studies lack good dose estimates for study participants. Some studies lack quantitative data altogether. For this reason, improved data on confounding factors and improved methods of human dosimetry would be valuable in any further human epidemiologic studies of arsenic, either in the workplace or in the general environment. Recent work has broadened the qualitative dose-response information beyond the highly exposed Taiwanese population, but additional studies of persons with lower exposure levels would be especially valuable for risk assessments for the U.S. population. From a public health standpoint, well designed studies of common noncancer health outcomes (e.g., cardiovascular disease and diabetes) could be more important than additional studies of cancer. Availability of methods for biomonitoring of exposure are discussed below.

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Biomarkers of Exposure and Effect.

Exposure. There are sensitive and specific methods for measuring arsenic in blood, urine, hair, nails, and other tissues, and this is the approach normally employed for measuring arsenic exposure in humans. Usually total arsenic is measured, but methods are available for measuring inorganic arsenic and each of the organic derivatives separately. Urinary levels are generally considered to be the most reliable indication of recent exposures (Enterline et al. 1987a; Milham and Strong 1974; Pinto et al. 1976; Polissar et al. 1990), but if a high urinary level is present, care must be taken to account for the presence of nontoxic forms of arsenic from the diet. Blood levels are sometimes used to evaluate the status of acutely poisoned individuals (Driesback 1980; Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979, 1981), but this approach is not generally useful for biomonitoring of long-term exposure to low levels. Hair and nails provide a valuable indication of exposures that occurred 1–10 months earlier (Agahian et al. 1990; Bencko et al. 1986; Choucair and Ajax 1988; EPA 1977a, 1981b; Milham and Strong 1974; Valentine et al. 1979; Yamauchi et al. 1989), although care must be taken to exclude external contamination of these samples. Cumulative urinary arsenic levels may be used to derive a quantitative estimate of exposure (Enterline et al. 1987a; Pinto et al. 1976), but data on the quantitative relation between exposure and arsenic levels in nails and hair were not located. Efforts to establish an algorithm for estimating past exposure levels from hair or nail levels would be valuable in quantifying average long-term exposure levels in people where repeated urinary monitoring is not feasible.

Effect. The effects of arsenic are mainly nonspecific, but the combined presence of several of the most characteristic clinical signs (e.g., nausea, diarrhea, peripheral neuropathy, anemia, vascular lesions, hyperkeratinization, hyperpigmentation) is usually adequate to suggest arsenic intoxication. Although there are standard clinical methods for detecting and evaluating each of these effects, there are no recognized methods for identifying early (preclinical) effects in exposed persons. Neurophysiological measurements of nerve conduction velocity or amplitude have been investigated (Goebel et al. 1990; Jenkins 1966; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981), but at present, this approach does not seem to offer much advantage over a standard neurological examination. Changes in urinary excretion levels of several heme-related metabolites appear to be a good indication of preclinical effects of arsenic toxicity in animals (Albores et al. 1989; Sardana et al. 1981; Woods and Fowler 1978; Woods and Southern 1989), but this has not been established in humans and is not specific for arsenic-induced effects. Further efforts to develop these approaches and to identify other more specific biochemical or physiological indicators of arsenic-induced effects would be very valuable in monitoring the health of persons exposed to low levels of arsenic in the environment or near waste sites.

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Absorption, Distribution, Metabolism, and Excretion. Available data from toxicokinetic studies in humans reveal that arsenates and arsenites are well absorbed following both oral and inhalation exposure. Data on distribution are limited, but it appears that arsenic is transported to nearly all tissues. Metabolism involves mainly reduction-oxidation reactions that interconvert As(+5) and As(+3) and methylation of As(+3) to yield MMA and DMA. Most arsenic is rapidly excreted in the urine as a mixture of inorganic arsenics, MMA, and DMA, although some may remain bound in tissues (especially skin, hair, and fingernails). These findings are strongly supported by numerous studies in animals. Because methylation represents a detoxification pathway, an area of special interest is the capacity of the human body to methylate inorganic arsenic. Limited data suggest that the methylation system might begin to become saturated at intakes of about 0.2–1 mg As/day (Buchet et al. 1981b; Marcus and Rispin 1988), but this is uncertain. Further studies to define the rate and saturation kinetics of whole-body methylation in humans would be especially helpful in evaluating human health risk from the low levels of arsenic intake that are usually encountered in the environment. Along the same line, further studies to determine the nature and magnitude of individual variations in methylation capacity and how this depends on diet, age, and other factors would be very useful in understanding and predicting which members of a population are likely to be most susceptible.

The toxicokinetics of dermal exposure have not been studied. It is usually considered that dermal uptake of arsenates and arsenites is sufficiently slow that this route is unlikely to be of health concern (except that due to direct irritation), but studies to test the validity of this assumption would be valuable. Also, dermal uptake of organic arsenicals could be of concern, and quantitative data on the rate and extent of this would be helpful in evaluating risks from application of arsenical pesticides or exposures to organic arsenicals in waste sites.

Comparative Toxicokinetics. Available toxicity data indicate that arsenic causes many of the same effects in animals that are observed in humans, but that animals are significantly less sensitive. The basis for this difference in susceptibility is not certain but is probably mainly a result of differences in absorption, distribution, metabolism, or excretion. For example, rats strongly retain arsenic in red blood cells (Lanz et al. 1950), while humans (and most other species) do not. Similarly, marmoset monkeys do not methylate inorganic arsenic (Vahter and Marafante 1985; Vahter et al. 1982), while humans and other animal species do. Because of these clear differences in toxicity and toxicokinetics between species, further comparative toxicokinetic studies that focus on the mechanistic basis for these differences would be very valuable. At a minimum, this would help clarify which laboratory species are the most useful

3. HEALTH EFFECTS

models for humans and could ultimately lead to development of a PBPK model that would permit reliable extrapolation of observations across species.

Methods for Reducing Toxic Effects. There are a number of general methods for reducing the absorption of arsenic in the gastrointestinal tract and skin, but there are currently no methods for reducing the absorption of arsenic from the lungs. The removal of arsenic from the gastrointestinal tract is usually facilitated by the use of emetics, cathartics, lavages, or activated charcoal (Agency for Toxic Substances and Disease Registry 1990a; Aposhian and Aposhian 1989; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; Mitra et al. 2004; Stutz and Janusz 1988). Studies that investigate the effects of phosphate-binding chemicals (aluminum hydroxide) and nonabsorbable sulfhydryl compounds on the absorption of pentavalent and trivalent arsenic, respectively, may be useful in developing treatments that are more specific to arsenic intoxication. Once arsenic is in the body, treatment usually involves the use of one or more chelators, such as BAL or penicillamine. However, these agents often exhibit adverse side effects (Agency for Toxic Substances and Disease Registry 1990a; Ellenhorn and Barceloux 1988), and are generally only applied following high-dose acute exposure. Further studies investigating the efficacy of less toxic arsenic chelators, such as DMSA, DMPA, DMPS, and N-acetyl cysteine, may lead to the development of safer treatment methods. Studies on the efficacy of chelators and agents to enhance methylation and elimination in treatment of chronic arsenic exposure would also be helpful, as available treatment methods for chronic arsenic exposure are limited. Trivalent arsenic is generally believed to exert toxic effects by binding to the vicinal sulfhydryl group of key enzymes, thereby interfering with a number of biological processes, such as gluconeogenesis and DNA repair (Li and Rossman 1989; Szinicz and Forth 1988). Since pentavalent arsenic may need to be reduced in the body to the trivalent state before it can exert toxic effects, studies that investigate methods for blocking this conversion may lead to a method for interfering with the mechanism of action for pentavalent arsenic. The insufficient intake of calcium, animal protein, folate, selenium, and fiber may enhance the toxic effects of inorganic arsenic (Mitra et al. 2004), but it is not known if dietary supplementation will prove effective in patients who already show arsenic-induced symptoms.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

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A majority of the data on the effects of exposure of humans to arsenic has focused on adults. Although a few studies of acute poisoning and chronic exposure specifically describe children (Borgoño et al. 1980; Concha et al. 1998a, 1998b, 1999; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldívar 1974; Zaldívar and Guillier 1977), in general, data are lacking. Specifically, although there is a substantial database on the effect of arsenic on animal development, there are few data describing developmental effects in humans. Additional research in this area, using populations in areas of endemic arsenic exposure, would be useful.

Although there is no reason to suspect that the pharmacokinetics of arsenic differs in children and adults, there are few data available on this topic. Research on absorption, distribution, metabolism, and excretion in children would aid in determining if children are at an increased risk, especially in areas where chronic exposure to an environmental source occurs. With regard to exposure during development, additional research on maternal kinetics, and transfer via breast milk would be useful in obtaining a more complete picture of prenatal and neonatal development, especially with regard to neural development and the possible development of childhood cancer.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of arsenic. Table 3-18 summarizes studies being sponsored by agencies of the U.S. federal government (FEDRIP 2007). Additional research is being sponsored by industry groups and other agencies, and research is also ongoing in a number of foreign countries.

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Table 3-18. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Ahsan, H	Columbia University, New York, New York	Chemoprevention of arsenic-induced skin cancer	NCI
Ahsan, H	Columbia University, New York, New York	Genetic susceptibility to arsenic-induced skin cancer	NCI
Andrew, A	Dartmouth College, Hanover, New Hampshire	Bladder cancer prognostic indicators	NCI
Beckman, K	Children's Hospital and Research Center, Oakland, California	Fetal arsenic-nutrient interaction in adult-onset cancer	NIEHS
Bodwell, J	Dartmouth College, Hanover, New Hampshire	Arsenic effects on glucocorticoid receptor action	NIEHS
Calderon, R	EPA, Research Triangle Park, North Carolina	Arsenic-induced skin conditions identified in Southwest United States	HEERL
Christiani, D	Harvard University, Boston, Massachusetts	Arsenic and health in Bangladesh	NIEHS
Dong, Z	University of Minnesota, Minneapolis, Minnesota	Molecular basis of arsenic-induced cell transformation	NCI
Finnell, R	Texas A & M University College Station, Texas	Sensitive genotypes to arsenic as a model environmental toxicant	NIEHS
Frenkel, K	New York University, New York, New York	Metal induced inflammatory factors, oxidative stress, and suppression	NIEHS
Futscher, B	University of Arizona, Tucson, Arizona	Epigenetic remodeling by environmental arsenicals	NCI
Gamble, M	Columbia University, New York, New York	Nutritional influences on arsenic toxicity	NIEHS
Germolec, D	NIH, Research Triangle Park, North Carolina	The role of growth factors and inflammatory mediators in arsenic-induced dermatotoxicity	NIEHS
Guallar, E	Johns Hopkins University, Baltimore, Maryland	Mercury, arsenic, and carotid atherosclerosis	NIEHS
He, K	Northwestern University, Chicago, Illinois	Trace elements and CVD risks factors among young adults	NHLBI
Hei, T	Columbia University, New York, New York	Mechanisms of arsenic carcinogenesis	NIEHS
Huang, C	New York University, New York, New York	Effects of arsenic on PI-3K signaling pathway	NCI
Hudgens, E	EPA, Research Triangle Park, North Carolina	Study of individuals chronically exposed to arsenic in drinking water	HEERL
Hughes, M	EPA, Research Triangle Park, North Carolina	Biomarkers of exposure: a case study with inorganic arsenic	HEERL
Hughes, M	EPA, Research Triangle Park, North Carolina	Tissue dosimetry, metabolism, and excretion of pentavalent arsenic	HEERL
Jing, Y	New York University, New York, New York	Arsenic trioxide and acute myeloid leukemia	NCI

3. HEALTH EFFECTS

Table 3-18. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Jung, M	Georgetown University, Washington, DC	Epigenetic regulation by poly(ADP-ribose) in response to arsenite	NIEHS
Karin, M	University of California San Diego, La Jolla, California	Interaction of heavy metal ions with the human genome	NIEHS
Kelsey, K	Harvard University, Boston, Massachusetts	Arsenic mode of action in cancer—models of epigenetic mechanism	NIEHS
Liu, K	University of New Mexico, Albuquerque, New Mexico	Oxidative mechanisms of arsenic-induced carcinogenesis	NIEHS
Markowski, V	University of Southern Maine, Portland, Maine	Developmental arsenic exposure produces cognitive impairment	NIEHS
Martin, M	Georgetown University, Washington, DC	Arsenic and epigenetic regulation of gene expression	NIEHS
Muscarella, D	Cornell University Ithaca, Ithaca, New York	Arsenite effects on CD40 signaling and B-cell apoptosis	NIEHS
Nichols, R	Dartmouth College, Hanover, New Hampshire	Effect of arsenic on cytochrome P450	NIEHS
Nriagu, J	University of Michigan, Ann Arbor, Michigan	Arsenic exposure and bladder cancer in Michigan	NCI
Rosen, B	Wayne State University, Detroit, Michigan	Mechanisms of arsenical transport	NIGMS
Rosen, B	Wayne State University, Detroit, Michigan	Metal binding domains in metallo-regulatory proteins	NIAID
Rosenblatt, A	University of Miami, Coral Gables, Florida	Environmental arsenic and androgen receptor regulation	NIEHS
Rossman, T	New York University, New York, New York	Investigation and genetic analysis of the human arsenite efflux pump	NIEHS
Schwartz, J	Harvard University, Boston, Massachusetts	Epigenetic effects of particles and metals on cardiac health of an aging cohort	NIEHS
Self, W	University of Central Florida, Orlando, Florida	Impact of arsenicals on selenoprotein synthesis	NIEHS
Sens, D	University of North Dakota, Grand Forks, North Dakota	Metallothionein isoform-3 urinary marker bladder cancer	NIEHS
Sheldon, L	Dartmouth College, Hanover, New Hampshire	Arsenic, histone modification, and transcription	NIEHS
Shi, X	University of Kentucky, Lexington, Kentucky	Mechanism of arsenic-induced carcinogenesis	NCI
Smith, A	University of California, Berkeley, California	Arsenic biomarker epidemiology	NIEHS
Spallholz, J	Texas Tech University, Lubbock, Texas	Selenium against arsenic toxicity and skin lesions	NCI
States, C	University of Louisville, Louisville, Kentucky	Arsenic induced mitotic arrest associated apoptosis	NIEHS
Styblo, M	University of North Carolina, Chapel Hill, North Carolina	Metabolism and toxicity of arsenic in human liver	NIEHS

3. HEALTH EFFECTS

Table 3-18. Ongoing Studies on Health Effects of Arsenic, Federally Funded

Investigator	Affiliation	Title	Sponsor
Taylor, P	Division of Cancer Epidemiology and Genetics, NCI, Bethesda, Maryland	Biologic specimen bank for early lung cancer markers in Chinese tin miners	NCI
Taylor, B	University of Louisville, Louisville, Kentucky	Arsenite inhibition of mitotic progression	NIEHS
Vaillancourt, R	University of Arizona, Tucson, Arizona	Modulation of Prostaglandins by Arsenic	NIEHS
Willett, W	Harvard University, Boston, Massachusetts	Prospective studies of diet and cancer in men and women	NCI
Wright, R	Brigham and Women's Hospital, Boston, Massachusetts	Metal mixtures and neurondevelopment	NIEHS
Zhang, D	University of Arizona, Tucson, Arizona	The protective role of Nrf2 in arsenic-induced toxicity and carcinogenicity	NIEHS

EPA = Environmental Protection Agency; NHEERL = National Health and Environmental Effects Research Laboratory; NCI = National Cancer Institute; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health Sciences; NIAID= National Institute of Allergy and Infectious Diseases; NIGMS = National Institute of General Medical Sciences; NIH = National Institute of Health

Source: FEDRIP 2007

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of arsenic and some common inorganic and organic arsenic compounds are located in Tables 4-1 and 4-2, respectively.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of arsenic and some common inorganic and organic arsenic compounds is located in Tables 4-3 and 4-4, respectively.

Arsenic appears in Group 15 (V) of the periodic table, below nitrogen and phosphorus. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. Elemental arsenic, which is also referred to as metallic arsenic, (As(0)) normally occurs as the α -crystalline metallic form, which is a steel gray and brittle solid. The β -form is a dark gray amorphous solid. Other allotropic forms of arsenic may also exist. In compounds, arsenic typically exists in one of three oxidation states, -3, +3, and +5 (Carapella 1992). Arsenic compounds can be categorized as inorganic, compounds without an arsenic-carbon bond, and organic, compounds with an arsenic-carbon bond.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds^a

Characteristic	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Synonym(s)	Arsenic black; colloidal arsenic; gray arsenic, metallic arsenic	Orthoarsenic acid	Arsenic(V) oxide; arsenic acid anhydride; diarsenic pentoxide	Arsenic(III) oxide; arsenious acid; arsenious oxide; white arsenic
Registered trade name(s)	No data	Zotox; Hi-Yield Desiccant H-10; Desiccant L-10; Crab Grass Killer	No data	White Arsenic; Arsenicum Album
Chemical formula	As	H ₃ AsO ₄	As ₂ O ₅	As ₂ O ₃
Chemical structure	As	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HO}-\text{As}-\text{OH} \\ \\ \text{OH} \end{array}$	[As ⁵⁺] ₂ [O ²⁻] ₅	[As ³⁺] ₂ [O ²⁻] ₃
Identification numbers:				
CAS registry	7440-38-2	7778-39-4	1303-28-2	1327-53-3
NIOSH RTECS ^b	CG0525000	CG0700000	CG2275000	CG3325000
EPA hazardous waste	D004	D004, P010	D004, P011	D004, P012
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN1558/IMDG 6.1	UN1553 (liquid)/ UN1554 (solid)/ IMDG 6.1 (liquid and solid)	UN1559/IMDG 6.1	UN1561/ IMDG 6.1
HSDB	509	431	429	419
EINECS	231-148-6	231-901-9	215-116-9	215-481-4
NCI	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds^a

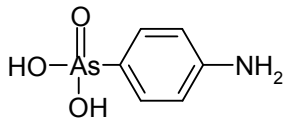
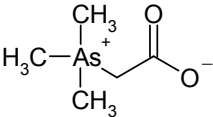
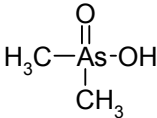
Characteristic	Calcium arsenate	Gallium arsenide	Sodium arsenate	Sodium arsenite
Synonym(s)	Calcium ortho-arsenate; arsenic acid, calcium salt	Gallium mono-arsenide	Disodium arsenate, dibasic; disodium hydrogen arsenate; arsenic acid, disodium salt	Arsenous acid, sodium salt; sodium meta-arsenite
Registered trade name(s)	Pencal; Security; Turf-Cal; Chip-Cal; SPRA-Cal	No data	No data	Atlas "A"; Penite; Kill-All; Chem-Sen 56; Chem Pels C; Progalumol Double
Chemical formula	Ca ₃ (AsO ₄) ₂	GaAs	Na ₂ HAsO ₄	NaAsO ₂
Chemical structure	$\left[\text{Ca}^{2+} \right]_3 \left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O}^- - \text{As} - \text{O}^- \\ \parallel \\ \text{O}^- \end{array} \right]_2$	Ga:As	$\left[\text{Na}^+ \right]_2 \text{HO} - \begin{array}{c} \text{O} \\ \parallel \\ \text{As} - \text{O}^- \\ \parallel \\ \text{O}^- \end{array} \quad \begin{array}{c} \text{O} \\ \parallel \\ \text{As} - \text{O}^- \end{array} \text{Na}^+$	
Identification numbers:				
CAS registry	7778-44-1	1303-00-0	7778-43-0	7784-46-5
NIOSH RTECS ^b	CG0830000	LW8800000	CG0875000	CG3675000
EPA hazardous waste	D004	D004	D004	D004
OHM/TADS	No data	No data	No data	7800057
DOT/UN/NA/IMDG shipping	UN1573/IMDG 6.1	UN 2803; Gallium/IMDG 8.0; Gallium	UN 1685/IMDG 6.1	UN1686 (aqueous solution)/UN2027 (solid)/IMDG 6.1
HSDB	1433	4376	1675	693
EINECS	233-287-8	215-114-8	231-902-4	232-070-5
NCI	No data	No data	No data	No data

^aAll information obtained from HSDB 2007 and CHEMIDplus 2007, except where noted.^bRTECS 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

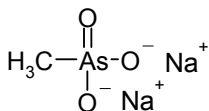
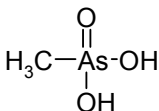
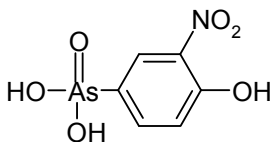
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds^a

Characteristic	Arsanilic acid	Arsenobetaine	Dimethylarsinic acid
Synonym(s)	(4-Aminophenyl)arsonic acid; antoxylic acid; atoxylic acid, Pro-Gen	Arsonium, (carboxymethyl)-trimethyl-, hydroxide, inner salt	Cacodylic acid; hydroxydimethyl-arsine oxide; DMA; DMAA
Registered trade name(s)	No data	No data	510; Arsan; Phytar 560; Rad-E-Cate 35
Chemical formula	C ₆ H ₈ AsNO ₃	C ₅ H ₁₁ AsO ₂	C ₂ H ₇ AsO ₂
Chemical structure			
Identification numbers:			
CAS registry	98-50-0	64436-13-1	75-60-5
NIOSH RTECS ^b	CF7875000	CH9750000	CH7525000
EPA hazardous waste	D004	No data	U136/D004
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	UN1572/IMDG 6.1
HSDB	432	No data	360
EINECS	202-674-3	No data	200-883-4
NCI	No data	No data	No data

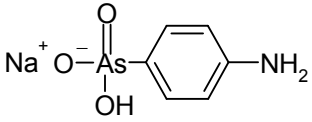
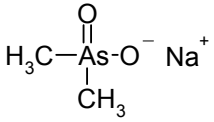
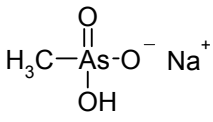
4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds^a

Characteristic	Disodium methane- arsonate	Methanearsonic acid	3-Nitro-4-hydroxy-phenyl- arsonic acid
Synonym(s)	DSMA; disodium monomethane arsonate	Arsonic acid, methyl-; monomethylarsonic acid	Roxarsone; 3-nitro- 4-hydroxyphenylarsonic acid; 3-Nitro-10
Registered trade name(s)	Ansar 8100; Arrhenal; Ansar DSMA Liquid; Dinate; Crab-E-Rad; Chipco Crab Kleen; Arsinyl; Sodar; Methar; Drexel DSMA Liquid; Di- Tac; Ansar 184; Weed-E- Rad; Versar DSMA-LQ; Calar-E-Rad; Dal-E-Rad; Jon-Trol; Namate	No data	No data
Chemical formula	CH ₃ AsO ₃ Na ₂	CH ₃ AsO ₃	C ₆ H ₆ AsNO ₆
Chemical structure			
Identification numbers:			
CAS registry	144-21-8	124-58-3	121-19-7
NIOSH RTECS ^b	PA2275000	PA1575000	CY5250000
EPA hazardous waste	D004	D004	D004
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	1701	845	4296
EINECS	205-620-7	204-705-6	204-453-7
NCI	No data	No data	C5608

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Chemical Identity of Selected Organic Arsenic Compounds^a

Characteristic	Sodium arsanilate	Sodium dimethylarsinate	Sodium methanearsonate
Synonym(s)	(4-Aminophenyl)arsonic acid sodium salt; arsanilic acid sodium salt; arsamin; atoxyl; soamin; trypoxyl	Sodium cacodylate; cacodylic acid, sodium salt; sodium dimethylarsonate	Arsonic acid, methyl-, monosodium salt; monosodium acid metharsonate; MSMA
Registered trade name(s)	No data	Ansar 160; Ansar 560; Bolls-Eye; Chemaide; Phytar 560, component of (with 012501); Rad-E-Cate 25.	Ansar 529; Ansar 170; Target MSMA; Phyban H.C.; Deconate; Mesamate; Bueno; Monate Merge 823; Dal-E-Rad; Weed-S-Rad; Arsanote liquid; Silvisar 550.
Chemical formula	C ₆ H ₇ AsNO ₃ Na	C ₂ H ₆ AsO ₂ Na	CH ₄ AsO ₃ Na
Chemical structure			
Identification numbers:			
CAS registry	127-85-5	124-65-2	2163-80-6
NIOSH RTECS ^b	CF9625000	CH7700000	PA2625000
EPA hazardous waste	D004	D004	D004
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN2473/IMDG 6.1	UN1688/IMDG 6.1	No data
HSDB	5189	731	754
EINECS	204-869-9	204-708-2	218-495-9
NCI	C61176	No data	C60071

^aAll information obtained from HSDB 2007 and CHEMIDplus 2007, except where noted.^bRTECS 2007

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Dept. of Transportation/United Nations/North America/Intergovernmental Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Chemical Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds^a

Property	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Molecular weight	74.9216	141.944	229.840	197.841
Color	Silver-gray or tin-white	White ^b	White	White
Physical state	Solid	Solid ^b	Solid	Solid
Melting point	817 °C (triple point)	35 °C	Decomposes at ~300 °C	313 °C (claudetite) 274 °C (arsenolite)
Boiling point	614 °C sublimes	Loses H ₂ O at 160 °C ^b	No data	460 °C
Density	5.778 g/cm ³ at 25 °C	~2.2 g/cm ³	4.32 g/cm ³	3.865 g/cm ³ (cubes) 4.15 g/cm ³ (rhombic crystals)
Odor	Odorless	No data	No data	Odorless
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	302 g/L at 12.5 °C ^b	2,300 g/L at 20 °C	17 g/L at 16 °C
Organic solvent(s)	No data	Soluble in alcohol, glycerol ^b	Soluble in alcohol	Practically insoluble in alcohol, chloroform, ether; soluble in glycerol
Other	Insoluble in caustic and nonoxidizing acids	No data	Soluble in acid, alkali	Soluble in dilute hydrochloric acid, alkali hydroxide, carbonate solution
Partition coefficients:				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
pK _a	No data	pK _{a1} =2.22; pK _{a2} =6.98 pK _{a3} =11.53 ^c	No data	No data
Vapor pressure	7.5x10 ⁻³ mmHg at 280 °C	No data	No data	2.47x10 ⁻⁴ mmHg at 25 °C
Autoignition temperature	No data	No data	No data	Not flammable
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds^a

Property	Calcium arsenate	Gallium arsenide	Disodium arsenate	Sodium arsenite
Molecular weight	398.072	144.64	185.91	130.92
Color	Colorless	Dark gray	Colorless ^d	White to gray-white
Physical state	Solid	Solid	Solid ^d	Solid
Melting point	Decomposes on heating	1,238 °C	57 °C ^d	No data
Boiling point	No data	No data	No data	No data
Density	3.620 g/cm ³	5.3176 g/cm ³ at 25 °C	1.87 g/cm ^d	1.87 g/cm ³
Odor	Odorless	Garlic odor	Odorless ^d	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	0.13 g/L at 25 °C	<1 mg/mL at 20 °C	Soluble 1:3 parts in water ^d	Freely soluble in water
Organic solvents	Insoluble	<1 mg/mg dimethyl sulfoxide, ethanol, methanol, acetone	Slightly soluble in alcohol; soluble in glycerol ^d	Slightly soluble in alcohol
Other	Soluble in dilute acids	Soluble in hydrochloric acid	Slightly soluble in alkaline solution ^d	No data
Partition coefficients:				
Log K _{ow}	No data	No data	No data	No data
Log K _{oc}	No data	No data	No data	No data
pK _a	No data	No data		
Vapor pressure	~0 mmHg at 20 °C	No data	No data	No data
Autoignition temperature	Not combustible	No data	No data	Not combustible
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

^aAll information from HSDB 2007, except where noted.^bValue for arsenic acid hemihydrate^cNRC 1999^dValue for disodium arsenate heptahydrate

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds^a

Property	Arsenilic acid	Arsenobetaine	Dimethylarsinic acid
Molecular weight	217.06	196.1 ^b	138.00
Color	White	No data	Colorless
Physical state	Solid	Solid ^b	Solid
Melting point	232 °C	203–210 °C (decomposes) ^b	195 °C
Boiling point		No data	>200 °C
Density	1.9571 g/cm ³ at 10 °C	No data	No data
Odor	Practically odorless	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	Slightly soluble in cold water; soluble in hot water	No data	2,000 g/L at 25 °C
Organic solvent(s)	Slightly soluble in alcohol; soluble in amyl alcohol; insoluble in ether, acetone, benzene, chloroform	No data	Soluble in alcohol; insoluble in diethyl ether
Acids	Slightly soluble in acetic acid; soluble in alkali carbonates; moderately soluble in concentrated mineral acids; insoluble in dilute mineral acids	No data	Soluble in acetic acid
Partition coefficients:			
Log K _{ow}	No data	No data	No data
Log K _{oc}	No data	No data	No data
pK _a	No data	2.2 ^c	1.57
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	Nonflammable
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds^a

Property	Methanearsonic acid	3-Nitro-4-hydroxy-phenylarsonic acid	Sodium arsanilate
Molecular weight	139.97	263.03	239.04
Color	White	Pale yellow	White or creamy white
Physical state	Solid	Solid	Solid
Melting point	160.5 °C	No data	No data
Boiling point	No data	No data	No data
Density	No data	No data	No data
Odor	No data	No data	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	256 g/L at 20 °C	Slightly soluble in cold water; soluble in about 30 parts boiling water	Soluble 1 part in 3 parts water
Organic solvents	Soluble in ethanol	Soluble in methanol, ethanol, acetone; insoluble in ether, ethyl acetate	Soluble 1 part in 150 parts alcohol; practically insoluble in chloroform, ether
Acids	No data	Soluble in acetic acid, alkalies; sparingly soluble in dilute mineral acids	No data
Partition coefficients:			
Log K _{ow}	No data	No data	No data
Log K _{oc}	No data	No data	No data
pK _a	pK _{a1} =4.1; pK _{a2} =9.02	No data	No data
Vapor pressure at 25 °C	<7.5x10 ⁻⁸ mmHg	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	No data	No data	No data
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-4. Physical and Chemical Properties of Selected Organic Arsenic Compounds^a

Property	Disodium methanearsonate	Sodium dimethylarsinate	Sodium methanearsonate
Molecular weight	183.93	159.98	161.95
Color	White	Colorless to light yellow	White
Physical state	Solid	Solid	Solid
Melting point	>355 °C	200 °C	130–140 °C
Boiling point	No data	No data	No data
Density	1.04 g/cm ³	>1 g/cm ³ at 20 °C	1.55 g/mL ^d
Odor	No data	Odorless	Odorless
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	432 g/L at 25 °C	200 g/L at 25 °C	580 g/L at 20 °C
Organic solvents	Soluble in methanol; practically insoluble in most organic solvents	No data	Insoluble in most organic solvents
Acids	No data	No data	No data
Partition coefficients:			
Log K _{ow}	<1	No data	-3.10
Log K _{oc}	No data	No data	No data
pK _a	pK _{a1} =4.1; pK _{a2} =8.94	6.29	pK _{a1} =4.1; pK _{a2} =9.02
Vapor pressure at 25 °C	10 ⁻⁷ mmHg	No data	7.8x10 ⁻⁸ mmHg
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability	Nonflammable	No data	Nonflammable
Conversion factors	No data	No data	No data
Explosive limits	No data	No data	No data

^aAll information from HSDB 2007, except where noted.^bCannon et al. 1981 (arsenobetaine as monohydrate)^cTeräsahde et al. 1996^dValue for Ansar 6.6

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5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Arsenic is presently obtained as a byproduct of the smelting of copper, lead, cobalt, and gold ores.

Arsenic trioxide is volatilized during smelting and accumulates in the flue dust, which may contain up to 30% arsenic trioxide. The crude flue dust is further refined by mixing with small amounts of galena or pyrite to prevent the formation of arsensites and roasting to yield arsenic trioxide of 90–95% purity. By successive sublimations, a purity of 99% can be obtained. Elemental arsenic can be prepared by the reduction of arsenic oxide with charcoal. Demand for elemental arsenic is limited and thus, about 95% of arsenic is marketed and consumed in combined form, principally as arsenic trioxide, which is subsequently converted to arsenic acid (Carapella 1992; Hanusch et al. 1985; USGS 2006a).

Since 1985, when the ASARCO smelter in Tacoma, Washington ceased operation, there has been no domestic production of arsenic trioxide or elemental arsenic and consequently, the United States remains entirely dependent on imports (U.S. Bureau of Mines 1988, 1990; USGS 2006a). Prior to its cessation, U.S. production of arsenic trioxide had been 7,300 metric tons in 1983, 6,800 metric tons in 1984, and 2,200 metric tons in 1985 (U.S. Bureau of Mines 1988). In 2005, arsenic trioxide was obtained from the treatment of nonferrous ores or concentrates in 14 countries. In 2005, the world's largest producer of arsenic trioxide was China, followed by Chile and Peru. China is the world leader in the production of commercial-grade arsenic followed by Japan. The United States, with an apparent demand of 8,800 metric tons in 2005, is the world's leading consumer of arsenic, mainly for CCA. This is an increase over 2004 with an apparent demand of 6,800 metric tons, but far less than that of 2003, 21,600 metric tons (USGS 2006a).

Tables 5-1 and 5-2 list facilities in each state that manufacture or process arsenic and arsenic compounds, respectively, as well as the intended use and the range of maximum amounts of arsenic or arsenic compounds that are stored on site. In 2004, there were 58 and 361 reporting facilities that produced, processed, or used arsenic and arsenic compounds, respectively, in the United States. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI04 2006). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Current U.S. manufacturers of selected arsenic compounds are given in Table 5-3.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Arsenic

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	1	1,000,000	9,999,999	1, 13
AL	18	0	9,999,999	1, 2, 3, 5, 7, 8, 11, 12, 13, 14
AR	4	1,000	999,999	7, 8
AZ	9	0	99,999	1, 3, 4, 5, 8, 12, 13
CA	31	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
CO	8	0	999,999	2, 7, 8, 11, 12
FL	10	1,000	999,999	1, 3, 5, 7, 8, 11, 12
GA	16	100	49,999,999	2, 3, 4, 6, 7, 8, 11, 12, 13, 14
HI	1	10,000	99,999	8
IA	4	100	99,999	6, 7, 8
ID	7	0	49,999,999	1, 2, 3, 5, 6, 7, 9, 12, 13
IL	16	0	999,999	1, 3, 4, 5, 6, 7, 8, 12, 14
IN	17	0	999,999	1, 3, 5, 6, 7, 8, 9, 12, 13
KY	9	0	999,999	1, 2, 3, 5, 6, 7, 8, 11
LA	8	0	999,999	1, 2, 3, 7, 8, 12, 13
MA	5	1,000	999,999	3, 7, 8
MD	9	0	999,999	1, 2, 4, 5, 6, 7, 8
MI	10	0	999,999	3, 7, 8, 12, 13
MN	5	100	99,999	1, 7, 8, 13
MO	6	100	999,999	1, 2, 3, 4, 5, 6, 7, 8
MS	9	1,000	49,999,999	2, 3, 4, 7, 8, 9
NC	21	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
ND	2	0	99,999	8
NE	1	0	99	8
NJ	9	0	99,999	1, 2, 3, 5, 7, 8, 9
NM	2	10,000	999,999	7, 12
NV	6	1,000	99,999,999	1, 2, 4, 5, 6, 7, 8, 11, 12, 13
NY	4	0	99,999	7, 8, 12
OH	15	0	999,999	1, 2, 3, 4, 5, 8, 9, 12, 13
OK	9	0	99,999	1, 2, 5, 6, 7, 9, 11, 12, 13
OR	6	10,000	999,999	1, 5, 7, 8, 12
PA	24	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
PR	3	1,000	99,999	8, 11
SC	9	0	9,999,999	1, 2, 3, 5, 6, 8, 12
SD	1	10,000,000	49,999,999	1, 7, 11, 13
TN	11	0	999,999	1, 2, 3, 6, 7, 8, 11, 12, 14
TX	29	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14
VA	8	0	999,999	2, 3, 7, 8, 10

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-1. Facilities that Produce, Process, or Use Arsenic

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
WA	3	0	99,999	5, 7, 8
WI	9	0	99,999	1, 2, 3, 4, 5, 6, 7, 8, 12
WV	19	100	999,999	1, 2, 3, 5, 7, 8, 10, 11, 12
WY	1	100	999	1, 13

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI04 2006 (Data are from 2004)

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Arsenic Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AK	6	1,000	49,999,999	1, 5, 7, 12, 13, 14
AL	37	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
AR	20	1,000	99,999,999	1, 2, 3, 7, 8, 9, 11, 12, 13, 14
AZ	29	100	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	40	100	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CO	9	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
DE	1	10,000	99,999	1, 5, 9
FL	30	0	999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
GA	50	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
HI	6	1,000	99,999	7, 8, 11
IA	22	0	9,999,999	1, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
ID	6	10,000	9,999,999	1, 3, 5, 6, 7, 8, 9, 12, 13
IL	44	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	54	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KS	14	0	999,999	1, 3, 4, 5, 6, 7, 8, 12, 13, 14
KY	29	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	32	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
MA	9	0	999,999	1, 4, 5, 6, 7, 8
MD	19	0	999,999	1, 4, 5, 7, 8, 9, 11, 12, 13
ME	2	1,000	99,999	7
MI	32	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MN	13	0	999,999	1, 3, 4, 5, 7, 8, 9, 11, 12, 13
MO	32	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MS	28	1,000	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
MT	8	1,000	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 12, 13, 14
NC	65	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	11	1,000	99,999	1, 5, 8, 9, 11, 12, 13, 14
NE	6	1,000	999,999	1, 2, 3, 4, 5, 6, 8, 9, 12, 13
NH	2	1,000	99,999	8, 11
NJ	35	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13
NM	11	1,000	499,999,999	1, 5, 7, 12, 13
NV	31	1,000	10,000,000,000	1, 2, 3, 5, 6, 7, 9, 11, 12, 13, 14
NY	27	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13
OH	50	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
OK	14	100	9,999,999	1, 2, 3, 4, 5, 6, 8, 12, 13, 14
OR	12	100	99,999	1, 2, 3, 7, 8, 12
PA	53	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
PR	8	1,000	99,999	1, 2, 3, 5, 8, 11
RI	7	100	99,999	7, 8

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-2. Facilities that Produce, Process, or Use Arsenic Compounds

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
SC	34	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
SD	6	1,000	99,999,999	1, 5, 6, 7, 8, 11, 12, 13
TN	29	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
TX	54	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
UT	23	0	499,999,999	1, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
VA	24	0	499,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
WA	14	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
WI	13	100	99,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11
WV	26	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14
WY	9	1,000	99,999	1, 3, 4, 5, 7, 8, 9, 12, 13

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI04 2006 (Data are from 2004)

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Table 5-3. Current U.S. Manufacturers of Selected Arsenic Compounds^a

Company	Location(s)
Arsenic acid	
Arch Wood Protection, Inc.	Conley, Georgia
Osmose Wood Preserving, Inc.	Millington, Tennessee
Arsanilic acid	
Fleming Laboratories, Inc.	Charlotte, North Carolina
Copper Chromated Arsenic (CCA)	
Arch Wood Protection, Inc.	Conley, Georgia; Kalama, Washington; Smyrna, Georgia ^b ; Valparaiso, Indiana
Chemical Specialties, Inc. ^b	Charlotte, North Carolina
Osmose Wood Preserving, Inc. ^b	Buffalo, New York
Calcium acid methanearsonate (CAMA)	
Drexel Chemical Company (formulator) ^c	No information provided
Disodium methanearsonate (DSMA)	
Drexel Chemical Company	Tunica, Mississippi
Monosodium methyl arsonate (MSMA)	
Drexel Chemical Company	Tunica, Mississippi
Gallium arsenide	
Atomergic Chemetals Corporation	Farmingdale, New York

^aDerived from Stanford Research Institute (SRI 2006), except where otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or \$10,000 in value annually) by the companies listed.

^bUSGS 2006a

^cMeister et al. 2006

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2 IMPORT/EXPORT

Since U.S. production ceased in 1985, all arsenic consumed in the United States is imported. Imports of arsenic (metal and compounds combined) have increased substantially since the mid-1980s, reaching 8,810 metric tons (as arsenic content) in 2005, of which 812 metric tons was as elemental arsenic. In 2005, 11,000 metric tons of arsenic trioxide was imported into the United States. China is the major import source for elemental arsenic from 2001 to 2004, supplying 81%, followed by Japan (15%) and Hong Kong (2%). China is also the major import source in 2001–2004 for arsenic trioxide, supplying 59% to the United States, followed by Morocco (22%), Chile (7%), and Mexico (5%) (USGS 2006a, 2006b).

U.S. exports of elemental arsenic were 220 metric tons in 2004 and are estimated to be 200 metric tons in 2005 (USGS 2006b). In 2005, U.S. import of arsenic was approximately 8.1×10^5 kilograms (810 metric tons) (ITA 2007a, 2007b).

5.3 USE

In 2003, the United States was the world's largest consumer of arsenic, with an apparent demand of 21,600 metric tons. In 2005, the United States was still the world's largest consumer of arsenic, mainly for CCA. Production of wood preservatives, primarily CCA, $\text{CrO}_3 \cdot \text{CuO} \cdot \text{As}_2\text{O}_5$, accounted for >90% of domestic consumption of arsenic trioxide prior to 2004. In 2005, about 65% of domestic consumption of arsenic trioxide was used for the production of CCA. The remainder was used for the production of agricultural chemicals, including herbicides, and insecticides. The major U.S. producers of CCA in 2005 included Arch Wood Protection, Inc., Smyrna Georgia; Chemical Specialties Inc., Charlotte, North Carolina; and Osmose Wood Preserving, Inc., Buffalo, New York (USGS 2006a). CCA is the most widely used wood preservative in the world. Wood treated with CCA is referred to as 'pressure treated' wood (American Wood Preservers Association 2007; Page and Loar 1993). In 1997, approximately 727.8 million cubic feet (20.6 million cubic meters) of wood products were pressure treated in the United States. CCA is a water-based product that protects several commercially available species of western lumber from decay and insect attack. It is widely used in treating utility poles, building lumber, and wood foundations. CCA comes in three types, A, B, and C, which contain different proportions of chromium, copper, and arsenic oxides. Type C, the most popular type, contains CrO_3 , CuO , and As_2O_5 in the proportions 47.5, 18.5, and 34.0%, respectively. The retention levels are 0.25 pounds per cubic feet (pcf) for above ground use such as fencing and decking, 0.40 pcf for lumber used in ground contact such as

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

fence posts and deck posts, and 0.60 pcf for all weather wood foundations (Chicago Flameproof 2000; Permapost 2000). Piling used for fresh and saltwater contact should contain 0.80 and 2.5 pcf of CCA, respectively. Ammoniacal copper zinc arsenate (ACZA) is another arsenic containing preservative used to treat wood; however, it is not as widely used as CCA-C (Lebow et al. 2000).

In 2003, U.S. manufacturers of arsenical wood preservatives began a voluntary transition from CCA to other wood preservatives in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; wood treated prior to this date could still be used and structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications (EPA 2003a).

Elemental arsenic is used as an alloying element in ammunition and solders, as an anti-friction additive to metals used for bearings, and to strengthen lead-acid storage battery grids. In the past, the predominant use of arsenic was in agriculture. The uses of lead arsenate as a growth regulator on citrus, calcium arsenate as an herbicide on turf, sodium arsenite as a fungicide on grapes, and arsenic acid as a desiccant on okra for seed and cotton were voluntarily cancelled in the late 1980s and the early 1990s (EPA 2006). The herbicides, MSMA and DSMA, are registered for weed control on cotton, for turf grass and lawns, and under trees, vines, and shrubs; calcium acid methanearsonate (CAMA) is registered for postemergent weed control on lawns. Cacodylic acid, a defoliant and herbicide, is registered for weed control under nonbearing citrus trees, around buildings and sidewalks, and for lawn renovation (EPA 2006).

Approximately 3 million pounds of MSMA or DSMA, and 100,000 pounds of cacodylic acid are applied in the U.S. annually based on EPA's Screening Level Use Analysis data. Data were not available for CAMA. Application to cotton and turf (residential and golf courses) are the major uses of organic arsenical herbicides. Currently, there are approximately 90, 25, 4, and 35 end-use products containing MSMA, DSMA, CAMA, and cacodylic acid, respectively (EPA 2006).

Other organic arsenicals used in agriculture include arsanilic acid, sodium arsanilate, and 3-nitro-4-hydroxyphenylarsonic acid (roxarsone), which are antimicrobials used in animal and poultry feeds (Beerman 1994). While the U.S. Food and Drug Administration (FDA) has authorized the use of these compounds as medicinal feed additives, only one of the arsenical compounds may be used at a time as the sole source of organic arsenic in the feed (EPA 1998k). In 1999–2000, about 70% of the broiler industry added roxarsone to broiler poultry feed; concentrations of roxarsone in feed range from 22.7 to 45.4 g/ton (Garbarino et al. 2003).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

From the mid-nineteenth century to the introduction of organic pesticides in the 1940s, inorganic arsenic compounds were the dominant pesticides available to farmers and fruit growers. Calcium arsenate was formerly used to control the boll weevil and cotton worm and was used as an herbicide. Lead arsenate was used on apple and other fruit orchards as well as on potato fields. Sodium arsenite was used to control weeds on railroad right-of-ways, potato fields, and in industrial areas, as well as in baits and to debark trees. Sodium arsenate had some application in ant traps. The use of inorganic arsenic compounds in agriculture has virtually disappeared beginning around the 1960s (Azcue and Nriagu 1994; Meister 1987; Merwin et al. 1994; Sanok et al. 1995). Food uses were voluntarily cancelled in 1993 as was the use of arsenic acid as a defoliant on cotton plants; inorganic arsenic's remaining allowable uses are in ant baits and wood preservatives (EPA 1999h). In 1987, EPA issued a preliminary decision to cancel the registration of most inorganic arsenicals used as nonwood pesticides (Loebenstein 1994) (see Chapter 8). According to the California Department of Pesticide Regulation, arsenic acid, arsenic pentoxide, and arsenic trioxide are registered currently as pesticides in the United States; there are no active registrants listed for calcium arsenate, lead arsenate, or sodium arsenite (NPIRS 2007).

High-purity arsenic (99.9999%) is used by the electronics industry for gallium-arsenide semiconductors for telecommunications, solar cells, and space research (USGS 2006b). Arsenic trioxide and arsenic acid were used as a decolorizer and fining agent in the production of bottle glass and other glassware (Carapella 1992).

Arsenic compounds have a long history of use in medicine. Inorganic arsenic was used as a therapeutic agent through the mid-twentieth century, primarily for the treatment of leukemia, psoriasis, and chronic bronchial asthma; organic arsenic antibiotics were extensively used in the treatment of spirochetal and protozoal disease (NRC 1999). The availability of inorganic arsenicals in Western medicines ended in the 1970s, although they may still be encountered in non-Western traditional medicines. By the 1980s, the only remaining medicinal organic arsenical was melarsoprol for treatment of the meningoencephalitic stage of African trypanosomiasis. There has been renewed interest in arsenic as a therapeutic agent, namely the use of arsenic trioxide in the treatment of acute promyelocytic leukemia (APL) (Gallagher 1998; Kroemer and de Thé 1999; Miller 1998; Wang 2001). In 2000, the FDA approved arsenic trioxide for this use (FDA 2000).

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5.4 DISPOSAL

Wastes containing arsenic are considered hazardous wastes, and as such, their treatment, storage, and disposal are regulated by law (see Chapter 8). The main route of disposal of solid wastes containing arsenic is landfilling. EPA has promulgated rules and treatment standards for landfilling liquid arsenical wastes (EPA 1990e). Arsenic-containing electronic components such as relays, switches, and circuit boards are disposed of at hazardous waste sites, and the elemental arsenic is not reclaimed. Process water at wood treatment plants that contained arsenic contained was reused. Gallium-arsenide scrap from the manufacture of semiconductor devices was reprocessed for arsenic recovery. Arsenic was not recovered from arsenical residues and dusts at domestic nonferrous smelters (USGS 2006b).

CCA-treated wood is classified as nonhazardous waste under the Federal Resource Conservation and Recovery Act (RCRA). CCA-treated wood is disposed of with regular municipal trash (i.e., municipal solid waste, not yard waste). It should not be burned in open fires, stoves, residential boilers, or fire places and should not be composted or used as mulch. Treated wood from commercial or industrial applications may only be burned in commercial or industrial incinerators in accordance with state and federal regulations (Adobe Lumber 2002; EPA 2005a).

Arsenic is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1995c). Disposal of wastes containing arsenic is controlled by a number of federal regulations (see Chapter 8).

6. POTENTIAL FOR HUMAN EXPOSURE

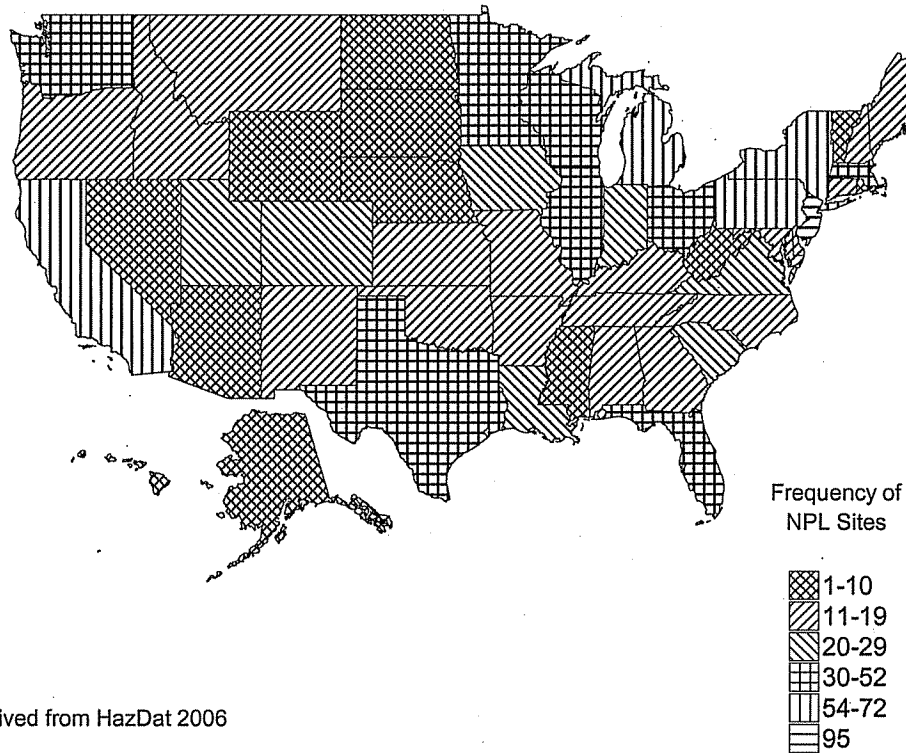
6.1 OVERVIEW

Arsenic has been identified in at least 1,149 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for arsenic is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,134 are located within the United States and 11, 2, and 2 are located in the Commonwealth of Puerto Rico, the Virgin Islands, and Guam (not shown).

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in nature in minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al. 2001; Carapella 1992). While arsenic is released to the environment from natural sources such as wind-blown soil and volcanoes, releases from anthropogenic sources far exceed those from natural sources. Anthropogenic sources of arsenic include nonferrous metal mining and smelting, pesticide application, coal combustion, wood combustion, and waste incineration. Most anthropogenic releases of arsenic are to land or soil, primarily in the form of pesticides or solid wastes. However, substantial amounts are also released to air and water.

Arsenic found in soil either naturally occurring or from anthropogenic releases forms insoluble complexes with iron, aluminum, and magnesium oxides found in soil surfaces, and in this form, arsenic is relatively immobile. However, under reducing conditions, arsenic can be released from the solid phase, resulting in soluble mobile forms of arsenic, which may potentially leach into groundwater or result in runoff of arsenic into surface waters. In aquatic systems, inorganic arsenic occurs primarily in two oxidation states, As(V) and As(III). Both forms generally co-exist, although As(V) predominates under oxidizing conditions and As(III) predominates under reducing conditions. Arsenic may undergo a variety of reactions in the environment, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Pongratz 1998; Welch et al. 1988). These reactions are influenced by Eh (the oxidation-reduction potential), pH, metal sulfide and sulfide ion concentrations, iron concentration, temperature, salinity, and distribution and composition of the biota (EPA 1979; Wakao et al. 1988). Much of the arsenic will adsorb to particulate matter and sediment. Arsenic released to air exists mainly in the form of particulate matter. Arsenic released from combustion processes will

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Figure 6-1. Frequency of NPL Sites with Arsenic Contamination

Derived from HazDat 2006

6. POTENTIAL FOR HUMAN EXPOSURE

generally occur as highly soluble oxides. These particles are dispersed by the wind and returned to the earth in wet or dry deposition. Arsines that are released to the atmosphere as a result of microbial action are oxidized to nonvolatile species that settle back to the ground.

Because arsenic is a natural component of the Earth's crust, low levels of the element are found in all environmental media. Atmospheric levels of arsenic in remote locations (away from human releases) range from 1 to 3 ng/m³, while concentrations in urban areas may range from 20 to 100 ng/m³. Concentrations in water are usually <10 µg/L, although higher levels may occur near natural mineral deposits or anthropogenic sources. Natural levels of arsenic in soil usually range from 1 to 40 mg/kg, with a mean of 5 mg/kg, although much higher levels may occur in mining areas, at waste sites, near high geological deposits of arsenic-rich minerals, or from pesticide application. Arsenic is also found in many foods, at concentrations that usually range from 20 to 140 µg/kg. Total arsenic concentrations may be substantially higher in certain seafoods. However, the general consensus in the literature is that about 85–>90% of the arsenic in the edible parts of marine fish and shellfish is organic arsenic (e.g., arsenobetaine, arsenocholine, dimethylarsinic acid) and that approximately 10% is inorganic arsenic (EPA 2003b). Drinking water in the United States generally contains an average of 2 µg/L of arsenic (EPA 1982c), although 12% of water supplies from surface water sources in the north Central region of the United States and 12% of supplies from groundwater sources in the western region have levels exceeding 20 µg/L (Karagas et al. 1998). In January 2001, EPA adopted a new standard that arsenic levels in drinking water were not to exceed 10 µg/L, replacing the previous standard of 50 µg/L. The date for compliance with the new MCL was January 23, 2006 (EPA 2001).

For most people, diet is the largest source of exposure to arsenic. Mean dietary intakes of total arsenic of 50.6 µg/day (range of 1.01–1,081 µg/day) and 58.5 µg/day (range of 0.21–1,276 µg/day) has been reported for females and males (MacIntosh et al. 1997). U.S. dietary intake of inorganic arsenic has been estimated to range from 1 to 20 µg/day, with grains and produce expected to be significant contributors to dietary inorganic arsenic intake (Schoof et al. 1999a, 1999b). The predominant dietary source of arsenic is generally seafood. Inorganic arsenic in seafood sampled in a market basket survey of inorganic arsenic in food ranged from <0.001 to 0.002 µg/g (Schoof et al. 1999a, 1999b). Intake of arsenic from air and soil are usually much smaller than that from food and water (Meacher et al. 2002).

People who produce or use arsenic compounds in occupations such as nonferrous metal smelting, pesticide manufacturing or application, wood preservation, semiconductor manufacturing, or glass production may be exposed to substantially higher levels of arsenic, mainly from dusts or aerosols in air.

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Exposure at waste sites may occur by a variety of pathways, including inhalation of dusts in air, ingestion of contaminated soil or water, or through the food chain. The magnitude of the exposures can only be evaluated on a site-by-site basis; however, exposures generally do not exceed background intakes from food and drinking water.

Tables 4-1, 4-2, 4-3, and 4-4 summarize all of the names, abbreviations, and structures of the various arsenic compounds that are discussed in Chapter 6.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005k). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005k).

6.2.1 Air

Estimated releases of 4,800 pounds (~2.2 metric tons) of arsenic to the atmosphere from 58 domestic manufacturing and processing facilities in 2004, accounted for about 0.52% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). Estimated releases of 0.13 million pounds (~59 metric tons) of arsenic compounds to the atmosphere from 361 domestic manufacturing and processing facilities in 2004, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases for arsenic and arsenic compounds are summarized in Table 6-1 and 6-2, respectively.

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Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic^a

State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Reported amounts released in pounds per year ^b		
							Total release		
							On-site ^j	Off-site ^k	On- and off-site
AL	1	51	162	0	110,264	0	110,425	52	110,477
AR	2	0	0	No data	0	0	No data	0	0
AZ	2	10	0	0	20,717	0	20,727	0	20,727
CA	3	13	14	0	5,482	0	13	5,497	5,510
FL	2	4	0	0	0	4,950	4	4,950	4,954
GA	4	8	10	0	1,603	5	13	1,613	1,626
IA	1	0	1	0	0	0	0	1	1
ID	1	39	0	0	361,252	0	361,291	0	361,291
IL	2	250	129	0	14,087	0	379	14,087	14,466
IN	1	5	5	0	13,250	250	5	13,505	13,510
KS	1	0	0	No data	0	0	No data	0	0
KY	1	0	1	0	0	6	1	6	7
MI	2	0	5	0	0	750	5	750	755
MN	1	15	47	0	14,504	0	15	14,551	14,566
MO	1	5	0	0	0	4,040	5	4,040	4,045
MS	2	0	0	0	0	0	0	0	0
NC	4	35	8	0	1	1	43	2	45
NV	1	0	0	0	0	0	0	0	0
NY	4	0	1	0	26,525	1	26,401	126	26,527
OH	2	13	0	0	0	0	13	0	13
OR	1	0	0	0	92,606	0	92,606	0	92,606
PA	5	166	8	0	14,362	26,140	199	40,477	40,676
SC	3	10	10	0	0	1,002	15	1,007	1,022
TN	3	3,988	0	0	0	0	3,988	0	3,988
TX	5	139	376	168,563	12,600	0	181,636	42	181,678

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic^a

Reported amounts released in pounds per year ^b									
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
WI	2	15	0	0	760	0	15	760	776
WV	1	0	0	0	10,135	0	10,135	0	10,135
Total	58	4,766	778	168,563	698,149	37,145	807,935	101,466	909,401

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic Compounds^a

State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Reported amounts released in pounds per year ^b		
							Total release		
							On-site ^j	Off-site ^k	On- and off-site
AK	1	511	0	1,400,000	1,200,000	0	2,600,511	0	2,600,511
AL	19	4,299	18,127	0	853,469	7,555	875,876	7,574	883,450
AR	12	0	0	0	133	26,435	0	26,568	26,568
AZ	5	5,421	0	0	402,335	422	394,749	13,429	408,178
CA	5	65	14	0	355,660	86,396	160,673	281,461	442,134
CO	1	11	0	0	4,094	0	4,105	0	4,105
CT	1	0	0	0	0	0	No data	0	0
FL	15	3,208	503	0	343,508	4,057	346,310	4,966	351,276
GA	23	8,643	7,823	0	422,124	5,127	437,496	6,221	443,717
HI	1	0	0	0	0	0	No data	0	0
IA	4	1,291	482	0	0	35,324	1,773	35,324	37,097
ID	3	332	20	0	1,056,904	0	1,057,256	0	1,057,256
IL	11	3,960	3,110	0	96,093	21,038	71,819	52,382	124,202
IN	21	13,786	8,282	0	768,297	42,808	632,704	200,470	833,174
KS	4	924	0	0	12,082	1	13,006	1	13,007
KY	18	14,406	8,427	0	616,074	95,285	578,080	156,112	734,192
LA	7	265	23	0	25,426	0	25,563	151	25,714
MA	1	0	0	0	0	500	0	500	500
MD	8	1,870	291	0	34,130	114,115	2,661	147,745	150,406
MI	10	1,123	2,310	68,924	101,857	1,059	77,505	97,769	175,274
MN	2	10	130	0	19,270	0	19,410	0	19,410
MO	6	462	116	0	27,855	936	10,026	19,343	29,369
MS	6	61	121	0	11,676	46	11,228	676	11,904
MT	3	630	0	0	2,138,190	37	2,138,820	37	2,138,857
NC	15	5,626	4,732	0	168,030	2,429	178,388	2,429	180,818
ND	6	6,326	5	0	318,175	0	137,961	186,545	324,506
NE	2	180	0	0	11,000	0	11,180	0	11,180
NJ	2	0	1	0	0	8	0	9	9
NM	2	130	0	0	18,326	0	18,456	0	18,456
NV	10	3,041	30,017	0	98,894,564	0	98,927,328	294	98,927,622
NY	3	67	36	0	27,059	802	27,141	823	27,964
OH	17	8,595	8,352	81,024	741,730	274	668,157	171,818	839,975
OK	4	115	13	0	25,000	4,202	115	29,215	29,330
OR	4	0	5	0	0	4,012	5	4,012	4,017
PA	23	18,963	2,166	0	666,753	69,053	403,582	353,353	756,935
PR	3	0	0	0	0	0	No data	0	0
RI	1	0	8	0	0	1,006	8	1,006	1,014

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Arsenic Compounds^a

Reported amounts released in pounds per year ^b										
State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release			
							On-site ^j	Off-site ^k	On- and off-site	
SC	13	2,178	1,443		0	25,817	22,705	29,438	22,705	52,143
SD	1	0	0		0	0		No data	0	0
TN	13	3,379	25,878		0	292,914	17,219	258,643	80,746	339,389
TX	17	4,616	199	33,148		196,385	31,557	226,751	39,155	265,906
UT	5	6,715	4,500		0	6,368,500	3,500	6,379,715	3,500	6,383,215
VA	11	1,911	2,773		0	160,154	8,463	164,789	8,512	173,301
WA	4	0	0		0	0		No data	0	0
WI	4	94	21		0	1,313	9,216	223	10,421	10,644
WV	12	2,693	2,417		0	536,628	10,000	441,237	110,501	551,738
WY	2	3,300	0		0	10,800	0	14,100	0	14,100
Total	361	129,205	132,347	1,583,096	116,952,326	625,588	117,346,787	2,075,775	119,422,562	

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

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Arsenic naturally occurs in soil and will be present in the atmosphere as airborne dust. It is also emitted from volcanoes and in areas of dormant volcanism (e.g., fumaroles). Gaseous alkyl arsenic compounds may be released from soil that has been treated with inorganic arsenic compounds as a result of biogenic processes (Schroeder et al. 1987; Tamaki and Frankenberger 1992). Arsenic naturally occurs in sea water and vegetation and is released into the atmosphere in sea salt spray and forest fires. Anthropogenic sources of arsenic include nonferrous metal smelting, coal, oil and wood combustion, and municipal waste incineration. Arsenic naturally occurs in coal and oil and therefore, coal- and oil-fired power plants release arsenic to the atmosphere in their emissions (Pacyna 1987). Arsenic's use in agriculture and industrial processes also contributes to its emissions. One important source of arsenic emissions is cotton ginning in which the cotton seeds are removed from the raw cotton.

The National Air Toxics Assessment reported that total anthropogenic emissions for arsenic compounds in the United States in 1996 were 355 tons/year (EPA 2005b). EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate air quality (Rosenbaum et al. 1999). Using 1990 data, the total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling was estimated to be 3.0 tons/day with 90% of emissions coming from point sources and 5% each from area and mobile sources. U.S. emissions of arsenic to the atmosphere were estimated as 3,300 metric tons per year between 1979 and 1986 (Pacyna et al. 1995). There is evidence that anthropogenic emissions, at least from smelters, are lower than they had been in the early 1980s. It is likely that air releases of arsenic decreased during the 1980s due to regulations on industrial emissions (EPA 1986f), improved control technology for coal-burning facilities, and decreased use of arsenical pesticides.

Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated worldwide emissions of arsenic to the atmosphere for 1983. Estimates of yearly emissions from anthropogenic sources ranged from 12,000 to 25,600 metric tons with a median value of 18,800 metric tons. Natural sources contributed 1,100–23,500 metric tons annually. Chilvers and Peterson (1987) estimated global natural and anthropogenic arsenic emissions to the atmosphere as 73,500 and 28,100 metric tons per year, respectively. Copper smelting and coal combustion accounted for 65% of anthropogenic emissions. A U.S. Bureau of Mines study on the flow of mineral commodities estimated that global emissions of arsenic from metal smelting, coal burning, and other industrial uses ranged from 24,000 to 124,000 metric tons per year compared to natural releases, mostly from volcanoes, ranging from 2,800 to 8,000 metric tons per year (Loebenstein 1994).

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Pirrone and Keeler (1996) compared trends of trace element emissions from major anthropogenic sources in the Great Lakes region with ambient concentrations observed in urban areas of the region. They found that arsenic emissions increased about 2.8% per year from 1982 to 1988 and then decreased steadily by about 1.4% per year to 1993. Coal combustion in electric utilities and in residential, commercial, and industrial facilities was an important source of arsenic in the region, accounting for about 69% of the total emissions. Iron-steel manufacturing accounted for about 13% of the region wide arsenic emissions and nonferrous metals production for 17%.

Arsenic in the particulate phase is the predominant (89–98.6%) form of arsenic in the troposphere (Matschullat 2000). Inorganic species, most commonly trivalent arsenic, is the dominant form of arsenic in the air over emission areas; methylated forms of arsenic are probably of minor significance. Arsenic-containing air samples of smelter or coal-fired power plant origin consist largely of trivalent arsenic in both vapor and particulate form (Pacyna 1987). Oxides are the primary species evolved from fossil fuel and industrial processes. Additionally, arsenic trisulfide has also been reported from coal combustion, organic arsines from oil combustion, and arsenic trichloride from refuse incineration.

Arsenic has been identified in 59 air samples collected from 1,684 current or former NPL hazardous waste sites where it was detected in some environmental media (HazDat 2006).

6.2.2 Water

Estimated releases of 780 pounds (~0.35 metric tons) of arsenic to surface water from 58 domestic manufacturing and processing facilities in 2004, accounted for about 0.09% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). Estimated releases of 1.3x10⁵ pounds (~59 metric tons) of arsenic compounds to surface water from 361 domestic manufacturing and processing facilities in 2004, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

Arsenic may be released to water from the natural weathering of soil and rocks, and in areas of vulcanism. Arsenic may also leach from soil and minerals into groundwater. Anthropogenic sources of arsenic releases to water include mining, nonferrous metals, especially copper, smelting, waste water, dumping of sewage sludge, coal burning power plants, manufacturing processes, urban runoff, atmospheric deposition and poultry farms (Garbarino et al. 2003; Nriagu and Pacyna 1988; Pacyna et al. 1995). A contributory

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part of mining and coal burning power plants is leaching from abandoned mine tailing and fly ash waste piles. Significant amounts of arsenic are released in liquid effluents from gold-milling operations using cyanide (Environment Canada 1993). Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into rivers, lakes, and oceans for 1983; annual estimated inputs ranged from 11,600 to 70,300 metric tons with a median value of 41,800 metric tons. Arsenic was detected in 58% of samples of urban storm water runoff from 8 of 15 cities surveyed in the National Urban Runoff Program at concentrations ranging from 1 to 50.5 µg/L (Cole et al. 1984).

Leaching of arsenic from soil, landfills, or slag deposits is a source of arsenic in groundwater (Francis and White 1987; Wadge and Hutton 1987). The arsenic in soil may be naturally-occurring or a result of the application of arsenic-containing pesticides or sludge. Wood treated with CCA is used in piers, piling and bulkheads and arsenic can leach from the treated wood (Breslin and Adler-Ivanbrook 1998; Brooks 1996; Cooper 1991; Sanders et al. 1994; Weis et al. 1998). Ammoniacal copper zinc arsenate (ACZA) is another arsenic-containing waterborne preservative; however, it is not as widely used as CCA (Lebow et al. 2000).

Arsenic has been identified in 846 groundwater and 414 surface water samples collected from 1,684 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2006).

6.2.3 Soil

Estimated releases of 0.70 million pounds (~320 metric tons) of arsenic to soils from 58 domestic manufacturing and processing facilities in 2004, accounted for about 77% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). An additional 0.17 million pounds (~77 metric tons), constituting about 19% of the total environmental emissions, were released via underground injection (TRI04 2006). Estimated releases of 117 million pounds (~5.3x10⁴ metric tons) of arsenic compounds to soils from 361 domestic manufacturing and processing facilities in 2004, accounted for about 98% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). An additional 1.6 million pounds (~720 metric tons), constituting about 1.3% of the total environmental emissions, were released via underground injection (TRI04 2006). These releases for arsenic and arsenic compounds are summarized in Tables 6-1 and 6-2, respectively.

The soil receives arsenic from a variety of anthropogenic sources, including ash residue from power plants, smelting operations, mining wastes, and municipal, commercial, and industrial waste. Ash from

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power plants is often incorporated into cement and other materials that are used for roads and construction. Arsenic may be released from such material into soil. Nriagu and Pacyna (1988) and Pacyna et al. (1995) estimated global anthropogenic inputs of arsenic into soil for 1983. Excluding mine tailings and smelter slag, annual estimated inputs ranged from 52,000 to 112,000 metric tons with a median value of 82,000 metric tons. Mine tailings and smelter slag were estimated to add an additional 7,200–11,000 and 4,500–9,000 metric tons, respectively. Old abandoned mine tailings undoubtedly contribute still more. Wood treated with CCA used in foundations or posts could potentially release arsenic into the surrounding soil. CCA preservatives have been shown to leach to varying degrees from wood, as well as through soils in both field and laboratory studies (Chirenje et al. 2003a; Hingston et al. 2001; Lebow et al. 2000; Rahman et al. 2004; Stilwell and Graetz 2001; USDA/USDT 2000). Arsenic may also be released on land through the application of pesticides and fertilizer. Senesi et al. (1999) reported the range of arsenic in 32 fertilizers as 2.2–322 ng/g. Roxarsone (3-nitro-4-hydroxyphenyl-arsonic acid), which was used to treat poultry feed in approximately 70% of the broiler poultry operations in 1999–2000, is excreted unchanged in the manure. Poultry litter (manure and bedding) is routinely used as fertilizer to cropland and pasture. In 2000, assuming 70% of the 8.3 billion broiler poultry produced in the United States were fed roxarsone-treated feed, the resulting manure would contain approximately 2.5×10^5 kg of arsenic (Garbarino et al. 2003). Land application of sewage sludge is another source of arsenic in soil. Arsenic was detected in sewage sludge samples from 23 cities at concentrations of 0.3–53 µg/g (Mumma et al. 1984).

Arsenic has been identified in 758 soil and 515 sediment samples collected from 1,684 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2006).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Arsenic in soil may be transported by wind or in runoff or may leach into the subsurface soil. However, because many arsenic compounds tend to partition to soil or sediment under oxidizing conditions, leaching usually does not transport arsenic to any great depth (EPA 1982c; Moore et al. 1988; Panssar-Kallio and Manninen 1997; Welch et al. 1988). Arsenic is largely immobile in agricultural soils; therefore, it tends to concentrate and remain in upper soil layers indefinitely. Downward migration has been shown to be greater in a sandy soil than in a clay loam (Sanok et al. 1995). Arsenic from lead arsenate that was used for pest control did not migrate downward below 20 cm in one fruit orchard; in another orchard, 15 years after sludge amendments and deep plowing, essentially all arsenic residues

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remained in the upper 40 cm of soil (Merwin et al. 1994). Leaching of arsenic in polluted wetland soil was low; leaching was correlated with the amount of dissolved organic matter in the soil (Kalbitz and Wennrich 1998). The effect of soil characteristics, namely pH, organic matter content, clay content, iron oxide content, aluminum oxide content, and cation exchange capacity (CEC), on the adsorption of various metals, including the metalloid arsenic, to 20 Dutch surface soils was assessed by regression analysis (Janssen et al. 1997). The most influential parameter affecting arsenic adsorption was the iron content of the soil.

Arsenic that is adsorbed to iron and manganese oxides may be released under reducing conditions, which may occur in sediment or flooding conditions (LaForce et al. 1998; McGeehan 1996; Mok and Wai 1994). In addition to reductive dissolution, when nutrient levels are adequate, microbial action can also result in dissolution (LaForce et al. 1998). Interestingly, drying of the previously flooded soil increases arsenic adsorption, possibly due to alterations in iron mineralogy (McGeehan et al. 1998).

Darland and Inskeep (1997) conducted a study to determine the effects of pH and phosphate competition on the transport of arsenate ($\text{H}_x\text{AsO}_4^{x-3}$) through saturated columns filled with sand containing free iron oxides. At pH 4.5 and 6.5, arsenate transport was strongly retarded, while at pH 8.5, it was rapid. The enhanced transport of arsenate at pH 8 is consistent with the pH dependence of surface complexation reactions describing arsenate sorption by metal oxide minerals that can be categorized as a ligand exchange mechanism. Phosphate was shown to compete effectively with arsenate for adsorption sites on the sand, but the competition was not sufficient to desorb all of the arsenate in batch column experiments, even when the applied phosphate exceeded the column adsorption capacity by a factor of two. The researchers concluded that arsenate desorption kinetics may play an important role in the transport of arsenate through porous media. In a study looking at the effect of competing anions on the adsorption of arsenite and arsenate on ferrihydrite, the effect of phosphate on arsenate adsorption was greater at higher pH than at low pH and the opposite trend was observed for arsenite. While sulfate did not change the affinity of arsenate for ferrihydrite, sulfate reduced the adsorption of arsenite at pHs below 7.0 (Jain and Loeppert 2000).

Smith et al. (1999) investigated the sorption properties of both As(V) and As(III) in 10 Australian soils of widely different chemistry and mineralogy at commonly found arsenic levels. Adsorption of both arsenate and arsenite was rapid (1 hour). The amount of As(V) sorbed varied widely (1.7–62.0 L/kg); soils with lower amounts of oxidic material adsorbed much less arsenic than those with higher amounts of these minerals. Arsenate sorption was highly correlated with the iron oxide content of the soil and this

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factor probably accounts for much of the variation in soil adsorptivity. Considerable leaching of arsenic occurred at a separate site where cattle were treated with a dip containing arsenic (cattle dip site) and that contained similar soil properties to that studied by Smith et al. (1999). Arsenite adsorption, which was investigated in four of the Australian soils, was sorbed to a lesser extent than was arsenate. This was attributed to soil mineralogy and the species of As(V) (arsenate) and As(III) (arsenite) present in solution; at pH 5–7, the dominant As(V) species are H_2AsO_4^- and HAsO_4^{2-} and neutral H_3AsO_3 is the dominant As(III) species. For soils containing low amounts of oxidic minerals, pH had little effect on As(V) sorption, while for oxidic soils, a decrease in sorption was evident as the pH increased. In contrast, As(III) sorption increased with increasing pH (Smith et al. 1999). Jain et al. (1999) reported similar results where arsenite were both found to bind strongly to iron oxides; however, the adsorption of arsenate decreases with increasing pH, while the adsorption of arsenite increases with increasing pH (Jain et al. 1999). As(III), which exists in a neutral form as arsenous acid, H_3AsO_3 ($\text{pK}_a=9.23, 12.13, 13.4$), is less strongly adsorbed on mineral surfaces than the oxyanions of arsenic acid, H_3AsO_4 , ($\text{pK}_a=2.22, 6.98, 11.53$) (NRC 1999). Based on its pK_a values, arsenic acid would exist as a mixture of arsenate anions, H_2AsO_4^- and HAsO_4^{2-} , under most environmental conditions (pH 5–9).

The practice of liming to remediate contaminated soils and mine tailings has the potential to mobilize arsenic. Experiments performed by Jones et al. (1997) indicate that the increased mobility appears to be consistent with the pH dependence of sorption reactions of arsenic on iron oxide minerals rather than dissolution-precipitation reactions involving arsenic. They recommend that remediation of acidic mine tailings or other arsenic-contaminated soils be carefully evaluated with respect to potential arsenic mobilization, especially at contaminated sites hydraulically connected to surface or groundwaters.

Transport and partitioning of arsenic in water depends upon the chemical form (oxidation state and counter ion) of the arsenic and on interactions with other materials present. Soluble forms move with the water, and may be carried long distances through rivers (EPA 1979). However, arsenic may be adsorbed from water onto sediments or soils, especially clays, iron oxides, aluminum hydroxides, manganese compounds, and organic material (EPA 1979, 1982c; Welch et al. 1988). Under oxidizing and mildly reducing conditions, groundwater arsenic concentrations are usually controlled by adsorption rather than by mineral precipitation. The extent of arsenic adsorption under equilibrium conditions is characterized by the distribution coefficient, K_d , which measures the equilibrium partitioning ratio of adsorbed to dissolved contaminant. The value of K_d depends strongly upon the pH of the water, the arsenic oxidation state, and the temperature. In acidic and neutral waters, As(V) is extensively adsorbed, while As(III) is relatively weakly adsorbed. Trivalent inorganic arsenic exists predominantly as arsenous acid (H_3AsO_3)

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at environmental pH and is not strongly adsorbed to suspended solids and sediments in the water column. Pentavalent inorganic arsenic exists predominantly as H_2AsO_4^- and HAsO_4^{2-} in most environmental waters, which has considerably greater adsorption characteristics than arsenous acid. While in acidic and neutral waters, As(V) is more strongly adsorbed relative to As(III), in high-pH waters (pH >9) aquifer K_d values are considerably lower for both oxidation states (Mariner et al. 1996). Sediment-bound arsenic may be released back into the water by chemical or biological interconversions of arsenic species (see Section 6.3.2).

Arsenic enters rivers from where mining operations occurred and is transported downstream, moving from water and sediment into biofilm (attached algae, bacterial, and associated fine detrital material), and then into invertebrates and fish. The source of arsenic in the water column may be resuspended sediment. While arsenic bioaccumulates in animals, it does not appear to biomagnify between trophic levels (Eisler 1994; Farag et al. 1998; Williams et al. 2006).

Most anthropogenic arsenic emitted to the atmosphere arises from high temperature processes (e.g., coal and oil combustion, smelting operations, and refuse incineration) and occurs as fine particles with a mass median diameter of about 1 μm (Coles et al. 1979; Pacyna 1987). These particles are transported by wind and air currents until they are returned to earth by wet or dry deposition. Their residence time in the atmosphere is about 7–9 days, in which time the particles may be transported thousands of kilometers (EPA 1982b; Pacyna 1987). Long-range transport was evident in analyzing deposition of arsenic in countries like Norway; there was no indication that the marine environment contributed significantly to the deposition (Steinnes et al. 1992). Atmospheric fallout can be a significant source of arsenic in coastal and inland waters near industrial areas. Scudlark et al. (1994) determined the average wet depositional flux of arsenic as 49 $\mu\text{g As/m}^2/\text{year}$ for two sites in Chesapeake Bay, Maryland from June 1990 to July 1991. They found a high degree of spatial and temporal variability. The elemental fluxes derived predominantly from anthropogenic sources. Golomb et al. (1997) report average total (wet + dry) deposition rates to Massachusetts Bay of 132 $\mu\text{g/m}^2/\text{year}$, of which 21 $\mu\text{g/m}^2/\text{year}$ was wet deposition during the period September 15, 1992–September 16, 1993. Hoff et al. (1996) estimated the following arsenic loadings into the Great Lakes for 1994 (lake, wet deposition, dry deposition): Superior, 11,000 kg/year, 3,600 kg/year; Michigan, 5,000 kg/year, 1,800 kg/year; Erie, 5,500 kg/year, 1,800 kg/year; and Ontario, 3,000 kg/year, 580 kg/year. The measured dry deposition fluxes of arsenic at four sampling sites around Lake Michigan ranged approximately from 0.01 to 1.5 $\mu\text{g As/m}^2/\text{day}$; estimated inputs of arsenic into Lake Michigan were reported to be 1.4×10^3 kg/year (Shahin et al. 2000).

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Terrestrial plants may accumulate arsenic by root uptake from the soil or by absorption of airborne arsenic deposited on the leaves, and certain species may accumulate substantial levels (EPA 1982b). Yet, even when grown on highly polluted soil or soil naturally high in arsenic, the arsenic level taken up by the plants is comparatively low (Gebel et al. 1998b; Pitten et al. 1999). Kale, lettuce, carrots, and potatoes were grown in experimental plots surrounding a wood preservation factory in Denmark where waste wood was incinerated to investigate the amount and pathways for arsenic uptake by plants (Larsen et al. 1992). On incineration, the arsenate in the wood preservative was partially converted to arsenite; the arsenic emitted from the stack was primarily particle bound. Elevated levels of inorganic arsenic were found in the test plants and in the soil around the factory. Statistical analyses revealed that the dominating pathway for transport of arsenic from the factory to the leafy vegetables (kale) was by direct atmospheric deposition, while arsenic in the root crops (potatoes and carrots) was a result of both soil uptake and atmospheric deposition. Arsenic accumulation by plants is affected by arsenic speciation. Uptake of four arsenic species (arsenite, arsenate, methylarsonic acid, and dimethylarsinic acid) by turnips grown under soilless culture conditions showed that while uptake increased with increasing arsenic concentration in the nutrient, the organic arsenicals showed higher upward translocation than the inorganic arsenical (Carbonell-Barrachina et al. 1999). The total amount of arsenic taken up by the turnip plants (roots and shoots) followed the trend methylarsenate (MMA)<dimethylarsinic acid (DMA)<arsenite<arsenate. In a similar experiment, conducted with tomato plants, the total amount of arsenic taken up by the tomato plants followed the trend DMA<MMA<arsenate≈arsenite, with arsenic concentrations in the plants increasing with increasing arsenic concentration in the nutrient solution. Arsenic was mainly accumulated in the root system (85%) with smaller amounts translocating to the fruit (1%). However, plants treated with MMA and DMA had higher arsenic concentrations in the shoots and fruit than those treated with arsenite or arsenate (Burlo et al. 1999). Terrestrial plants growing on land bordering arsenic-contaminated waters show relatively little arsenic content, even though the sediments have arsenic concentrations as high as 200 µg/g (Tamaki and Frankenberger 1992). Arsenic concentrations in vegetables grown in uncontaminated soils and contaminated soils containing arsenic, as well as other metals and organic contaminants, were generally <12 µg/kg wet weight. A maximum arsenic concentration of 18 µg/kg wet weight was found in unpeeled carrots grown in soil, which contained a mean arsenic concentration of 27 mg/kg dry weight (Samsøe-Petersen et al. 2002).

In a study by Rahman et al. (2004), CCA-treated lumber was used to construct raised garden beds to determine how far the components of CCA migrated in the soil and the uptake of these components by crops grown in the soil. Arsenic was found to diffuse laterally into the soil from the CCA-treated wood, with the highest concentrations found at 0–2 cm from the treated wood and a steady decline in

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concentration with increased distance. The highest average arsenic concentrations found in soil closest (0–2 cm) to the CCA-treated wood were 56 and 46 $\mu\text{g/g}$ in loamy sand and sandy loam soils, respectively. At a distance of 30–35 cm from the CCA-treated wood, arsenic concentrations were approximately 7 $\mu\text{g/g}$ in both soils. All samples were of the top 0–15 cm of soil. Crops grown in both soil types within 0–2 cm of the CCA-treated wood contained higher concentrations of arsenic, 0.186 and 10.894 $\mu\text{g/g}$ for carrots without peal and bean leaves and stems, respectively, than those grown at 1.5 m from the CCA-treated wood, 0.006 and 0.682 $\mu\text{g/g}$ for bean pods and bean leaves and stems, respectively. However, based on FDA guidelines on tolerance limits, these crops would be considered approved for human consumption. Studies by Chirenje et al. (2003a) also showed that elevated arsenic concentrations were found in surface (0–5 cm) soils immediately surrounding, within the first 0.3 m, of utility poles, fences, and decks made with CCA-treated wood. Factors such as the preservative formula, fixation temperature, post treatment handling, and timber dimensions of CCA-treated wood, as well as the pH, salinity, and temperature of the leaching media can affect the leach rates from CCA-treated wood (Hingston et al. 2001). Studies of leaching of the components of CCA- and ACZA-treated wood used to construct a boardwalk in wetland environments reported elevated arsenic levels in soil and sediment below and adjacent to these structures. Generally, these levels decreased with increasing distance from the structure (Lebow et al. 2000). Increased concentrations of arsenic were also observed under CCA-treated bridges. Arsenic levels declined with distance from the bridge and were near background levels at 1.8–3 m from the bridge's perimeter (USDA/USDT 2000).

In a study by Lebow et al. (2003), the use of a water repellent finish on CCA-treated wood significantly reduces the amount of arsenic, as well as copper and chromium, in the run-off water. It was also observed the exposure to UV radiation caused a significant increase in leaching from both finished and unfinished samples of CCA-treated wood. Small amounts of arsenic can be transferred from CCA-treated wood to skin from touching CCA-treated wood surfaces (Hemond and Solo-Gabriele 2004; Kwon et al. 2004; Shalat et al. 2006; Ursitti et al. 2004; Wang et al. 2005).

Breslin and Adler-Ivanbrook (1998) examined the leaching of the copper, chromium, and arsenic from CCA-treated wood in laboratory studies using samples of treated southern yellow pine in solutions simulating estuarine waters. The tank leaching solutions were frequently sampled and replaced to approximate field conditions. Initial 12-hour fluxes ranging from 0.2×10^{-10} to 5.2×10^{-10} $\text{mol/mm}^2 \text{ d}$ was reported for arsenic. After 90 days, arsenic fluxes decreased to 0.5×10^{-11} – 3.1×10^{-11} $\text{mol/mm}^2 \text{ d}$. A study by Cooper (1991) demonstrated that the buffer system used in leaching studies of components from CCA-treated wood can significantly change the amount arsenic released from treated wood. Samples of four

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species of CCA-treated wood were exposed to four acidic leaching solutions. In the samples exposed to water adjusted to pHs of 3.5, 4.5, and 5.5, losses of arsenic after 13 days were generally <7%. However, when a leaching solution of sodium hydroxide and citric acid buffer (pH 5.5) was used, the percent of arsenic leached ranged from 27.4 to 46.7% (Cooper 1991).

Arsenic bioaccumulation depends on various factors, such as environmental setting (marine, estuarine, freshwater), organism type (fish, invertebrate), trophic status within the aquatic food chain, exposure concentrations, and route of uptake (Williams et al. 2006). Bioaccumulation refers to the net accumulation of a chemical by aquatic organisms as a result of uptake from all environmental sources, such as water, food, and sediment, whereas bioconcentration refers to the uptake of a chemical by an aquatic organism through water (EPA 2003b). Biomagnification in aquatic food chains does not appear to be significant (EPA 1979, 1982b, 1983e, 2003b; Mason et al. 2000; Williams et al. 2006).

Bioconcentration of arsenic occurs in aquatic organisms, primarily in algae and lower invertebrates. Both bottom-feeding and predatory fish can accumulate contaminants found in water. Bottom-feeders are readily exposed to the greater quantities of metals, including the metalloid arsenic, which accumulate in sediments. Predators may bioaccumulate metals from the surrounding water or from feeding on other fish, including bottom-feeders, which can result in the biomagnification of the metals in their tissues. An extensive study of the factors affecting bioaccumulation of arsenic in two streams in western Maryland in 1997–1998 found no evidence of biomagnification since arsenic concentrations in organisms tend to decrease with increasing trophic level (Mason et al. 2000). Arsenic is mainly accumulated in the exoskeleton of invertebrates and in the livers of fish. No differences were found in the arsenic levels in different species of fish, which included herbivorous, insectivorous, and carnivorous species. The major bioaccumulation transfer is between water and algae, at the base of the food chain and this has a strong impact on the concentration in fish. National Contaminant Biomonitoring data produced by the Fish and Wildlife Service were used to test whether differences exist between bottom-feeders and predators in tissue levels of metals and other contaminants. No differences were found for arsenic (Kidwell et al. 1995). The bioconcentration factors (BCFs) of bryophytes, invertebrates, and fish (livers) in Swedish lakes and brooks impacted by smelter emissions were 8,700, 1,900–2,200, and 200–800, respectively (Lithner et al. 1995). EPA (2003b) assessed a large dataset of bioaccumulation data for various fish and invertebrate species. BCF values in this dataset ranged from 0.048 to 1,390.

Williams et al. (2006) reviewed 12 studies of arsenic bioaccumulation in freshwater fish, and proposed that BCF and bioaccumulation factor (BAF) values are not constant across arsenic concentrations in

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water. BCF or BAF values from these 12 studies ranged from 0.1 to 3,091. Williams et al. (2006) found that BCF and BAF values appear to be the highest within the range of ambient arsenic concentrations, and decline steeply to relatively low levels as the arsenic concentrations in water increase. Based on this analysis, arsenic concentrations in tissue and BAF values may be a power function of arsenic concentrations in water. EPA (2007b) also reported that for many nonessential metals, including arsenic, accumulation is nonlinear with respect to exposure concentration.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Arsenic is released into the atmosphere primarily as arsenic trioxide or, less frequently, in one of several volatile organic compounds, mainly arsines (EPA 1982b). Trivalent arsenic and methyl arsines in the atmosphere undergo oxidation to the pentavalent state (EPA 1984a), and arsenic in the atmosphere is usually a mixture of the trivalent and pentavalent forms (EPA 1984a; Scudlark and Church 1988). Photolysis is not considered an important fate process for arsenic compounds (EPA 1979).

6.3.2.2 Water

Arsenic in water can undergo a complex series of transformations, including oxidation-reduction reactions, ligand exchange, precipitation, and biotransformation (EPA 1979, 1984a; Sanders et al. 1994; Welch et al. 1988). Rate constants for these various reactions are not readily available, but the factors most strongly influencing fate processes in water include Eh, pH, metal sulfide and sulfide ion concentrations, iron concentrations, temperature, salinity, distribution and composition of the biota, season, and the nature and concentration of natural organic matter (EPA 1979; Farago 1997; Redman et al. 2002; Wakao et al. 1988). Organic arsenical pesticides, such as MSMA, DSMA, and DMA do not degrade by hydrolysis or by aquatic photolysis (EPA 2006). No formation of arsine gas from marine environments has been reported (Tamaki and Frankenberger 1992).

Inorganic species of arsenic are predominant in the aquatic environment. In the pH range of natural waters, the predominant aqueous inorganic As(V) species are the arsenate ions, H_2AsO_4^- and HAsO_4^{2-} ; the predominant inorganic As(III) species is $\text{As}(\text{OH})_3$ (Aurillo et al. 1994; EPA 1982c). As(V) generally dominates in oxidizing environments such as surface water and As(III) dominates under reducing conditions such as may occur in groundwater containing high levels of arsenic. However, the reduction of arsenate to arsenite is slow, so arsenate can be found in reducing environments. Conversely, the oxidation of arsenite in oxidizing environments is moderately slow (half-life, 0.4–7 days in coastal

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systems) and therefore, arsenite can be found in oxidizing environments (Mariner et al. 1996; Sanders et al. 1994). The main organic species in fresh water are MMA and DMA; however, these species are usually present at lower concentrations than inorganic arsenic species (Eisler 1994). (The toxicities of MMA and DMA are discussed in Chapter 3.) Aquatic microorganisms may reduce the arsenate to arsenite, as well as methylate arsenate to its mono- or dimethylated forms (Aurillo et al. 1994; Benson 1989; Braman and Foreback 1973; Edmonds and Francesconi 1987; Sanders et al. 1994). Methylated species are also produced by the biogenic reduction of more complex organoarsenic compounds like arsenocholine or arsenobetaine. Water samples from a number of lakes and estuaries, mostly in California, show measurable concentrations of methylated arsenic (equivalent to 1–59% of total arsenic) (Anderson and Bruland 1991). Within the oxic photic zone, arsenate and DMA were the dominant species. A seasonal study of one lake demonstrated that DMA was the dominant form of arsenic in surface waters during late summer and fall. Methylated species declined and arsenate species increased when the lake turned over in late fall. Mono Lake, a highly alkaline body of water, and four rivers did not have measurable concentrations of methylated arsenic. It was hypothesized that the reason why methylated forms were not detected in Mono Lake was that the extremely high inorganic arsenic concentrations in the lake, 230 μM (17 mg/L), could overwhelm the analysis of small amounts of organic forms. Other possibilities are that the high alkalinity or very high phosphate levels in the water, 260 μM (25 mg/L), are not conducive to biogenic methylation (Anderson and Bruland 1991). Both reduction and methylation of As(V) may lead to increased mobilization of arsenic, since As(III), dimethylarsinates, and monomethylarsonates are much less particle-reactive than As(V) (Aurillo et al. 1994). In the estuarial Patuxet River, Maryland, arsenate concentrations peaked during the summer, at 1.0 $\mu\text{g/L}$ in 1988–1989 (Sanders et al. 1994). In contrast, winter to spring levels were around 0.1 $\mu\text{g/L}$. Arsenite concentrations were irregularly present at low levels during the year. Peaks of DMA occurred at various times, particularly in the winter and late spring and appeared to be linked with algal blooms. The DMA peak declined over several months that was followed by a rise in MMA. The MMA was thought to be occurring as a degradation product of DMA. A similar seasonal pattern of arsenic speciation was observed in Chesapeake Bay. Arsenite methylation took place during the warmer months leading to changes down the main stem of the bay; arsenite production dominated the upper reaches of the bay and methylated species dominated the more saline lower reaches. In coastal waters, reduced and methylated species are present in lower concentrations, around 10–20% of total arsenic (Sanders et al. 1994). In groundwater, arsenic generally exists as the oxyanion of arsenate ($\text{H}_x\text{AsO}_4^{3-x}$) or arsenite ($\text{H}_x\text{AsO}_3^{3-x}$), or both; however, the distribution between arsenite and arsenate is not always predictable based on oxidation-reduction potential (Robertson 1989; Welch et al. 1988).

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6.3.2.3 Sediment and Soil

In soil, arsenic is found as a complex mixture of mineral phases, such as co-precipitated and sorbed species, as well as dissolved species (Roberts et al. 2007). The degree of arsenic solubility in soil will depend on the amount of arsenic distributed between these different mineral phases. The dissolution of arsenic is also affected by particle size. The distribution between these phases may reflect the arsenic source (e.g., pesticide application, wood treatment, tanning, or mining operations), and may change with weathering and associations with iron and manganese oxides and phosphate minerals in the soil (Roberts et al. 2007; Ruby et al. 1999). Davis et al. (1996) reported that in soil in Anaconda, Montana, a smelting site from 1860 to 1980, contained arsenic that is only in a sparingly soluble form, consisting of primarily arsenic oxides and phosphates.

The arsenic cycle in soils is complex, with many biotic and abiotic processes controlling its overall fate and environmental impact. Arsenic in soil exists in various oxidation states and chemical species, depending upon soil pH and oxidation-reduction potential. Under most environmental conditions, inorganic As(V) will exist as a mixture of arsenate anions, H_2AsO_4^- and HAsO_4^{2-} , and inorganic As(III) will exist as H_3AsO_3 . The arsenate and arsenite oxyanions have various degrees of protonation depending upon pH (EPA 1982b; McGeehan 1996). As(V) predominates in aerobic soils, and As(III) predominates in slightly reduced soils (e.g., temporarily flooded) or sediments (EPA 1982b; Sanders et al. 1994). As(III) commonly partitions to the aqueous phase in anoxic environments, and would be more mobile. As(V) usually remains bound to minerals, such as ferrihydrite and alumina, limiting its mobility and bioavailability (Rhine et al. 2006).

Arsenite is moderately unstable in the presence of oxygen; however, it can be found under aerobic conditions as well (Sanders et al. 1994). While arsenate is strongly sorbed by soils under aerobic conditions, it is rapidly desorbed as the system becomes anaerobic. Once it is desorbed, arsenate can be reduced to arsenite, which exhibits greater mobility in soils (McGeehan 1996). Transformations between the various oxidation states and species of arsenic occur as a result of biotic or abiotic processes (Bhumbla and Keefer 1994). While degradation of an organic compound is typically considered complete mineralization, in the case of organic arsenic compounds, the element arsenic itself cannot be degraded. However, the organic portion of the molecule can be metabolized (Woolson 1976).

Arsenicals applied to soils may be methylated by microorganisms to arsines, which are lost through volatilization, and organic forms may be mineralized to inorganic forms. Gao and Burau (1997) reported

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that the overall percentage of DMA and MMA mineralized after 70 days ranged from 3 to 87% in air-dry soil and a soil near saturation, respectively. The rate of demethylation of DMA increased with soil moisture. Over the same 70-day period, arsenic losses as volatile arsines were much lower than mineralization, ranging from 0.001 to 0.4%. Arsine evolution rates followed the order: DMA>MMA>arsenite=arsenate (Gao and Burau 1997). Woolson and Kearney (1973) reported that ^{14}C -labeled DMA degraded differently in soils under aerobic and anaerobic conditions. Under anaerobic conditions, 61% of the applied DMA was converted to a volatile alkyl arsine after 24 weeks, and lost from the soil system. Under aerobic conditions, 35% was converted to a volatile organo-arsenic compound, possibly dimethyl arsine, and 41% was converted to $^{14}\text{CO}_2$ and arsenate after 24 weeks. Similar to microorganisms in soils, Reimer (1989) reported that microorganisms found in natural marine sediments and sediments contaminated with mine-tailings are also capable of methylating arsenic under aerobic and anaerobic conditions. Von Endt et al. (1968) reported that the degradation of ^{14}C -labelled monosodium methanearsonate (MSMA) was found to range from 1.7 to 10% in Dundee silty clay loam soil and Sharkey clay soil after 60 days, respectively. MSMA decomposition to CO_2 was a slow process without a lag period. Sterilized soils were found to produce essentially no $^{14}\text{CO}_2$ (0.7%) after 60 days, indicating that soil bacteria contributed to the decomposition of MSMA (Von Endt et al. 1968). Akkari et al. (1986) studied the degradation of MSMA in various soils. At 20% water content, half-lives of 144, 88, and 178 days were reported in Sharkey clay, Taloka silt loam, and Steele-Crevasse sand loam, respectively. The Sharkey soil with the highest clay content was expected to have the greatest adsorptive capacity for both water and MSMA, reducing the amount of MSMA available in the soil solution to microorganisms that degrade the MSMA. The half-lives were 25, 41, and 178 days under anaerobic (flooded) conditions in Sharkey clay, Taloka silt loam, and Steele-Crevasse sand loam, respectively. Under flooded conditions, MSMA degradation occurs by reductive methylation to form arsinite and alkylarsine gas. The authors attributed the longer half-lives for MSMA degradation in the Steele-Crevasse sand loam soil to its low organic matter content, which may have supported fewer microbial populations needed for oxidation demethylation under aerobic conditions. Under flooded conditions, anaerobiosis is expected to be slowest in low organic matter sandy loam soils (Akkari et al. 1986).

Organic arsenical pesticides, such as MSMA, DSMA, and DMA, do not degrade by hydrolysis or by soil photolysis (EPA 2006).

Roxarsone (3-nitro-4-hydroxyphenylarsonic acid) used in poultry feed is found excreted unchanged in poultry litter (bedding and manure). Roxarsone found in poultry litter, which is used to amend agricultural soil, was found to degrade to arsenate in approximately 3–4 weeks upon composting

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(Garbarino et al. 2003). In addition, the arsenic in poultry litter was found to be easily mobilized by water; however, its leach rate from amended soils was slow enough that it accumulated in soils (Rutherford et al. 2003).

A sequential fractionation scheme was used to assess the chemical nature, and thus the potential bioavailability, of arsenic at cattle dip sites in Australia where sodium arsenite was used extensively in cattle dips from the turn of the century until the early 1950s (McLaren et al. 1998). Most sites contained substantial amounts, 13% on the average, of arsenic in the two most labile fractions indicating a high potential for bioaccessibility and leaching. The bulk of the arsenic appeared to be associated with amorphous iron and aluminum minerals in soil. Similarly, arsenic in soil and mine waste in the Tamar Valley in England was found to be concentrated in a fraction associated with iron and organic-iron (Kavanagh et al. 1997). Laboratory studies were performed to assess the phase partitioning of trace metals, including the metalloid arsenic, to sediment from the Coeur d'Alene River, a mining area of Idaho, and the release of metals under simulated minor and major flooding events (LaForce et al. 1998). Arsenic was primarily associated with the iron and manganese oxides as seen by its large release when these oxides were reduced. Arsenic levels were comparatively low in the organic fraction and remaining residual fraction and negligible in the extractable fractions.

6.3.2.4 Other Media

Carbonell-Barrachina et al. (2000) found the speciation and solubility of arsenic in sewage sludge suspensions to be affected by pH and Eh. Under oxidizing conditions, the solubility of arsenic was low, with a major portion of the soluble arsenic present as organic arsenic compounds, mainly dimethylarsinic acid (approximately 74% of the total arsenic in solution). Under moderately reducing conditions (0–100 mV), inorganic arsenic accounted for the majority (90%) of the total arsenic in solution, and the solubility of arsenic was increased due to dissolution of iron oxyhydroxides. Under strongly reducing conditions (-250 mV), arsenic solubility was decreased by the formation of insoluble sulfides. The pH of the solution was also found to influence the speciation and solubility of arsenic. At neutral pH, the solubility of arsenic was at its maximum, and decreased under acidic or alkaline conditions. Inorganic arsenic species were the dominant species at pH 5.0; at pH 6.5, the major soluble forms were organic arsenic species. The biomethylation of arsenic was limited at acidic pH, and was at its maximum at near neutral pH (Carbonell-Barrachina et al. 2000).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to arsenic depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of arsenic in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on arsenic levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring arsenic in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Arsenic in ambient air is usually a mixture of particulate arsenite and arsenate; organic species are of negligible importance except in areas of substantial methylated arsenic pesticide application or biotic activity (EPA 1984a). Mean levels in ambient air in the United States have been reported to range from <1 to 3 ng/m^3 in remote areas and from 20 to 30 ng/m^3 in urban areas (Davidson et al. 1985; EPA 1982c; IARC 1980; NAS 1977a). EPA conducted a modeling study with the Assessment System for Population Exposure Nationwide (ASPEN) in which estimates of emissions of hazardous air pollutants were used to estimate ambient concentrations (Rosenbaum et al. 1999). Using 1990 data to estimate total emissions of arsenic in the conterminous 48 states, excluding road dust or windblown dust from construction or agricultural tilling, the 25th percentile, median, and 75th percentile arsenic concentration were estimated to be 9 , 20 , and 30 ng/m^3 , respectively. Maps illustrating the amount of toxic air pollutant emissions, including arsenic compounds, by county in 1996 for the 48 coterminous states of the United States as well as Puerto Rico and the Virgin Islands are available on the internet at <http://www.epa.gov/ttn/atw/-nata/mapemis.html>, as of March 2005. Schroeder et al. (1987) listed ranges of arsenic concentrations in air of 0.007 – 1.9 , 1.0 – 28 , and 2 – $2,320 \text{ ng/m}^3$ in remote, rural, and urban areas, respectively. The average annual arsenic concentration in air at Nahant, Massachusetts, just north of Boston, between September 1992 and September 1993, was 1.2 ng/m^3 ; 75% of the arsenic was associated with fine ($<2.5 \mu\text{m}$) particles. The long-term means of the ambient concentrations of arsenic measured in urban areas of the Great Lakes region from 1982 to 1993 ranged from 4.2 to 9.6 ng/m^3 (Pirrone and Keeler 1996). Large cities generally have higher arsenic air concentrations than smaller ones due to emissions from coal-fired power plants (IARC 1980), but maximum 24-hour concentrations generally are $<100 \text{ ng/m}^3$ (EPA 1984a). In the spring of 1990, aerosols and cloud water that were sampled by aircraft at an altitude of 1.2 – 3 km above the Midwestern United States had a mean mixed layer arsenic concentration of $1.6 \pm 0.9 \text{ ng/m}^3$ (Burkhard et al. 1994). A mean arsenic concentration of $1.0 \pm 0.5 \text{ ng/m}^3$ was reported at

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Mayville, New York, a site 400 km to the northwest of the sampling area and directly downwind on most days.

Arsenic was monitored at an application site in the San Joaquin Valley, California and at four sites in nearby communities in 1987 where sodium arsenite was used as a fungicide on tokay grapes (Baker et al. 1996). The maximum arsenic concentration measured 15–20 meters from the edge of the field was 260 ng/m³. The maximum arsenic concentration at four community sites in the area was 76 ng/m³. The concentration at an urban background site was 3 ng/m³ (Baker et al. 1996). Sodium arsenite is no longer registered in California (Baker et al. 1996). The highest historic arsenic levels detected in the atmosphere were near nonferrous metal smelters, with reported concentrations up to 2,500 ng/m³ (IARC 1980; NAS 1977a; Schroeder et al. 1987).

Arsenic air concentrations measured in several indoor public places (e.g., cafeteria, coffee house, music club, Amtrak train, and several restaurants) with environmental tobacco smoke (ETS) ranged from <0.1 to 1 ng/m³, with a mean of 0.4±0.3 ng/m³. Sites that were ETS-free (university office and library) had arsenic concentrations <0.13 ng/m³ (Landsberger and Wu 1995). The Toxic Exposure Assessment at Columbia/Harvard (TEACH) study measured levels of various toxics in New York City air in 1999. Exposures were assessed in a group of 46 high school students in West Central Harlem. Mean arsenic concentrations in summer home outdoor, home indoor, and personal air of the participants were 0.37, 0.40, and 0.45 ng/m³, respectively (Kinney et al. 2002). Detected arsenic concentrations in indoor and outdoor air collected as part of the National Human Exposure Assessment Survey (NHEXAS) in Arizona ranged from 3.4 to 22.3 and from 3.5 to 25.7 ng/m³, respectively, with 71 and 68% below the detection limit (1.8–14.3 ng/m³) (O'Rourke et al. 1999).

6.4.2 Water

Arsenic is widely distributed in surface water, groundwater, and finished drinking water in the United States. A survey of 293 stations in two nationwide sampling networks on major U.S. rivers found median arsenic levels to be 1 µg/L; the 75th percentile level was 3 µg/L (Smith et al. 1987). Arsenic was detected in 1,298 of 3,452 surface water samples recorded in the STORET database for 2004 at concentrations ranging from 0.138 to 1,700 µg/L in samples where arsenic was detected (EPA 2005c). Two streams in western Maryland that were the focus of a major bioaccumulation study in 1997–1998 had arsenic concentrations of 0.370±0.200 and 0.670±0.460 µg/L (Mason et al. 2000). Surface water will be impacted by runoff from polluted sites. An average arsenic concentration of 5.12 µg/L was reported in

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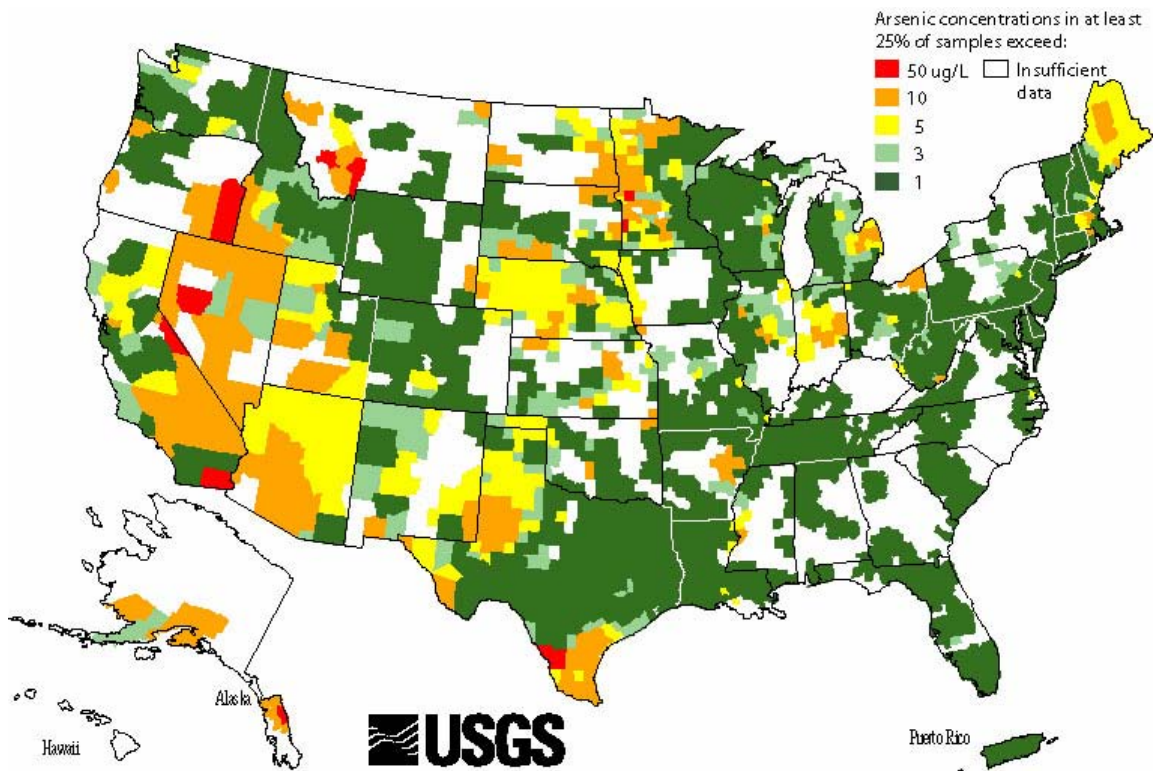
water from Moon Lake, a Mississippi River alluvial floodplain in northwest Mississippi. Intensive cultivation has occurred in this area, including cotton, soybeans, and rice (Cooper and Gillespie 2001). Hard-rock mining activities occurred in the southern part of Colorado and New Mexico north of Taos since the latter part of the 19th century until recently, which have impacted the Rio Grande and its tributaries. A mean arsenic concentration of approximately 0.8 µg/L was reported for the main stem of the Rio Grande sampled in June and September 1994. Arsenic concentrations in the Alamosa River, Colorado were 0.11 and 0.14 µg/L in June and September 1994, respectively, and 1.4 µg/L in Big Arsenic Spring, New Mexico in September 1994 (Taylor et al. 2001). Arsenic concentrations in water from watersheds in Black Hills, South Dakota, an area impacted by gold mining activities ranged from 2.5 to 55 µg/L and from 1.7 to 51 µg/L in unfiltered and filtered samples, respectively; concentrations from reference areas ranged from 1.1 to 3.4 µg/L and from 0.9 to 1.9 µg/L in unfiltered and filtered samples, respectively (May et al. 2001). Arsenic concentrations ranged from 0.29 to 34.0 µg/L in water samples from Wakulla River and St. Joseph Bay North, along the Florida Panhandle; arsenic contamination in this area is likely to result from nonpoint source pollution (Philp et al. 2003).

Data on total arsenic in surface water from a number of seas and oceans show levels of <1 µg/L, except in the Antarctic Ocean and Southwest Pacific Oceans where the levels are 1.1 and 1.2 µg/L, respectively. Levels in coastal waters and estuaries are generally somewhat higher, in the range of 1–3 µg/L. However, estuarine water in Salinas, California had arsenic levels of 7.42 µg/L (Francesconi et al. 1994). The dissolved arsenic concentration in water at 40 sites in the Indian River Lagoon System in Florida ranged from 0.35 to 1.6 µg/L with a mean of 0.89 ± 0.34 µg/L (Trocine and Trefry 1996). Thermal waters generally have arsenic levels of 20–3,800 µg/L, although levels as high as 276,000 µg/L have been recorded (Eisler 1994).

Arsenic levels in groundwater average about 1–2 µg/L, except in some western states with volcanic rock and sulfidic mineral deposits high in arsenic, where arsenic levels up to 3,400 µg/L have been observed (IARC 1980; Page 1981; Robertson 1989; Welch et al. 1988). In western mining areas, groundwater arsenic concentrations up to 48,000 µg/L have been reported (Welch et al. 1988). Arsenic concentrations in groundwater samples collected from 73 wells in 10 counties in southeast Michigan in 1997 ranged from 0.5 to 278 µg/L, with an average of 29 µg/L. Most (53–98%) of the arsenic was detected as arsenite (Kim et al. 2002). The U.S. Geological Survey mapped concentrations of arsenic in approximately 31,350 groundwater samples collected between 1973 and 2001; the counties in which at least 25% of wells exceed various levels are shown in Figure 6-2 (USGS 2007a). Most arsenic in natural waters is a

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Figure 6-2. Counties in Which at Least 25% of Wells Exceed Different Arsenic Levels



Source: USGS 2007a

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mixture of arsenate and arsenite, with arsenate usually predominating (Braman and Foreback 1973; EPA 1982c, 1984a). Methylated forms have also been detected in both surface water and groundwater, at levels ranging from 0.01 to 7.4 µg/L (Braman and Foreback 1973; Hood 1985), with most values below 0.3 µg/L (Hood 1985). In a survey of shallow groundwater quality in the alluvial aquifer beneath a major urban center, Denver, Colorado, arsenic levels in the 30 randomly-chosen wells sampled had median levels of <1 µg/L; the maximum level was 33 µg/L (Bruce and McMahon 1996). Arsenic levels in groundwater sometimes exceeded the EPA maximum contaminant level (MCL), which was 50 µg/L at the time, in the Willamette Valley, Oregon and a nine-county region of southeastern Michigan (USGS 1999b, 1999c).

Arsenic has also been detected in rainwater at average concentrations of 0.2–0.5 µg/L (Welch et al. 1988). This range is consistent with that found in a 1997–1998 study in western Maryland, which was the focus of a major bioaccumulation study (Mason et al. 2000). Arsenic levels in wet deposition in the watershed as well as throughfall into the two streams were 0.345 ± 0.392 , 0.400 ± 0.400 , and 0.330 ± 0.250 µg/L, respectively. Median arsenic concentrations in 30-day rainwater composite samples collected May–September 1994 from eight arctic catchments in northern Europe at varying distances and wind directions from the emissions of a Russian nickel ore mining, roasting, and smelting industry on the Kola Peninsula ranged from 0.07 to 12.3 µg/L (Reimann et al. 1997). Rain and snow samples were collected during the fall of 1996 and winter of 1997 at eight locations in a semi-circular pattern radiating out (2–15 km) in the direction of the prevailing wind from the Claremont incinerator located in New Hampshire. This incinerator processes 200 tons of solid waste per day. Arsenic concentrations in rainwater and snow ranged from 0.020 to 0.079 µg/L and from 0.80 to 1.28 µg/L, respectively (Feng et al. 2000).

Drinking water is one of the most important sources of arsenic exposure. Surveys of drinking water in the United States have found that >99% of public water supplies have arsenic concentrations below the EPA MCL, which was 50 µg/L at the time (EPA 1984a). In an EPA study of tap water from 3,834 U.S. residences, the average value was 2.4 µg/L (EPA 1982c).

Before the MCL for arsenic in drinking water was lowered from 50 to 10 µg/L, studies were undertaken to ascertain how different standards would affect compliance. One such survey sponsored by the Water Industry Technical Action Fund was the National Arsenic Occurrence Survey (NAOS). NAOS was based on a representational survey of public water systems defined by source type, system size, and geographical location. Additionally, it included a natural occurrence factor, a stratifying variable that could qualitatively describe the likelihood of arsenic occurrence in the supply. To predict finished water

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arsenic concentrations, data on the water treatment options, efficiency, and frequency of use were factored in. The results of the NAOS are presented in Table 6-3. The NAOS results are in general agreement with two older and more limited national surveys, EPA's National Inorganics and Radionuclides Survey (NIRS) and the Metropolitan Water District of Southern California Survey (MWDSC). The percentages of water systems that would be out of compliance are estimated to be 1.7, 3.6, 9.3, and 20.7% for arsenic MCLs of 20, 10, 5, and 2 µg/L, respectively. Arsenic concentrations were determined in drinking in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin) as part of the NHEXAS; mean arsenic concentration in flushed and standing tap water were both 1.1 µg/L (Thomas et al. 1999). A review by Frost et al. (2003) of existing data from the EPA Arsenic Occurrence and Exposure Database, as well as additional data from state health and environmental departments and water utilities found that 33 counties in 11 states had estimated mean drinking water arsenic concentrations of 10 µg/L or greater. Eleven counties had mean arsenic concentrations of ≥ 20 µg/L, and two counties had mean arsenic concentrations of ≥ 50 µg/L (Frost et al. 2003).

The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. In a study of drinking water from New Hampshire, arsenic concentrations ranged from <0.01 to 180 µg/L in the 793 households tested. More than 10% of the private wells had arsenic concentrations >10 µg/L, and 2.5% had levels >50 µg/L (Karagas et al. 1998). In New Hampshire, 992 randomly selected household water samples were analyzed for arsenic levels and the results for domestic well users were compared with those for users of municipal water supplies (Peters et al. 1999). The concentrations ranged from <0.0003 to 180 µg/L, with water from domestic wells containing significantly more arsenic than water from municipal supplies; the median concentration of the former was about 0.5 µg/L and the latter was 0.2 µg/L. None of the municipal supplies exceeded an arsenic concentration of 50 µg/L, and 2% of the domestic wells were found to have arsenic concentrations that exceeded 50 µg/L. Approximately 2% of the municipal water users have water with arsenic levels exceeding 10 µg/L compared with 13% of domestic wells. Twenty-five percent of domestic wells and 5% of municipal supplies were found to have arsenic concentrations exceeding 2 µg/L. The highest arsenic levels in New Hampshire are associated with bedrock wells in the south eastern and south central part of the state (Peters et al. 1999). In a study of arsenic in well water supplies in Saskatchewan, Canada, 13% of samples were >20 µg/L and one sample exceeded 100 µg/L (Thompson et al. 1999). It was noted that the samples with high arsenic levels were derived from sites that were in near proximity to each other, indicating the presence of 'hot spots' with similar geological characteristics. As part of an epidemiological study, Engel and Smith (1994) investigated the levels of arsenic in drinking

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Table 6-3. Regional Occurrence of Arsenic in U.S. Water Sources and Finished Drinking Water

Geographical region	Arsenic concentration in µg/L			
	<1	1–5	5–20	>20
<i>Occurrence in U.S. surface water sources</i>				
Region 1. New England	50	50	0	0
Region 2. Mid-Atlantic	84	12	4	0
Region 3. South East	93	7	0	0
Region 4. Midwest	24	76	0	0
Region 5. South Central	32	55	13	0
Region 6. North Central	33	22	33	0
Region 7. Western	42	58	0	0
<i>Occurrence in U.S. groundwater sources</i>				
Region 1. New England	71	21	7	0
Region 2. Mid-Atlantic	81	4	11	4
Region 3. South East	82	14	2	0
Region 4. Midwest	40	40	15	5
Region 5. South Central	68	27	15	0
Region 6. North Central	30	40	30	0
Region 7. Western	24	34	28	14
<i>Occurrence in U.S. finished surface water supplies</i>				
Region 1. New England	88	12	0	0
Region 2. Mid-Atlantic	92	8	0	0
Region 3. South East	100	0	0	0
Region 4. Midwest	73	27	0	0
Region 5. South Central	74	19	7	0
Region 6. North Central	44	44	0	12
Region 7. Western	42	58	0	0
<i>Occurrence in U.S. finished groundwater supplies</i>				
Region 1. New England	79	21	0	0
Region 2. Mid-Atlantic	81	4	11	4
Region 3. South East	94	4	2	0
Region 4. Midwest	58	27	12	3
Region 5. South Central	61	27	12	0
Region 6. North Central	40	50	10	0
Region 7. Western	20	40	22	12

Source: National Arsenic Occurrence Survey (Frey and Edwards 1997)

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water throughout the United States between 1968 and 1984. They found that 30 counties in 11 states had mean arsenic levels of >5 $\mu\text{g/L}$, with a range of 5.4–91.5 $\mu\text{g/L}$; 15 counties had mean levels from 5 to 10 $\mu\text{g/L}$; 10 counties had mean levels from 10 to 20 $\mu\text{g/L}$; and 5 counties had levels >20 $\mu\text{g/L}$. The highest levels were found in Churchill County, Nevada, where 89% of the population was exposed to a mean arsenic concentration of 100 $\mu\text{g/L}$ and 11% to a mean of 27 $\mu\text{g/L}$. A study by Frost et al. (2003) identified 33 counties from 11 states in which the average arsenic concentration of at least 75% of public wells was >10 $\mu\text{g/L}$. Arsenic concentrations in drinking water from these counties ranged from 10.3 to 90.0 $\mu\text{g/L}$ in Pinal, Arizona and Churchill, Nevada, respectively (Frost et al. 2003).

Many communities have high levels of arsenic in their drinking water because of contamination or as a result of the geology of the area. In Millard County, Utah, seven towns had median and maximum arsenic levels of 18.1–190.7 and 125–620 $\mu\text{g/L}$, respectively, in their drinking water (Lewis et al. 1999). The mean arsenic concentration in tap water from homes in Ajo, Arizona, about 2 miles from an open pit copper mine and smelter was 90 $\mu\text{g/L}$ (Morse et al. 1979). The town's water was supplied from five deep wells.

Countries such as Mexico, Bangladesh, India, Chile, Argentina, and Vietnam have highly elevated levels of arsenic in drinking water in some regions (Bagla and Kaiser 1996; Berg et al. 2001; Tondel et al. 1999; WHO 2001; Wyatt et al. 1998a, 1998b). In Bangladesh and West Bengal, the soil naturally contains high levels of arsenic, which leaches into the shallow groundwater that is tapped for drinking water. In West Bengal, India, it is estimated that more than one million Indians are drinking arsenic-laced water and tens of millions more could be at risk in areas that have not been tested for contamination. Analysis of 20,000 tube-well waters revealed that 62% have arsenic at levels above the World Health Organization (WHO) permissible exposure limit (PEL) in drinking water of 10 $\mu\text{g/L}$, with some as high as 3,700 $\mu\text{g/L}$ (Bagla and Kaiser 1996). Analysis of 10,991 and 58,166 groundwater samples from 42 and 9 arsenic-affected districts in Bangladesh and West Bengal were found to have arsenic levels that were 59 and 34%, respectively, above 50 $\mu\text{g/L}$ (Chowdhury et al. 2000). Berg et al. (2001), studied the arsenic contamination of the Red River alluvial tract in Hanoi, Vietnam and the surrounding rural areas. Arsenic concentrations in groundwater from private small-scale tube-wells averaged 159 $\mu\text{g/L}$, ranging from 1 to 3,050 $\mu\text{g/L}$. Arsenic concentrations ranged from 37 to 320 $\mu\text{g/L}$ in raw groundwater pumped from the lower aquifer for the Hanoi water supply (Berg et al. 2001). Several investigators have noticed a correlation between high levels of arsenic and fluoride in drinking water (Wyatt et al. 1998a, 1998b). Arsenic concentrations in drinking water from four villages in Bangladesh ranged from 10 to 2,040 $\mu\text{g/L}$ (Tondel et al. 1999).

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6.4.3 Sediment and Soil

Arsenic is widely distributed in the Earth's crust, which contains about 3.4 ppm arsenic (Wedepohl 1991). It is mostly found in nature minerals, such as realgar (As_4S_4), orpiment (As_2S_3), and arsenolite (As_2O_3), and only found in its elemental form to a small extent. There are over 150 arsenic-bearing minerals (Budavari et al. 2001; Carapella 1992). Arsenic concentrations in soils from various countries can range from 0.1 to 50 $\mu\text{g/g}$ and can vary widely among geographic regions. Typical arsenic concentrations for uncontaminated soils range from 1 to 40 $\mu\text{g/g}$, with the lowest concentrations in sandy soils and soils derived from granites. Higher arsenic concentrations are found in alluvial soils and soils with high organic content (Mandal and Suzuki 2002). Arsenic in soil may originate from the parent materials that form the soil, industrial wastes, or use of arsenical pesticides. Geological processes that may lead to high arsenic concentrations in rock and subsequently the surrounding soil include hydrothermic activity and pegmatite formation (Peters et al. 1999). In the first case, thermal activity results in the dissolution and transport of metals, including the metalloid arsenic, which are precipitated in fractures in rocks. In the second process, cooling magmas may concentrate metals that are injected into rocks, crystallizing as pegmatites. Areas of volcanic activity include large areas of California, Hawaii, Alaska, Iceland, and New Zealand.

The U.S. Geological Survey reports the mean and range of arsenic in soil and other surficial materials as 7.2 and <0.1 –97 $\mu\text{g/g}$, respectively (USGS 1984). The concentrations of arsenic in 445 Florida surface soils ranged from 0.01 to 50.6 $\mu\text{g/g}$ (Chen et al. 1999). The median, arithmetic mean, and geometric mean were 0.35, 1.34 ± 3.77 , and 0.42 ± 4.10 $\mu\text{g/g}$, respectively. Chirenje et al. (2003b) reported a geometric mean arsenic concentrations of 0.40 (0.21–660) and 2.81 (0.32–110) $\mu\text{g/g}$ in surface soil samples (0–20 cm) collected in May–June 2000 from Gainesville and Miami, Florida, respectively. The geometric mean arsenic concentration in 50 California soils was 2.8 $\mu\text{g/g}$ (Chen et al. 1999). In the Florida surface soils, arsenic was highly correlated ($\alpha=0.0001$) with the soil content of clay, organic carbon, CEC, total iron, and total aluminum. Arsenic tends to be associated with clay fractions and iron and manganese oxyhydroxides. Soils of granitic origin are generally low in arsenic, about 4 $\mu\text{g/g}$, whereas arsenic in soils derived from sedimentary rocks may be as high as 20–30 $\mu\text{g/g}$ (Yan-Chu 1994). Soils overlying arsenic-rich geologic deposits, such as sulfide ores, may have soil concentrations two orders of magnitude higher (NAS 1977a).

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Soils in mining areas or near smelters may contain high levels of arsenic. Arsenic concentrations up to 27,000 µg/g were reported in soils contaminated with mine or smelter wastes (EPA 1982b). Soils at an abandoned mining site in the Tamar Valley in southwest England have arsenic concentrations that may exceed 50,000 µg/g (Erry et al. 1999). The average arsenic levels in the top 2 cm of different soil types in the vicinity of a former copper smelter in Anaconda, Montana, ranged from 121 to 236 µg/g; levels were significantly related to proximity and wind direction to the smelter site (Hwang et al. 1997a). Smelter fallout can contaminate land miles from the source. Soils in mainland southern King County were studied for the presence of arsenic and lead (WSDOE 2005). Soil samples were collected in the fall of 1999 and the spring of 2001 from locations around the ASARCO smelter, which operated in Ruston from the 1890s to 1986. The study area ran roughly from the I-90 corridor south to the King-Pierce county line, from the Puget Sound shore to the Cascade foothills. Almost all of the contamination was found was in the 0–6-inch depths of the cores samples; 62 of the 75 samples were found to have arsenic levels above 20 ppm (WSDOE 2005).

Soil on agricultural lands treated with arsenical pesticides may retain substantial amounts of arsenic. One study reported an arsenic concentration of 22 µg/g in treated soil compared to 2 µg/g for nearby untreated soil (EPA 1982b). Arsenic was measured in soil samples taken from 10 potato fields in Suffolk County on Long Island, New York, where sodium arsenite had been used for vine control and fall weed control for many years. Lead arsenate also may have been used as an insecticide in certain areas. The mean arsenic levels taken at a depth of 0–18 cm from each of the 10 fields ranged from 27.8±5.44 µg/g dry weight (n=10) to 51.0±7.40 µg/g dry weight (n=10). These levels were markedly higher than the level of 2.26±0.33 µg/g (n=10) for untreated control soils (Sanok et al. 1995). A survey was conducted in 1993 to determine the concentrations of arsenic and lead in soil samples from 13 old orchards in New York State. Lead arsenate was used for pest control in fruit orchards for many years, mainly from the 1930s to 1960s, and residues remain in the soil. Concentrations of arsenic ranged from 1.60 to 141 µg/g dry weight (Merwin et al. 1994). Arsenic and lead concentrations were also measured in former orchard soils contaminated by lead arsenate from the Hanford site in Washington State. The mean arsenic concentration in surface (5–10 cm) and subsurface (10–50 cm) soils were 30 (2.9–270) and 74 (32–180) µg/g dry weight, respectively (Yokel and Delistraty 2003). Average arsenic concentration of 5.728, 5.614, and 6.746 µg/g were reported in soils, lake sediments, and wetland sediments, respectively, from Moon Lake, a Mississippi River alluvial floodplain in northwest Mississippi. Intensive cultivation has occurred in this area, including cotton, soybeans, and rice (Cooper and Gillespie 2001). A geometric mean arsenic concentration of 20.6 mg/kg (range 4.6–340 mg/kg) was reported soil collected during the

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summer and fall of 2003 from 85 homes in Middleport, New York, where historical pesticide manufacturing was associated with arsenic in the soil (Tsuji et al. 2005).

The Washington State Area-wide Soil Contamination Project provides various data on arsenic contamination in soils across Washington State (Washington State 2006). Arsenic concentrations within areas affected by area-wide soil contamination are highly variable, ranging from natural background levels to >3,000 ppm in smelter areas. Generally, average arsenic concentrations in soil at developed properties are <100 ppm. Areas affected by smelter emissions in King, Pierce, Snohomish, and Stevens Counties have a higher likelihood of arsenic soil contamination than other areas of the State due to historical emissions from metal smelters located in Tacoma, Harbor Island, Everett, Northport, and Trail, British Columbia. Areas where apples and pears were historically grown, such as Chelan, Spokane, Yakima, and Okanogan Counties, also have a higher likelihood of arsenic soil contamination than other areas due to the past use of lead arsenate pesticides. Generally, arsenic contamination in soils from historical smelter emissions and historical use of lead-arsenate pesticides is found in the upper 6–18 inches of soil (Washington State 2006).

The New Jersey Department of Environmental Protection (Historic Pesticide Contamination Task Force 1999) reported on the analysis of soil samples collected from 18 sites for various pesticide residues, including arsenic, from current and former agricultural sites in New Jersey in order to assess contamination from historic pesticide use. Arsenic was detected in all 463 samples, with concentrations ranging from 1.4 to 310 ppm.

Natural concentrations of arsenic in sediments are usually <10 µg/g dry weight, but can vary widely around the world (Mandal and Suzuki 2002). Sediment arsenic concentrations reported for U.S. rivers, lakes, and streams range from about 0.1 to 4,000 µg/g (Eisler 1994; Heit et al. 1984; NAS 1977a; Welch et al. 1988). During August through November 1992 and August 1993, bed sediment in the South Platte River Basin (Colorado, Nebraska, and Wyoming) was sampled and analyzed for 45 elements, including arsenic. The range of arsenic found was 2.8–31 µg/g dry weight and the geometric mean (n=23) was 5.7 µg/g (Heiny and Tate 1997). The arsenic concentration in surface sediment (0–2 cm) at 43 sites in the Indian River Lagoon System in Florida ranged from 0.6 to 15 µg/g dry weight with a mean of 5.0±3.9 µg/g (Trocine and Trefry 1996). Arsenic levels were well correlated with those of aluminum. Correlation with aluminum levels is used to normalize sediment level concentrations to natural levels in Florida estuaries. Surficial sediments collected from 18 locations in 3 major tributaries to Newark Bay, New Jersey, were analyzed for 7 toxic metals, including arsenic (Bonnevie et al. 1994). The highest

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concentrations of arsenic were found in the Rahway River adjacent to a chemical plant, 58 µg/g dry weight, and in the Hackensack River adjacent to a coal-fired power plant, 49 µg/g. The average arsenic concentration for all sediments was 17±16 µg/g. Sediments collected from seven sites in Baltimore Harbor, Maryland, at five seasonal periods between June 1987 and June 1988 had a geometric mean maximum of 7.29 µg/g dry weight and a geometric mean minimum of 1.25 µg/g (Miles and Tome 1997). This harbor is one of two sub-tributaries of the Chesapeake Bay where contaminants have been discharged on a large scale.

The upper Clark Fork River basin in western Montana is widely contaminated by metals from past mining, milling, and smelting activities. In a 1991 study, arsenic levels were determined in sediment along the river and in a reservoir 205 km downstream. Total arsenic in sediments from Clark Fork River decreased from 404 µg/g dry weight at the farthest upstream sampling station to 11 µg/g, 201 km downstream. Sediment samples from the Milltown Reservoir had arsenic concentrations ranging from 6 to 56 µg/g (Brumbaugh et al. 1994). Total recoverable arsenic in nonfiltered pore water from the Clark Fork River decreased from 1,740 µg/L at the farthest upstream sampling station to 31 µg/L at the 201 km station (Brumbaugh et al. 1994). The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity and 3 reference sites. The mean arsenic levels in sediment at the mining sites ranged from 8.3 to 179.0 µg/g dry weight, compared to 2.4–13.1 µg/g dry weight at the reference sites. The mean arsenic levels in biofilm adhering to rock in the water at the mining sites ranged from 7.5 to 155.8 µg/g dry weight, compared to 7.2–27.3 µg/g dry weight at the reference sites. In Whitewood Creek, South Dakota, where as much as 100 million tons of mining and milling waste derived from gold mining activities were discharged between 1876 and 1977, mean and maximum sediment arsenic concentrations were 1,920 and 11,000 µg/g, respectively (USGS 1987). Uncontaminated sediment had mean arsenic levels of 9.2 µg/g. Arsenic concentrations in surface (0–5 cm) sediments from watersheds in Black Hills, South Dakota, an area impacted by gold mining activities, ranged from 23 to 1,951 µg/g dry weight; concentrations from reference areas ranged from 10 to 58 µg/g dry weight (May et al. 2001). Swan Lake, a sub-bay of Galveston Bay in Texas is a highly industrial area that received runoff from a tin smelter in the 1940s and 1950s. Surface sediments at 17 sites where oysters and mussels were collected ranged from 4.53 to 103 µg/g (Park and Presley 1997). A site in the channel leading from the old smelter had arsenic levels of 568 µg/g. Surface sediment was less contaminated than deeper sediment, indicating less arsenic input recently than in the past as a result of the smelter closing.

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It has been suggested that the wood preservative most commonly used in dock pilings and bulkheads, CCA, can be toxic to estuarine organisms. Wendt et al. (1996) measured arsenic in surface sediments and oysters from creeks with high densities of docks and from nearby reference creeks with no docks. The average concentrations in the sediments ranged from 14 to 17 $\mu\text{g/g}$ throughout the study area, which is within the range of natural background levels. Weis et al. (1998) sampled sediments along a 10-m transect from CCA-treated wood bulkheads from four Atlantic coast estuaries. Arsenic concentrations were highest in the fine-grained portion of the sediments near the CCA-treated bulkhead (0–1 m); arsenic concentrations were generally at reference levels at distances >1 m from the bulkheads (Weis et al. 1998).

Soils below and around play structures constructed from CCA-treated wood in the City of Toronto, Canada were sampled and analyzed for inorganic arsenic (Ursitti et al. 2004). A mean arsenic concentration of 2.1 $\mu\text{g/g}$ (range 0.5–10 $\mu\text{g/g}$) was reported in soil samples taken within 1 m of the CCA-treated wood for all play structures. Soil samples that were collected 10 m from the play structures served as a background had arsenic concentration of 2.4 $\mu\text{g/g}$ (range 0.5–13 $\mu\text{g/g}$). A mean arsenic concentration of 6.2 $\mu\text{g/g}$ (range 0.5–47.5 $\mu\text{g/g}$) was reported in soil samples taken below CCA-treated wood for all play structures. Of the 217 play structures in the study, 32 had arsenic concentrations under the play structures that exceeded the Canadian federal soil guidelines with arsenic concentrations ranging from 12.4 to 47.5 $\mu\text{g/g}$. From this study, the authors concluded that arsenic does not migrate laterally, but does accumulate in soil under elevated platforms constructed from CCA-treated wood (Ursitti et al. 2004).

6.4.4 Other Environmental Media

Low levels of arsenic are commonly found in food; the highest levels are found in seafood, meats, and grains. Typical U.S. dietary levels of arsenic in these foods range from 0.02 mg/kg in grains and cereals to 0.14 mg/kg in meat, fish, and poultry (Gartrell et al. 1986). Shellfish and other marine foods contain the highest arsenic concentrations and are the largest dietary source of arsenic (Gunderson 1995a; Jelinek and Corneliussen 1977; Tao and Bolger 1999). Arsenic levels in various fish and shellfish are presented in Table 6-4. In the U.S. Food and Drug Administration (FDA) Total Diet Study, 1991–1997, seafood contained the highest levels of arsenic, followed by rice/rice cereal, mushrooms, and poultry. Concentrations in canned tuna (in oil), fish sticks, haddock (pan-cooked), and boiled shrimp were 0.609–1.470, 0.380–2.792, 0.510–10.430, and 0.290–2.681 mg/kg, respectively (Tao and Bolger 1999). Typically, arsenic levels in foods in the Total Diet Study, 1991–1996 were low, <0.03 mg/kg; only 63 of the 264 foods contained arsenic above this level. Similar results were reported in the Total Diet Study,

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Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration ^a (µg/g)	Comments	Reference
Yellowtail flounder		Samples collected from Northwest Atlantic 1993	Hellou et al. 1998
Muscle (n=8)	8–37		
Liver (n=6)	7–60		
Gonad (n=6)	1.2–9.4		
Marine organisms		Belgian fish markets in 1991; inorganic arsenic ranged from 0.003 to 0.2 µg/g	Buchet and Lison 1998
Ray (n=8)	16.4		
Cod (n=8)	4.7		
Plaice (n=8)	19.8		
Sole (n=8)	5.1		
Sea-bream (n=8)	2.4		
Mussell (n=8)	3.5		
Bluefin tuna (<i>Thunnus thynnus</i>) (n=14)	3.2	Virgin Rocks, Grand Banks of Newfoundland, Canada, 1990	Hellou et al. 1992
Fish		National Contaminant Biomonitoring Program, 1984–1985, 112 stations	Kidwell et al. 1995
Bottom feeding (n=2,020)	0.16±0.23 wet weight		
Predatory (n=12)	0.16±0.140 wet weight		
Oysters		South Carolina, private residential docks on tidal creeks, 1994	Wendt et al. 1996
<1 m from docks (n=10)	8.3±1.1		
>10 m from docks (n=10)	7.6±0.9		
Reference (no docks) (n=10)	8.4±1.3		
Clams (n=22)	12±1.1	Indian River Lagoon, Florida, 22 sites, 1990	Trocine and Trefry 1996
Marine organisms		Swan Lake, Galveston Bay, Texas, 1993	Park and Presley 1997
Snails	13.3±17.0		
Blue crab	6.61		
Fish	0.82		
Shrimp	1.37±0.64		
Whole crab	5.35±2.51		
Oysters (n=10, pooled)	7.28±1.32		
Mussels (n=7, pooled)	7.75±2.15		
Marine organisms		GPNEP, 1992, Galveston Bay, Texas	Park and Presley 1997
Blue crab	2.31±2.15		
Fish	2.46		
Oysters, two areas		NOAA NS&T Program, 1986–1990	Park and Presley 1997
n=78, pooled	4.50±1.08	Galveston Bay	
n=874, pooled	9.67±7.00	Gulf of Mexico	

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Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration ^a (µg/g)	Comments	Reference
Marine crustaceans			
<i>Parapenaeus longirostris</i> (pink shrimp) (n=826, 10 pools)	34.84±19.21 (12.01–62.60)	Commercial crustaceans from the Mediterranean Sea (Italy)	Storelli and Marcotrigiano 2001
<i>Aristeus antennatus</i> (red shrimp) (n=387, 8 pool)	17.09±3.49 (10.45–20.82)		
<i>Plesionika martia</i> (shrimp) (n=456, 7 pools)	40.82±2.50 (36.37–44.06)		
<i>Nephrops norvegicus</i> (Norway lobster) (n=270, 5 pools)	43.48±14.21 (35.63–69.15)		
Freshwater fish			
Sabalo (<i>Brycon melanopterus</i>) (n=3)	0.015–0.101	Fish samples (muscle) were collected in August 1997 from the Candamo River, Peru; a pristine rainforest valley prior to the start of oil-drilling activities	Gutleb et al. 2002
Huazaco (<i>Hoplias malabaracus</i>) (n=4)	nd–0.005		
Bagre (<i>Pimelodus ornatus</i>) (n=8)	nd–0.201		
Boquichio (<i>Prochilodus nigricans</i>) (n=1)	0.063		
Doncello (<i>Pseudo-platystoma sp.</i>) (n=1)	0.055		
Freshwater fish			
Bowfin (n=59)	0.32±0.04 wet weight	Savannah River, along and below the Department of Energy's Savannah River Site (SRS); samples analyzed were edible fillets	Burger et al. 2002
Bass (n=47)	0.03±0 wet weight		
Channel catfish (n=50)	0.09±0.02 wet weight		
Chain pickerel (n=19)	0.05±0.01 wet weight		
Yellow perch (n=51)	0.05±0.01 wet weight		
Black crappie (n=52)	0.04±0.01 wet weight		
American eel (n=24)	0.04±0.01 wet weight		
Shellcracker (n=52)	0.06±0 wet weight		
Bluegill (n=52)	0.05±0.02 wet weight		
Redbreast (n=43)	0.07±0.01 wet weight		
Spotted sucker (n=35)	0.03±0 wet weight		

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Table 6-4. Levels of Arsenic in Fish and Shellfish—Recent Studies

Sample type	Arsenic concentration ^a (µg/g)	Comments	Reference
Horseshoe crabs			
Apodeme (n=74)	7.034±0.65 wet weight	Overall mean in tissues of crabs collected from New Jersey in 2000	Burger et al. 2003
Egg (n=63)	5.924±0.345 wet weight		
Leg (n=74)	14.482±0.685 wet weight		
Apodeme (n=40)	7.513±0.835 wet weight	Overall mean in tissues of crabs collected from Delaware in 2000	
Egg (n=35)	6.766±0.478 wet weight		
Leg (n=40)	18.102±1.489 wet weight		

^aConcentrations are means±standard deviation, unless otherwise stated. Concentrations are in a dry weight basis, unless otherwise stated.

GM = geometric mean; GPNEP = Galveston Bay National Estuary Program; nd = not detected;
NOAA NS&T = National Oceanic and Atmospheric Administration National Status and Trends

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1991–1997, where the mean arsenic concentration in all foods was 0.036 mg/kg dry weight and arsenic was not detectable in about 88% of the foods and was detected at trace levels in another 7.8% of foods. The foods with the highest mean arsenic levels were haddock, canned tuna, fish sticks, shrimp, and fish sandwiches, with arsenic concentrations ranging from 5.33 to 0.568 mg/kg dry weight (Capar and Cunningham 2000). Nriagu and Lin (1995) analyzed 26 brands of wild rice sold in the United States and found arsenic levels ranging from 0.006 to 0.142 µg/g dry weight. Arsenic concentrations ranging from 0.05 to 0.4 µg/g are typically reported for rice from North America, Europe, and Taiwan (Meharg and Rahman 2003).

During a comprehensive total diet study extending from 1985 to 1988, foods were collected in six Canadian cities and processed into 112 composite food samples (Dabeka et al. 1993). The mean, median, and range of total arsenic in all samples were 0.0732, 0.0051, and <0.0001–4.840 µg/g, respectively. Food groups containing the highest mean arsenic levels were fish (1.662 µg/g), meat and poultry (0.0243 µg/g), bakery goods and cereals (0.0245 µg/g), and fats and oils (0.0190 µg/g). Of the individual samples, marine fish had the highest arsenic levels, with a mean of 3.048 µg/g for the cooked composites and 2.466 µg/g for the raw samples. Canned fish (1.201 µg/g) and shellfish (2.041 µg/g) also contained high means. Cooked poultry, raw mushrooms, and chocolate bars contained 0.100, 0.084, and 0.105 µg/g, respectively.

National monitoring data from the Food Safety and Inspection Service National Residue Program (NRP) (1994–2000) found that the mean total arsenic concentration in livers of young chickens ranged from 0.33 to 0.43 µg/g, with an overall mean of 0.39 µg/g (Lasky et al. 2004). The mean arsenic concentrations in liver for mature chickens, turkeys, hogs, and all other species over the same time period ranged from 0.10 to 0.16 µg/g. Lasky et al. (2004) used the NRP arsenic data in livers of young chickens to estimate the concentrations of arsenic in muscle tissue, the most commonly consumed part of the chicken. Assuming that 65% of the arsenic in poultry and meat is inorganic, at a mean level of chicken consumption of 60 g/person/day, people may ingest an estimated 1.38–5.24 µg/day of inorganic arsenic from chicken.

A Danish study (Pedersen et al. 1994) reports the arsenic levels in beverages as the mean (range) in µg/L as follows: red wine, 9 (<2–25); white wine, 11 (<2–33); fortified wine, 5 (<2–11); beer, 7 (4–11); soft drinks, 3 (<2–8); miscellaneous juices, 8 (3–13); instant coffee, 4 (0.7–7); and instant cocoa, 5.6 (1.6–12.8).

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In a study of dietary arsenic exposure in the Indigenous Peoples of the western Northwest Territories, Canada, fish contained the highest arsenic concentrations in foods consumed by the Dene and Métis populations with the highest concentration, 1.960 µg/g, found in smoked/dried cisco (fish). Other foods derived from land mammals, birds, and plants contained lower arsenic concentrations. A mean arsenic intake of <1.0 µg/kg/day was reported for this population (Berti et al. 1998).

The general consensus in the literature is that about 85–90% of the arsenic in the edible parts of marine fish and shellfish is organic arsenic (e.g., arsenobetaine, arsenocholine, dimethylarsinic acid) and that approximately 10% is inorganic arsenic (EPA 2003b). However, the inorganic arsenic content in seafood may be highly variable. For example, a study in the Netherlands reported that inorganic arsenic comprised 0.1–41% of the total arsenic in seafood (Vaessen and van Ooik 1989). Buchet et al. (1994) found that, on the average, 3% of the total arsenic in mussels was inorganic in form. Some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al. 2003). Arsenic concentrations ranging from 17 to 88 mg/kg dry weight were found in commercially available seaweeds (van Netten et al. 2000). Other arsenic compounds that may be found in seafood are arsenic-containing ribose derivatives called arsenosugars. Arsenosugars are the common organoarsenicals found in marine algae; they are also found in mussels, oysters, and clams (Le et al. 2004). Less information about the forms of arsenic in freshwater fish is known at this time (EPA 2003b).

Schoof et al. (1999a) reported on the analysis of 40 commodities anticipated to account for 90% of dietary inorganic arsenic intake. In this study, the amount of inorganic arsenic was measured in these foods. Consistent with earlier studies, total arsenic concentrations were highest in the seafood sampled (ranging from 160 ng/g in freshwater fish to 2,360 ng/g in marine fish). In contrast, average inorganic arsenic in seafood ranged from <1 to 2 ng/g. The highest inorganic arsenic concentrations were found in raw rice (74 ng/g), followed by flour (11 ng/g), grape juice (9 ng/g), and cooked spinach (6 ng/g).

Tobacco contains an average arsenic concentration of 1.5 ppm, or about 1.5 µg per cigarette (EPA 1998j). Before arsenical pesticides were banned, tobacco contained up to 52 mg As/kg, whereas after the ban, maximum arsenic levels were reduced to 3 µg/g (Kraus et al. 2000). An international literature survey reports arsenic yields of 0–1.4 µg/cigarette for mainstream (inhaled) cigarette smoke (Smith et al. 1997). The wide range of arsenic yields for flue-cured cigarettes suggests that the field history, soil, and fertilizer conditions under which the tobacco is grown will affect the arsenic concentration (Smith et al. 1997).

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Arsenic emission factors of 0.015–0.023 $\mu\text{g}/\text{cigarette}$ (mean $0.018 \pm 0.003 \mu\text{g}/\text{cigarette}$) have been measured for sidestream smoke from a burning cigarette (Landsberger and Wu 1995).

A median arsenic concentration of 2.1 $\mu\text{g}/\text{g}$ and a deposition rate of 0.008 $\mu\text{g}/\text{m}^2/\text{day}$ was reported in house dust in homes evaluated as part of the German Environmental Survey in 1990–1992. A mean arsenic concentration of 7.3 $\mu\text{g}/\text{g}$ was reported in house dust from 48 residences in Ottawa, Canada (Butte and Heinzow 2002). These arsenic concentrations are expected to be representative of background levels. In general high arsenic concentrations were found in household dust collected from homes in areas with known arsenic contamination. Mean arsenic concentrations of 12.6 (2.6–57) and 10.8 (1.0–49) $\mu\text{g}/\text{g}$ were reported in house dust collected from the entryway and child play areas, respectively, from homes in a community in Washington State with a history of lead arsenate use (Wolz et al. 2003). Arsenic was detected in all 135 indoor floor dust samples collected as part of the NHEXAS from Arizona mining communities, ranging from 0.3–50.6 $\mu\text{g}/\text{g}$, (O'Rourke et al. 1999). A geometric mean arsenic concentration of 10.8 $\mu\text{g}/\text{g}$ (range 1.0–172 $\mu\text{g}/\text{g}$) was reported in house dust from 96 homes in Middleport, New York, with historical pesticide manufacture, collected during the summer and fall of 2003 (Tsuji et al. 2005).

Arsenic has also been detected in several homeopathic medicines at concentrations up to 650 $\mu\text{g}/\text{g}$ (Kerr and Saryan 1986). Some Asian proprietary medicines that are manufactured in China, Hong Kong, and other Asian countries have been reported to contain levels of inorganic arsenic ranging from 25 to 107,000 $\mu\text{g}/\text{g}$ (Chan 1994). Fifty medicinally important leafy samples that were analyzed for elemental concentrations contained arsenic at levels ranging from 0.12 to 7.36 $\mu\text{g}/\text{g}$, with a mean of $2.38 \pm 1.2 \mu\text{g}/\text{g}$ (Reddy and Reddy 1997). Arsenic concentrations ranged from 0.005 to 3.77 $\mu\text{g}/\text{g}$ in 95 dietary supplements purchased from retail stores in the Washington, DC area in 1999 (Dolan et al. 2003). Commercially available samples of Valarian, St. John's Wort, Passion Flower, and Echinacea were purchased in the United States and analyzed for various contaminants; arsenic concentrations were 0.0016–0.0085, 0.0065–0.017.8, 0.0024–0.0124, and 0.0021–0.0102 $\mu\text{g}/\text{g}$, respectively, in these samples (Huggett et al. 2001). Concentrations of heavy metals including the metalloid arsenic were evaluated in 54 samples of Asian remedies that were purchased in stores in Vietnam and Hong Kong that would be easily accessible to travelers, as well as in health food and Asian groceries in Florida, New York, and New Jersey. Four remedies were found to contain daily doses exceeding 0.1 mg. Two of these contained what would have been a potentially significant arsenic dose, with daily doses of 16 and 7.4 mg of arsenic (Garvey et al. 2001).

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The possible presence of toxic compounds in waste materials has raised concerns about the fate of these compounds either during the composting process or when the composted product is applied to soils. Three waste compost products generated at the Connecticut Agricultural Experiment Station had arsenic levels of 12.8, 9.8, and 13 $\mu\text{g/g}$ dry weight, respectively (Eitzer et al. 1997). The arsenic levels in municipal solid waste composts from 10 facilities across the United States ranged from 0.9 to 15.6 $\mu\text{g/g}$ dry weight with a mean of 6.7 $\mu\text{g/g}$ (He et al. 1995). These are lower than the EPA 503 regulatory limit for arsenic of 41 $\mu\text{g/g}$ for agricultural use of sewage sludge (EPA 1993b). Concentrations of arsenic in U.S. sewage sludges, which are sometimes spread on soil, were <1 $\mu\text{g/g}$. Arsenic is a common impurity in minerals used in fertilizers. A comprehensive Italian study found that the arsenic content in a number of mineral and synthetic fertilizers ranged from 2.2 to 322 mg/kg with a sample of triple superphosphate having the highest level (Senesi et al. 1999). Arsenic naturally occurs in coal and crude oil at levels of 0.34–130 and 0.0024–1.63 ppm, respectively, which would account for its presence in flue gas, fly ash, and bottom ash from power plants (Pacyna 1987).

Background arsenic levels in living organisms are usually <1 $\mu\text{g/g}$ wet weight (Eisler 1994). Levels are higher in areas with mining and smelting activity or where arsenical pesticides were used. Eisler (1994) has an extensive listing of arsenic levels in terrestrial and aquatic flora and fauna from literature sources to about 1990. The U.S. Fish and Wildlife Service's National Contaminant Biomonitoring Program have analyzed contaminants in fish at 116 stations (rivers and the Great Lakes) across the United States. The geometric mean concentration of arsenic for the five collection periods starting in 1976 were (period, concentration wet weight basis): 1976–1977, 0.199 $\mu\text{g/g}$; 1978–1979, 0.129 $\mu\text{g/g}$; 1980–1981, 0.119 $\mu\text{g/g}$; 1984, 0.106 $\mu\text{g/g}$; and 1986, 0.083 $\mu\text{g/g}$ (Schmitt et al. 1999). In 1986, the maximum and 85th percentile arsenic levels were 1.53 and 0.24 $\mu\text{g/g}$, respectively. The highest concentrations of arsenic for all five collection periods were in bloaters from Lake Michigan at Sheboygan, Wisconsin. Arsenic levels declined by 50% at this site between 1976–1997 and 1984. The major source of arsenic into Lake Michigan was a facility at Marinette, Wisconsin, which manufactured arsenic herbicides. Table 6-4 contains arsenic levels in aquatic organisms from more recent studies. The Coeur d'Alene river basin in northern Idaho has been contaminated with heavy metals from mining and smelting operations since 1885 (Farag et al. 1998). A 1994 study determined the metal content of sediment, biofilm, and invertebrates at 13 sites in the basin, 10 with historic mining activity, and 3 reference sites. The mean arsenic levels in benthic macroinvertebrates at the mining sites ranged from 2.2 to 97.0 $\mu\text{g/g}$ dry weight, compared to 2.1–2.4 $\mu\text{g/g}$ dry weight at the reference sites. A study of aquatic organism in Swan Lake, a highly polluted sub-bay of Galveston Bay, Texas showed that arsenic concentrations were in the order snail>oyster>crab>shrimp>fish (Park and Presley 1997). In contrast to metals like silver, cadmium,

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copper, and zinc, arsenic concentrations in oysters and mussels were less than in the sediment from which they were collected. No significant correlation was found between levels of arsenic in clams in the Indian River Lagoon in Florida with those found in sediment or water samples (Trocine and Trefry 1996). Small animals living at mining sites ingest more arsenic in their diet and have higher arsenic levels in their bodies than those living on uncontaminated sites (Erry et al. 1999). Seasonal variations in both arsenic intake and dietary composition may affect the amount of arsenic taken up by the body and transferred to predator animals. Tissue arsenic content of wood mice and bank voles living on both arsenic-contaminated mining sites and uncontaminated sites were greater in autumn than spring. The lower tissue arsenic levels in spring of rodents living on contaminated sites suggest that there is no progressive accumulation of arsenic in overwintering animals.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure to arsenic may include exposure to the more toxic inorganic forms of arsenic, organic forms of arsenic, or both. While many studies do not indicate the forms of arsenic to which people are exposed, this information may often be inferred from the source of exposure (e.g., fish generally contain arsenic as arsenobetaine). Yost et al. (1998) reported that the estimated daily dietary intake of inorganic arsenic for various age groups ranged from 8.3 to 14 $\mu\text{g}/\text{day}$ and from 4.8 to 12.7 $\mu\text{g}/\text{day}$ in the United States and Canada, respectively, with 21–40% of the total dietary arsenic occurring in inorganic forms.

Drinking water may also be a significant source of arsenic exposure in areas where arsenic is naturally present in groundwater. While estimates of arsenic intake for typical adults drinking 2 L of water per day average about 5 $\mu\text{g}/\text{day}$ (EPA 1982c), intake can be much higher (10–100 $\mu\text{g}/\text{day}$) in geographical areas with high levels of arsenic in soil or groundwater (see Figure 6-2). It is assumed that nearly all arsenic in drinking water is inorganic (EPA 2001).

In the United States, food intake of arsenic has been estimated to range from 2 $\mu\text{g}/\text{day}$ in infants to 92 $\mu\text{g}/\text{day}$ in 60–65-year-old men (see Table 6-5) (Tao and Bolger 1999). The average intake of inorganic arsenic are estimated to range from 1.34 $\mu\text{g}/\text{day}$ in infants to 12.54 $\mu\text{g}/\text{day}$ in 60–65-year-old men. Tao and Bolger (1999) assumed that 10% of the total arsenic in seafood was inorganic and that 100% of the arsenic in all other foods was inorganic. The greatest dietary contribution to total arsenic was seafood (76–96%) for all age groups, except infants. For infants, seafood and rice products contributed 42 and 31%, respectively. Adult dietary arsenic intakes reported for other countries range

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Table 6-5. Mean Daily Dietary Intake of Arsenic for Selected U.S. Population Groups

Mean daily intake (µg/kg body weight/day)	Date of study		
	1984–1986 ^a	1986–1991 ^b	1991–1997 ^c
Provisional tolerable daily intake (PTDI) ^d	2.1	2.1	2.1
6–11 months	0.82	0.5	0.31
2 years	1.22	0.81	1.80
14–16 years, female	0.54	0.36	0.41
14–16 years, male	0.60	0.39	0.24
25–30 years, female	0.66	0.44	0.44
25–30 years, male	0.76	0.51	0.72
60–65 years, female	0.71	0.46	1.08
60–65 years, male	0.74	0.48	1.14

^aGunderson 1995a^bGunderson 1995b^cTao and Bolger 1999^dNo agreement has been reached on a maximum acceptable intake for total arsenic; the FAO/WHO has assigned a PTDI for inorganic arsenic of 2.1 µg/kg body weight for adults. Data from FDA studies. FDA does not recommend daily intake levels for Arsenic.

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from 11.7 to 280 µg/day (Tao and Bolger 1999). Schoof et al. (1999b) estimated that intake of inorganic arsenic in the U.S. diet ranges from 1 to 20 µg/day, with a mean of 3.2 µg/day. In contrast, these estimates of inorganic arsenic intakes are based on measured inorganic arsenic concentrations from a market basket survey.

The FDA conducted earlier Total Diet Studies in 1984–1986 and 1986–1991. For the sampling period of June 1984 to April 1986, the total daily intake of arsenic from foods was 58.1 µg for a 25–30-year-old male with seafood contributing 87% of the total (Gunderson 1995a). For the sampling period from July 1986 to April 1991, the total daily intake of arsenic from foods was lower, 38.6 µg for a 25–30-year-old male. Seafood again was the major source of arsenic, contributing 88% of the total (Gunderson 1995b). Results of the two Total Diet Studies for selected population groups are shown in Table 6-5. The Total Diet Study for the sampling period from September 1991 to December 1996, shows that arsenic, at ≥ 0.03 µg/g, was found in 55 (21%) of the 261–264 foods/mixed dishes analyzed. The highest concentrations again were found in seafood, followed by rice/rice cereal, mushrooms, and poultry. The estimated total daily intake of arsenic from foods was 56.6 µg for a 25–30-year-old male. Seafood was the major contributor, accounting for 88–96% of the estimated total arsenic intake of adults.

Average daily dietary exposures to arsenic were estimated for approximately 120,000 U.S. adults by combining data on annual diet, as measured by a food frequency questionnaire, with residue data for table-ready foods that were collected for the annual FDA Total Diet Study. Dietary exposures to arsenic were highly variable, with a mean of 50.6 µg/day (range, 1.01–1,081 µg/day) for females and 58.5 µg/day (range, 0.21–1,276 µg/day) for males (MacIntosh et al. 1997). Inorganic arsenic intake in 969 men and women was assessed by a semi-quantitative food frequency questionnaire in combination with a database for total arsenic content in foods and by toenail concentrations of arsenic. The mean estimated average daily consumption of inorganic arsenic was 10.22 µg/day with a range of 0.93–104.89 µg/day. An assumption of 1.5% of the total arsenic in fish and 20% of the total arsenic in shellfish was inorganic arsenic was used in this assessment (MacIntosh et al. 1997).

During a comprehensive total diet study extending from 1985 to 1988, the estimated daily dietary ingestion of total arsenic by the average Canadian was 38.1 µg and varied from 14.9 µg for the 1–4 year-old-age group to 59.2 µg for 20–39-year-old males (Dabeka et al. 1993). Daily intakes of arsenic from food by women in the Shiga Prefecture, Japan, were investigated by the duplicate portion method and by the market basket method. In 1991 and 1992, the daily intakes determined by the duplicate portion

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method were 206 and 210 μg , respectively. Those determined by the market basket method were 160 and 280 μg , respectively (Tsuda et al. 1995b).

Arsenic concentrations in human breast milk have been reported to range from 4 to <10 $\mu\text{g/L}$ in pooled human milk samples from Scotland and Finland to 200 $\mu\text{g/L}$ in samples from Antofagasta, Chile, where there is a high natural environmental concentration of arsenic (Broomhall and Kovar 1986). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 $\mu\text{g/L}$, with a median of 4.22 $\mu\text{g/L}$ (Ulman et al. 1998). Sternowsky et al. (2002) analyzed breast milk from 36 women from three different regions in Germany. These regions included the city of Hamburg, a rural area, Soltau, Lower Saxony, and Munster, the potentially contaminated area. Arsenic was not detected (<0.3 $\mu\text{g/L}$) in 154 of 187 samples, with the highest concentration, 2.8 $\mu\text{g/L}$, found in a sample from the rural area. The geometric means from the three areas were comparable.

The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46, and 4.93 $\mu\text{g/L}$, compared to 5.25 $\mu\text{g/L}$ for cows kept in sheds and fed commercial pellet feed and municipal water (Ulman et al. 1998). Mean arsenic concentrations in cow's milk ranging from 18.6 to 17.1 $\mu\text{g/L}$ and from 16.7 to 18.0 $\mu\text{g/L}$ were reported for cow's grazing in nonindustrial and an industrial regions, respectively, in Turkey (Erdogan et al. 2004).

A Danish study found that carrots grown in soil containing 30 $\mu\text{g/g}$ of arsenic, which is somewhat above the 20 $\mu\text{g/g}$ limit for total arsenic set by Denmark for growing produce, contained 0.014 $\mu\text{g/g}$ fresh weight of arsenic, all in the form of inorganic As(III) and As(V) (Helgesen and Larsen 1998). An adult consuming 376 grams of vegetables a day (90th percentile) represented solely by carrots would consume 5.3 μg of arsenic a day. The study concluded that the estimated intake of arsenic from produce grown in soil meeting regulatory limits was low compared with other food sources and water.

If vegetables are grown in planters made of wood treated with CCA, arsenic may leach out of the wood and be taken up by the vegetables. In a study by Rahman et al. (2004), arsenic was found to diffuse into the soil from the CCA-treated wood, with the highest concentrations found at 0–2 cm from the CCA-treated wood and a steady decline in concentration with increased distance from the wood. Crops grown within 0–2 cm of the CCA-treated wood contained higher concentrations of arsenic than those grown at 1.5 m from the treated wood. However, the concentrations are below U.S. FDA tolerance limits that have been set for arsenic in select food items. In addition, food grown in this manner is unlikely to constitute a significant part of a person's diet.

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In 2003, U.S. manufacturers of arsenical wood preservatives began a voluntary transition from CCA to other wood preservatives in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; wood treated prior to this date could still be used and structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications (EPA 2003a). EPA's Consumer Awareness Program (CAP) for CCA is a voluntary program established by the manufacturers of CCA products to inform consumers about the proper handling, use, and disposal of CCA-treated wood. Additional information about this program can be found from EPA (2007a).

The arsenic content in the human body is 3–4 mg and tends to increase with age. Arsenic concentrations in most tissues of the human body are <0.3 to 147 µg/g dry weight, excluding hair, nails, and teeth. Mammals tend to accumulate arsenic in keratin-rich tissues such as hair and nails. The normal concentrations of arsenic range from about 0.08 to 0.25 µg/g in hair, and 0.34 µg/g in nails. The normal concentration of arsenic in urine can range from 5 to 40 µg per day (total) (Mandal and Suzuki 2002). Table 6-6 contains arsenic levels in various human tissues.

A German study investigated the transfer of arsenic from the environment to humans in the northern Palatine region, a former mining area characterized by high soil levels of arsenic (<2–605 µg/g) in residential areas compared to a region in southern lower Saxony with nonelevated levels of arsenic in soil (Gebel et al. 1998a). None of the residents were occupationally exposed to arsenic and the arsenic levels in drinking water were generally below 0.015 mg/L. The mean levels of arsenic in urine and hair were lower in the reference area than in the former mining area (see Table 6-6), although within the mining area, there was a slight increase in arsenic levels in hair and arsenic excreted in urine with increasing arsenic content in soil. Children in the Palatine region did not have higher contents of arsenic in their hair or urine. The most significant factor contributing to elevated levels of arsenic in hair and urine was seafood consumption. In the combined population of people living in mining areas containing high levels of arsenic in soil and other areas, the level of arsenic in urine was positively associated with the extent of seafood consumption. However, the study also showed that seafood consumption does not lead to an extreme increase in excretion of arsenic in the urine. There are apparently other, unidentified factors affecting the urine levels. Only arsenic in urine, not in hair, was significantly correlated with age. The level of arsenic in urine was very slightly, but significantly correlated with the consumption of home-grown produce. Tobacco smoking had no correlation with the arsenic content of either hair or urine (Gebel et al. 1998a).

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Table 6-6. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site population	Sample	Concentration		Units	Reference
		Mean ^a	Range		
Fort Valley, Georgia, Pesticide manufacturing facility (Superfund site)					
40 workers (samples collected at end of work week)	Urine, random	11.6	<1–57	µg/L	Hewitt et al. 1995
	Urine, 24-hour	11.0	<1–54	µg/L	
	Hair	0.78	<0.01–6.3	µg/g	
	Fingernails	0.79	<0.01–6.1	µg/g	
Hermosa, Sonora, Mexico					
Children, ages 7–11, exposed to arsenic in water (mean concentration [mean dose]):	Urine, 24-hour				Wyatt et al. 1998a, 1998b
9 µg/L [0.481 µg/kg/day]		10.26	4.05–19.68	µg/day	
15 µg/L [0.867 µg/kg/day]		10.54	2.82–20.44	µg/day	
30 µg/L [1.92 µg/kg/day]		25.18	5.44–93.28	µg/day	
Glasgow, Scotland					
Adults, normal (n=1,250)	Hair	0.650	0.20–8.17	µg/g	Raie 1996
Adults, postmortem (n=9)	Liver	0.048 [0.024]	0.011–0.152	µg/g	
Infants, postmortem (n=9)	Liver	0.0099 [0.007]	0.0034–0.019	µg/g	
Adults, postmortem (n=8)	Lung	0.044 [0.022]	0.0121–0.125	µg/g	
Infants, postmortem (n=9)	Lung	0.007 [0.0055]	0.0011–0.015	µg/g	
Adults, postmortem (n=9)	Spleen	0.015 [0.008]	0.001–0.063	µg/g	
Infants, postmortem (n=8)	Spleen	0.0049 [0.0045]	0.0011–0.0088	µg/g	
Palatinate Region, Germany (high As) ^b					
Residents (n=199)	Urine, 24-hour	3.96 [3.21]	<0.1–18.32	µg/g	Gebel et al. 1998a
Residents (n=211)	Hair	0.028 [0.016]	<0.005–0.154	µg/g	
Saxony, Germany (low As—reference) ^b					
Residents (n=75)	Urine, 24-hour	7.58 [6.20]	0.29–23.78	µg/g	Gebel et al. 1998a
Residents (n=74)	Hair	0.069 [0.053]	0.013–0.682	µg/g	
Ismir, Turkey, (volcanic area with high thermal activity)					
Nonoccupationally exposed women (n=35)	Breast milk	4.23 [4.26]	3.24–5.41	µg/L	Ulman et al. 1998
Erlangen-Nurenberg Germany 1/92–12/93					
Nonoccupationally exposed people (n=50)	Lung	5.5	<1–13.0	ng/g ww	Kraus et al. 2000
		28.4	<1–73.6	ng/g dw	

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Table 6-6. Levels of Arsenic in Human Tissue and Urine—Recent Studies

Site population	Sample	Concentration		Units	Reference
		Mean ^a	Range		
Tarragona (Catalonia, Spain) 1997–1999					
Nonoccupationally exposed people (n=78)	Lung	<0.05		µg/g ww	Garcia et al. 2001
	Bone	<0.05			
	Kidney	<0.05			
	Liver	<0.05			
	Lung	<0.05			
West Bengal, India					
Residents consuming arsenic-contaminated water (n=47)	Fingernail	7.32	2.14–40.25	µg/g	Mandal et al. 2003
	Hair	4.46	0.70–16.17		
Residents consuming nonarsenic-contaminated water (n=15)	Fingernail	0.19	0.11–0.30		
	Hair	0.07	0.03–0.12		
Middleport, NY, USA					
Children <7 years (n=77)	Urine	15.1 ^c	2.1–59.6	µg/L	Tsuji et al. 2005
Children <13 years (n=142)	Urine	15.7 ^c	2.1–59.9		
Children ≥7 years and adults (n=362)	Urine	15.8 ^c	3.9–773		
All participants	Urine	15.7 ^c	2.1–773		

^aMedians, if reported, are in brackets.^bThe reference group (Saxony) had significantly higher levels of arsenic in urine and hair. However, data from both groups correspond to normal range reference data.^cGeometric mean, total arsenic

dw = dry weight; ww = wet weight

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A study was performed to look at the arsenic levels, as well as the arsenic species present, in hair and nail samples from individuals in an arsenic-affected area in West Bengal, India. Mean arsenic concentrations in hair and fingernails of the chronically arsenic exposed population were 4.46 and 7.32 $\mu\text{g/g}$, respectively and were 0.07 and 0.19 $\mu\text{g/g}$ in a control population. Fingernail samples were found to contain mostly inorganic arsenic (>80%) as a mixture of As(III) and As(V), as well as DMA(III) and DMA(V). Hair samples also mostly contained inorganic arsenic (>90%), as well as MMA(V) and DMA(V) (Mandal et al. 2003).

Arsenic in soil in communities surrounding former smelters is a public health concern, especially for infants and children who may consume significant quantities of soil. Since lead arsenate was used in apple and other fruit orchards, often at very high application rates, and this compound would be expected to accumulate and persist in surface soil, there are concerns to human health when these when old orchards are converted into subdivisions or when they are used to grow food crops or forage. However, arsenic in soil may be imbedded in minerals or occur as insoluble compounds such as sulfides and therefore, not be taken up by the body from the gastrointestinal tract. In addition, oxidation of mineral surfaces may result in armoring the primary mineral grain by a secondary reaction product. Arsenic-bearing solids are often encapsulated in insoluble matrices such as silica, further diminishing arsenic availability (Davis et al. 1992).

Sarkar and Datta (2004) examined the bioavailability of arsenic from two soils with different arsenic retention capacities. In this study, Immokalee (Florida) and Orelia (Texas) soils were incubated after spiking with sodium arsenate for 4 months. The Immokalee soil is a sandy spodosol with low Fe/Al, Ca/Mg, and P contents and is likely to have minimal arsenic retention capacity. The Orelia soil is a sandy clay that is expected to have strong arsenic retention capacity. Arsenic speciation and bioavailability were studied immediately after spiking and after 4 months of incubation. Approximately 85% of the total arsenic (soluble and exchangeable fractions) was considered bioavailable and phytoavailable immediately after pesticide application for the Immokalee soil; after 4 months of incubation, this decreased to approximately 46%. Immediately after pesticide application, the amounts of arsenic extracted in the soluble/exchangeable and Fe/Al-bound fractions were similar that of the Immokalee soil. After 4 months, the soluble arsenic decreased to approximately 45% and the Fe/Al-bound arsenic increased to about 40%. Experiments looking at the bioavailability of arsenic from these two soils indicated that the potentially irreversible adsorption of arsenic by the Orelia soil rendered a significant portion of the total arsenic unavailable for absorption by the human gastrointestinal system. Initially after pesticide application,

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100% of the arsenic was bioavailable; after 4 months, the bioavailable fraction was found to decrease to 88 and 69% in the Immokalee and Orelia soils, respectively (Sarkar and Datta 2004).

Hamel et al. (1998) used synthetic gastric juice to estimate the bioaccessible fraction of metals in the stomach with varying liquid to solid ratios. They found that the bioaccessibility may vary in different soils and with varying liquid to solid ratios. Bioaccessibility was defined as the amount of metal that is soluble in synthetic gastric juice and therefore, potentially available for uptake across the intestinal lumen, while bioavailability was defined as the amount that was actually taken across the cell membranes.

Arsenic bioaccessibility for National Institute of Standards and Technology (NIST) Montana Soil SRM 2710, with a certified arsenic concentration of 626 $\mu\text{g/g}$, was fairly consistent across the liquid-to-solid ratios and ranged from 41.8 ± 18 to $56 \pm 21\%$. The extractability of a hazardous waste contaminated soil from Jersey City, New Jersey, was different than that observed for the Montana NIST soil. For the Jersey City soil, which had an arsenic concentration of 1,120 $\mu\text{g/g}$, there was an increase in the bioaccessible arsenic as the liquid-to-solid ratio increased. Bioaccessible arsenic ranged from 4.5 ± 0.8 (at a liquid-to-solid ratio of 100:1) to $25 \pm 9\%$ (at a ratio of 5,000:1). Similarly, smelter impacted soils from Anaconda, Montana contain metal-arsenic oxides and phosphates whose bioaccessibility is limited by solubility restraints for residence times typical of the gastrointestinal tract (Davis et al. 1992, 1996).

Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. For example, the dose to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3 (see Section 6.4.1) would be about 0.4–0.6 $\mu\text{g}/\text{day}$. However, smokers may be exposed to arsenic by inhalation of mainstream smoke. Assuming that 20% of the arsenic in cigarettes is present in smoke, an individual smoking two packs of cigarettes per day would inhale about 12 μg of arsenic (EPA 1984a). However, a German study of the arsenic levels in lung tissue of 50 unexposed deceased people (see Table 6-6) found no significant difference in lung arsenic concentrations of smokers versus nonsmokers, nor were there any significant age- or sex-related differences (Kraus et al. 2000). Before arsenical pesticides were banned, tobacco contained up to 52 $\mu\text{g As/g}$, whereas after the ban, maximum arsenic levels were reduced to 3 $\mu\text{g/g}$.

Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing, and arsenical pesticide production and application. Since arsenic compounds are used as a desiccant for cotton, workers involved in harvesting and ginning cotton may be exposed to arsenic. Occupational exposure would be via inhalation and dermal contact. Should any arsenic be retained in the cotton, workers handling the fabric and the general

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public would be exposed. The electronics industry is expanding the use of gallium arsenide in the production of electro-optical devices and integrated circuits, and workers in the industry where gallium arsenide is used may be exposed to hazardous substances such as arsenic, arsine, and various acids (Sheehy and Jones 1993). Occupational exposure to arsenic is generally assessed by measuring urinary excretion of arsenic. Past exposure is commonly assessed by arsenic levels in hair. Different types of occupational exposures may result in different uptakes of arsenic because of the bioavailability of the form of arsenic to which workers are exposed. For example, maintenance workers at a Slovak coal-fired power plant exposed to 8-hour TWA arsenic air concentrations of $48.3 \mu\text{g}/\text{m}^3$ (range, 0.17–375.2) had urinary total arsenic levels of $16.9 \mu\text{g As/g creatinine}$ (range, 2.6–50.8), suggesting that bioavailability of arsenic from airborne coal fly ash is about one-third that from in copper smelters and similar settings (Yager et al. 1997). Approximately 90% of the arsenic-containing particulates were $\geq 3.5 \mu\text{m}$. Apostoli et al. (1999) monitored 51 glass workers exposed to arsenic trioxide by measuring dust in the breathing zone. The mean concentration of arsenic in air was $82.9 \mu\text{g}/\text{m}^3$ ($1.5\text{--}312 \mu\text{g}/\text{m}^3$); exposure was higher for workers involved in handling the particulate matter. The occupation exposures to principal contaminants, including arsenic, at five coal-fired power plants were evaluated during June–August 2002. Eight air samples were collected per similar exposure group at four of the five facilities; inorganic arsenic concentrations in all samples were below the limit of detection ($0.37\text{--}0.72 \mu\text{g}/\text{m}^3$), as well as being below the OSHA permissible exposure limit (PEL) of $10 \mu\text{g}/\text{m}^3$ (Bird et al. 2004).

NIOSH researchers conducted a study of arsenic exposures and control systems for gallium arsenide operations at three microelectronics facilities during 1986–1987 (Sheehy and Jones 1993). Results at one plant showed that in all processes evaluated but one, the average arsenic exposures were at or above the OSHA action level of $5 \mu\text{g}/\text{m}^3$, with a maximum exposure of $8.2 \mu\text{g}/\text{m}^3$. While cleaning the Liquid Encapsulated Czochralski (LEC) pullers, the average potential arsenic exposure of the cleaning operators was 100 times the OSHA PEL of $10 \mu\text{g}/\text{m}^3$. Area arsenic samples collected at the plant in break-rooms and offices, 20–60 feet from the process rooms, had average arsenic concentrations of $1.4 \mu\text{g}/\text{m}^3$. At the other two plants, personal exposures to arsenic were well controlled for all processes evaluated.

A study has been conducted to examine the relationship between total arsenic levels in hair of employees in a semiconductor fabrication facility and job responsibility, a surrogate variable for arsenic exposure (de Peyster and Silvers 1995). Airborne arsenic was found in areas where equipment was cleaned but not in administrative areas. The highest airborne arsenic level found in the study, $15 \mu\text{g}/\text{m}^3$, was collected from the breathing zone of a maintenance employee who was cleaning a source housing over a period of 2 hours in an area with local exhaust ventilation. A concentration of $2 \mu\text{g}/\text{m}^3$ was found during the

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remainder of the cleaning period (~53 minutes). Workers in maintenance who were regularly assigned to cleaning equipment, and therefore presumed to have the highest exposure potential, had a mean hair arsenic level of 0.042 $\mu\text{g/g}$. This was higher than the mean of 0.033 $\mu\text{g/g}$ observed in administrative controls, but the difference was not significant. Maintenance workers who only occasionally cleaned and maintained arsenic-contaminated equipment had a mean hair arsenic level of 0.034 $\mu\text{g/g}$, which was comparable to the controls. The highest group mean hair arsenic level of 0.044 $\mu\text{g/g}$, surprisingly, was found in supervisors and engineers who were presumed to have the lowest exposure potential of all workers in the process areas. However, the highest concentrations of hair arsenic in engineers, 0.076 and 0.106 $\mu\text{g/g}$, were observed in two heavy smokers who smoked 1–2 packs of cigarettes per day. A 2-way analysis of variance indicated that smoking appeared to be a significant contributing factor whereas occupational exposure was not.

Hwang and Chen (2000) evaluated arsenic exposure in 21 maintenance engineers (exposed group) and 10 computer programmers (control group) at 3 semiconductor manufacturing facilities. Samples of air, wipe, and urine, as well as used cleaning cloths and gloves were collected to determine arsenic exposure. Arsenic was undetectable in 46 of the 93 air samples, and most samples were generally below the recommended occupational exposure limit (10 $\mu\text{g}/\text{m}^3$) in work areas during ion implanter maintenance. Arsenic was detectable in 22 of the 45 area air samples and in 15 of the 35 personal air samples; however, all concentrations were well below the occupational exposure limit of 50 ppb (160 $\mu\text{g}/\text{m}^3$). Mean arsenic concentrations ranged from not detected to 4.0 ppb (15 $\mu\text{g}/\text{m}^3$) in area air samples, and the mean arsenic concentration of personal air for maintenance engineers was 4.3 ppb (14 $\mu\text{g}/\text{m}^3$). Arsenic concentrations in wipe samples, used cleaning cloths, and gloves, varied from not detected to 146 $\mu\text{g}/\text{cm}^2$. During ion implanter maintenance, urinary arsenic levels were found to increase (1.0–7.8 $\mu\text{g/g}$ creatinine) in the maintenance engineers, from a mean baseline concentration of 3.6 $\mu\text{g/g}$ creatinine. The average urinary arsenic level for the computer programmers was 3.8 $\mu\text{g/g}$ creatinine (Hwang and Chen 2000). Mean arsenic concentrations in blood of 103 workers in the optoelectronic industry and 67 controls were 8.58 and 7.85 $\mu\text{g/L}$, respectively (Liao et al. 2004).

Concentrations of various metals, including arsenic, were measured in autopsy tissues (liver, lung, kidney, brain, and bone) collected from 78 nonoccupationally exposed subjects from Tarragona County, Spain between 1997 and 1999. In general, arsenic concentrations were under the analytical detection limit (0.05 $\mu\text{g/g}$ wet weight) in all tissues (Garcia et al. 2001).

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CCA preservatives are commonly used for treating timber used in constructions in marine and other humid environments or in contact with the ground. Exposure to CCA compounds may occur through dermal contact and inhalation of dust while working with the treated timber. Nygren et al. (1992) investigated the occupational exposure to airborne dust, chromium, copper, and arsenic in six joinery shops in Sweden where impregnated wood was used for most of their production. The mean airborne concentration of arsenic around various types of joinery machines ranged from 0.54 to 3.1 $\mu\text{g}/\text{m}^3$. No increased concentrations of arsenic were found in the workers' urine. A study was carried out in Denmark to evaluate arsenic exposure in taxidermists, workers impregnating wood with CCA solutions, fence builders, construction workers, and workers impregnating electric pylons with arsenic solution (Jensen and Olsen 1995). Airborne arsenic exposure was documented in 19 of 27 individuals working with products containing arsenic. The maximum exposure concentration was 17.3 $\mu\text{g}/\text{m}^3$, found for a single worker who was filling an impregnation container with CCA paste. Median exposures for indoor workers producing garden fences and weekend cottages were 3.7 and 0.9 $\mu\text{g}/\text{m}^3$, respectively. The maximum urine concentration reported in the study was 294.5 nanomoles arsenic per millimole creatinine (195 $\mu\text{g As/g creatinine}$) and was from the injector impregnating electric pylons. The median concentration in workers on electric pylons was 80 nanomoles arsenic per millimole creatinine (53 $\mu\text{g As/g creatinine}$), which was 6 times the concentration in reference individuals. Urine arsenic levels in workers producing garden fences and in taxidermists were 2.9 and 1.8 times the reference level, respectively.

The NIOSH National Occupational Exposure Survey (NOES) conducted in 1981–1983 estimated that about 55,000 workers were potentially exposed to arsenic (NOES 1990). The NOES was based on field surveys of 4,490 facilities that included virtually all workplace environments, except mining and agriculture, where eight or more persons are employed. The principal exposure pathway is probably inhalation of arsenic adsorbed to particulates, but ingestion and possibly dermal exposure may also be common. Since arsenic is no longer produced in the United States (see Section 5.1) and many arsenical pesticide uses have been banned (see Chapter 8), it is likely that the number of workers occupationally exposed to arsenic has decreased markedly in more recent years.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

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Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

As with adults, most children are exposed to arsenic largely through their diet. Since the greatest dietary intake of arsenic is from fish and seafood, infants and young children for whom a substantial part of their food is milk, would not be exposed to arsenic from dietary sources as much as older children. Even when mothers consume large amounts of seafood, there does not appear to be any major transfer of arsenobetaine, the major form of arsenic in seafood, from seafood to milk (Grandjean et al. 1995).

Arsenic concentrations were very low in human milk sampled from 88 mothers in the Faroe Islands, where the seafood diet includes pilot whale meat and blubber. The total arsenic concentrations ranged from 0.1 to 4.4 µg/kg, with a median of 1.6 µg/kg (Grandjean et al. 1995). The arsenic concentration in the breast milk of 35 women in Ismir, Turkey, a volcanic area with high thermal activity ranged from 3.24 to 5.41 µg/L, with a median of 4.22 µg/L (Ulman et al. 1998). The mean arsenic levels in three groups of cows in the region that grazed on land impacted by lava and thermal activity were 4.71, 4.46, and 4.93 µg/L, compared to 5.25 µg/L for cows kept in sheds and fed commercial pellet feed and municipal water. The arsenic levels in the urine of pregnant women and the cord blood of their infants were 0.625 ± 0.027 and 0.825 ± 0.079 µg/L, respectively. The authors concluded that there was no harmful exposure to arsenic in volcanic areas with high arsenic levels from suckling infants or feeding them local cow's milk, nor was there harm to the newborns from their mother's diet. Sternowsky et al. (2002) analyzed breast milk from 36 women from three different regions in Germany. These regions included the city of Hamburg, a rural area, Soltau, Lower Saxony, and Munster, the potentially contaminated area. Arsenic was not detected (<0.3 µg/L) in 154 of 187 samples, with the highest concentration, 2.8 µg/L, found in a sample from the rural area. The geometric mean arsenic concentrations from the three areas were comparable. Calculated oral intakes of arsenic were between 0.12 and 0.37 µg/day for an infant at 3 months of age and weighing 6 kg.

According to the FDA study of 1986–1991, the mean daily intakes of arsenic are 0.5 and 0.81 µg/kg body weight per day for a 6–11-month-old infant and 2-year-old child, respectively (Gunderson 1995b). This

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can be compared to a mean daily intake of 0.51 $\mu\text{g/kg}$ -body weight per day for a 25–30-year-old male (see Table 6-5). A Total Diet Study, from September 1991 to December 1996, estimated that the average inorganic arsenic intake for children of various age/sex groups were (age-sex group, total arsenic intake in $\mu\text{g/day}$, inorganic arsenic intake in $\mu\text{g/day}$): 6–11 months, 2.15, 1.35; 2 years, 23.4, 4.41; 6 years, 30.3, 4.64; 10 years, 13.3, 4.21; and 14–16 years (females), 21.8, 5.15; 14–16 years (males), 15.4, 4.51 (Tao and Bolger 1999). The greatest dietary contribution (76–96%) of total arsenic intake for all age groups other than infants was seafood. For infants, 41 and 34% of the estimated total arsenic intakes are from seafood and rice/rice cereals, respectively (Tao and Bolger 1999). Only for toddlers does the intake approach the World Health Organization's (WHO) provisional tolerable daily intake (PTDI) for inorganic arsenic (see Table 6-5). A 1985–1988 Canadian total diet study estimated that 1–4-year-olds ingested 14.9 μg of total arsenic per day compared with 38.1 μg by the average Canadian and 59.2 μg for 20–39-year-old males (Dabeka et al. 1993). Yost et al. (2004) estimated the mean dietary intake for inorganic arsenic for children (1–6 years of age) to be 3.2 $\mu\text{g/day}$, with a range of 1.6–6.2 $\mu\text{g/day}$ for the 10th and 95th percentiles, respectively. Inorganic arsenic intake was predominantly contributed by grain and grain products, fruits and fruit juices, rice and rice products, and milk (Yost et al. 2004). Total arsenic and arsenobetaine concentrations were measured in 16 baby food samples obtained from manufactures in Spain; total arsenic concentrations ranged from 2.042 to 0.270 $\mu\text{g/g}$ in plaice with vegetables and sole with white sauce, respectively. Arsenobetaine, which is the arsenical commonly found in fish, accounted for essentially 100% of the arsenic present in the samples (Vinas et al. 2003).

Arsenic exposure from drinking water may be elevated especially in groundwater from areas where arsenic occurs naturally in soil such as the western and north central sections of the United States (see Table 6-3 and Figure 6-2).

Arsenic exposure in communities near mining and smelting facilities or where arsenic had formerly been applied to agricultural land are a public health concern, especially for infants and children. Since arsenic remains in the surface soil indefinitely and long past land uses may be forgotten, people may not realize that they are living in areas where high levels of arsenic may occur in soil. Contaminated soils pose a particular hazard to children because of both hand-to-mouth behavior and intentional ingestion of soil (pica) that contains metals and other contaminants (Hamel et al. 1998). In these communities, arsenic may contaminate carpeting or may have been tracked in from outside. Children may be exposed to this arsenic while crawling around or playing on contaminated carpeting. Exposure may also result from dermal contact with the soil, or by inhaling the dust and then swallowing it after mucociliary transport up

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out of the lungs. Because much of the arsenic in soil is embedded in or adsorbed to soil particles or insoluble, it may not be in a form accessible for uptake by the body.

Hwang et al. (1997b) studied the arsenic exposure of children in Anaconda, Montana, in the vicinity of a former copper smelter from the summer of 1992 through the summer of 1993. Environmental samples and first morning voided urine samples from 414 children <72 months old were collected. Attention was focused on that fraction of the environmental source that was thought to be of the greatest risk to the child (i.e., arsenic in small particles [$<250\text{ }\mu\text{m}$]) that could most readily adhere to hands and toys and could be inadvertently ingested. Average arsenic levels in different types of soil ranged from 121 to 236 $\mu\text{g/g}$. Several studies have reported mean soil ingestion values for children ranging from 9 to 1,834 $\mu\text{g/day}$. Assuming that high arsenic exposure areas have average arsenic levels in soil from 60 to 150 $\mu\text{g/g}$, the resulting daily arsenic intake from soil could range from 1 to 275 $\mu\text{g/day}$ per child. The geometric mean of speciated urinary arsenic (combined As(III), As(V), MMA and DMA) was $8.6\pm 1.7\text{ }\mu\text{g/L}$ ($n=289$) in the Hwang study. A nationwide survey on arsenic exposure in the vicinity of smelter sites revealed that children without excess arsenic exposure had average total urinary arsenic levels ranging from 5 to 10 $\mu\text{g/L}$ (Hwang et al. 1997a). Compared to these values, the mean total urinary arsenic values found in the Hwang study were markedly higher, but they were still well below the WHO-recommended maximum excretion level for total arsenic of 100 $\mu\text{g/L}$ as an action level for intervention. The investigators hypothesized that the relatively low urinary arsenic levels found in the study were probably a reflection of the low bioavailability of some forms of arsenic in contaminated soil. Hwang et al. (1997a) stated that arsenic intake through skin contact is insignificant and may be neglected in the assessment of childhood arsenic exposure. They recommend that parents or guardians pay more attention to their children's activity, especially hand-to-mouth behavior, even though the environmental contaminants might be elevated only slightly. Children in the northern Palatine region of German study, a former mining area characterized by high levels of arsenic ($<2\text{--}605\text{ }\mu\text{g/g}$) in residential areas did not show higher arsenic levels in their hair or urine than children from a reference area of Germany (Gebel et al. 1998a).

While CCA registrants voluntarily canceled the production of CCA-treated wood for residential use in 2003, there is a potential for exposure to arsenic from existing structures (Zartarian et al. 2006). Based on a review of existing studies, Hemond and Solo-Gabriele (2004) estimated that children with contact with CCA-treated wood may be subjected to doses in the range of tens of micrograms of arsenic per day. The most important route of exposure appeared to be by hand-to-mouth activities after contact with the CCA-treated wood. Kwon et al. (2004) compared the amounts of water-soluble arsenic on hands of children in

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contact with CCA-treated wood structures or sand in playgrounds. The mean amount of water-soluble arsenic on children's hands from playgrounds without CCA-treated wood was 0.095 μg (range 0.011–0.41 μg). A mean amount of water-soluble arsenic on children's hands from playgrounds with CCA-treated wood was 0.5 μg (range 0.0078–3.5 μg) (Kwon et al. 2004). Additional data from the study by Kwon et al. (2004) showed that total arsenic collected in hand-washing water (insoluble arsenic on the filter combined with the water-soluble arsenic in the filtrate) was 0.934 and 0.265 μg for the CCA playgrounds and the non-CCA playgrounds, respectively (Wang et al. 2005). Two wood surface swab samples collected from 217 play structures constructed from CCA-treated wood in the City of Toronto, Canada were sampled and analyzed for inorganic arsenic (Ursitti et al. 2004). Dislodgeable arsenic concentrations were found to vary widely from nondetectable (0.08–0.25 $\mu\text{g}/100\text{ cm}^2$) to 521 $\mu\text{g}/100\text{ cm}^2$ (mean = 41.6 $\mu\text{g}/100\text{ cm}^2$), and were found to not be a useful predictor of soil arsenic levels (Ursitti et al. 2004).

Shalat et al. (2006) evaluated postexposure hand rinses and urine for total arsenic for 11 children (13–71 months) in homes in Miami-Dade County, Florida, with and without CCA-treated playgrounds. Seven playgrounds were included in this study, and five of these contained either CCA-treated or partially CCA-treated wood. In addition, samples of wood, soil (5–8 cm from the base of the playground structure), mulch (when present), and synthetic wipes were analyzed for total arsenic. Wood and soil arsenic concentration were <2.0 and <3 mg/kg for the non-CCA-treated playgrounds, respectively. Mean arsenic concentrations of 2,380 mg/kg (range 1,440–3,270 mg/kg) and 19 mg/kg (4.0–42 mg/kg) were reported for wood and soil, respectively, in the playgrounds with CCA-treated wood. An arsenic concentration in mulch at one playground without CCA-treated wood was 0.4 mg/kg, and arsenic concentrations were 0.6 and 69 mg/kg in mulch at two of the playgrounds with CCA-treated wood. The amount of arsenic removed by synthetic wipes from the non-CCA-treated wood was <0.5 μg , while the mean amount of arsenic removed from the CCA-treated wood was 117 μg (range 1.0–313 μg). The amount of arsenic in hand rinses from children who played at the playgrounds with non-CCA-treated wood and at the playgrounds with CCA-treated wood were <0.2 and 0.6 μg (range <0.2–1.9 μg), respectively. The mean urinary total arsenic concentration was 0.0136 $\mu\text{g}/\text{L}$ (range 0.0072–0.0231 $\mu\text{g}/\text{L}$) for all children. No association between assess to CCA-treated playgrounds and urinary arsenic levels was found (Shalat et al. 2006).

The potential exposure children may receive from playing in play structures constructed from CCA-treated wood is generally smaller than that they would receive from food and water. For comparison, Yost et al. (2004) estimated the mean dietary intake for inorganic arsenic for children (1–6 years of age)

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to be 3.2 µg/day, with a range of 1.6–6.2 µg/day for the 10th and 95th percentiles, respectively. In a Total Diet Study, from September 1991 to December 1996, estimated average total intakes for children aged 6–11 months, 2 years, 6 years, and 10 years were 2.15, 23.4, 30.3, and 13.3 µg/day, respectively. Average inorganic arsenic intakes for the same age groups were estimated as 1.35, 4.41, 4.64, and 4.21 µg/day, respectively, based on data for total arsenic in foods and the assumption that 10% of the total arsenic in seafood was inorganic and that 100% of the arsenic in all other foods was inorganic (Tao and Bolger 1999). Hand washing after play would reduce the potential exposure to children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water (Kwon et al. 2004).

Concentrations of several toxic metals, including the metalloid arsenic, were measured in the placentas of 200 women in two urban cities in Ukraine, Kyiv and Dniprodzerzhinsk. Arsenic was detected in only 5% of the samples with concentrations ranging from <0.156 to 0.378 µg/g. In a study in Bulgaria, placental arsenic concentrations of 7 and 23 µg/g were reported in a control and smelter area, respectively. A placental arsenic concentration of 34 µg/g was reported in a region of Argentina with high concentrations of arsenic in drinking water (Zadorozhnaja et al. 2000).

Parents can inadvertently carry hazardous materials home from work on their clothes, skin, hair, and tools, and in their vehicles (DHHS 1995). Falk et al. (1981b) reported a case of hepatic angiosarcoma in a child that could be associated with arsenic contamination of a parent's clothing, the water supply, and the environment. The father worked in a copper mine and smelter area where his clothing was contaminated with dust containing arsenic. His daughter, who exhibited a high degree of pica, ate soil from the yard, and licked soil off her father's shoes. In a study of arsenic levels in homes in Hawaii, Klemmer et al. (1975) found higher levels in homes of employees of firms that used arsenic for pesticides or wood preservation, compared to homes where residents' work did not involve arsenic. The concentration of arsenic in dust from the homes of workers exposed to arsenic ranged from 5.2 to 1,080 µg/g, compared to concentrations of 1.1–31 µg/g in dust from control homes.

While the harmful effects of many components of tobacco smoke are well known, those due to heavy metals in the smoke have not been sufficiently emphasized. The adverse health effects of these toxic metals on the fetus through maternal smoking are of special concern (Chiba and Masironi 1992). The concentration of arsenic in tobacco is relatively low, usually below detectable limits (<1 µg/g). Although the concentrations of inorganic and organic arsenic in the urine of adults do not appear to be influenced by smoking, a positive association was found between urinary arsenic levels in children and parental

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smoking habits. As detailed in a WHO report, the mean arsenic level in the urine of children of nonsmoking parents was 4.2 µg/g creatinine, in children with one smoking parent, it was 5.5 µg/g, and in children with both parents smoking, it was 13 µg/g (Chiba and Masironi 1992). Tsuji et al. (2005) reported geometric mean concentrations of total arsenic of 15.1 and 15.7 µg/L in children <7 and <13 years old, respectively, from households in Middleport, New York, where historical pesticide manufacture was associated with arsenic in soil. Geometric mean concentrations of inorganic arsenic, MMA, and DMA were 0.81, 0.54, and 2.5 µg/L, respectively, in children <7 years old and 0.83, 0.55, and 3.0 µg/L, respectively, in children <13 years old (Tsuji et al. 2005).

The use of Chinese herbal medicines (CHM) appears to be common among Chinese women. Both CHM and Chinese proprietary medicines (CPM) are used for treatment of minor ailments in babies and children. Herbal medicines are available in capsule or tablet form in drug stores, supermarkets, and by mail. The CPM “Sin Lak Pill,” “Lu Shen Wan,” and other anti-asthma preparations have been found to contain inorganic arsenic levels ranging from 25 to 107,000 µg/g, and cases of acute arsenic poisoning have been found in children and adults using these CPM (Chan 1994). Babies and children are particularly at risk because they may be given higher doses of these preparations per kg of body weight than adults would normally consume. They may also lack the hepatic enzymes responsible for drug biotransformation and detoxification (Chan 1994). Concentrations of heavy metals, including arsenic, were evaluated in 54 samples of Asian remedies that were purchased in stores in Vietnam and Hong Kong that would be easily accessible to travelers, as well as in health food and Asian groceries in Florida, New York, and New Jersey. One remedy that was recommended to treat children’s fever would expose a 15 kg child to approximately 5.0 mg of arsenic per day (Garvey et al. 2001). A folk remedy, purchased in California, for the treatment of chicken pox, flu-like symptoms, and nasal congestion, which had been given to two children in Wisconsin, was found to contain 36% arsenic acid. One-half teaspoon of this powder (about 500 mg of arsenic) was dissolved in hot water and taken 2–3 times per day (Werner et al. 2001).

Various metallic pigments and colors in the form of salts or lakes are used in toy production. Therefore, children may be exposed to toxic metals while playing with toys, especially when they lick, suck, or swallow a toy or a piece of a toy. Toys produced in European Union Markets must conform to restrictions concerning the bioavailability of toxic metals, including arsenic. The maximum limit for bioavailability of arsenic from the accessible parts of a toy is set to 0.1 µg/day. This corresponds to an arsenic migration limit of 25 µg/g for all toy material, including modeling clay and paints (Rastogi and Pritzl 1996). A study was carried out to determine whether crayons, water colors, and water-based paints

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conform with the migration limits for toxic metals (Rastogi and Pritzl 1996). For the analysis, 94 samples representing 48 products were obtained from China, Taiwan, Japan, the United States, and European countries. Fifty-two samples showed migration of arsenic, ranging from 0.01 to 3.75 µg/g.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to arsenic (see Section 6.5), there are several groups within the general population that have potentially high exposures (higher than background levels) to arsenic. These populations include individuals living in proximity to sites where arsenic was produced, used (e.g., as a pesticide), or disposed, and individuals living near one of the 1,684 NPL hazardous waste sites where arsenic has been found at elevated levels in some environmental media (HazDat 2006). It also includes point sources such as smelters, coal-fired power plants, and municipal incinerators. People living in areas of volcanic activity may be exposed to higher levels of arsenic since high levels are more likely to be present in the environment. Other populations at risk of potentially high levels of exposure include those whose water supply contains high levels of arsenic and those consuming large amounts of seafood or seaweed. However, as pointed out previously (see Section 6.4.4), arsenic in fish and shellfish, is largely in the form of the less harmful organic arsenical, arsenobetaine; however, some commercially available seaweeds, especially brown algae varieties, may have high percentages of the total arsenic present as inorganic arsenic (>50%) (Almela et al. 2002; Laparra et al. 2003). While elevated urinary arsenic excretion levels have been associated with the consumption of fish and seafood, in a study of 32 sport fish consumers from Lakes Erie, Huron, and Michigan, only 6 (19%) had detectable urine arsenic concentrations, >4 µg/L, and 5 of these consumed fish from Lake Huron (Anderson et al. 1998). Exposure of high levels of arsenic in drinking water is more apt to be absorbed by the body and be harmful than exposure to arsenic in seafood. For example, a group of 36 people in Zimapan, Mexico who consumed water from an aquifer with 1.0 mg As/L had hair arsenic levels of 2.6–14.1 µg/g (10 µg/g average), compared with 2.4–13.9 µg/g (6.19 µg/g average) for a reference population that consumed bottled water with <0.014 mg/L arsenic (Armienta et al. 1997).

A study was conducted to determine if significant arsenic exposure was occurring at a Superfund site in Fort Valley, Georgia (Hewitt et al. 1995). Random urine, 24-hour urine, hair, and fingernail samples were collected at the end of the workweek from 40 employees at an active pesticide manufacturing facility where arsenical pesticides had been produced for over 50 years prior to the mid-1970s. Measurement of arsenic in the urine is considered to be the best method for monitoring recent exposure in industrial populations. Hair and fingernail analyses may provide an indication of exposures that occurred

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up to several months prior to testing, but both can adsorb and strongly retain arsenic from external sources. Since arsenic is rapidly cleared from the blood (half-life of 3–4 hours), blood arsenic levels are not considered suitable for monitoring populations for chronic low-level arsenic exposure. Results of the Hewitt study are summarized in Table 6-6. Urinary arsenic levels for all workers were well within the commonly accepted normal range of <100 µg/L.

As noted above, workers in a number of industries may have high exposures to arsenic, especially if proper safety procedures are not followed. For members of the general population, above-average exposure to arsenic from drinking water is possible in areas of high natural arsenic levels in groundwater or elevated arsenic levels in drinking water due to industrial discharges, pesticide applications, or leaching from hazardous waste facilities. Individuals living in the vicinity of large smelters and other industrial emitters of arsenic may be exposed to above-average arsenic levels both in the air, and as a result of atmospheric deposition, in water and soil and subsequent uptake into crops.

People sawing or drilling arsenic-treated wood without protective masks or burning this wood may be exposed to elevated levels of arsenic in air.

Recreational and subsistence fishers who consume appreciably higher amounts of locally caught fish from contaminated bodies of water may be exposed to higher levels of arsenic associated with dietary intake. Arsenic contamination has triggered the issuance of several human health advisories (EPA 1998g). As of December 1997, arsenic was identified as the causative pollutant in a restricted consumption advisory for the general population for all fish in a 7-mile area including Devil's Swamp Lake and Bayou Baton Rouge in Louisiana. A public health advisory has been issued for consumption of fish and shellfish from the Duwamish River, Seattle, Washington due to arsenic and other chemicals (WSDOE 2005).

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

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The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The chemical and physical properties of the arsenic species of chief toxicological and environmental concern are sufficiently well characterized to allow estimation of the environmental fates of these compounds. However, more information regarding the K_{ow} and K_{oc} values of the organic arsenicals would help predict the fate of these compounds in the environment.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

While arsenic has not been produced in the United States since 1985, the United States is the largest consumer of arsenic and substantial quantities of arsenic are imported, primarily as arsenic trioxide (USGS 2006a). The agricultural use of inorganic arsenic pesticides have been discontinued in the United States. However, some organic arsenicals still may be used in agriculture. Current production and use data for individual arsenical pesticides and other arsenic compounds would help to estimate human exposure to the various arsenic species. Because arsenical pesticides are so persistent, a more complete picture of past use of these products would enable us to predict what areas may contain high levels of arsenic in soil.

Comprehensive estimates on emissions of arsenic date to the early 1980s (Nriagu and Pacyna 1988). The industrial picture has changed considerably since then and emission controls are being mandated more and more. For example, emission factors for Canadian smelters calculated in 1993 were grossly lower than those estimated in 1983 (Skeaff and Dubreuil 1997). There is a need for accurate and up-to-date measurements of atmospheric arsenic releases from both natural and anthropogenic sources to better assess human exposure to arsenic and guide environmental protection measures.

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Environmental Fate. The interconversion of the various arsenic species and transport among the environmental media is complex and not all aspects are well-studied. Additional quantitative data on the rates of oxidation, reduction, and biotransformation reactions of arsenic compounds, and how these depend on environmental conditions would be useful in evaluating and predicting the fate and transport of arsenic at hazardous waste sites and other areas.

Bioavailability from Environmental Media. Toxicokinetic and toxicity studies establish that bioaccessible (e.g., soluble, not strongly adsorbed to soil or embedded in minerals) arsenic is highly absorbed following inhalation and oral exposure (see Sections 3.4.1.2 and 3.4.1.1). Some work has been done on the effect of environmental matrix (soil, food) on accessibility and absorption of arsenic (Davis et al. 1992, 1996; Hamel et al. 1998; Roberts et al. 2002, 2007), but additional data would be valuable. Limited data suggests that dermal absorption of arsenic is very low (see Section 3.4.1.3) (Lowney et al. 2005), further data would be useful to establish whether arsenic uptake occurs from contact with contaminated soil or water, since humans may be exposed by these routes near hazardous waste sites.

Food Chain Bioaccumulation. Bioconcentration factors have been measured for several freshwater and marine species. While some species (mainly marine algae and shellfish) tend to bioconcentrate arsenic (EPA 1980a; Roper et al. 1996), it is not biomagnified through the food chain (Eisler 1994; EPA 1979, 1982b, 1983e, 2003b; Williams et al. 2006).

Carrots growing on land containing somewhat more than the permissible of arsenic in crop land did not contain levels of arsenic that were harmful (Helgesen and Larsen 1998). However, further research on the uptake of arsenic by a variety of plants in a wide range of arsenic polluted sites (e.g., mining area, orchards previously treated with lead arsenate) would be valuable in assessing human exposure near such sites through the consumption of vegetables from home gardens.

Exposure Levels in Environmental Media. Additional reliable monitoring data for the levels of arsenic in contaminated media at hazardous waste sites are needed or need to be made available, so that the information obtained on levels of arsenic in the environment can be used in combination with the known body burden of arsenic to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

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Extensive monitoring data are available for total arsenic in all environmental media. Additional monitoring studies, specifically those that include identification of arsenic species, would allow more precise estimation of current exposure levels and possible human health risks.

Exposure Levels in Humans. Arsenic has been detected in human tissues, including blood, urine, hair, nails, and internal organs. Data are available for populations exposed in the workplace and for the general population (de Peyster and Silvers 1995; Jensen and Olsen 1995; Nygren et al. 1992), and some studies have been published on exposures near waste sites (Hwang et al. 1997a; Tsuji et al. 2005). Additional biomonitoring studies of residents near waste sites that contain arsenic would be helpful in evaluating the likely human health risks from these sites.

While some data are available on the speciation of arsenic in food, additional data on the particular species of arsenic, rather than just the total arsenic concentration, present in foods, especially seafood, are needed to better estimate the potential hazards to human health by the consumption of these foods (Ryan et al. 2001).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Contaminated soils pose a particular hazard to children because of pica and hand-to-mouth activities. Some studies have been performed on exposure and body burden (Hwang et al. 1997a), but additional studies, including investigations of unique pathways for exposures of children and the amount of soil a child ingests, would provide valuable data. Small amounts of arsenic were found to be transferred to hands of children playing on play structures constructed from CCA-treated wood (Hemond and Solo-Gabriele 2004; Kwon et al. 2004; Shalat et al. 2006; Ursitti et al. 2004; Wang et al. 2005). Based on a review of existing studies, Hemond and Solo-Gabriele (2004) estimated that children with contact with CCA-treated wood may be subjected to doses in the range of tens of micrograms of arsenic per day and suggested that exposure by this route warrants further study. The PTDI assigned by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO) applies to adults. Studies are needed to assess whether children are different in their weight adjusted intake of arsenic. No childhood-specific means for reducing exposure were identified.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

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Exposure Registries. No exposure registries for arsenic were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2006) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-7.

The U.S. Geological Survey, along with other federal and state agencies, industry, and academia, is conducting the National Geochemical Survey (NGS) in order to produce a body of geochemical data for the United States based primarily on stream sediments that have been analyzed using a consistent set of analytical methods. The goal of the NGS is to analyze at least one stream sediment sample in every 289 km² area by a single analytical method across the entire United States (USGS 2007b).

EPA is conducting a 4-year (2000–2003) national screening-level study of contaminants in freshwater fish, referred to as the National Fish Tissue Study (EPA 2004c). This study will allow the EPA to develop national estimates of the mean concentrations of 268 chemicals in tissues of fish from lakes and reservoirs of the coterminous United States. EPA analysis of the data from this study was scheduled to begin in January 2005, with the final report scheduled to be released in 2006. Interim raw data have been released each year, and are available from EPA. Fish samples have been analyzed for total inorganic arsenic (As(III) and As(V) combined), arsenic(III), arsenic(V), MMA(V), and DMA(V). Analysis for total arsenic was not performed as part of this study.

The American Water Works Association Research Foundation (AWWARF) supports research on arsenic in drinking water.

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Table 6-7. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic

Investigator	Affiliation	Research description	Sponsor
Basta, NT	Ohio State University, School of Natural Resources, Columbus, Ohio	Heavy metal and trace element biogeochemistry in soils; chemical speciation, bioavailability, and toxicity	USDA
Blum, CB	Columbia University Health Sciences, New York, New York	Bioavailability lead and arsenic in soil to humans	NIEHS
Hamilton, JW	Dartmouth College, Hanover, New Hampshire	Toxic metals—biological and environmental implications	NIEHS
Hoppin, J	Not specified	Monitoring of arsenic and other compounds in the blood and urine of a cohort of pregnant women in Norway	NIEHS
Kpomblekou, AK; Ankumah, RO	Tuskegee University, Agriculture and Home Economics, Tuskegee, Alabama	Biochemical processes in soils treated with trace-element-enriched broiler litter; to determine total arsenic and other metal concentrations and the distribution of their chemical forms in soils under long-term broiler litter treatments	USDA
Loeppert, RH	Texas A&M University, Soil and Crop Sciences, College Station, Texas	Inorganic chemical processes influencing soil and water quality	USDA
Peryea, FJ	Wenatchee Tree Fruit Research & Extension Center Washington State University, Pullman, Washington	Quantification of biogeochemical processes in lead arsenate-contaminated orchard soils and development of soil and plant management practices to minimize the toxicity risks that these soils impose on agricultural crops and to human and environmental health	USDA
Miller, DM; DeLaune, P; Miller, WP	University of Arkansas, Crop, Soil and Environmental Sciences, Fayetteville, Arkansas	Arsenic levels in soils of northwest Arkansas	USDA
van Geen, A	Columbia University, Lamont-Doherty Earth Observatory, Palisades, New York	Studies on arsenic in groundwater in Bangladesh	NSF

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Table 6-7. Ongoing Studies on the Environmental Fate and Exposure of Humans to Arsenic

Investigator	Affiliation	Research description	Sponsor
Walker, MJ et al.	University of Nevada, Natural Resources and Environmental Sciences, Reno, Nevada	Arsenic in Churchill County, Nevada domestic water supplies	USDA
Zheng, Y	Columbia University Health Sciences, New York, New York	Arsenic mobilization in Bangladesh groundwater	NIEHS

NIEHS = National Institute of Environmental Health Sciences; NSF = National Science Foundation; USDA = U.S. Department of Agriculture

Source: FEDRIP 2006

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring arsenic, its metabolites, and other biomarkers of exposure and effect to arsenic. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Atomic absorption spectrophotometry (AAS) is the most common analytical procedure for measuring arsenic in biological materials (Curatola et al. 1978; Foà et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin and Vahter 1981; Sotera et al. 1988). In AAS analysis, the sample is heated in a flame or in a graphite furnace until the element atomizes. The ground-state atomic vapor absorbs monochromatic radiation from a source and a photoelectric detector measures the intensity of transmitted radiation (APHA 1989b). Inductively-coupled plasma atomic emission spectrometry (ICP-AES) and ICP-mass spectrometry (ICP-MS) are increasingly common techniques for the analysis of arsenic; both methods can generally provide lower detection limits than absorbance detection methods.

Samples may be prepared for AAS in a variety of ways. Most often, the gaseous hydride procedure is employed (Curatola et al. 1978; Foà et al. 1984; Johnson and Farmer 1989; Norin and Vahter 1981). In this procedure, arsenic in the sample is reduced to arsine (AsH_3), a gas that is then trapped and introduced into the flame. This approach measures total inorganic arsenic, but may not detect all organic forms unless preceded by a digestion step. Digestion or wet-ashing with nitric, sulfuric, and/or perchloric acids degrades the organic arsenic species to inorganic arsenic so that recovery of total arsenic from biological materials can be achieved (Maher 1989; Mushak et al. 1977; Versieck et al. 1983). In microwave assisted digestion, harsh oxidation conditions are used in conjunction with microwave heating (Benramdane et al. 1999b). For accurate results, it is important to check the completeness of the oxidation; however, this is seldom done (WHO 1981).

7. ANALYTICAL METHODS

The arsenic concentration in biological fluids and tissues may also be determined by neutron activation analysis (NAA) (Landsberger and Simsons 1987; Versieck et al. 1983). In this approach, the sample is irradiated with a source of neutrons that converts a portion of the arsenic atoms to radioactive isotopes, which can be quantified after separation from radioisotopes of other chemicals. Neutron activation has limited use because of the limited number of nuclear reactors in the United States providing this service and the need to dispose of radioactive waste. X-ray fluorescence is also capable of measuring arsenic in biological materials (Bloch and Shapiro 1986; Clyne et al. 1989; Nielson and Sanders 1983) and environmental samples (see Section 7.2). This method has the advantage that no sample digestion or separation steps are required. Hydride generation combined with atomic fluorescence spectroscopy (HG-AFS) is a relatively new technique that provides freedom from interference offered by hydride generation with sensitivity better than to 20 parts per trillion and linearity up to 10 ppm (PSA 2000).

Speciation of arsenic (i.e., analysis of organic arsenic compounds or different inorganic species, rather than total arsenic) is usually accomplished by employing separation procedures prior to introduction of the sample material into a detection system. Various types of chromatography or chelation-extraction techniques are most commonly used in combination with AAS, ICP-AES, or ICP-MS detection methods (Dix et al. 1987; Foà et al. 1984; Johnson and Farmer 1989; Mushak et al. 1977; Norin et al. 1987; Thomas and Sniatecki 1995). In one method, high performance liquid chromatography (HPLC) is combined with HG-AFS to quantify As(III), dimethylarsinic acid (DMA), monomethyl arsonic acid (MMA), and As(V) (PSA 2000). Another approach involves selective reduction of arsenate and arsenite (permitting quantification of individual inorganic arsenic species), and selective distillation of methyl arsines to quantify MMA and DMA (Andreae 1977; Braman et al. 1977; Crecelius 1978). Most methods for measuring arsenic in biological samples are unable to measure arsenobetaine with any accuracy because it does not form a hydride and it gives a different response from inorganic arsenic in electrothermal AAS. Ebdon et al. (1999) successfully employed HPLC coupled with ICP-MS to determine arsenic speciation in blood plasma, which was entirely arsenobetaine. Øygard et al. (1999) developed a simple method to determine inorganic arsenic in biological samples. Their method, which involves initially distilling inorganic arsenic from the sample as AsCl_3 using HCl, avoids separating and quantifying all of the different arsenic species, which is both costly and time-consuming.

Table 7-1 summarizes a variety of methods for measuring total arsenic and individual arsenic species in biological materials. None of these methods have been standardized by EPA or other federal agencies.

7. ANALYTICAL METHODS

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
<i>Methods for total arsenic:</i>					
Blood	Digestion with nitric acid and hydrogen peroxide; dry ash with magnesium oxide/magnesium nitrate; reduction with sodium borohydride	HGAAS	0.5 µg/L	95–102	Foà et al. 1984
Blood, hair	Wet ash with nitric/perchloric acids; reduction with sodium borohydride	HGAAS	0.1 µg/L ^a	95–105	Valentine et al. 1979
Serum	Irradiation; digestion with nitric/perchloric/sulfuric acids; extraction with toluene	NAA	0.088 ng/mL ^a	94–98	Versieck et al. 1983
Urine	Irradiate epithermally	NAA	40–100 ng/g	93–109	Landsberger and Simsons 1987
Urine	Digestion with nitric and perchloric acid; reduction with tin chloride; generation arsine by addition of zinc; reaction with SDDC	Colorimetric photometry	0.5 µg/sample	90–110	Pinto et al. 1976
Urine	Pretreatment with L-cysteine; reduction with potassium iodide/ascorbic acid	Flow injection HGAAS	0.1 µg/L	95–100	Guo et al. 1997
Urine	Drying sample; irradiation with x-rays	XRF	0.2 µg/L ^a	92–108	Clyne et al. 1989
Hair	Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride	HGAAS	0.06 µg/g	93	Curatola et al. 1978
Soft tissue	Digestion with nitric/sulfuric acids; complexation with DDDC in potassium iodide; extraction with chloroform	GFAAS	0.2 ppm	79.8	Mushak et al. 1977
Nails	Wet ashing with nitric/sulfuric acids and hydrogen peroxide; reduction to arsine with sodium borohydride	HGAAS	1.5 µg/g	No data	Agahian et al. 1990
<i>Methods for arsenic speciation:</i>					
Urine	Separation of As ⁺³ , As ⁺⁵ , MMA, and DMA on anion/cation exchange resin column; reduction to respective arsines with sodium borohydride	IEC/HGAAS	0.5 µg/L	93–106	Johnson and Farmer 1989
Urine	Reduction of As ⁺³ , As ⁺⁵ , MMA, and DMA to arsines with sodium borohydride	HGAAS	0.08 µg/L	97–104	Norin and Vahter 1981

7. ANALYTICAL METHODS

Table 7-1. Analytical Methods for Determining Arsenic in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Reduction of As ⁺³ , As ⁺⁵ , MMA, and DMA to arsines; collection in cold trap; selective distillation by slow warming	Atomic emission (direct-current plasma)	≤1 ng for all four species	No data	Braman et al. 1977
Urine	Extraction with chloroform/methanol; column separation with chloroform/methanol; elution on cation exchange column with ammonium hydroxide	HGAAS/TLC/HRMS	0.34 mg/sample ^a	No data	Tam et al. 1982
Blood/tissue	Acidification with hydrochloric acid; complexation with TGM; extraction into cyclohexane; separation on capillary column	GLC/ECD	0.1 mg/mL	No data	Dix et al. 1987
Blood plasma	Separation by HPLC	HPLC/ICP-MS	2.5 ng As/mL	~100	Ebdon et al. 1999
Urine	Separation by anion exchange chromatography; detection by direct coupling of column to ICP-MS	IEC/ICP-MS	<0.45 µg/L for all species	No data	Inoue et al. 1994
Marine biota	Extraction with methanol-water; removal of fats by liquid-liquid extraction or solid-phase cartridge	HPLC/ICP-MS	6–25 ng/mL	94.6 (fish muscle CRM)	Sniatecki 1994
Marine biota	Separation by anion exchange coupled with HPLC; on-line microwave oxidation	HPLC/HGAAS	0.3–0.9 ng	95–110 (recovery of spike in fish tissue)	López-González et al. 1994
Biological samples—Inorganic arsenic	Distill inorganic arsenic as AsCl ₃ using HCl after prereduction of As(V) with KI/HCl	Flow-injection HGAAS	0.045 mg/kg (dry matter)	No data	Øygard et al. 1999

^aLowest reported concentration

CRM = certified reference material; DDDC = diethylammonium diethyldithiocarbamate; DMA = dimethylarsinate; ECD = electron capture detector; GFAAS = graphite furnace atomic absorption spectrometry; GLC = gas-liquid chromatography; HGAAS = hydride generation atomic absorption spectrometry; HRMS = high resolution mass spectrometry; ICP-MS = inductively-coupled plasma mass spectrometry; IEC = ion exchange chromatography; HPLC = high-performance liquid chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; SDDC = silver diethyldithiocarbamate; TGM = thioglycolic acid methylester; TLC = thin layer chromatography; XRF = x-ray fluorescence

7. ANALYTICAL METHODS

Detection limits in blood and urine are about 0.1–1 ppb for most techniques; limits for hair and tissues are usually somewhat higher.

7.2 ENVIRONMENTAL SAMPLES

Arsenic in environmental samples is also measured most often by AAS techniques, with samples prepared by digestion with nitric, sulfuric, and/or perchloric acids (Dabeka and Lacroix 1987; EPA 1983b, 1994a, 1994b; Hershey et al. 1988). Other methods employed include a spectrophotometric technique in which a soluble red complex of arsine and silver diethyldithiocarbamate (SDDC) is formed (APHA 1977; EPA 1983c, 1983d), ICP-AES (EPA 2000c; NIOSH 2003), graphite furnace AAS (EPA 1983b, 1994b; NIOSH 1994b), ICP-MS (EPA 1991, 1994a, 1998j), and x-ray fluorescence (Khan et al. 1989; Nielson and Sanders 1983).

HPLC is currently the most common technique for separation of the species of arsenic found in seafood (Benramdane et al. 1999b; Guerin et al. 1999; Kumaresan and Riyazuddin 2001). An advantage of HPLC over other separation methods (e.g., gas chromatography [GC]) is that the arsenic species do not need to be derivatized prior to separation, avoiding concerns over complete conversion to the derivative for detection.

Since arsenic in air is usually associated with particulate matter, standard methods involve collection of air samples on glass fiber or membrane filters, acid extraction of the filters, arsine generation, and analysis by SDDC spectrophotometry or AAS (APHA 1977; NIOSH 1984).

Methods standardized by the EPA for measuring total arsenic in water and waste water, solid wastes, soil, and sediments include: ICP-MS (EPA 1998j, 1994a, 1991), ICP-AES (EPA 1996d), graphite furnace AAS (EPA 1994b), quartz furnace hydride generation AAS (EPA 1996h), and an electrochemical method using anodic stripping voltammetry (ASV) (EPA 1996e). A modification using cryogenic GC to EPA Method 1632 (HG/AAS) allows the technique to be adopted for the species As(III), As(V), MMA, and DMA to the 0.003 ppb level (EPA 1998l). Similar methods are recommended by APHA for water using AAS/hydride generation (APHA 1989c), AAS/graphite furnace technique (APHA 1989b), ICP (APHA 1989d), or SDDC spectrophotometry (APHA 1989a). The AAS/hydride generation method is generally resistant to matrix and chemical interferences (APHA 1989a). Techniques to compensate for these interferences have been described by EPA (1982b).

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Analysis for arsenic in foods is also most frequently accomplished by AAS techniques (Arenas et al. 1988; Dabeka and Lacroix 1987; Hershey et al. 1988; Tam and Lacroix 1982). Hydride generation is the sample preparation method most often employed (Arenas et al. 1988; Hershey et al. 1988), but interferences must be evaluated and minimized.

Speciation of inorganic arsenic in environmental samples is usually accomplished by chromatographic separation, chelation-extraction or elution of As(III), and then reduction of As(V) with subsequent similar treatment (Butler 1988; López-González et al. 1994; Mok et al. 1988; Rabano et al. 1989).

Methods are also available for quantifying organic arsenicals in environmental media, including arsenobetaine in fish (Beauchemin et al. 1988; Cannon et al. 1983) and other organic forms of arsenic in water, soil, and foods using hyphenated methods of separation and detection (HPLC/ICP-MS, HPLC/HGAAS, IC/ICP-MS) (Andreae 1977; Braman et al. 1977; Comber and Howard 1989; Crecelius 1978; Heitkemper et al. 1994; López-González et al. 1994; Odanaka et al. 1983; Teräsahde et al. 1996).

Methods have been developed for extraction of arsenic species from solid seafood samples that included treatment of the sample with mixtures of organic solvents (alcohols or chloroform) and water to extract the arsenic compounds that are soluble in water or polar organic solvents. These extracts can be subsequently analyzed by HPLC. Enzymatic digestion using trypsin has also been used to extract arsenic compounds from seafood samples (Benramdane et al. 1999b). These extraction techniques are used in place of digestion when speciated data are needed.

A summary of selected methods for analysis of total arsenic and individual inorganic and organic arsenic species in environmental samples is presented in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of arsenic is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of arsenic.

7. ANALYTICAL METHODS

Table 7-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
<i>Methods for total arsenic:</i>					
Air (particulates)	Collection on cellulose ester membrane filter; digestion with nitric acid, sulfuric acid, and perchloric acid	NIOSH Method 7900; HGAAS	0.02 µg/sample	No data	NIOSH 1994a
Air (particulate arsenic and arsenic trioxide vapor)	Collection on Na ₂ CO ₃ -impregnated cellulose ester membrane filter and H ₂ O ₂	NIOSH Method 7901; GFAAS	0.06 µg/sample	No data	NIOSH 1994b
Air	Collection on cellulose ester membrane filter; digestion with nitric acid, sulfuric acid, and perchloric acid	NIOSH Method 7300; ICP-AES	0.140 µg/filter	No data	NIOSH 2003
Water/waste water/solid wastes	Acid digestion	EPA Method 6010C; ICP-AES	35 µg/L	86	EPA 2000c
Water/waste water/solid wastes	Digestion with nitric and hydrochloric acids	EPA Method 200.7; ICP-AES	8 µg/L	106	EPA 1994c
Water/soil/solid waste	Digestion with nitric acid and hydrogen peroxide	EPA Methods 206.2 and 7060A; GFAAS with Ni(NO ₃) ₂ modifier	1 µg/L	85–106	EPA 1983b, 1994b
Water/waste water/solid waste	Digestion with nitric acid	EPA Methods 200.8, 6020 and 6020A ICP-MS	0.4 µg/L	97–114	EPA 1991, 1994a, 1998j
Water/soil/solid waste	Digestion with nitric/sulfuric acid; reduction to As ⁺³ with tin chloride; reduction to arsine with zinc in acid solution	EPA Method 206.3	2 µg/L	85–94	EPA 1983c
Water	Reduction to arsine in acid solution; reaction with SDDC	EPA Method 206.4; SDDC colorimetric spectrophotometry at 510 nm	10 µg/L	100	EPA 1983d
Water	Digestion with 6M HCl; reduction to arsine with sodium borohydride; cold trap and desorption into quartz furnace	EPA Method 1632; HGAAS	2 ng/L	No data	EPA 1998l

7. ANALYTICAL METHODS

Table 7-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Digestion with nitric acid; dry ashing with magnesium oxide; reduction with ascorbic acid; precipitation with APDC in presence of nickel carrier	GFAAS	10 ng	86–107	Dabeka and Lacroix 1987
Food	Digestion with nitric/sulfuric/perchloric acids; reduction to trivalent arsenic with potassium iodide; reduction to arsine with sodium borohydride	HGAAS	0.1 µg/g	98–110	Hershey et al. 1988
Soil, rock, coal	Preparation of pellet	XRF (backscatter)	4 mg/kg	SRM recoveries: 110±4 in soil; 100±1 in rock; 97±18 in coal	Nielson and Sanders 1983
<i>Methods for species of arsenic:</i>					
Air (particulate organo-arsenals)	Collection on PTFE filter	NIOSH Method 5022; ion chromatography/HGAAS	0.2 µg As/sample	No data	NIOSH 1994c
Air (arsine)	Collection on coconut shell charcoal; digestion with nitric acid	NIOSH Method 6001; GFAAS	0.004 µg/sample	No data	NIOSH 1994d
Air particulates (As ⁺³ and As ⁺⁵ only)	Collection on PTFE filter in high volume dichotomous virtual impactor; desorption with ethanolic hydrochloric acid; selective reduction of As ⁺³ to arsine with zinc in acid and reduction of As ⁺⁵ to arsine with sodium tetrahydroborate	HGAAS	1 ng/m ³	95±7 (As ⁺³); 100±8 (As ⁺⁵) on spiked materials	Rabano et al. 1989
Water	Selective elution of As ⁺³ with orthophosphoric acid; elution and conversion of As ⁺⁵ to As ⁺³ with sulfur dioxide	IEC/amperometric detector (detects As ⁺³ only)	0.9 µg/L	95% of converted As ⁺⁵ recovered	Butler 1988
Water/soil	Selective complexation of As ⁺⁵ with ammonium molybdate; extraction with isoamyl alcohol to separate from As ⁺³	Colorimetric spectrometry at 712 nm	No data	No data	Brown and Button 1979

7. ANALYTICAL METHODS

Table 7-2. Analytical Methods for Determining Arsenic in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Selective extraction of As ⁺³ with APDC into chloroform; back extraction with nitric acid; reduction of As ⁺⁵ to As ⁺³ with thiosulfate and extract	NAA	0.01 ppb	No data	Braman et al. 1977
Food (arsenobetaine in fish)	Extraction of arsenobetaine with methanol/chloroform; digestion with nitric acid/magnesium nitrate for remainder of As species	HPLC/ICP-MS	0.3 ng as arsenobetaine	101±4 recovery of arsenobetaine	Beauchemin et al. 1988
Water/waste water/soil (inorganic species)	Acidification or digestion with hydrochloric acid	EPA Method 7063; ASV	0.1 µg/L	96–102	EPA 1996e
Water (As(III), As(V), MMA, and DMA)	Cryogenic GC, Digestion with 6M HCl; reduction to arsine with sodium borohydride; cold trap and desorption into quartz furnace	EPA Method 1632 appendix; HGAAS	3 ng/L	No data	EPA 1998l
Water	Reduction to arsines; cold trap and selectively warm to separate arsine species	AAS	2 ng/L	91–109	Andreae 1977
Water	Reduction of MMA, DMA and inorganic As (control pH to select As ⁺³ or As ⁺⁵) to arsines with sodium tetrahydroborate; cold trap and selectively warm to separate arsine species	HGAAS	0.019–0.061 ng	No data	Comber and Howard 1989
Water/soil	Extraction with sodium bicarbonate; reduction of inorganic arsenic, MMA and DMA to hydrides with sodium borohydride; cold trap arsines in n-heptane	HG-HCT/GC-MID	0.2–0.4 µg/L	97–102	Odanaka et al. 1983

AAS = atomic absorption spectrophotometry; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anodic stripping voltammetry; DMA = dimethylarsinate; EPA = Environmental Protection Agency; GC-MID = gas chromatography-multiple ion detection; GFAAS = graphite furnace atomic absorption spectrometry; HGAAS=hydride generation-atomic absorption spectroscopy; HG-HCT = hydride generation-heptane cold trap; HPLC = high performance liquid chromatography; ICP-AES = inductively coupled plasma-atomic emission spectrometry; ICP-MS = inductively coupled plasma-mass spectrometry; IEC = ion exchange chromatography; MMA = monomethylarsonate; NAA = neutron activation analysis; NIOSH = National Institute of Occupational Safety and Health; PTFE = polytetrafluoroethylene; SDDC = silver diethyldithiocarbamate; SRM = standard reference material; XRF = x-ray fluorescence

7. ANALYTICAL METHODS

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. The most common biomarker for arsenic exposure is analysis of total arsenic in urine (Hughes 2006). Existing methods are sufficiently sensitive to measure background levels of arsenic in various tissues and biological fluids for average persons, and to detect increases as a result of above-average exposure (Agahian et al. 1990; Clyne et al. 1989; Curatola et al. 1978; Foà et al. 1984; Gebel et al. 1998b; Landsberger and Simsons 1987; Mushak et al. 1977; Pinto et al. 1976; Valentine et al. 1979; Versieck et al. 1983). The precision and accuracy of these methods are documented. Methods are also available that can distinguish nontoxic forms of arsenic (arsenobetaine) from inorganic and organic derivatives that are of health concern (Braman et al. 1977; Dix et al. 1987; Johnson and Farmer 1989; Norin and Vahter 1981; Tam et al. 1982). Further efforts to improve accuracy, reduce interferences, and detect multiple species using a single analysis would be valuable. Arsenic is believed to act by inhibition of numerous cellular and molecular processes. However, these effects are not specific to arsenic, and most can only be measured in tissue extracts.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Arsenic is ubiquitous in the environment. It is found in air, water, soil, sediments, and food in several inorganic and organic forms. Analytical methods exist for the analysis of arsenic species in all of these environmental media, and these methods have the sensitivity to measure background levels and to detect elevated concentrations due to emissions from sources such as smelters, chemical plants, or hazardous waste sites (APHA 1977, 1989c; EPA 1982b, 1983b, 1983c, 1983d, 1991, 1994b, 1994c, 1996f, 1996h, 1998j, 2000c; NIOSH 1994a, 1994b, 2003). However, further research to reduce chemical and matrix interferences may improve the speed and accuracy of the analyses.

Le et al. (2004) pointed out that there is a need for the development of certified reference materials (CRMs) for speciation analysis. A shortcoming of many CRMs is that they are only certified for the total concentration of arsenic, and only limited information is available on the identity and concentrations of specific arsenic species in some CRMs.

7. ANALYTICAL METHODS

Continued improvement of the methods for determination of the particular species of arsenic, rather than just the total arsenic concentration, present in foods, especially seafood, is needed since different arsenic species poses different hazards to individuals consuming these foods.

7.3.2 Ongoing Studies

The information in Table 7-3 was found as a result of a search of the Federal Research in Progress database (FEDRIP 2006).

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Table 7-3. Ongoing Studies on Analytical Methods for Arsenic in Environmental and Biological Samples

Investigator	Affiliation	Research description	Sponsor
Styblo, M	University of North Carolina Chapel Hill, Chapel Hill, North Carolina	Optimized hydride generation system for arsenic analysis	Fogarty International Center
Dietze, WT	Tracedetect, Inc., Seattle, Washington	A continuous monitor for arsenic in drinking water	NIEHS
Dasgupta, PK	Texas Tech University, Department of Chemistry, Lubbock, Texas	A green fieldable analyzer for arsenic	NSF

NIEHS = National Institute of Environmental Health Sciences; NSF = National Science Foundation

Source: FEDRIP 2006

8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines pertaining to arsenic and its metabolites in air, water, and other media are summarized in Table 8-1.

ATSDR has not derived inhalation MRLs or an intermediate-duration oral MRL for inorganic arsenic, or any MRLs for organic arsenic, due to lack of suitable data.

ATSDR has derived an acute-duration oral MRL for inorganic arsenic of 0.005 mg As/kg/day based on a LOAEL of 0.05 mg As/kg/day for gastrointestinal effects and facial edema in Japanese people who ingested arsenic-contaminated soy sauce for 2–3 weeks (Mizuta et al. 1956). An uncertainty factor of 10 (10 for use of a LOAEL and 1 for human variability) was applied.

ATSDR has derived a chronic-duration oral MRL of 0.0003 mg/kg/day for inorganic arsenic based on a NOAEL of 0.0008 mg As/kg/day for dermal effects in a Taiwanese farming population exposed to arsenic in well water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 (for human variability) was applied.

EPA (IRIS 2007) has derived a chronic oral reference dose (RfD) of 0.0003 mg As/kg/day for inorganic arsenic, based on a NOAEL of 0.0008 mg As/kg/day for dermal effects and possible vascular complications in a Taiwanese farming population exposed to arsenic in well water (Tseng 1977; Tseng et al. 1968). An uncertainty factor of 3 (to account for the lack of reproductive data and uncertainty in whether the NOAEL accounts for all sensitive individuals) was applied. No reference concentration (RfC) for chronic inhalation exposures to arsenic was reported. EPA is currently revising the assessment for inorganic arsenic.

The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen (NTP 2005). The EPA has determined that inorganic arsenic is a human carcinogen and has assigned it the cancer classification, Group A (IRIS 2007). EPA's quantitative estimates of carcinogenic risk from oral exposures include a cancer slope factor of 1.5 mg/kg/day and a drinking water unit risk of 5×10^{-5} µg/L. The inhalation unit risk for cancer is 0.0043 µg/m³ (IRIS 2007).

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification for arsenic and arsenic compounds	Group 1 ^a	IARC 2004
WHO	Air quality guidelines	1.5x10 ⁻³ unit risk ^b	WHO 2000
	Drinking water quality guidelines for arsenic	0.01 mg/L ^c	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (TWA) for arsenic and inorganic compounds	0.01 mg/m ³	ACGIH 2004
EPA	Hazardous air pollutant (arsenic and inorganic compounds, including arsine)	Yes	EPA 2004b 42 USC 7412
NIOSH	REL (15-minute ceiling limit) for arsenic and inorganic compounds ^d	0.002 mg/m ³	NIOSH 2005a
	IDLH for arsenic and inorganic compounds ^d	5 mg/m ³	
OSHA	PEL (8-hour TWA) for general industry for arsenic organic compounds	0.5 mg/m ³	OSHA 2005d 29 CFR 1910.1000
	PEL (8-hour TWA) for general industry for arsenic inorganic compounds	10 µg/m ³	OSHA 2005c 29 CFR 1910.1018
	PEL (8-hour TWA) for construction industry for arsenic organic compounds	0.5 mg/m ³	OSHA 2005b 29 CFR 1926.55
	PEL (8-hour TWA) for shipyard industry for arsenic organic compounds	0.5 mg/m ³	OSHA 2005a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2005d 40 CFR 116.4
	Arsenic pentoxide, arsenic trioxide, calcium arsenate, and sodium arsenite		
	Drinking water standards and health advisories for arsenic		EPA 2004a
	DWEL	0.01 mg/L	
	National primary drinking water standards for arsenic		EPA 2002a
	MCLG	Zero	
	MCL	0.01 mg/L ^e	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act		EPA 2005e 40 CFR 117.3
	Arsenic pentoxide, arsenic trioxide, calcium arsenate, sodium arsenite	1 pound	

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
EPA	Water quality criteria for human health consumption of arsenic:		EPA 2002b
	Water + Organism	0.018 µg/L ^f	
	Organism only	0.14 µg/L ^f	
c. Food			
EPA	Tolerances for residues		
	Dimethylarsinic acid		EPA 2005i
	Cotton (undelinted seed)	2.8 ppm	40 CFR 180.311
	Methanearsonic acid		EPA 2005j
	Cotton (undelinted seed)	0.7 ppm	40 CFR 180.289
	Cotton, hulls	0.9 ppm	
	Fruit, citrus	0.35 ppm	
FDA	Bottled drinking water	0.01 mg/L	FDA 2005 21 CFR 165.110
USDA	Nonsynthetic substances prohibited for use in organic crop production	Arsenic	USDA 2004 7 CFR 205.602
d. Other			
ACGIH	Carcinogenicity classification for arsenic and arsenic compounds	A1 ^g	ACGIH 2004
	Biological exposure indices for inorganic arsenic plus methylated metabolites in urine at the end of the workweek	35 µg As/L	
EPA	Carcinogenicity classification	Group A ⁱ	IRIS 2007
	Oral slope factor	1.5 per mg/kg/day	
	Inhalation unit risk	4.3x10 ⁻³ per µg/m ³	
	RfC	No data	
	RfD	3x10 ⁻⁴ mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance		EPA 2005f
	Reportable quantity		40 CFR 302.4
	Arsenic	Not applicable ^j	
	Arsenic acid, arsenic pentoxide, arsenic trioxide, calcium arsenate, dimethylarsinic acid, and sodium arsenite	1 pound	
	Effective date of toxic chemical release reporting for arsenic	01/01/87	EPA 2005h 40 CFR 372.65

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Arsenic and Arsenic Compounds

Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
EPA	Superfund, emergency planning, and community right-to-know		
	Extremely hazardous substances		EPA 2005g
	Reportable quantity		40 CFR 355, Appendix A
	Arsenic pentoxide, calcium arsenate, and sodium arsenite	1 pound	
	Threshold planning quantities		
	Arsenic pentoxide	100/10,000 pounds	
	Calcium arsenate and sodium arsenite	500/10,000 pounds	
NTP	Carcinogenicity classification	Known human carcinogen	NTP 2005

^aGroup 1: carcinogenic to humans^bCancer risk estimates for lifetime exposure to a concentration of 1 µg/m³.^cProvisional guideline value: as there is evidence of a hazard, but the available information on health effects is limited.^dNIOSH potential occupational carcinogen^eMCL will become effective on 01/23/06.^fThis criterion is based on carcinogenicity of 10⁻⁶ risk.^gA1: confirmed human carcinogen^hA3: confirmed animal carcinogen with unknown relevance to humansⁱGroup A: known human carcinogen^jIndicates that no reportable quantity is being assigned to the generic or broad class.

ACGIH = American Conference of Governmental Industrial Hygienists; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NAS/NRC = National Academy of Sciences/National Research Council; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; USDA = United States Department of Agriculture; WHO = World Health Organization

8. REGULATIONS AND ADVISORIES

EPA is currently revising the assessment for inorganic arsenic. The International Agency for Research on Cancer (IARC) cites sufficient evidence of a relationship between exposure to arsenic and human cancer. IARC classification of arsenic is Group 1 (IARC 2004). The American Conference of Governmental Industrial Hygienists (ACGIH) classifies arsenic (elemental and inorganic compound) as a confirmed human carcinogen, cancer category A1 (ACGIH 2004).

ATSDR has derived an intermediate-duration oral MRL of 0.1 mg MMA/kg/day for MMA based on a BMDL₁₀ of 12.38 mg MMA/kg/day for diarrhea observed in rats exposed to MMA in the diet for 13 weeks (Arnold et al. 2003) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.01 mg MMA/kg/day for MMA based on a BMDL₁₀ of 1.09 mg MMA/kg/day for increased incidence of progressive nephropathy in male mice exposed to MMA in the diet for 2 years (Arnold et al. 2003) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ATSDR has derived a chronic-duration oral MRL of 0.02 mg DMA/kg/day for DMA based on a BMDL₁₀ of 1.80 mg DMA/kg/day for increased vacuolization of the urothelium in the urinary bladder of female mice exposed to DMA in the diet for 2 years (Arnold et al. 2006) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

EPA has not derived RfD values for organic arsenicals (IRIS 2007).

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

10. GLOSSARY

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

10. GLOSSARY

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

10. GLOSSARY

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1^* —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

10. GLOSSARY

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose₍₅₀₎ (TD₅₀)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

10. GLOSSARY

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Inorganic Arsenic
CAS Number: 7440-38-2
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: ☐ Inhalation ☒ Oral
Duration: ☒ Acute ☐ Intermediate ☐ Chronic
Graph Key: 29
Species: Human

Minimal Risk Level: 0.005 ☒ mg/kg/day ☐ ppm

Reference: Mizuta N, Mizuta M, Ito F, et al. 1956. An outbreak of acute arsenic poisoning caused by arsenic-contaminated soy-sauce (shōyu): A clinical report of 220 cases. Bull Yamaguchi Med Sch 4(2-3):131-149.

Experimental design: Mizuta et al. (1956) summarized findings from 220 poisoning cases associated with an episode of arsenic contamination of soy sauce in Japan. The soy sauce was contaminated with approximately 0.1 mg As/mL, probably as calcium arsenate. Arsenic intake in the cases was estimated by the researchers to be 3 mg/day (0.05 mg/kg/day, assuming 55 kg average body weight for this Asian population). Duration of exposure was 2–3 weeks in most cases. Clinical symptoms were recorded. Seventy patients were examined ophthalmologically. Laboratory tests were performed on some patients and included hematology, urinalysis, fecal exam, occult blood in gastric and duodenal juice, biochemical examination of blood, liver function tests, electrocardiograph, and liver biopsy.

Effects noted in study and corresponding doses: The primary symptoms were edema of the face, and gastrointestinal and upper respiratory symptoms initially, followed in some patients by skin lesions and neuropathy. Other effects included mild anemia and leukopenia, mild degenerative liver lesions and hepatic dysfunction, abnormal electrocardiogram, and ocular lesions. For derivation of the acute oral MRL, facial edema and gastrointestinal symptoms (nausea, vomiting, diarrhea), which were characteristic of the initial poisoning and then subsided, were considered to be the critical effects.

Dose and end point used for MRL derivation: 0.05 mg As/kg/day

☐ NOAEL ☒ LOAEL

Uncertainty factors used in MRL derivation:

☐ 1 ☐ 3 ☒ 10 (for use of a LOAEL)
☐ 1 ☐ 3 ☐ 10 (for extrapolation from animals to humans)
☒ 1 ☐ 3 ☐ 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

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Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by the case of a man and wife in upstate New York who experienced gastrointestinal symptoms (nausea, diarrhea, abdominal cramps) starting almost immediately after beginning intermittent consumption of arsenic-tainted drinking water at an estimated dose of 0.05 mg As/kg/day (Franzblau and Lilis 1989). Gastrointestinal symptoms have been widely reported in other acute arsenic poisoning reports as well, although in some cases, the doses were higher and effects were severe, and in other cases, dose information was not available. The UF of 1 for intrahuman variability reflects the fact that the database includes persons of various ethnicities and age groups, including infants.

Agency Contact (Chemical Manager): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Inorganic Arsenic
 CAS Number: 7440-38-2
 Date: August 2007
 Profile Status: Post-Public Comment, Final Draft
 Route: ☐ Inhalation ☒ Oral
 Duration: ☐ Acute ☐ Intermediate ☒ Chronic
 Graph Key: 134
 Species: Human

Minimal Risk Level: 0.0003 ☒ mg/kg/day ☐ ppm

References: Tseng, WP, Chu HM, How SW, et al. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J Natl Cancer Inst 40:453-463.

Tseng, WP. 1977. Effects and dose-response relationships of cancer and Blackfoot disease with arsenic. Environ Health Perspect 19:109-119.

Experimental design: Tseng et al. (1968) and Tseng (1977) investigated the incidence of Blackfoot disease and dermal lesions (hyperkeratosis and hyperpigmentation) in a large number of poor farmers (both male and female) exposed to high levels of arsenic in well water in Taiwan. A control group consisting of 17,000 people was identified. The authors stated that the incidence of dermal lesions increased with dose, but individual doses were not provided. However, incidence data were provided based on stratification of the exposed population into low (<300 µg/L), medium (300–600 µg/L), or high (>600 µg/L) exposure levels. Doses were calculated from group mean arsenic concentrations in well water, assuming the intake parameters described by Abernathy et al. (1989). Accordingly, the control, low-, medium-, and high-exposure levels correspond to doses of 0.0008, 0.014, 0.038, and 0.065 mg As/kg/day, respectively. The NOAEL identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was <20 years of age and the incidence of skin lesions increased as a function of age, and because the estimates of water intake and dietary arsenic intake are highly uncertain. Schoof et al. (1998) estimated that dietary intakes of arsenic from rice and yams may have been 15–211 µg/day (mean 61 µg/day), based on arsenic analyses of foods collected in Taiwan in 1993–1995. Use of the 50 µg/day estimate would result in an approximate doubling of the NOAEL (0.0016 mg/kg/day).

Effects noted in study and corresponding doses: A clear dose-response relationship was observed for characteristic skin lesions:

0.0008 mg As/kg/day	= control group (NOAEL)
0.014 mg As/kg/day	= hyperpigmentation and keratosis of the skin (less serious LOAEL)
0.038–0.065 mg As/kg/day	= increased incidence of dermal lesions

Dose and end point used for MRL derivation: 0.0008 mg As/kg/day

☒ NOAEL ☐ LOAEL

Uncertainty factors used in MRL derivation:

☐ 1 ☐ 3 ☐ 10 (for use of a LOAEL)
☐ 1 ☐ 3 ☐ 10 (for extrapolation from animals to humans)

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[] 1 [x] 3 [] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? The arithmetic mean concentration of arsenic in well water for the control group (0.009 mg/L) was converted to a NOAEL of 0.0008 mg As/kg/day as described below:

$$\left[\left(\frac{0.009 \text{ mg}}{\text{L}} \times \frac{4.5 \text{ L}}{\text{day}} \right) + \frac{0.002 \text{ mg}}{\text{day}} \right] \div 55 \text{ kg} = 0.0008 \text{ mg As / kg / day}$$

This NOAEL conversion assumed a water intake of 4.5 L/day and a body weight of 55 kg, and includes an estimation of arsenic intake of 0.002 mg As/kg/day from food. These assumptions are detailed in Abernathy et al. (1989). This approach to deriving a chronic oral MRL is identical to EPA's approach to deriving a chronic oral RfD.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The MRL is supported by a number of well conducted epidemiological studies that identify reliable NOAELs and LOAELs for dermal effects. EPA (1981b) identified a NOAEL of 0.006–0.007 mg As/kg/day for dermal lesions in several small populations in Utah. Harrington et al. (1978) identified a NOAEL of 0.003 mg As/kg/day for dermal effects in a small population in Alaska. Guha Mazumder et al. (1988) identified a NOAEL of 0.009 mg As/kg/day and a LOAEL of 0.006 mg As/kg/day for pigmentation changes and hyperkeratosis in a small population in India. Haque et al. (2003) identified a LOAEL of 0.0043 mg As/kg/day for hyperpigmentation and hyperkeratosis in a case-control study in India. Cebrian et al. (1983) identified a NOAEL of 0.0004 mg As/kg/day and a LOAEL of 0.022 mg As/kg/day in two regions in Mexico. Borgoño and Greiber (1972) and Zaldívar (1974) identified a LOAEL of 0.02 mg As/kg/day for abnormal skin pigmentation in patients in Chile, and Borgoño et al. (1980) identified a LOAEL of 0.01 mg As/kg/day for the same effect in school children in Chile. Valentine et al. (1985) reported a NOAEL of 0.02 mg As/kg/day for dermal effects in several small populations in California. Collectively, these studies indicate that the threshold dose for hyperpigmentation and hyperkeratosis is approximately 0.002 mg As/kg/day.

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Monomethylarsonic acid (MMA)
CAS Number: 124-58-3
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☒ Intermediate ☐ Chronic
Graph Key: 12
Species: Rat

Minimal Risk Level: 0.1 ☒ mg MMA/kg/day ☐ ppm

References: Arnold LL, Eldan M, van Gemert M, et al. 2003. Chronic studies evaluating the carcinogenicity of monomethylarsonic acid in rats and mice. Toxicology 190:197-219.

Crown S, Nyska A, Waner T. 1990. Methanearsonic acid: Combined chronic feeding and oncogenicity study in the rat. Conducted by Life Science Research Israel Ltd., Ness Ziona Israel. Submitted to EPA Office of Pesticide Programs (MRID 41669001).

Experimental design: Groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 50, 400, or 1,300 ppm MMA in the diet for 104 weeks. Using the average doses for weeks 1–50 reported in an unpublished version of this study (Crown et al. 1990), doses of 0, 3.5, 30.2, and 106.9 mg MMA/kg/day and 0, 4.2, 35.9, and 123.3 mg MMA/kg/day were calculated for males and females, respectively. Body weights, food consumption, and water intake were monitored regularly. Blood was taken at 3, 6, and 12 months for clinical chemistry measurements, and urine samples were collected at the same interval.

Effects noted in study and corresponding doses: Mortality was increased in high-dose males and females during the first 52 weeks of the study. Body weights were decreased in the mid- and high-dose groups of both sexes; however, at 51 weeks, only the body weight for the high-dose males was <10% of the control weight (14.5%). Food and water consumption was increased in the mid- and high-dose groups. Diarrhea was observed in 100% of the high-dose males and females and in 16.7 and 40% of the mid-dose males and females during the first 52 weeks of exposure. Diarrhea first occurred after 3 weeks of exposure to the high dose and 4 weeks of exposure to the mid-dose group; the severity of the diarrhea was dose-related. The gastrointestinal system was the primary target in animals dying early; numerous macroscopic and histological alterations were observed.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-1) for diarrhea in male and female rats exposed to MMA in the diet for 1–52 weeks (incidence data reported in Crown et al. 1990) was conducted. All available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) were fit to the data. Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all models, with the exception of the quantal linear model for male incidence data and the quantal linear model for female incidence data, provided an adequate fit ($X^2 p > 0.1$) (Table A-2). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC). As assessed by AIC, the gamma model for the males (Figure A-1) and the 2-degree polynomial multi-stage model for the females (Figure A-2) provide the best fit to the data. The predicted BMD₁₀ and BMDL₁₀ are 28.25 mg MMA/kg/day and 22.99 mg MMA/kg/day for the male rat incidence data and 16.17 mg MMA/kg/day, and 12.38 mg MMA/kg/day for the female rat incidence data.

Table A-1. Incidences of Diarrhea in Rats Exposed to MMA in the Diet for 1–52 Weeks

Dietary concentration (ppm)	Dose (mg MMA/kg/day)	Incidence
Male rats		
0	0	2/60
50	3.5	0/60
400	30.2	10/60
1,300	106.9	60/60
Female rats		
0	0	0/60
50	4.2	0/60
400	35.9	24/60
1,300	123.3	60/60

Sources: Arnold et al. 2003; Crown et al. 1990

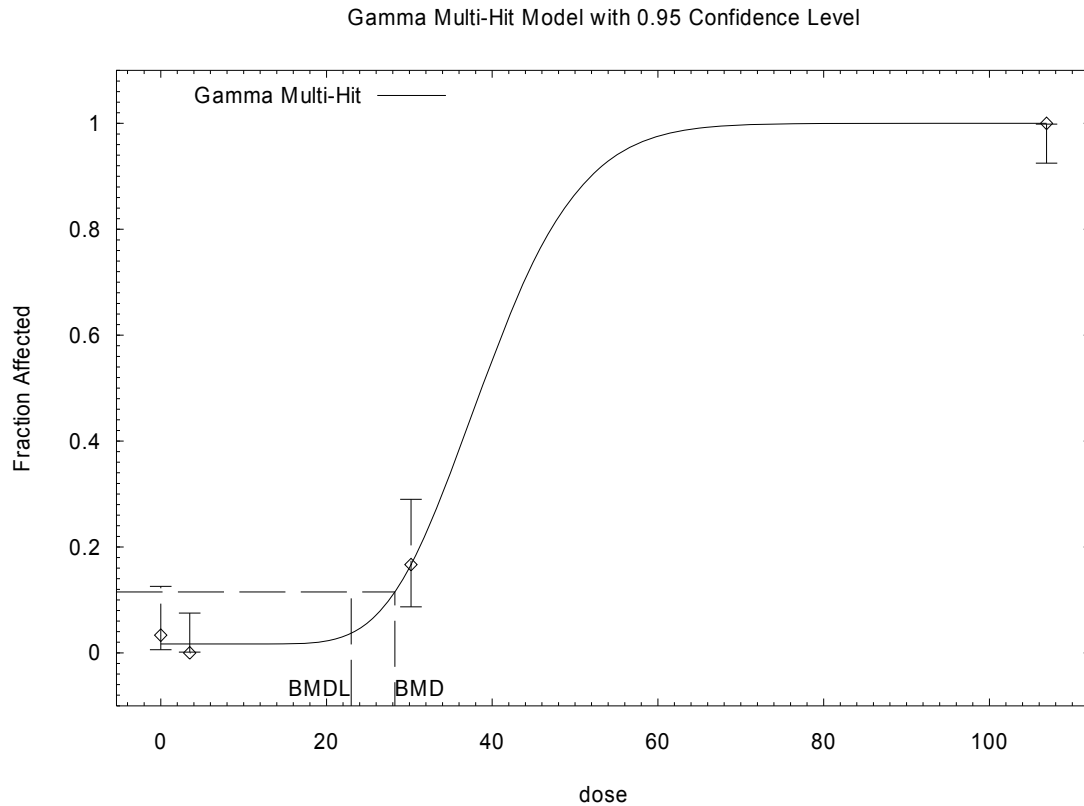
Table A-2. Modeling Predictions for the Incidence of Diarrhea in Rats Exposed to MMA in the Diet for 1–52 Weeks

Model	BMD ₁₀ (mg MMA/kg/day)	BMDL ₁₀ (mg MMA/kg/day)	χ^2 p-value	AIC
Male rats				
Gamma^a	28.25	22.99	0.36	78.41
Logistic	24.60	20.19	0.16	79.59
Log-logistic ^b	29.32	24.73	0.15	80.41
Multi-stage ^c	25.74	19.90	0.35	78.51
Probit	23.11	18.67	0.11	80.02
Log-probit ^b	28.79	24.47	0.15	80.41
Quantal linear	6.317	5.079	0.00	123.06
Weibull ^a	27.99	20.66	0.15	80.41
Female rats				
Gamma ^a	26.81	15.18	1.00	84.76
Logistic	32.85	21.49	1.00	84.76
Log-logistic ^b	31.97	20.16	1.00	84.76
Multi-stage^c	16.17	12.38	0.90	83.88
Probit	29.89	19.11	1.00	84.76
Log-probit ^b	28.95	18.87	1.00	84.76
Quantal linear	5.33	4.33	0.00	106.52
Weibull ^a	27.83	13.58	1.00	84.76

Sources: Arnold et al. 2003; Crown et al. 1990

^aRestrict power ≥ 1 .^bSlope restricted to >1 .^cRestrict betas ≥ 0 ; lowest degree polynomial with an adequate fit is reported; degree of polynomial=3.^dRestrict betas ≥ 0 ; lowest degree polynomial with an adequate fit is reported; degree of polynomial=2.

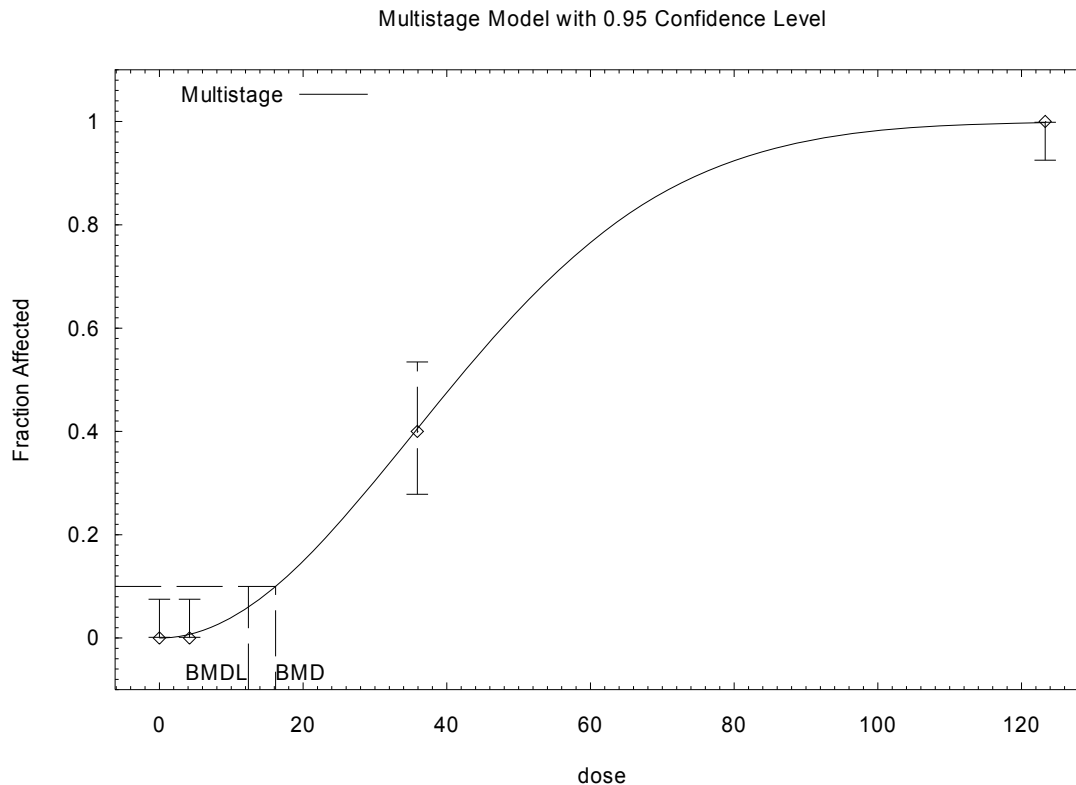
Figure A-1. Predicted and Observed Incidence of Diarrhea in Male Rats Exposed to MMA in the Diet for 1–52 Weeks*



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*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg MMA/kg/day.

Figure A-2. Predicted and Observed Incidence of Diarrhea in Female Rats Exposed to MMA in the Diet for 52 Weeks*



*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg MMA/kg/day.

The BMDL₁₀ of 12.38 mg MMA/kg/day for female rats was selected as the point of departure for deriving the intermediate-duration oral MRL because it was lower than the BMDL₁₀ (22.99 mg MMA/kg/day) calculated using the male incidence data.

☐ NOAEL ☐ LOAEL ☒ BMDL

Uncertainty factors used in MRL derivation: 100

- ☐ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses calculated using the average of the achieved doses for weeks 1–50 reported in Crown et al. (1990): 0, 3.5, 30.2, and 106.9 mg MMA/kg/day for males and 0, 4.2, 35.9, and 123.3 mg MMA/kg/day for females.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

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Other additional studies or pertinent information that lend support to this MRL: Increases in the incidence of diarrhea has also been observed in dogs administered via capsule 2 mg MMA/kg/day for 52 weeks (Waner and Nyska 1988); the increased incidence of diarrhea started during weeks 25–28. At 35 mg MMA/kg/day, vomiting was also observed in the dogs. Diarrhea has also been observed in rats and mice exposed to MMA for 2 years (Arnold et al. 2003); the LOAELs are 25.7 and 67.1 mg MMA/kg/day, respectively.

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Monomethylarsonic acid (MMA)
CAS Number: 124-58-3
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Graph Key: 21
Species: Mouse

Minimal Risk Level: 0.01 ☒ mg MMA/kg/day ☐ ppm

References: Arnold LL, Eldan M, van Gemert M, et al. 2003. Chronic studies evaluating the carcinogenicity of monomethylarsonic acid in rats and mice. Toxicology 190:197-219.

Gur E, Piraic H, Waner T. 1991. Methanearsonic acid: Combined oncogenicity study in the mouse. Conducted by Life Science Research Israel Ltd., Ness Ziona Israel. Submitted to EPA Office of Pesticide Programs (MRID 42173201).

Experimental design: Groups of 52 male and 52 female B6C3F₁ mice were exposed to 0, 10, 50, 200, or 400 ppm of MMA in the diet for 104 weeks. The reported MMA doses were 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day (males) and 0, 1.4, 7.0, 31.2, and 101 mg MMA/kg/day (females). Body weights, food consumption, and water intake were monitored regularly. Blood was taken at 3, 6, 12, 18, and 24 months for white cell counts. At sacrifice, complete necropsies were performed, including histological examination of at least 13 organs.

Effects noted in study and corresponding doses: No treatment-related increases in mortality were observed. Significant decreases in body weights were observed in males and females exposed to 32.2 or 48.5 mg As/kg/day, respectively; at week 104, the males weighed 17% less than controls and females weighed 23% less. Food consumption was increased in females exposed to 101 mg MMA/kg/day, and water consumption was increased in 67.1 mg MMA/kg/day males and 31.2 and 101 mg MMA/kg/day females. Loose and mucoid feces were noted in mice exposed to 67.1/101 mg MMA/kg/day. No changes were seen in white cell counts of either sex. Small decreases in the weights of heart, spleen, kidney, and liver were seen in some animals, but the decreases were not statistically significant. Squamous metaplasia of the cecum, colon, and rectum was observed at 67.1/101 mg MMA/kg/day. The incidences of metaplasia in the cecum, colon, and rectum were 29/49, 14/49, and 39/49 in males and 38/52, 17/52, and 42/52 in females; metaplasia was not observed in other groups of male or female mice. An increased incidence of progressive glomerulonephropathy (incidence of 25/52, 27/52, 38/52, 39/52, and 46/52 in the 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day) was observed in males; the incidence was significantly higher (Fisher Exact Test) than controls at ≥ 6.0 mg MMA/kg/day. Significant increases in the incidence of nephrocalcinosis was observed in the males at 24.9 and 67.1 mg MMA/kg/day (Fisher Exact Test) (incidence of 25/52, 30/52, 30/52, 45/52, 45/51 and 0/52, 1/52, 1/52, 2/52, and 5/52 in males and females, respectively). The investigators noted that the kidney lesions were consistent with the normal spectrum of spontaneous renal lesions and there was no difference in character or severity of the lesions between groups. A reduction in the incidence of cortical focal hyperplasia in the adrenal gland of male mice exposed to 67.1 mg MMA/kg/day was possibly related to MMA exposure; the toxicological significance of this effect is not known.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-3) for progressive glomerulonephropathy in male mice exposed to MMA in the diet for 2 years

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(incidence data reported in Gur et al. 1991) was conducted. All available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) were fit to the data. Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all models, with the exception of the log-probit model, provided an adequate fit ($X^2 p > 0.1$) (Table A-4). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC). As assessed by AIC, the log-logistic model (Figure A-3) provided the best fit to the data. The predicted BMD₁₀ and BMDL₁₀ for the incidence data are 2.09 and 1.09 mg MMA/kg/day.

Table A-3. Incidence of Progressive Glomerulonephropathy in Male Mice Exposed to MMA in the Diet for 2 Years

Dietary Concentration (ppm)	Dose (mg MMA/kg/day)	Incidence
0	0	25/52
10	1.2	27/52
50	6.0	38/52
200	24.9	39/52
400	67.1	46/52

Sources: Arnold et al. 2003; Gur et al. 1991

Table A-4. Modeling Predictions for the Incidence of Progressive Glomerulonephropathy in Male Mice Exposed to MMA in the Diet for 2 Years

Model	BMD ₁₀ (mg MMA/kg/day)	BMDL ₁₀ (mg MMA/kg/day)	x^2 <i>p</i> -value	AIC
Gamma ^a	4.60	3.15	0.18	309.33
Logistic	6.09	4.45	0.13	310.15
Log-logistic^b	2.09	1.09	0.38	307.47
Multi-stage ^c	4.60	3.15	0.18	309.33
Probit	6.62	5.00	0.11	310.43
Log-probit ^b	8.54	5.50	0.08	311.11
Quantal linear	4.60	3.15	0.18	309.33
Weibull ^a	4.60	3.15	0.18	309.33

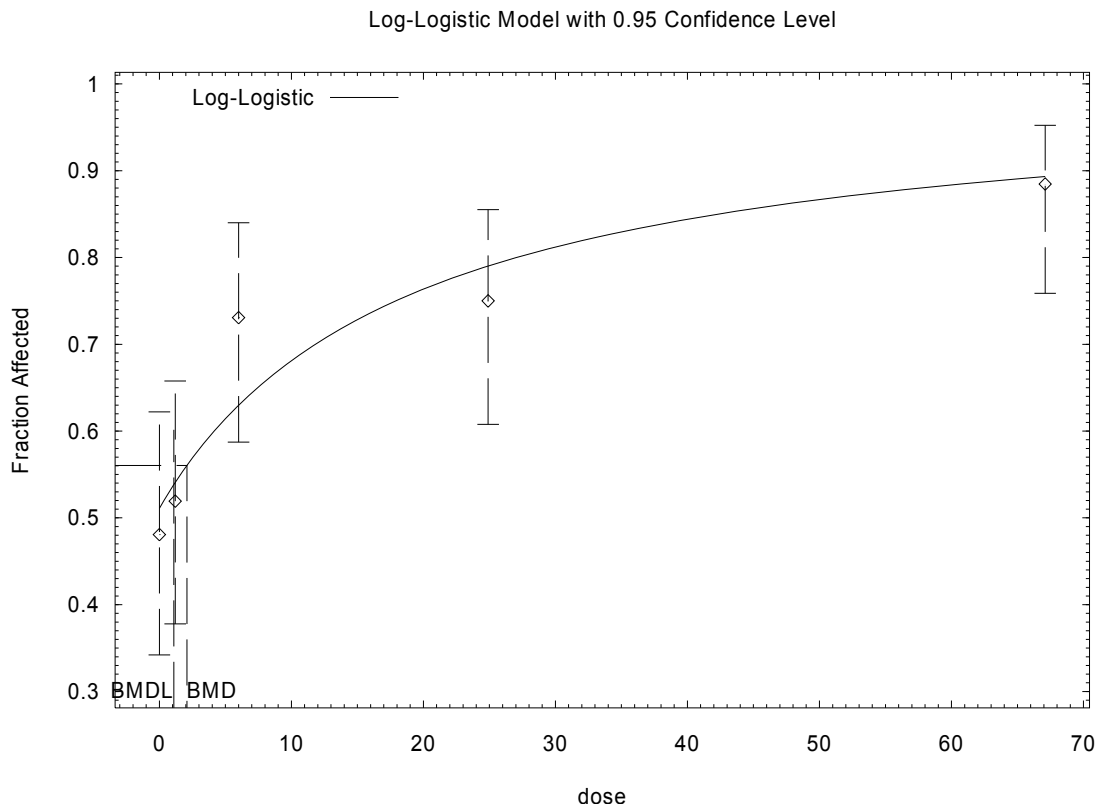
Sources: Arnold et al. 2003; Gur et al. 1991

^aRestrict power ≥ 1 .

^bSlope restricted to > 1 .

^cRestrict betas ≥ 0 ; lowest degree polynomial with an adequate fit is reported; degree of polynomial=1.

Figure A-3. Predicted and Observed Incidence of Progressive Glomerulonephropathy in Male Mice Exposed to MMA*



10:57 08/03 2007

*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg MMA/kg/day.

The BMDL₁₀ of 1.09 mg MMA/kg/day for male mice was selected as the point of departure for deriving the chronic-duration oral MRL.

☐ NOAEL ☐ LOAEL ☒ BMDL

Uncertainty factors used in MRL derivation: 100

- ☐ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses calculated using the average of the achieved doses reported in Gur et al. (1991): 0, 1.2, 6.0, 24.9, and 67.1 mg MMA/kg/day for males and 0, 1.4, 7.0, 31.2, and 101 mg MMA/kg/day for females.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

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Other additional studies or pertinent information that lend support to this MRL: An exacerbation of chronic progressive nephropathy (an increase in the severity of the nephropathy) has also been observed in rats exposed to ≥ 33.9 mg MMA/kg/day for 2 years (Arnold et al. 2003).

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Dimethylarsinic acid (DMA)
CAS Number: 75-60-5
Date: August 2007
Profile Status: Post-Public Comment, Final Draft
Route: ☐ Inhalation ☒ Oral
Duration: ☐ Acute ☐ Intermediate ☒ Chronic
Graph Key: 35
Species: Mouse

Minimal Risk Level: 0.02 ☒ mg DMA/kg/day ☐ ppm

References: Arnold LL, Eldan M, Nyska A, et al. 2006. Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in F344 rats and B6C3F₁ mice. Toxicology 223:82-100.

Gur E, Nyska A, Pirak M, et al. 1989b. Cacodylic acid: Oncogenicity study in the mouse. Conducted by Life Science Research Israel Ltd., Ness Ziona Israel. Submitted to EPA Office of Pesticide Programs (MRID 41914601).

Experimental design: Groups of 56 male and 56 female B6C3F₁ mice were exposed to 0, 8, 40, 200, or 500 ppm DMA in the diet for 2 years. The investigators reported the dietary doses were equivalent to approximately 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day. The following parameters were used to assess toxicity: clinical observations, body weight, food consumption, water consumption, differential leukocyte levels measured at 12, 18, and 24 months in mice in the control and 94 mg DMA/kg/day groups, organ weights (brain, kidneys, liver, and testes), and histopathological examination of major tissues and organs.

Effects noted in study and corresponding doses: No deaths were observed. Decreases in body weight gain were observed in the male mice exposed to 94 mg DMA/kg/day; the difference was <10% and was not considered adverse. An increase in water consumption was observed in males exposed to 94 mg DMA/kg/day during weeks 60–96. No treatment-related clinical signs were observed. In the female mice exposed to 94 mg DMA/kg/day, a statistically significant decrease in lymphocytes and increase in monocytes were observed at 24 months. Treatment related nonneoplastic alterations were observed in the urinary bladder and kidneys. In the urinary bladder, increases in the vacuolization of the superficial cells of the urothelium were observed in males exposed to 37 or 94 mg DMA/kg/day (0/44, 1/50, 0/50, 36/45, 48/48) and in females exposed to 7.8, 37, or 94 mg DMA/kg/day (1/45, 1/48, 26/43, 47/47, 43/43); incidence data reported in Gur et al. (1989b). An increased incidence of progressive glomerulonephropathy was observed in males at 37 mg DMA/kg/day (16/44, 22/50, 17/50, 34/45, 30/50) and an increased incidence of nephrocalcinosis was also observed in male mice at 94 mg DMA/kg/day (30/44, 25/50, 27/50, 29/50, 45/50). Neoplastic alterations were limited to an increased incidence of fibrosarcoma of the skin in females exposed to 94 mg DMA/kg/day; the incidence was 3/56, 0/55, 1/56, 1/56, and 6/56 in the 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day groups, respectively; however it was concluded that this lesion was not related to DMA exposure.

Dose and end point used for MRL derivation: Benchmark dose analysis of the dose-response data (Table A-5) for vacuolization of the urothelium in the urinary bladder in female mice exposed to DMA in the diet for 2 years (incidence data reported in Gur et al. 1989b) was conducted. All available dichotomous models in EPA's Benchmark Dose Software (version 1.4.1) were fit to the data. Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all models, with the exception of the quantal linear model, provided an adequate fit ($X^2 p > 0.1$) (Table A-6). Comparing across models, a better fit is generally indicated by a lower AIC. The AIC

values were similar for the logistic, multi-stage, and probit models; of these three models, the multi-stage had the lowest BMD₁₀ and was selected for the analysis (see Figure A-4). The predicted BMD₁₀ and BMDL₁₀ for the incidence data are 2.68 and 1.80 mg DMA/kg/day.

Table A-5. Incidence of Vacuolization of Urothelium in Urinary Bladder of Female Mice Exposed to DMA in the Diet for 2 Years

Dietary concentration (ppm)	Dose (mg DMA/kg/day)	Incidence
0	0	1/45
8	1.3	1/48
40	7.8	26/43
200	37	47/47
500	94	43/43

Sources: Arnold et al. 2006; Gur et al. 1989b

Table A-6. Modeling Predictions for the Incidence of Vacuolization in of Urothelium in Urinary Bladder of Female Mice Exposed to DMA in the Diet for 2 Years

Model	BMD ₁₀ (mg DMA/kg/day)	BMDL ₁₀ (mg DMA/kg/day)	x ² p-value	AIC
Gamma ^a	5.01	1.85	1.00	83.03
Logistic	3.66	2.78	0.95	81.37
Log-logistic ^b	6.23	2.34	1.00	83.03
Multi-stage^c	2.68	1.80	0.90	81.69
Probit	3.20	2.46	0.89	81.60
Log-probit ^b	5.03	2.00	1.00	83.03
Quantal linear	0.98	0.76	0.07	91.75
Weibull ^a	4.77	1.88	1.00	83.03

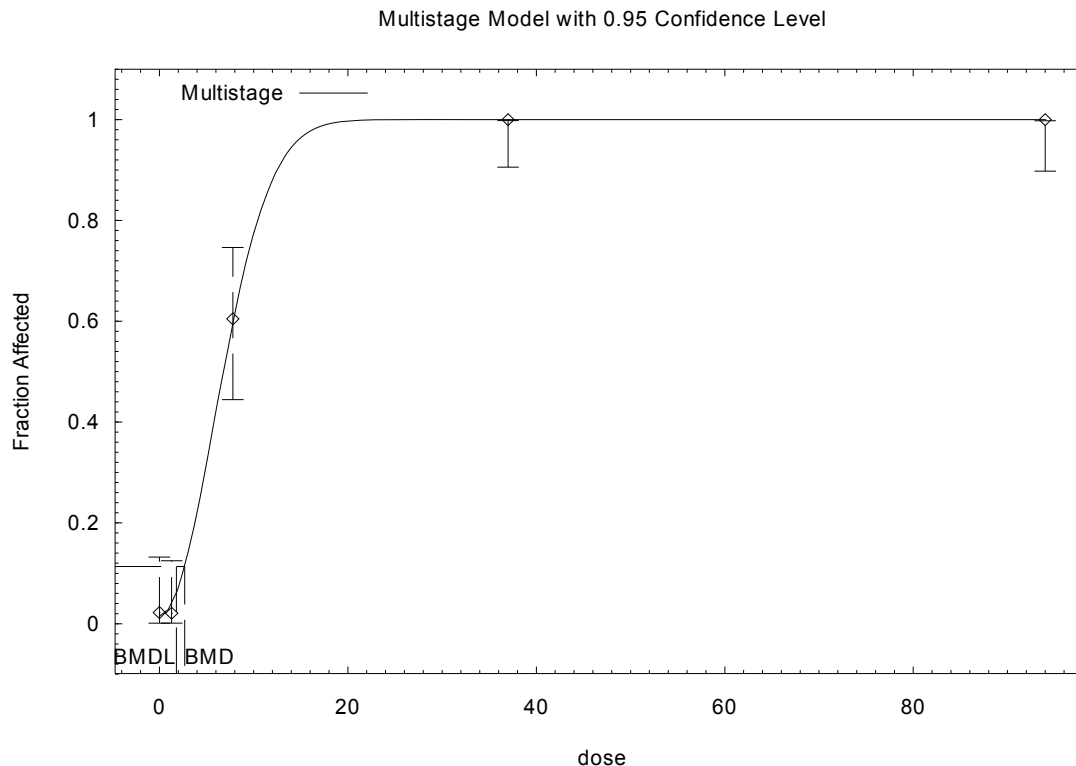
Sources: Arnold et al. 2006; Gur et al. 1989b

^aRestrict power ≥1.

^bSlope restricted to >1.

^cRestrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=2.

Figure A-4. Predicted and Observed Incidence of Vacuolization of Urothelium in Urinary Bladder of Female Mice*



13:25 08/03 2007

Source: Arnold et al. 2006

*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg DMA/kg/day.

The BMDL₁₀ of 1.80 mg DMA/kg/day for female mice was selected as the point of departure for deriving the chronic-duration oral MRL.

☐ NOAEL ☐ LOAEL ☒ BMDL

Uncertainty factors used in MRL derivation: 100

- ☐ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses reported in Gur et al. (1989b): 0, 1.3, 7.8, 37, and 94 mg DMA/kg/day.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

APPENDIX A

Other additional studies or pertinent information that lend support to this MRL: One other study has investigated the chronic toxicity of DMA in species other than rats. In this study, administration of 16 mg DMA/kg/day via a capsule for 52 weeks resulted in increases in the incidence of diarrhea; no histological alterations were observed (Zomber et al. 1989).

Agency Contacts (Chemical Managers): Selene Chou, Ph.D and Carolyn Harper, Ph.D.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND**See Sample LSE Table 3-1 (page B-6)**

- (1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).
- (7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

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which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See Sample Figure 3-1 (page B-7)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.
- (14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

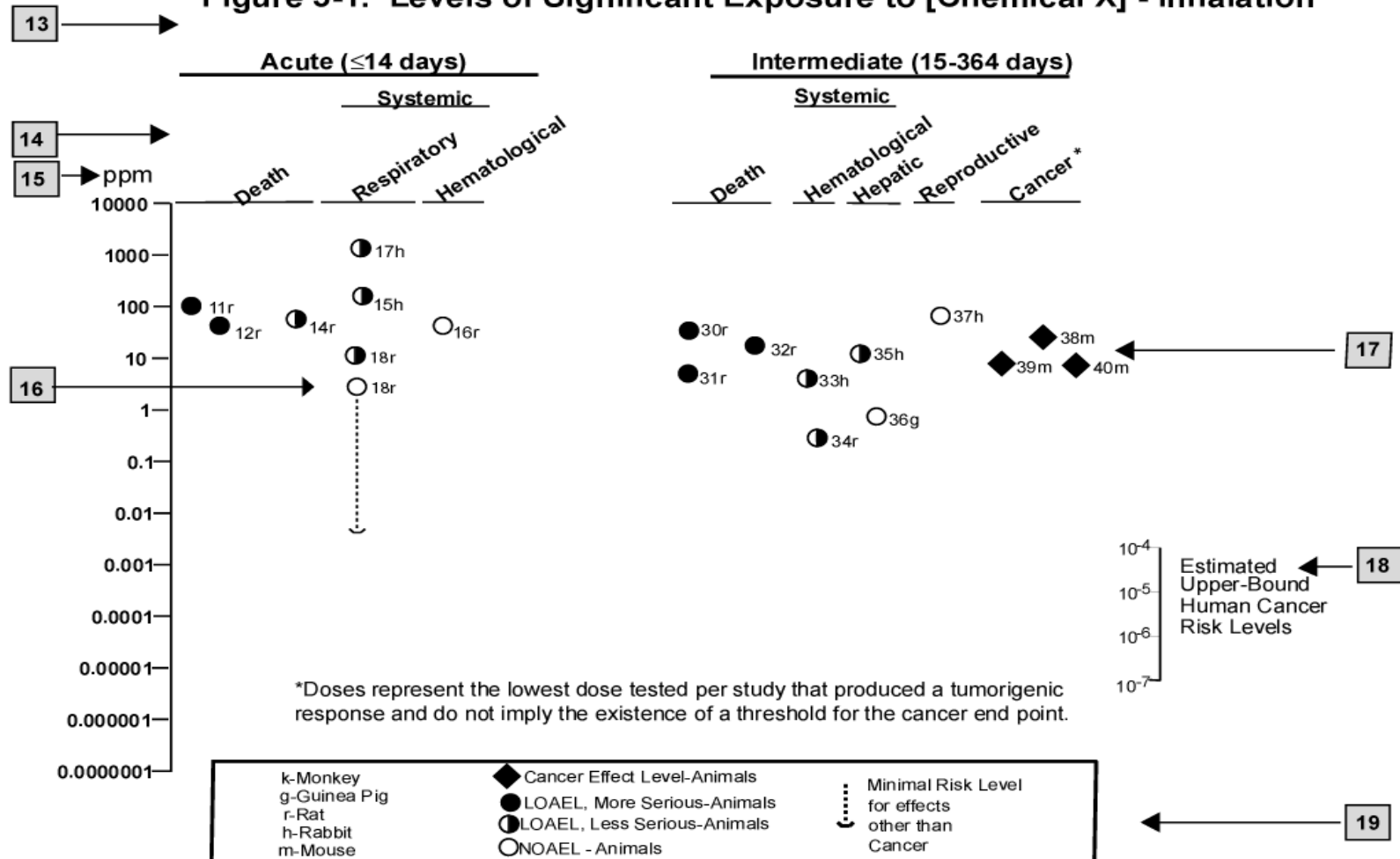
						LOAEL (effect)			
	Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	Less serious (ppm)	Serious (ppm)	Reference	
2	→	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10	
3	→	Systemic	↓	↓	↓	↓		↓	
4	→	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981	
		CHRONIC EXPOSURE							
		Cancer					11		
						↓			
		38	Rat	18 mo 5 d/wk 7 hr/d			20 (CEL, multiple organs)	Wong et al. 1982	
		39	Rat	89–104 wk 5 d/wk 6 hr/d			10 (CEL, lung tumors, nasal tumors)	NTP 1982	
		40	Mouse	79–103 wk 5 d/wk 6 hr/d			10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982	

12 →

^a The number corresponds to entries in Figure 3-1.^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

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DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

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MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

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OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD ₅₀	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

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$>$	greater than
\geq	greater than or equal to
$=$	equal to
$<$	less than
\leq	less than or equal to
$\%$	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
$-$	negative
$+$	positive
$(+)$	weakly positive result
$(-)$	weakly negative result

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Risk Assessment for Arsenic and Inorganic Arsenic Compounds

Executive Summary

In response to a request made by the North Carolina Division of Air Quality (DAQ), the Secretary's Science Advisory Board for Toxic Air Pollutants (NCSAB) has reassessed arsenic and arsenic-containing inorganic compounds and recommends an update to the Acceptable Ambient Level (AAL) for these compounds. An AAL is an airborne concentration above which a toxic air pollutant may be considered to have an adverse effect on human health. The current AAL for arsenic and inorganic arsenic-containing compounds, established in 1990, is 2.3×10^{-7} mg/m³, averaged annually. Upon review of the updated toxicological and epidemiological literature, the NCSAB recommends revising the AAL to 2.1×10^{-6} mg/m³, the central estimate within an exposure range from a lower bound of 1.6×10^{-6} mg/m³ to an upper bound of 3.0×10^{-6} mg/m³. This updated AAL is based on an estimated lifetime excess risk of 1 additional lung cancer death per 1,000,000 population over a 78-year lifespan.

I. Background Information

Arsenic (CAS 7440-38-2), abbreviated As, is a grey-colored allotropic metalloid that occurs naturally in the Earth's crust. It has an atomic number of 33 and a molecular weight of 74.92 g/mole. Arsenic commonly exists in the -3, 0, +3, and +5 oxidation states.

Arsenic is found at low concentrations (about 3 - 4 ppm) in soils and water throughout the world (California OEHHA 2001). Refining of arsenic-containing ores, including copper and lead smelting, is the major source of emissions of arsenic dust and inorganic arsenic compounds. Since 1985, the United States has had no domestic production of arsenic. Both arsenic and arsenic trioxide are imported, primarily from China and Japan (arsenic), and Chile and Morocco (arsenic trioxide), and have been important secondary sources (Brooks 2002). The most commonly produced form of inorganic arsenic is arsenic trioxide, As₂O₃. It is used as a raw material for the production of other inorganic arsenic compounds, organic arsenic compounds, and alloys. It is produced at an estimated 3000 tons per year: an estimated 1000 tons per year from mining and smelting by-products and 2000 tons per year reclaimed from metal and

electrical waste (European Chemicals Agency 2010). Galvanizing, soldering, and etching processes requiring the treatment of metal with strong acids are possible sources of arsine gas, AsH_3 . Arsine is used to provide arsenic as a doping agent in the semiconductor industry. Combustion of fossil fuels can also result in the emission of particulate arsenic compounds as well as arsine.

According to latest USEPA National Air Toxics Assessment (NATA) report (U.S. Environmental Protection Agency 2011) (of year 2005 data), the mean ambient air concentration of arsenic statewide in North Carolina is $3.8 \times 10^{-7} \text{ mg/m}^3$. Table 1 summarizes emissions by source type and percent contribution for North Carolina:

Table 1 – Contributions to Ambient Air from Source Types in North Carolina

Source Type	Approximate Contribution to Ambient Air Concentration, %
Point	3
Nonpoint	6
Mobile	3
Background	88

The most complete and current emissions inventory available containing source category data is the 2008 National Emissions Inventory (NEI). Using the 2008 NEI data, arsenic emissions were totaled by source category. The results indicate that Point Sources are the predominant source of arsenic emissions in NC (Table 2):

Table 2 – Arsenic Emissions by Source Category

Source Category	As Emissions, tons per year	As Emissions, % of total
Point	6.1	92
Mobile	0.5	7
Nonpoint	0.05	1

Using NAICS (North American Industrial Classification System) categories, the predominant industrial category for arsenic emissions is electrical power generation, transmission and distribution. Significant category contributors in North Carolina are shown in Table 3:

Table 3 – Arsenic Emissions, Contribution by NAICS Source Category

% Contribution to Arsenic Emissions	NAICS Category Description
74	Electrical Power Generation, Transmission and Distribution
13	Pulp, Paper and Paper Mills
6	Wood Products, Glass Mfg, Clay Mfg, Textiles, Pesticide Mfg, Polymers
4	National Security and International Affairs
3	Other

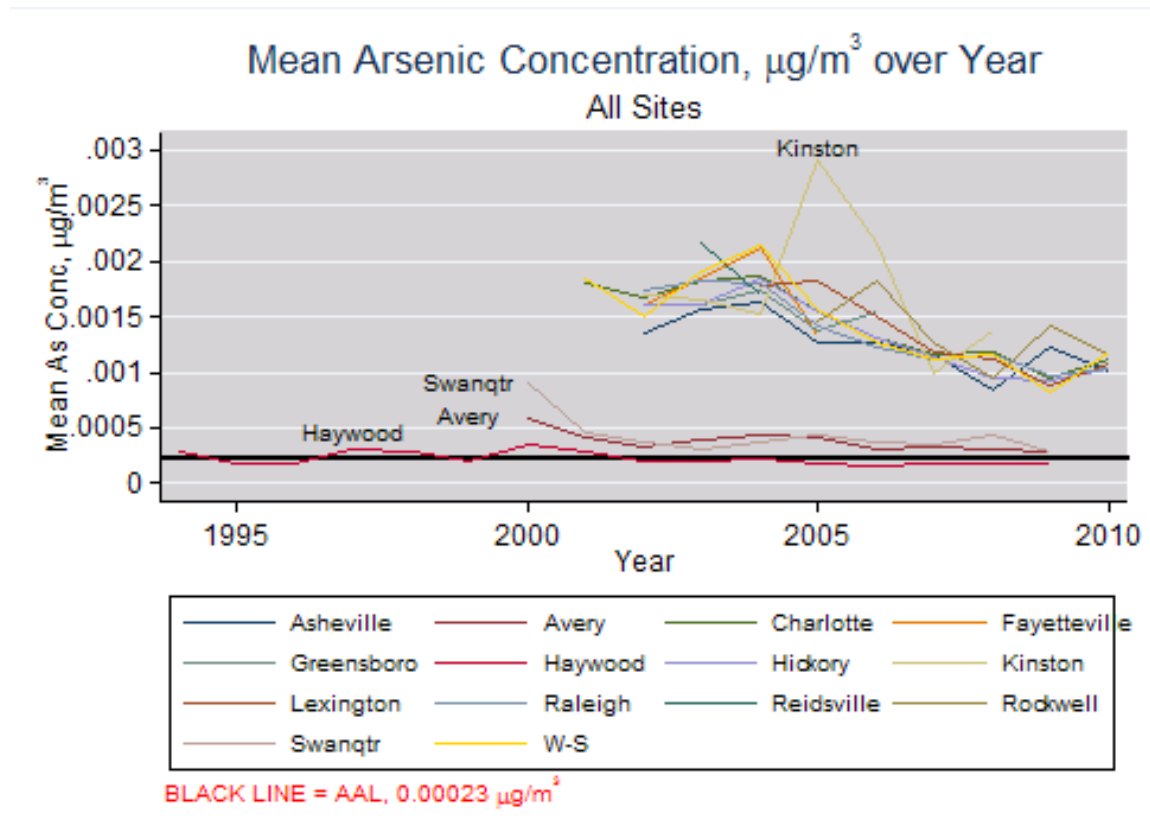
For electrical power generators, transmitters, and/or distributors, fuels used for power generation are reported in Table 4:

Table 4 – Arsenic Emissions by Fuel Type

Fuel	As Emissions, tons per year	As Emissions, % of total
Coal	5.9	96
Other	0.2	4

The NC Division of Air Quality has been analyzing particulate matter in the ambient air in North Carolina for arsenic since 1994. In Figure 1, mean arsenic concentration by monitoring location is plotted against year and compared with the current (historical) AAL:

Figure 1 – Arsenic Concentration in Ambient Air by Site and Year



Except for the monitoring location in Haywood County, the mean annual arsenic concentrations at all other monitoring locations exceed the AAL for every year in which sampling was performed. These data are available in the EPA Air Quality System (AQS) database.

Acceptable Ambient Level (AAL) History

The current AAL for arsenic and inorganic arsenic compounds of $2.3 \times 10^{-7} \text{ mg}/\text{m}^3$ became effective in 1990. This AAL was based on an EPA (U.S. Environmental Protection Agency 1984) Unit Risk Factor of $4.29 \times 10^{-3} (\mu\text{g}/\text{m}^3)^{-1}$, and was associated with an upper bound estimate of excess cancer risk of 10^{-6} :

$$AAL = \frac{\text{excess risk}}{IUR} = \frac{10^{-6}}{4.29 \times 10^{-3} \left(\frac{\mu g}{m^3} \right)^{-1}} = 2.3 \times 10^{-4} \frac{\mu g}{m^3} = 2.3 \times 10^{-7} \frac{mg}{m^3}$$

II. Animal Studies

Acute and Chronic Non-Cancer Endpoints

Developmental Studies

Mouse and rat studies have been conducted to determine the potential developmental toxicity of arsenic.

Nagymajtenyi et. al. (Nagymajtenyi, Selypes et al. 1985) investigated chromosomal damage and fetotoxic effects in pregnant CFLP mice exposed to various concentrations of As₂O₃ aerosol spray. Study details were poorly documented and provided no information on the generation and/or analysis of the chamber atmosphere. Four groups (8-11 per group) of pregnant mice were exposed to As₂O₃ aerosol spray for 4 hours per day on the 9th, 10th, and 12th gestational days. Control mice were exposed to distilled water aerosol. Mice were sacrificed on the 18th gestational day. No information was provided on maternal toxicity. Fetuses were removed and examined. Livers of ten fetuses from each exposure group were examined for chromosomal damage. Twenty mitoses in each fetus were scored for chromosomal damage and 10% of these were karyotyped. The experimental data are shown in Table 5.

Table 5 - Nagymajtenyi Data

Group	As ₂ O ₃ Exposure Concentration (mg/m ³)	Number of Litters	Avg. Number of Living Fetuses per Mother	Number of Fetuses Examined	Dead Fetuses (%)	Avg. Fetal Weight (g)	Number of Fetuses with Retarded Growth
Control	0	8	12.5	100	8	1.272 ±0.02	1
1	0.26 ±0.01	8	12.5	100	12	1.225 ±0.03*	2
2	2.9 ±0.04	8	12.8	100	13	1.146 ±0.03*	3
3	28.5 ±0.3	11	9.6	100	29	0.981 ±0.04*	51*

* Significantly different from Control (p < 0.05). NOTE: Nagymajtenyi et al analyzed body weights from several fetuses per litter but do not appear to have taken litter effects into account. When litter effects are ignored, statistical tests indicate greater statistical significance than is warranted by the data.

From the Nagymajtenyi data, the exposure concentration of 0.26 mg/m³ was determined by OEHHA (California OEHHA 2000) to be a LOAEL based on decreased fetal weight. ATSDR does not consider a % weight reduction from control of less than 10% to be significant (from these data, the weight reduction experienced at 0.26 mg/m³ was 3.7%), while OEHHA considers any statistically significant decrease in fetal weight a concern. The NCSAB agrees with the ATSDR approach, in that while a 3.7% decrease in fetal weight may be reported as statistically significant, it does not appear to be biologically significant. OEHHA based their Chronic Inhalation Reference Exposure Level of 0.03 µg As/m³ on these data (average exposure to LOAEL group = 33 µg As/m³, Total Uncertainty Factor = 1000). Holson (Holson, Stump et al. 1999) investigated developmental toxicity of inhaled As₂O₃ aerosol in female Crl:CD®(SD)BR rats under GLP conditions. A preliminary range-finding study (8-10 mated dams/group) was conducted in addition to a definitive exposure study. Exposure was to the whole body for 6 hours/day beginning 14 days before mating. Exposure was continued through mating to gestational day 19. Aerosol concentration was measured periodically to estimate exposure concentrations. Control animals in the range-finding study were kept in a separate room from the exposed animals. Controls for the definitive study were handled in the same manner as exposed animals, except they breathed filtered air. In the range-finding study, maternal mortality was seen at 25 mg/m³ and maternal rates were

observed in the 10 and 25 mg/m³ groups and; 10 mg/m³ was selected to be the highest exposure level in the definitive study. In the definitive study, groups of 24 female rats were exposed for 6 h/day to 0.3, 3, and 10 mg/m³ As₂O₃ aerosol (MMAD for lowest to highest exposure groups: 2.1, 1.9, and 2.2 µm). No significant maternal effects were reported for the control and two lower exposure groups. At 10 mg/m³, rats exhibited rales and dried red material around the nose, and it was observed that there were statistically significant differences in food consumption and net body weight gain in the high exposure group compared to controls. A NOAEL of 3 mg/m³ and a LOAEL of 10 mg/m³ were reported based on these maternal effects. Intrauterine parameters (mean numbers of corpora lutea, implantation sites, resorptions and viable fetuses, and mean fetal weights) were unaffected by treatment. No exposure-related malformations or variations were noted at any exposure level. Definitive study data are shown in the table below:

Table 6 - Holson Data

Group	As ₂ O ₃ Exposure Concentration (mg/m ³)	Number of Litters	Mean Net Maternal Body Wt Change (g+/- SD)	Number of Fetuses Examined	Total No. with Malformations (fetus/litter)	No. Live Fetuses per Litter (mean ± SD)	Avg. Fetal Weight (g ± SD)
Control	0	22	72.6±15.7	336	0/0	15.3 ± 2.16	3.7 ±0.17
1	0.3	23	72.6±16.9	354	1/1	15.4 ± 1.97	3.7 ±0.22
2	3.0	24	81.4±16.9	375	2/2	15.6 ± 3.15	3.7 ±0.20
3	10	23	60.1±14.1*	367	0/0	16.0 ± 1.64	3.5 ±0.32

* Significantly different from Control (p < 0.05)

In summary, exposure of female rats to arsenic trioxide dusts at levels up to 10 mg/m³ did not result in any evidence of developmental toxicity, but did cause maternal toxicity in this study. Findings seen in the Nagymajtenyi et al., 1985 study were not reproduced in the rat study that used a more robust study design. These findings may have been due to maternal toxicity at the high dose of 28.5 mg/m³ since the dose of 25 mg/m³ in the rat caused mortality.

Immunological Studies

Aranyi (Aranyi, Bradof et al. 1985) and co-workers investigated the effects of exposure to arsenic trioxide on bactericidal activity in the lung. CD-1 mice were exposed for 3 hours to As_2O_3 aerosol (MMAD = $0.4 \mu\text{m}$). Exposure concentrations ranged from 125 – $1000 \mu\text{g}/\text{m}^3$. Changes in infectivity were evaluated by observation of changes in susceptibility to a radiolabeled streptococcal aerosol, ^{35}S -labeled *Klebsiella pneumoniae*. Mortality increased significantly after infection challenge and decreases in bactericidal activity were noted after single 3-hour exposures to 270, 500, and $940 \mu\text{g As}/\text{m}^3$. It was also observed that multiple (5 and 20) 3-hour exposures to $500 \mu\text{g As}/\text{m}^3$ significantly increased mortality and decreased bactericidal activity. Decreases in bactericidal activity were noted only after 20 3-hour exposures at 125 or $250 \mu\text{g As}/\text{m}^3$. A NOAEL was reported at $0.123 \text{ mg}/\text{m}^3$.

Chronic Studies

ATSDR(ATSDR 2008) reports "...animal data on the health effects of inorganic arsenic following inhalation exposure are limited to studies that did not evaluate a suitable range of health effects. Lacking suitable studies upon which to base the MRLs, no inhalation MRLs were derived for inorganic arsenic." Additionally, the NCSAB finds that animal studies are not particularly robust, and should not be used as the basis for an AAL based on chronic exposure to arsenic.

Cancer Endpoints

Since human epidemiological studies were available for this risk assessment, animal studies were not reviewed in depth.

III. Human Studies

Acute and Chronic Non-Cancer Endpoints

ATSDR(ATSDR 2008) reports "...Adequate human studies evaluating dose-response relationships for noncancer end points were not located for inorganic arsenic..."

Perry(Perry, Bowler et al. 1948) reported on clinical manifestations of disease in workers in a factory that produced sodium arsenite powder. Airborne arsenic levels were determined by sampling. Hair and urine analyses were also performed. ATSDR(ATSDR 2008) reported a NOAEL for a respiratory endpoint of $0.613 \text{ mg As}/\text{m}^3$ for the Perry study based on observed

differences in chest x-rays and respiratory performance (vital capacity and exercise tolerance tests) in workers studied. ATSDR also reported a LOAEL of 0.078 mg As/m³ for a dermal endpoint (mild pigmentation keratosis of skin). Lagerkvist (Lagerkvist, Linderholm et al. 1986) investigated vasospastic (blood vessel spasm leading to vasoconstriction) tendency in 47 workers at a copper smelter. Lagerkvist reports that "...increased vasospastic reactivity in the fingers and Raynaud's phenomenon in smelter workers seems to be due to functional alterations in the vessels caused by inhalation of arsenic." ATSDR (ATSDR 2008) reports a LOAEL for this study to be 0.36 mg/m³. Lagerkvist (Lagerkvist and Zetterlund 1994) investigated nerve conduction velocity (NCV) in 43 copper smelter workers and 46 controls in a 5 year follow-up to a previous study (Blom, Lagerkvist et al. 1985). The results were extrapolated to a long term exposure of mean duration of 28 years. Lagerkvist reported the greatest difference in NCV was in the tibial and sural nerves. The time-weighted average exposure reported as a LOAEL for decreased NCV in ATSDR(ATSDR 2008) was 0.36 mg/m³. This time-weighted average (TWA) was derived from estimations of Lagerkvist et al. that the mean exposure duration to Rönnskär smelter arsenic workers was 23 years: 16 years at 500 µg/m³ and 7 years at 50 µg/m³.

Cancer Endpoints

Several epidemiological studies address the carcinogenicity of inhaled arsenic and arsenic compounds. These studies were conducted in smelter operations, where the predominant form of arsenic was particulate arsenic trioxide(ATSDR 2008).

A. Asarco Copper Smelter - Tacoma, Washington

Enterline and co-workers (Enterline and Marsh 1982; Enterline, Henderson et al. 1987a; Enterline, Marsh et al. 1987b; Enterline, Day et al. 1995) have been investigating risk of respiratory cancer in workers occupationally exposed to arsenic compounds at the Asarco copper smelter in Tacoma, Washington from 1940-1964. The 1995 update follows the cohort of Asarco workers (2,802 workers, 84,916 person-years) through 1986. Airborne arsenic levels were measured in the air of plant departments where arsenic levels were deemed to be elevated. While air sampling was begun in 1938 and conducted in only selected departments, urine samples were collected beginning in

1948 from all workers and analyzed for arsenic concentration. Information on worker smoking was not collected. Urinary arsenic levels were converted to air concentrations by comparison of actual air measurement data with urinary arsenic concentration of workers in sample plant departments. Also in the 1995 update, Enterline reported a cumulative mortality of 1,583 (1,061 deaths were reported in the 1987 update); 188 deaths due to respiratory cancer (104 reported in 1987). The SMR for respiratory cancer was reported to be 209.7 for the entire study cohort ($p < 0.01$). The cumulative arsenic exposure was reported to range from <0.75 -45+ $\text{mg}/\text{m}^3\text{-yr}$. Additional significant increases in Standard Mortality Ratios (SMR) related to arsenic exposure were found for cancers of the large intestine, bone, buccal cavity and larynx, rectum and kidney for this cohort.

B. Anaconda Copper Smelter - Montana

Brown and Chu (Brown and Chu 1983b; Brown and Chu 1983c), Lee-Feldstein (Lee-Feldstein 1986) and Lubin and co-workers (Lubin, Pottern et al. 2000; Lubin, Moore et al. 2008) have investigated the risk of respiratory cancer in a cohort of 8,014 workers occupationally exposed to arsenic during the years 1938-1958 at an Anaconda copper smelter in Montana. The cohort was divided into three categories based on level of arsenic exposure (low = $0.29 \text{ mg}/\text{m}^3$, medium = $0.58 \text{ mg}/\text{m}^3$, high = $11.3 \text{ mg}/\text{m}^3 \times$ exposure reduction factor due to use of personal protective equipment). Of the 8,014 workers in the original cohort, about 3,200 (approximately evenly split between those under 30 years old and those between 30-39 years old) quit their jobs. To minimize the impact of unmeasured exposures on workers who quit, Lubin not only analyzed data from the full cohort, but also on a "restricted cohort" consisting of current workers as well as those 50 years old or older who quit working at the smelter. Follow-up in this cohort of workers is through 1989 (256,850 person-years for full cohort; 144,851 for a restricted cohort). Lubin reported 446 lung cancer deaths in the follow-up study compared with 302 as reported by Lee-Feldstein. The range of cumulative arsenic exposure was reported to be 1 – 26.2+ $\text{mg}/\text{m}^3\text{-yr}$ with a mean cumulative arsenic exposure of $5.4 \text{ mg}/\text{m}^3\text{-yr}$. An SMR of 156 ($p < 0.001$) for respiratory cancer was

reported for the full cohort; an SMR of 187 ($p < 0.001$) was reported for a restricted cohort.

C. Rönnskär Copper Smelter - Sweden

Lung cancer mortality and arsenic exposure was investigated by Järup, et. al. (Jarup, Pershagen et al. 1989) and by Viren, et.al. (Viren and Silvers 1994) using a cohort of 3,916 Swedish male smelter workers employed for at least three months from 1928-1967 (127,189 person-yrs of exposure). 106 lung cancer deaths were reported with an SMR of 372. Viren also reported that the SMR for those employees hired prior to 1940 was 428 compared with an SMR of 302 for those hired after 1940. This cohort was followed through 1981. Cumulative arsenic exposure was determined to range from $< 0.25 - 100+ \text{ mg}/(\text{m}^3\text{-yr})$. Järup reported an SMR of 372 ($p < 0.001$) for lung cancer and further stated that lung cancer mortality was related to average intensity of arsenic exposure, but not to duration – given a fixed level of cumulative arsenic exposure, inhalation of higher concentrations of arsenic over shorter durations of time were more hazardous than exposure to lower concentrations of arsenic over longer durations. With a 10 year minimum latency, an exposure intensity of $< 0.1 \text{ mg}/\text{m}^3$ was associated with a significant SMR of 317. Significant SMRs of 376 and 637 were noted with a cumulative arsenic exposure levels of < 0.25 and $(0.25 \text{ to } < 1) \text{ mg-years}/\text{m}^3$.

D. United Kingdom Tin Smelter

Binks (Binks, Doll et al. 2005) investigated lung cancer mortality and exposure to carcinogens (arsenic, lead, cadmium, polonium, antimony, sulfur dioxide) in a cohort of 1,462 workers (35,942 person-yrs of exposure) at the Copper Pass and Sons Limited tin smelter located in North Humberside, UK. This smelter was purchased in 1967 by Rio Tinto. The cohort consisted of workers employed for at least 12 months between November 1, 1967 and July 28, 1995. The latest year of follow-up was 2001. Binks reported an SMR of 161 for lung cancer (95% CI: 124 – 204) ($p < 0.001$). Jones (Jones, Atkin et al. 2007) combined the Binks mortality data with area and personal measurement data to investigate the relationship between lung cancer mortality and measures of exposure. Using available personnel records of employee work histories

and exposure measurements, matrices of exposure for several airborne particulates were compiled: arsenic, cadmium, lead, antimony, and polonium-210. To assess worker exposure prior to 1972 (where no exposure measurement data were collected), three extrapolation methods were devised to assess exposure: (A) Constant extrapolation in each process area, as the mean of the levels in the three earliest years for which data were available; (B) Extrapolation in each process area with a linear increasing trend from baseline to values 2-fold higher in the early 1940s, based on a weak trend seen in average exposure levels over the period 1972–91; (C) Extrapolation in each process area from baseline to values 2-fold higher in 1960, subsequently, declining linearly to values one-half of the baseline in 1937. Lung cancer mortality was investigated using Poisson regression on cumulative exposure. No significant association was determined between lung cancer mortality and cumulative exposure to arsenic. However, when cumulative exposure was weighted by time since exposure and age, a significant association was determined to exist. Increased prevalence of smoking with the cohort of workers studied enhances this association.

IV. Carcinogenic Mode of Action (MOA)

Arsenic is a known human carcinogen, but a definitive MOA for the various –cancer has not been generally accepted at this time. It is well accepted that the mechanisms of arsenic-induced carcinogenesis are complex and multifactorial and also may be target-site specific. As recently reviewed by Tokar (Tokar, Benbrahim-Tallaa et al. 2010) historically, conventional rodent cancer bioassays had provided -inconsistent evidence of the carcinogenicity of inorganic arsenic compounds. However, in a 2-year NTP inhalation bioassay, gallium arsenide did induce a dose-dependent increase in the incidence of lung adenomas and combined lung adenoma/carcinomas in female, but not male rats (NTP, 2000). Studies of inorganic arsenic using whole-life rodent exposures (i.e., including pre-natal and/or peri-natal exposures) have clearly demonstrated that arsenic does induce cancer in multiple organs ((Tokar, Benbrahim-Tallaa et al. 2010; Tokar, Diwan et al. 2011).

In addition, other in vivo rodent studies have established that inorganic arsenic can act together with other agents to enhance tumorigenesis (Tokar, Benbrahim-Tallaa et al. 2010). Regarding genotoxicity, there is little evidence that inorganic arsenic acts as a point mutagen, and a multitude of effects of arsenic on cell signaling have been reported. However, there are numerous other MOAs proposed for arsenic, including: cell proliferation, altered DNA repair, DNA methylation, oxidative stress, co-carcinogenesis, and tumor promotion.

(1) Genotoxicity

In Vitro Studies

Rossman (ATSDR 2008) reported that arsenite did not induce mutation in tests that selected for *E. coli* tryptophan⁺ revertants or in Chinese hamster ovary cells selecting for ouabain-(ATPase) or thioguanine-resistant (HPRT) mutants, while Hei (Hei, Liu et al. 1998) reported that arsenite does induce large deletion mutations in hamster-human hybrid cells.

There are multiple reports of dose-dependent chromosomal aberrations (chromatid gaps, breaks and fragmentation, endoreduplication, and chromosomal breaks), DNA-protein crosslinking, and sister chromatid exchanges in hamster embryo cells, human lymphocytes, and fibroblasts following exposure to inorganic arsenic (Rossman, Stone et al. 1980; Larramendy, Popescu et al. 1981; Lee, Huang et al. 1985b; Wiencke and Yager 1991; Jha, Noditi et al. 1992; Kochhar, Howard et al. 1996; Rasmussen and Menzel 1997). Arsenite is reported to be more potent than arsenate.

In Vivo Studies

DeKnudt and Tinwell (DeKnudt, Leonard et al. 1986; Tinwell, Stephens et al. 1991) have reported a linear dose-dependent increase in micronucleated polychromatic erythrocytes in somatic cells of mice administered arsenite. Chromatid gaps and breaks, and chromosomal rearrangements have been observed in bone marrow cells of mice administered arsenite (Das, RoyChoudbury et al. 1993; RoyChoudbury, Das et al. 1996). Studies have reported that clastogenic effects have been reduced in mice pre-treated with garlic extract before exposure to arsenite (Das, RoyChoudbury et al. 1993;

RoyChoudbury, Das et al. 1996). Tice (Tice, Yager et al. 1997) reported that hepatic methyl donor status may affect arsenic-induced genotoxicity.

(2) Co-Mutagenesis

Studies by Lee, Okui, and Li (Lee, Oshimura et al. 1985a; Okui and Fujiwara 1986; Li and Rossman 1991) indicate that inorganic arsenic (including arsenite, As_2O_3 , and arsenate) is co-mutagenic with other chemicals and UV light in mammalian cells: a synergistic increase in UV-induced chromatid and chromosomal aberrations and mutation at the HPRT locus in Chinese hamster ovary cells is produced after UV-treated cells are exposed to inorganic arsenic. Lee (Lee, Oshimura et al. 1985a) reported no co-mutagenic effect of arsenic with UV-induced sister chromatid exchanges or ouabain resistance. Wiencke (Wiencke and Yager 1991) reported that chromosomal aberrations in lymphocytes induced by diepoxybutane, a DNA crosslinking agent, are potentiated after exposure to arsenite. Jha (Jha, Noditi et al. 1992) reported that chromosomal aberrations induced by x-rays or UV light in fibroblasts are potentiated after exposure to arsenite.

(3) Gene Amplification

Lee (Lee, Tanaka et al. 1988) suggests that arsenic enhances amplification of the gene that codes for the enzyme dihydrofolate reductase, and that this gene amplification may play a role in its carcinogenic effect. Cells had a 2- to 11-fold increased copy number of the dihydrofolate reductase gene. Arsenite (active in the 0.2 – 0.8 μM range) was more potent than arsenate (active in the 1 – 4 μM range). This hypothesized MOA is based on observations that arsenic is carcinogenic, but not a point mutagen, and oncogenes are amplified in several animal and human tumors. Woloson (Woloson 1990) found arsenic-induced gene amplification in Syrian Hamster Embryo (SHE) cells, and Katakura (Katakura and Chang 1989) reported arsenite-resistant trypanosomes.

(4) Altered DNA Repair

Okui (Okui and Fujiwara 1986) reports that inorganic arsenic (arsenite more potent than arsenate) inhibits the DNA excision repair of thymine dimers in human fibroblasts. Li (Li and Rossman 1989) note that DNA ligase activity in nuclear extracts is decreased by

arsenite (55% at 10 μ M), but the enzyme is not directly inhibited (Li and Rossman 1989; Hu, Su et al. 1998). Hu noted that arsenite might indirectly inhibit DNA ligase activity by altering cellular redox levels or affecting signal transduction pathways or altering phosphorylation of proteins linked to DNA ligase activity. In addition, with purified human DNA repair enzymes, Hu observed that arsenite increased DNA polymerase beta, O⁶-methyl-guanine-DNA methyltransferase and DNA ligases I, II, and III. Yager (Yager and Wiencke 1997) observed a dose-dependent decrease of the enzyme poly(ADP-ribose) polymerase in human T-cell lymphoma cells (at 10 μ M arsenite, there is an approximately 50% decrease in enzyme activity and 80% cell viability). Kitchin (Kitchin 2001) states "...The theory that altered DNA repair is the cause of arsenic carcinogenesis is particularly attractive because trivalent arsenic species, such as arsenite, can bind strongly to dithiols as well as free sulfhydryl groups. Such protein binding could induce inhibited DNA repair, mutation in key genetic sites, or increased cell proliferation which can lead to subsequent mutation via inhibited DNA repair."

(5) Altered DNA Methylation

Counts (Counts and Goodman 1995) suggests that DNA methylation may have a prominent role in cancer development. Mass (Mass and Wang 1997) reported that arsenite increased resistance of the p53 promoter region to cleavage by the restriction enzyme *HpaII*. This resistance to cleavage indicates that more methylated cytosine was present within the p53 gene. Methylated cytosine can alter the ability of transcription factors to bind to DNA, which would modify gene expression. Arsenate was determined to be less potent than arsenite. Zhao (Zhao, Young et al. 1997) found that the DNA of arsenite-transformed rat liver TRL 1215 cells was globally hypomethylated and that the effect was dependent on dose and length of exposure. Zhong (Zhong and Mass 2001) observed both hypo- and hyper-methylation of DNA in human lung cells after several weeks of arsenite exposure, suggesting that altered methylation within a specific DNA sequence may be more important than the magnitude of DNA methylation.

(6) Oxidative Stress

Arsenic appears to induce oxidative stress both in in vivo and in vitro studies (Brown and Rush 1984; Keyse and Tyrell 1989). Liu (Liu, Athar et al. 2001) reports that within 5 minutes after exposure of human-hamster hybrid cells to arsenite, reactive oxygen species are detected. Wang (Wang and Huang 1994) found that catalase and superoxide dismutase reduce arsenite-induced micronuclei in CHO cells, and Nordenson (Nordenson and Beckman 1991) has reported that SCE were reduced as well. Lee (Lee and Ho 1994) found that the antioxidants vitamin E, methylamine, and benzyl alcohol reduced the killing of human fibroblasts by arsenite.

The main sources of reactive oxygen species generated after exposure to arsenite are NADPH oxidase (Brown and Chu 1983; U.S. Environmental Protection Agency 1984) (from (Sumi, Shinkai et al. 2010)); inhibition of mitochondrial respiration (Lee-Feldstein 1983); and inhibition of glutathione peroxidase (Higgins, Welch et al. 1982) and thioredoxin reductase (Enterline and Marsh 1982). In addition, in the presence of iron, arsenite undergoes a Fenton reaction and may generate reactive oxygen species directly (Brown and Chu 1983a) (from (Druwe and Vaillancourt 2010)). In vivo chronic exposure to arsenite (300 ug/L) in rats leads to depletion of glutathione and increased lipid peroxidation (Lee and Fraumeni 1969; Chaudury, Basu et al. 1999).

Oxidative DNA damage has been detected in many cell types exposed to arsenite (Brown and Chu 1983a; Chen, Lin-Shiau et al. 1998). Chronic oral dimethylarsenic acid (DMA^V) exposure was shown to lead to an increased incidence in lung tumors in *Ogg*^{-/-} mice (the mouse knockout for 8-oxoguanine DNA-glycosylase 1 which is key in repair of oxidative DNA damage) but not in the DNA-repair competent *Ogg*^{+/+} mice (Kinoshita et al., 2007), implicating some form of oxidative DNA damage as a possible means for tumor formation due to arsenic.

(7) Cell Proliferation

Brown (Brown and Kitchin 1996) reported increased ornithine decarboxylase (ODC) activity (an indicator of cell proliferation) in rat liver with arsenite exposure at 1.6 mg/kg. Germolec (Germolec, Yoshida et al. 1996) observed the proliferation of human keratinocytes after exposure to arsenite in culture, and also reported (Germolec,

Spalding et al. 1997) epidermal thickening and hyperkeratinosis in the skin of transgenic mice administered arsenite in drinking water. After an 8-week exposure to arsenite, Trouba (Trouba, Wauson et al. 2000a) observed that multiple genes and proteins involved in proliferative signaling and mitogenesis in murine fibroblasts were affected. A greater proportion of arsenite-exposed fibroblasts entered the S-phase of the cell cycle than controls. The exposed cells also expressed positive regulators of proliferation (*c-myc* and E2F-1) and decreased expression of negative regulators (MAP kinase phosphatase-1 and p27^{kip1}). Trouba (Trouba, Wauson et al. 2000b) also reported the inhibition of insulin/dexamethasone-induced differentiation of murine preadipocytes at nontoxic doses of arsenite. Vogt (Vogt and Rossman 2001) investigated expression of Cyclin D in arsenite-exposed normal human fibroblasts. After 14 days of exposure to a low dose (0.1 μ M) of arsenite, Cyclin D expression was increased. Since arsenite affects the cell cycle, arsenite may alter cell proliferation.

(8) Intracellular signaling pathways involved in cell proliferation and apoptosis

Arsenite-induced alterations in intracellular oxidation/reduction reactions, DNA methylation and/or DNA damage result in the activation of a number of signaling pathways. Activation of the early response genes is thought to be a response to arsenite-induced cellular stress via changes in intracellular redox status (Druwe and Vaillancourt 2010). Stress response transcription factors, such as activator protein-1 (AP-1) and nuclear factor-kappa B (NF- κ B) are an important part of these early responses, and regulate the expression of a variety of downstream target genes, such as pro-inflammatory genes that are involved in cellular antioxidant defense mechanisms (Kapahi, Takahashi et al. 2000). Activation of these stress response transcription factors is dependent upon arsenic concentration and cell type. In addition, arsenite activates Nrf2, a transcription factor which is a regulator of a number of antioxidant enzymes (Wang, Li et al. 2008).

A link between arsenite, reactive oxygen species and cell proliferation has been suggested through mitogen-activated protein kinases (MAPK). MAPK signaling is induced by inorganic and organic forms of arsenic in a variety of cell types (reviewed in

(Druwe and Vaillancourt 2010)). Some of the main kinases that have been studied include p38, Jnk, Erk, Pi3k/Akt (reviewed in (Sumi, Shinkai et al. 2010)).

With regard to other transcription factors that are responsible for DNA damage-induced signaling, p53 is thought to be a major target for arsenicals. Sumi, Shinkai et al. 2010 report, "It has been reported that iAsIII and As2O3, but not iAsV, caused p53 induction in a dose- and time-dependent manner in HeLa cells, human osteosarcoma U2OS cells and human gastric cancer MGC-803 cells (Salazar, Ostrosky-Wegman et al. 1997; Filippova and Duerksen-Hughes 2003; Zhang, Cao et al. 2005), and dimethylated arsenicals have also been shown to induce an increase in the cellular p53 level in U2OS cells, whereas monomethylated arsenicals had no effect (Filippova and Duerksen-Hughes 2003). This suggests that the ability of arsenic to activate p53 is dependent on its chemical composition and oxidation state."

V. Quantitative Assessment

Chronic Exposure, Non-Cancer Endpoints

The NCSAB, like ATSDR(ATSDR 2008) found limited evidence for the evaluation of chronic exposure to inorganic arsenic with non-cancer endpoints. Most of these studies have generated either negative or equivocal results (Tokar, Benbrahim-Tallaa et al. 2010). Further, the NCSAB has determined that an AAL based on a cancer endpoint is sufficient to protect the public from adverse health effects resulting from chronic exposure to arsenic-bearing particulate matter.

Chronic Exposure, Cancer Endpoints

Animal Studies

The NCSAB did not use animal studies as a basis for the revision of the arsenic AAL because these studies do not appear to be sufficiently robust to be used for this purpose.

Human Studies

Three epidemiological studies have been determined to be key studies:

- Enterline 1995 (Asarco copper smelter study)
- Lubin 2000 and Lubin 2008 (Montana copper smelter study)

- Järup 1989 (Rönnskär copper smelter).

The development of a revised AAL is based on the work of Valdez-Flores and Sielkin (Valdez-Flores and Sielkin 2011) as it was presented to the NCSAB at their January, 2011 meeting.

In the Valdez-Flores – Sielkin (V-S) analysis of the data from these selected studies, a Poisson dose-response model used was:

$$E(O_j) = \alpha \times E_{oj} \times (1 + \beta \times d_j)$$

where:

- $E(O_j)$ = expected number of cancer cases for exposure group j
- E_{oj} = expected number of background cancer cases for exposure group j
- α = accounts for possible differences in cancer background rates between study population and reference population
- β = slope factor by which background risk increases with cumulative exposure
- d_j = cumulative exposure for the jth exposure group j

Using this dose-response model, V-S derived maximum likelihood estimates of the model parameters, as shown in Table 6:

Table 7 – Maximum Likelihood Estimates of Model Parameters

Study	Intercept MLE (α)	Slope MLE (β) ($\mu\text{g}/\text{m}^3\text{-yr}$) ⁻¹	Standard Error Slope (β)	95% UCL Slope (β) ($\mu\text{g}/\text{m}^3\text{-yr}$) ⁻¹
Asarco	1.46 ^a 2.02 ^b	3.15e-05	1.48e-05	5.59e-05
Montana	0.94	5.75e-05	1.61e-05	8.4e-05
Ronnskar	2.37 ^a 2.81 ^b	2.92e-05	1.63e-05	5.61e-05

a: intercept for workers hired before 1940

b: intercept for workers hired after 1940

Modeling the combined (three studies) dose-response data with a common intercept model yields:

- β (MLE, combined data) = 5.46e-05 ($\mu\text{g}/\text{m}^3\text{-yr}$)⁻¹ and
- SE (combined data) = 9.84e-06 ($\mu\text{g}/\text{m}^3\text{-yr}$)⁻¹

A life table analysis was then conducted using this Poisson model, β (MLE, upper (95%) and lower (5%) confidence bounds, combined data), North Carolina age-specific lung cancer mortality rates (males, all races, 2009, http://www.cdc.gov/nchs/nvss/bridged_race/data_documentation.htm#vintage2009), baseline survival to beginning of age category data (U.S., all races, all sexes, 2000 census), with the intercept parameter α set equal to 1. Airborne concentrations of arsenic were iteratively input to the Poisson model until the resulting estimated lifetime excess risk of death from lung cancer was 1×10^{-6} . Based on the output from this life table analysis, Table 7 lists the following candidate AALs derived for constant and continuous 78-year exposures:

Table 8 – Candidate AALs

Exposure Range Category	AAL Candidate, mg/m³
Central Estimate	2.1×10^{-6}
Lower Bound	1.6×10^{-6}
Upper Bound	3.0×10^{-6}

The central estimate AAL candidate represents a 9-fold increase of the AAL from its current value of 2.3×10^{-7} mg/m³. As mentioned previously, the current arsenic AAL is based on an EPA unit risk factor derived in the 1984 EPA Health Assessment document (HAD) (U.S. Environmental Protection Agency 1984). This URF was derived as the geometric mean of the overall unit risk estimates for the occupational exposure studies at the Montana smelter and an occupational study at the Asarco smelter Table 7-35, page 7-114 of that report:

Table 9 – Unit Risk Estimates (from Table 7-35, 1984 EPA Health Assessment Document)

Exposure Source	Study	Unit Risk*	Geometric Mean Unit Risk	Final Estimated Unit Risk
Anaconda smelter (Montana)	Brown & Chu Lee-Feldstein Higgins	1.25×10^{-3}	2.56×10^{-3}	4.29×10^{-3}
		2.8×10^{-3}		
		4.9×10^{-3}		
ASARCO smelter (Tacoma)	Enterline & Marsh	6.81×10^{-3} 7.60×10^{-3}	7.19×10^{-3}	

* unit risk estimates were based on absolute-risk linear models

As described previously, these epidemiological data have been updated since the issuance of the 1984 EPA HAD to include a total of 341,766 person-years of follow up for the Montana and Tacoma smelters having 634 additional lung cancer deaths. Ronnskar smelter data with 127, 189 person-years of follow up and 106 lung cancer deaths was combined with the data from the Tacoma and Montana studies in the V-S analysis relied upon by the NCSAB.

VI. Recommendations

A. Chronic Endpoint

No recommendation.

B. Carcinogenic Endpoint

The NCSAB recommends that the current AAL for arsenic be revised to 2.1×10^{-6} mg/m³, the central estimate within an exposure range having a lower bound of 1.6×10^{-6} mg/m³ and an upper bound of 3.0×10^{-6} mg/m³. Because arsenic is a known human carcinogen, the Division of Air Quality has assigned an annual averaging time for this AAL.

VII. References

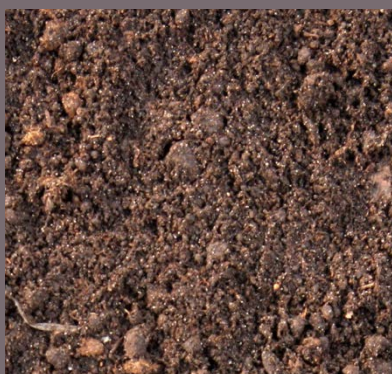
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PUBLIC STAKEHOLDER WORKSHOP
TO INFORM EPA'S UPCOMING IRIS

TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC




INTRODUCTION

Tuesday, January 8 &
Wednesday, January 9
RTP, North Carolina

HOSTED BY EPA'S NATIONAL CENTER
FOR ENVIRONMENTAL ASSESSMENT

 **EPA**
United States
Environmental Protection
Agency

Public Stakeholder Workshop – Development of Toxicological Review of Inorganic Arsenic



USEPA / ORD / NCEA
Presented by: Reeder Sams II

Office of Research and Development
National Center for Environmental Assessment

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Welcome to the Public Stakeholder Workshop

3



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Why is EPA holding this workshop?

- Human health
- Most recent IRIS assessment completed in 1988
- Support and use in EPA's program / regional risk assessments and state / local government risk assessments
- Past human health assessment efforts for inorganic arsenic
- Stakeholder comments and requests
- Congressional Request (HR 2055; HR 112-151)
 - Review by National Academy of Sciences (NAS)
- Recommendations from the NAS



Selected NAS Recommendations

From “Science and Decisions” (NAS 2009)

- Expand agency and interagency collaboration
- Implement scoping and problem formulation
- Consider feasibility/benefits of options in the design stages
- Uncertainty and variability into dose response analysis
- Incorporation of probabilistic and distributional methods into dose-response analysis
- Evaluate chemicals in terms of mode of action, background exposure, disease processes, and vulnerable populations
- Criteria to justify alternative assumptions in place of default assumptions



Selected NAS Recommendations

From Formaldehyde review (NAS 2011)

- Literature search strategy and literature evaluation criteria (e.g., systematic review)
- Weight of evidence evaluation for non-cancer endpoints
- Use HERO database to capture study information and data
- Sensitivity analyses for reference values and effect of uncertainty factors
- Harmonize characterization of uncertainty and variability
- Unify outcome consideration around common modes of action



Common Themes

(NAS 2011, 2009; EPA, 2005, 2000)

- Transparency- Explicitness in the health assessment process
- Clarity- Health assessment is free from obscure language and is easy to understand
- Consistency- Conclusions of the health assessment are characterized in harmony w/ other EPA actions
- Reasonableness- Health assessment is based on sound judgment

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Workshop Goals

- Ensure that EPA provides the public an opportunity to inform the Toxicological Review.
 - Gather scientific information and public dialogue
 - Many opportunities beyond this workshop
 - Submit information to the docket
 - Future public meetings
 - Webinar series
- Transparently communicate how EPA will produce an assessment that meets the needs of the Agency and the public.
 - Presentations during this workshop
 - NCEA website
 - Other tools (e.g., IRIS List-serve, blogs, etc.)

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Workshop Logistics

- Workshop is organized into 5 sessions
 - 1) Applying Systematic Review to the iAs Toxicological Review
 - 2) Hazard Identification for iAs
 - 3) Dose Response
 - 4) Roundtable Discussion on Planning and Scoping
 - 5) Opportunity for Additional Public Comment and Workshop Summary
- General format for each session
 - Panel Discussion (*State of the Science*)
 - Opportunity for Public Comment (Webinar & In Person)

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Workshop Logistics

- Webinar Participants
 - Please submit comments or questions at any time during the workshop. Comments or questions from webinar participants will be during the Discussion section for each session as indicated on the agenda.
 - If you experience technical difficulties, please type this in as a comment on the webinar or email: EPA_arsenic@icfi.com
- RTP Facility (in-person participants)
 - Comments and question from in-person participants will alternate with comments from the webinar

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Thank You...

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EXTRA SLIDES

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Past Efforts for the Toxicological Review of Inorganic Arsenic

- ✓ First arsenic assessment posted to IRIS database in 1988
- ✓ National Research Council (NRC)/National Academy of Sciences (NAS) review of scientific information: 1999
- ✓ Science Advisory Board completes review of EPA Arsenic Rule: 2001
- ✓ EPA establishes Primary Drinking Water Standard for Arsenic: 2001
- ✓ NRC assessment and review of EPA Drinking Water Standard: 2001
- ✓ EPA implements NRC 2001 recommendations in draft arsenic IRIS assessment and submits for Science Advisory Board review: 2005
- ✓ Science Advisory Board completes review of EPA 2005 draft: 2007
- ✓ Science Advisory Board completes review of EPA 2010 draft: 2011

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Common Themes (NAS 2011, 2009; EPA, 2005, 2000)

Principal	Definition	Criteria for a human health assessment
Transparency	Explicitness in the risk assessment process	<ul style="list-style-type: none"> -Describe assessment approaches, assumptions, extrapolations and model use -Describe plausible alternative assumptions -Identify data gaps -Distinguish science from policy -Describe uncertainty -Describe relative strength of assessment
Clarity	Assessment is free from obscure language and is easy to understand	<ul style="list-style-type: none"> -Employ brevity -Use plain English -Avoid technical terms -Use simple tables, graphics, equations

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Common Themes Continued

(NAS 2011, 2009; EPA, 2005, 2000)

Principal	Definition	Criteria for a human health assessment
Consistency	Conclusion of the risk assessment are characterized in harmony w/ other EPA actions	<ul style="list-style-type: none"> -Follow statutes -Follow Agency Guidance -Use Agency information systems -Define level of effort -Use review by peers
Reasonableness	Risk assessment is based on sound judgment	<ul style="list-style-type: none"> -Use review by peers -Use best available scientific information -Use good judgment -Use plausible alternatives



iAs Human Health Assessment -Considerations

- NAS recommendations for human health assessments (2011; 2009)
- Common themes with guidance documents (EPA, 2005; EPA, 2000)
- Social, behavioral, and physical impacts (epigenome)
- Useful reviews and documents: SAB (2011, 2007, 2001) NAS (2001, 1999)

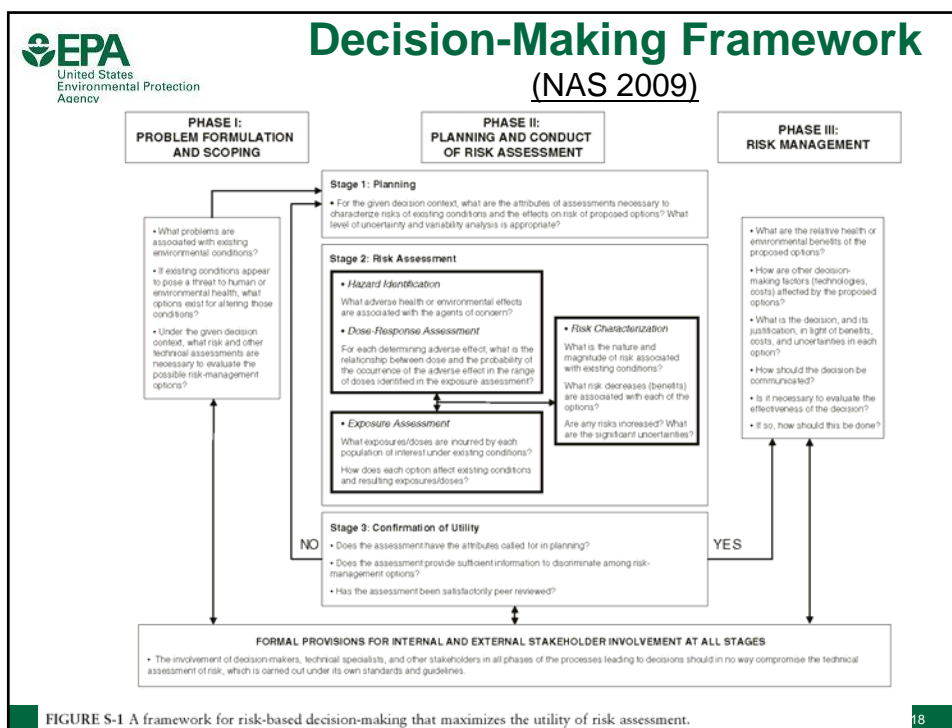
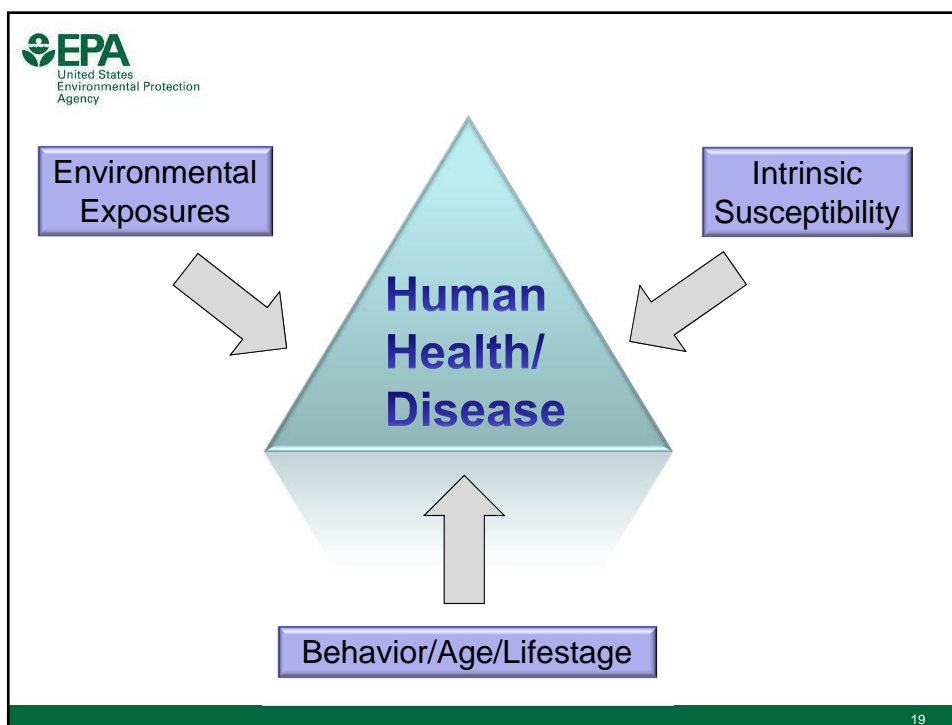


FIGURE S-1 A framework for risk-based decision-making that maximizes the utility of risk assessment.

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Useful Reviews and Documents:

- SAB (2011; 2007) were reviews of existing EPA iAs cancer assessments
- NAS (2001) was a human health assessment; NAS (1999) was a review of the state of the science
- Recommendations should be utilized as appropriate throughout the development of a new integrated assessment (e.g., criteria categories for evaluating epi literature)
- Some recommendations may not be as informative for developing a new assessment compared to revising an existing assessment
- State of the science and human health assessment approaches are evolving



Workshop Goals

- Communication (throughout the development of the assessment)
 - Efficient and effective means
 - iAs human health assessment project page (internal and external)
 - Arsenic Communication Committee
 - List-serve
 - Ongoing dialogue
 - Assessment schedule
- Clear understanding of current regulatory practices and challenges across the Agency



Workshop Goals

- Based upon the current regulatory practices and challenges, what are the needs of the Agency with respect to a new iAs human health assessment?
- Problem formulation / Scoping
- Provide input as to how the Agency can effectively engage outside stakeholders specifically for iAs
- Address how Agency partners can collaborate to develop an integrated assessment for iAs

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EXTRA SLIDES

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Selected SAB Recommendations

SAB Review of 2010 iAs Cancer Assessment (SAB 2011)

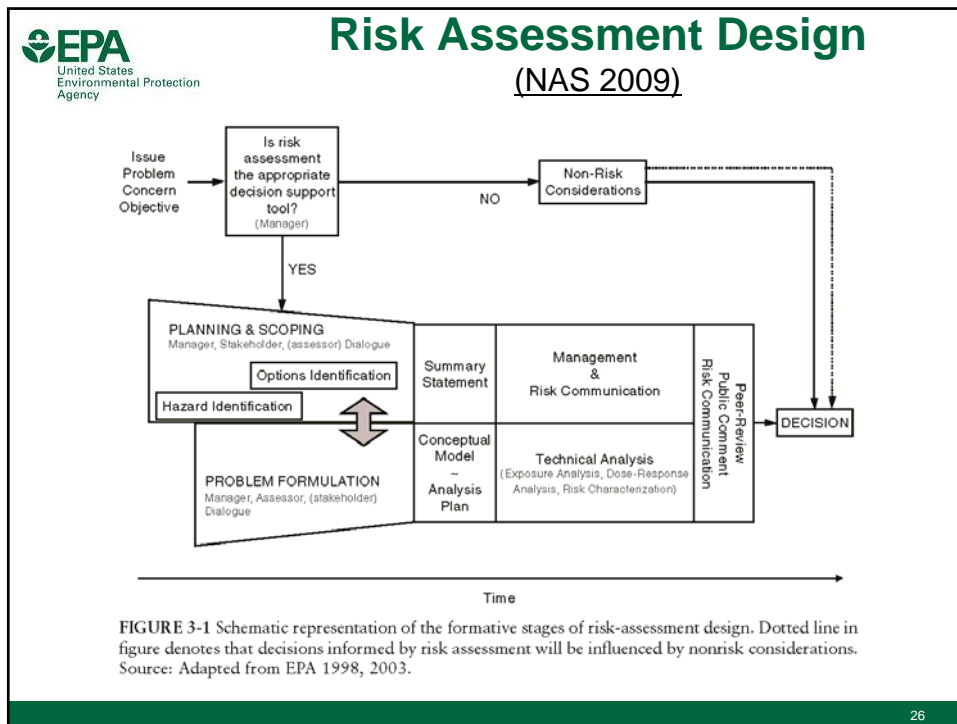
- Recommended EPA should more clearly state and utilize criteria to evaluate epidemiological data
- Improve the documentation of data sets utilized for sensitivity analyses;
- For complete EPA risk assessments provide context to the cancer risk estimate should be interpreted w/ respect to current cancer incidence in US populations
- Improve the documentation for selection and use of exposure assumptions for sensitivity analyses
- Commented on the importance of conducting integrated assessments (i.e., cancer and noncancer)



Selected SAB Recommendations


SAB Review of 2005 iAs Cancer Assessment (SAB 2007)

- Concluded that multiple modes of action are likely operable for the effects due to iAs
- Taiwanese dataset remains the most appropriate for dose-response analysis
- Epi studies of the US should be critically evaluated based upon a uniform set of criteria
- Information to determine a non-linear form of the dose-response and the linear default is most appropriate
- Recommendations regarding specific cancer modeling, exposure assumptions, and corresponding sensitivity analyses






DRAFT PLANNING AND SCOPING SUMMARY

 **EPA**
United States
Environmental Protection
Agency


Draft Planning and Scoping Summary for the Inorganic Arsenic (iAs) IRIS Assessment



John Cowden
U.S. EPA / ORD / NCEA
Research Triangle Park, NC

Office of Research and Development
National Center for Environmental Assessment

Disclaimer: the views expressed in this presentation are those of the speaker and do not necessarily represent the views or policies of the U.S. EPA.

 **EPA**
United States
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Agency

Key Terminology

IRIS Toxicological Review <ul style="list-style-type: none"> • Hazard identification • Dose-response assessment 	Risk Assessment <ul style="list-style-type: none"> • Hazard identification • Dose-response assessment • Exposure assessment • Risk characterization
Planning and Scoping <ul style="list-style-type: none"> • Establishes goals, breadth, depth, and focus of the toxicological review • Develops common understanding of why assessment is being developed, how assessment will be used, and data needed to answer key questions 	Problem Formulation <ul style="list-style-type: none"> • Describes specific technical details for the toxicological review • Consists of conceptual model and analysis plan

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NAS Guidance on Planning and Scoping


Scoping Elements	Considerations
Partner and Stakeholder needs	<ul style="list-style-type: none"> • Context and purpose • Areas of interest
Exposure	<ul style="list-style-type: none"> • Spatial and temporal considerations • Sources and source mitigation • Environmental exposure and exposure mitigation • Individual intake pathways and individual intake mitigations
Hazard Identification	<ul style="list-style-type: none"> • Direct and mitigation related hazards and stressors • Direct and mitigation-related adverse health outcomes • At-risk populations and populations at mitigation-related risk

Source: "Science and Decisions: Advancing Risk Assessment,"
National Research Council of the National Academies, 2009




Draft Planning and Scoping Summary

Considered	Limited Consideration	Outside the Scope
<ul style="list-style-type: none"> • Oral and inhalation exposure • Chronic exposure and exposure during susceptible life stages (e.g., in utero) • Cancer and non-cancer effects • Susceptibility – stressors and potential biomarkers of at-risk populations • Impact of uncertainty • Dose-response analysis indicating risk at potential exposure levels (including background levels) 	<ul style="list-style-type: none"> • Exposure sources (e.g., environmental sources and individual intake pathways) – <u>as related to dose-response analysis</u> • Arsenic speciation data – <u>as data inform hazard identification, mode of action analyses, or dose response analyses</u> • Bioavailability – <u>as related to dose-response analysis</u> 	<ul style="list-style-type: none"> • Options for mitigating exposure • Health effects related to clinical or ecological mitigation efforts • Dose-response analyses for mitigation related health effects • Cost benefit analysis on human health effects of iAs exposure or related mitigation efforts

 United States Environmental Protection Agency	<h2>Developing the Toxicological Review</h2>
PROPOSED PROCESS	PROPOSED DATE
Scoping and Problem Formulation Workshop	September 2012
Public Stakeholder Workshop	January 2013
NAS Public Workshops	January 24, 2013 April 4, 2013
Interim NAS Report	Fall 2013
Completed Draft iAs Toxicological Review	Spring 2014
Complete Internal Agency Review	Summer 2014
Complete Interagency Science Consultation	Summer 2014
Release draft to External Peer Review (NAS Review)	Fall 2014
Complete NAS Review of the iAs Toxicological Review	Winter 2015
Complete Internal Agency Review/Interagency Science Discussion	Spring 2016
Post to IRIS Website	Summer 2016

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 United States Environmental Protection Agency	<h2>Conclusions</h2>
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- **Planning and Scoping Summary**
 - DRAFT statement – discussion for Session 4
 - Context for discussions
- **Developing the IRIS Toxicological Review**
 - Multiple opportunities for public engagement
 - Importance of utility to partners and stakeholders
- **Next steps**
 - Meeting Report
 - Problem Formulation
 - NAS Public Meetings

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Additional Context: NAS Recommendations

From Formaldehyde review (NAS 2011)

- Literature search strategy and evaluation criteria (e.g., systematic review)
 - Use HERO database to capture study information and data
- Unify outcome consideration around common modes of action
- Weight of evidence evaluation for non-cancer endpoints
- Sensitivity analyses for reference values and effect of uncertainty factors
- Harmonize characterization of uncertainty and variability



Additional context: NAS Recommendations (con't)

From "Science and Decisions" (NAS 2009)

- Expand collaboration
- Implement scoping and problem formulation
- Criteria to justify alternative assumptions in place of default assumptions
- Consider feasibility/benefits of options in the design stages
- Evaluate chemicals in terms of mode of action, background exposure, disease processes, and vulnerable populations
- Incorporation of probabilistic and distributional methods into dose-response analysis
- Develop process to communicate and incorporate uncertainty and variability into analysis



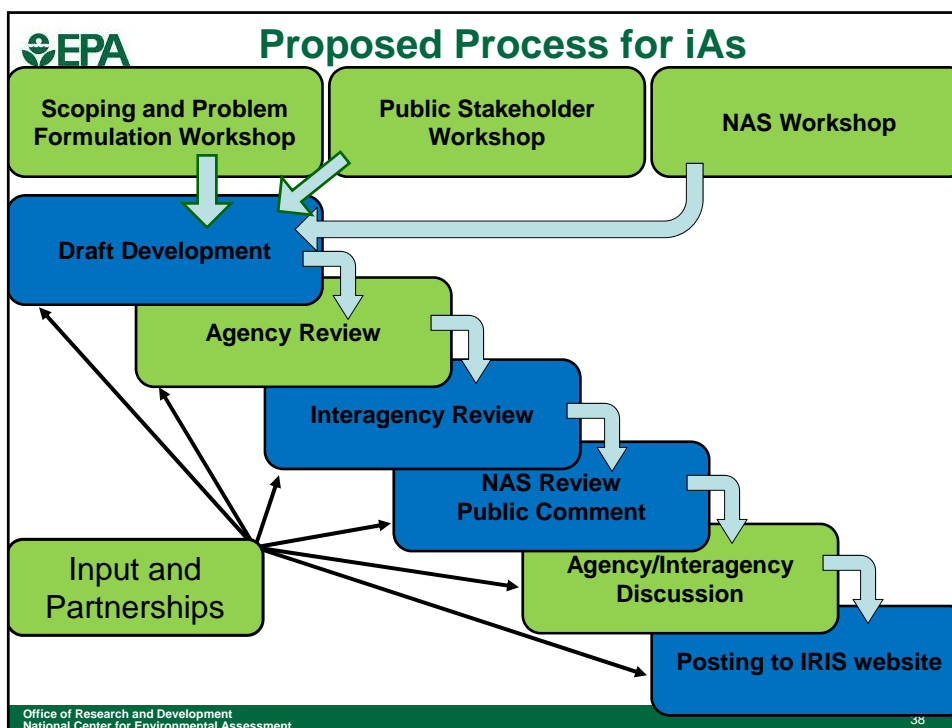
Outline

- **Drafting the IRIS Toxicological Review**
 - Draft planning and scoping summary
- **Developing the IRIS Toxicological Review**
 - Proposed timeline



Draft Planning and Scoping Summary

Considered	Limited Consideration	Outside the Scope
<ul style="list-style-type: none"> • Oral and inhalation exposure • Chronic exposure and exposure during susceptible life stages (e.g., in utero) • Cancer and non-cancer effects • Susceptibility – stressors and potential biomarkers of at-risk populations • Impact of uncertainty • Dose-response analysis indicating risk at potential exposure levels (including background levels) 	<ul style="list-style-type: none"> • Exposure sources (e.g., environmental sources and individual intake pathways) – <i>as related to dose-response analysis</i> • Arsenic speciation data – <i>as data inform hazard identification, mode of action analyses, or dose response analyses</i> • Bioavailability – <i>as related to dose-response analysis</i> 	<ul style="list-style-type: none"> • Options for mitigating exposure • Health effects related to clinical or ecological mitigation efforts • Dose-response analyses for mitigation related health effects • Cost benefit analysis on human health effects of iAs exposure or related mitigation efforts



EPA Selected NAS Recommendations

United States Environmental Protection Agency

From Formaldehyde review (NAS 2011)

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From “Science and Decisions” (NAS 2009)

- Expand agency and interagency collaboration
- Implement scoping and problem formulation
- Consider feasibility/benefits of options in the design stages
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- Incorporation of probabilistic and distributional methods into dose-response analysis
- Evaluate chemicals in terms of mode of action, background exposure, disease processes, and vulnerable populations
- Criteria to justify alternative assumptions in place of default assumptions

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Draft Planning and Scoping Summary

Scoping Elements	Considered	Limited Consideration	Beyond the Scope
Exposure	<ul style="list-style-type: none"> • Oral and inhalation exposure • Chronic exposure • Exposure during susceptible life stages (e.g., in utero) 	<ul style="list-style-type: none"> • Exposure sources (e.g., environmental sources and individual intake pathways) – <i>as related to dose-response analysis</i> 	<ul style="list-style-type: none"> • Options for mitigating exposure
Hazard Identification	<ul style="list-style-type: none"> • Cancer and non-cancer effects • Susceptibility – stressors and potential biomarkers of at-risk populations • Impact of uncertainty 	<ul style="list-style-type: none"> • Arsenic speciation data – <i>as data inform hazard identification</i> 	<ul style="list-style-type: none"> • Health effects related to clinical or ecological mitigation efforts
Dose-Response	<ul style="list-style-type: none"> • Dose-response analysis indicating risk at potential exposure levels (including background levels) • Impact of uncertainty 	<ul style="list-style-type: none"> • Bioavailability – <i>as related to dose-response analysis</i> • Arsenic speciation – <i>as related to mode of action/dose-response analysis</i> 	<ul style="list-style-type: none"> • Dose-response analyses for mitigation related health effects • Cost benefit analysis on human health effects of iAs exposure or related mitigation efforts

SOUTHERN ENVIRONMENTAL LAW CENTER

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Facsimile 919-929-9421

October 9, 2012

Sheila Holman
Division of Air Quality
1641 Mail Service Center
Raleigh, North Carolina 27699-1641

VIA ELECTRONIC MAIL (daq.publiccomments@ncdenr.gov)

**Re: Comments on Potential Amendments to the Air Toxics Rules Pursuant to
Section 1 and Section 3 of Session Law 2012-91**

Dear Ms. Holman:

The Southern Environmental Law Center, on behalf of itself, Clean Air Carolina, and Medical Advocates for Healthy Air, respectfully submits the following comments on potential changes to the North Carolina air toxics program. On September 5, 2012, the Division of Air Quality ("DAQ") published notice of its review of the air toxics rules pursuant to Section 3 of Session Law 2012-91. DAQ also stated its intention to consider potential amendments to the air toxics rules pursuant to Section 1 of Session Law 2012-91 at this time. On September 25, 2012, DAQ held a stakeholder meeting and presented an overview of possible changes to the air toxics rules.

In the public notice, DAQ stated that it would accept written comments through October 9, 2012. These comments are therefore timely. DAQ also declared that it would accept supplemental comments during the pendency of its review process. The Southern Environmental Law Center therefore reserves the right to provide additional comments.

Background

The air toxics program was established in 1990 "to protect public health."¹ The program fills gaps left by the federal hazardous air pollution program. As the North Carolina Department of Energy and Natural Resources ("DENR") explains, "[f]ederal programs [were] not intended to comprehensively address all air toxics emissions", but were instead "designed in anticipation that state and local air toxics programs would address local issues and federal program limitations."²

¹ See Control of Toxic Air Pollutants, 15A N.C.A.C. 2D .1101 (2012).

² Control of Toxic Air Pollutants in North Carolina, DENR, Division of Air Quality, Environmental Review Commission Meeting at 12 (Sept. 28, 2011), *available at* http://www.wral.com/asset/news/state/nccapitol/2011/09/28/10196478/Holman_presentation.PDF, Attachment A.

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October 9, 2012
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The air toxics program supplements the federal hazardous air pollution regulations in a number of key respects. First, the air toxics program covers 21 pollutants that are not subject to federal hazardous air pollutant regulations.³ These pollutants include acetic acid, ammonia, bromine, fluoride, hydrogen sulfide, and nitric acid.⁴ The air toxics program is the only source of protection against emissions of these air pollutants for the people of North Carolina. Second, while the federal program imposes technology-based standards, the state program institutes health-based standards to ensure that levels of pollution in the ambient air are safe. This protects the public in situations where a facility uses state-of-the-art pollution controls, but still contributes to unacceptable concentrations of ambient pollutants. Finally, the federal program applies on a source-by-source basis, so that some sources at a facility may not be subject to any limits. The air toxics program, on the other hand, applies to all sources at a regulated facility. In sum, the air toxics program safeguards public health where the federal program falls short.

Even so, only 75% of toxic air pollution is currently regulated under the state and federal rules combined.⁵ North Carolina is home to more hazardous air pollutant emissions than almost any other state, and ranks fourth in the nation according to the Toxics Release Inventory.⁶ Any attempts to weaken the North Carolina air toxics program would exacerbate this situation and the adverse health effects of toxic pollutants.

On June 28, 2012, the North Carolina legislature enacted amendments to the air toxics program.⁷ Section 1 of the amendments directs DENR to implement rules that exempt sources subject to federal hazardous air pollutant regulations from air toxics rules. But if an exempt source presents an “unacceptable risk to human health,” DENR must require the facility to eliminate this unacceptable risk. DENR must make a written finding of unacceptable risk, which can be based on modeling, epidemiological studies, monitoring data, or other information. Section 3 of the amendments requires DAQ to review the air toxics rules “to determine whether changes could be made to the rules or their implementation to reduce unnecessary regulatory burden and increase the efficient use of Division resources while maintaining protection of public health.” The amendments direct DAQ to “report the results of its review, including recommendations, if any, to the Environmental Review Commission”.

DAQ must take this opportunity to ensure that the new law is implemented in a way that promotes the overarching purpose of the act: the protection of public health.

³ See Toxic Air Pollutants Regulated by North Carolina, EPA and South Carolina 57-64, *available at* <http://www.ncleg.net/documentsites/committees/ERC/2011-2012%20ERC%20Documents/2%20-%20October%2012,%202011/Handouts%20and%20Presentations/2011-1012%20ERC%20Submittal%20-%20Attachments.pdf>, Attachment B.

⁴ *Id.*

⁵ Control of Toxic Air Pollutants in North Carolina, *supra* note 3, at 6.

⁶ *Id.* at 8.

⁷ See An Act to Exempt from State Air Toxics Emissions Controls Those Sources of Emissions That Are Subject to Certain Federal Emissions Requirements, 2012 N.C. Sess. Laws 91 (2012).

Section 1

1. DAQ's implementation of Section 1 is premature and unauthorized.

DAQ states that it has been implementing the session law since its effective date of June 28, 2012. As such, DAQ is currently exempting sources subject to the federal rules listed in section 1(a)(5)a, unless the agency determines that they present an unacceptable risk to human health.⁸

But DAQ's actions violate the plain language of the session law. If a statute is unambiguous, North Carolina courts will not defer to the interpretation of the agency charged with implementing the statute.⁹ Instead, the agency must apply the statute as written. Section 1(a)(5) states that the Department "shall implement *rules* adopted pursuant to this subsection as follows . . ." (emphasis added). DAQ has not adopted rules to exempt facilities that are subject to federal hazardous air pollutant regulations, and therefore it is prematurely granting exemptions without the regulatory framework mandated by the session law. This violates the plain language of the statute, and DAQ must cease implementing section 1(a)(5)a-b until it has adopted the legally required rules. Any exemptions that have been granted by DAQ so far are unauthorized and unlawful.

2. DAQ must define "unacceptable risk to human health."

Under the amendments to the air toxics program, the Department must determine whether increased toxic emissions from a new facility or a modification of a facility present an "unacceptable risk to human health."¹⁰ But "unacceptable risk" is not defined in the statute or in DAQ's regulations.

DAQ must provide a concrete, regulatory definition of "unacceptable risk" that protects the public from harmful levels of toxic air pollutants. This definition must be "commensurate with established air quality standards."¹¹ At the very least, any emission that causes or contributes to an exceedance of acceptable ambient levels ("AALs") should be defined as an "unacceptable risk." DAQ has indicated that an exceedance of an AAL would be considered an unacceptable risk, but it should codify this understanding to provide reassurance to the public and ensure that this interpretation is not abandoned in the future. Moreover, any exceedance of an AAL would endanger public health and contravene the purpose of the air toxics program. DAQ therefore cannot consider any AAL exceedance to be an acceptable risk. As explained in the following paragraphs, the regulations should also require DAQ to consider all potential exposure routes, impacts of multiple facilities and combinations of pollutants, and background pollution levels.

⁸ See 2012 N.C. Sess. Laws 91 § 1(a)(5)a.

⁹ See *Charlotte-Mecklenburg Hosp. Auth. v. N.C. HHS*, 201 N.C. App. 70, 72-73 (N.C. Ct. App. 2009).

¹⁰ 2012 N.C. Sess. Laws 91 § 1(a)(5)b.

¹¹ *Id.* § 1(a)(5).

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“Unacceptable risk” must be defined based on all relevant transmission pathways, not just inhalation. Human exposure to air pollutants occurs through multiple pathways, including water, soil, ingestion, and inhalation. For example, mercury that is emitted into the air eventually deposits into water bodies, where microbial action converts it into methylmercury. People are primarily exposed to methylmercury by eating fish¹² in which methylmercury accumulates and concentrates, rather than through inhalation of mercury.¹³ Mercury levels in the kinds of fish people eat can be hundreds of thousands to millions of times more concentrated than the water in which they swim.¹⁴ Mercury concerns are particularly salient in North Carolina, where all 13,123 water bodies in the state are listed as impaired for mercury.¹⁵ DAQ must therefore consider all exposure pathways to determine whether a facility’s emissions pose an unacceptable risk.

The current AALs fail to account for numerous exposure pathways, and therefore cannot alone be used to ensure that there is no unacceptable risk to human health. DENR relies on the North Carolina Scientific Advisory Board (“SAB”) to formulate recommendations for acceptable ambient concentrations for toxic air pollutants.¹⁶ The SAB conducts a number of assessments to determine the AALs, including an exposure assessment.¹⁷ According to SAB guidelines, exposure assessments “generally take into account potential inhalation exposures only.”¹⁸ The SAB *may* also consider dermal exposure and exposure due to deposition of airborne pollutants onto soil or water.¹⁹ But the SAB has not always done so when proposing AALs. For example, when the SAB conducted its latest review of mercury, it concluded that it was “unable to fulfill the request to develop an AAL based on indirect [i.e., non-inhalation] routes of exposure.”²⁰ The SAB explained that it lacked critical information on North Carolina freshwater systems, emission factors, and appropriate atmospheric models at that time.²¹ The current AALs therefore do not consider environmental fate and transport or likely routes of environmental exposure to mercury.²² DAQ must ensure that all exposure pathways are taken into account when determining whether the emission of any toxic air pollutant presents an unacceptable risk to human health, and cannot rely solely on AALs.

¹² EPA, Mercury Study Report to Congress, EPA-452/R-97-005 (Dec. 1997) (“Mercury Study”), Vol. 1, 0-2.

¹³ *Id.* at 2-5.

¹⁴ Environmental Protection Agency, Mercury, Human Exposure, <http://www.epa.gov/hg/exposure.htm#3> (last visited Oct. 9, 2012).

¹⁵ See North Carolina Mercury Total Maximum Daily Load (“TMDL”) at 4 (July 5, 2012).

¹⁶ Secretary’s Science Advisory Board on Toxic Air Pollutants, Internal Guidelines for Toxicological Evaluation of Chemicals Released to the Air, <http://daq.state.nc.us/toxics/risk/sab/sabtoxra.shtml>.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ North Carolina Science Advisory Board, Mercury in the Environment at 3, 68 (Dec. 5, 2000), *available at* <http://daq.state.nc.us/toxics/risk/sab/>, Attachment C.

²¹ *Id.* at 3.

²² *Id.* at 14.

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DAQ must also take into account other sources of emissions and background levels of pollutants in its unacceptable risk analysis. If emissions of multiple facilities exceed the AALs, the air toxics program requires the facilities to “apply additional controls or to otherwise reduce emissions.”²³ DAQ should clarify that the same principle applies when multiple facilities emit toxic pollutants that present an unacceptable risk. The purpose of the air toxics program is to protect public health, and DAQ cannot achieve this goal if it allows unacceptable risks to occur simply because multiple facilities contribute to the problem. Similarly, DAQ must also consider background levels of pollutants in its analysis. Otherwise it cannot ensure that a facility’s emissions will not further exacerbate existing pollutant levels to the point that they present an unacceptable risk of harm. The regulations should therefore explain that DAQ will consider these aggravating factors in its risk analysis.

DAQ must also consider the cumulative impact of multiple pollutants. The current air toxics regulations acknowledge that the effects of multiple pollutants may be additive.²⁴ The regulations should clarify that DAQ will take this into account when considering whether a facility poses an unacceptable risk.

Finally, DAQ should not create an exemption for facilities that are located in remote areas. Under the current air toxics program, facilities do not have to show that their emissions are below acceptable ambient levels, as long as they are located in areas that are unoccupied or uninhabitable.²⁵ But “uninhabitable” and “unoccupied” are vague, undefined terms in the regulations. For example, a facility could emit dangerous levels of toxic pollutants, thereby making it unsafe for anyone to live in the surrounding area. Such an area might be considered “uninhabitable,” but it would be absurd to allow a facility to create its own loophole in this manner. Similarly, a facility could emit toxic levels of pollutants in a habitable but unoccupied area, thereby effectively prohibiting people from moving into the vicinity. Moreover, pollutants with acute health effects may harm people even in uninhabited locations. People may fish and recreate in these areas, and thereby be exposed to toxic pollutants. In sum, it would be contrary to the purpose of the air toxics program for DAQ to exempt facilities from the unacceptable risk analysis based on their location in an uninhabitable or unoccupied area.

3. The regulations must authorize DAQ to collect sufficient data from a facility to determine whether there is an unacceptable risk.

Section 1 requires DAQ to review a facility’s application and determine whether its emissions present an unacceptable risk to human health.²⁶ But the law does not specify what information a facility must provide to allow DAQ to conduct its determination. DAQ should promulgate regulations that clarify what information a facility must give in its permit application. At a minimum, this information must include actual, potential, and permitted emission rates for toxic emissions from each source at an existing facility, and projected actual and potential

²³ 15A N.C.A.C. 2D .1107(a).

²⁴ *See id.* 2D .1108.

²⁵ Toxic Air Pollutant Procedures, 15A NCAC 2Q .0709(a)(2)(A) (2012).

²⁶ 2012 N.C. Sess. Laws 91 § 1(a)(5)b.

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emission rates for each source at a new facility. Facilities must provide these emission rates using mass balancing analysis, source testing, or other methods approved by the Director that provide an equivalently accurate estimate of the emission rate.²⁷ Without this data, DAQ could do nothing more than guess whether a facility presents an unacceptable risk to human health.

4. DAQ must specify the models and averaging times that it will use in making its determination.

DAQ must create regulations that identify the models it will rely on when determining whether a facility presents an unacceptable risk. Regulations currently prescribe standards for the models that DAQ may use to see whether a facility will exceed AALs.²⁸ DAQ should follow this approach and use models that are at least as rigorous and accurate as the model described in 40 C.F.R. 51.166(l) or its equivalent.

In addition, DAQ must specify what time period it will use to evaluate a facility's impact on human health (i.e., a one-hour or 24-hour averaging period for emissions). DAQ should conduct its analysis and set emission limits based on averaging times that correspond to the health risks for each pollutant. Thus, for pollutants that that present risks to people from short-term, higher-level exposures, DAQ should evaluate a facility's emissions and set limits for short-term peak emissions. Where chronic exposure to low-levels of pollutants pose a risk to people's health and welfare, DAQ should evaluate emissions and set limits on that basis. Notably, some pollutants may present risks at short-term, peak concentrations as well as from chronic exposure to lower concentrations. In such cases, the evaluation and resulting emission limits must address the full range of health risk scenarios.

5. DAQ should clarify that facilities with non-exempt sources must still comply with the air toxics program.

Under the amendments to the air toxics program, a source subject to federal hazardous air pollution regulations is no longer subject to the air toxics rules. But 15A N.C.A.C. 2Q .0711 states that an air toxic permit is required for any facility whose emissions from "all sources" are greater than any TPERs. Therefore, if a facility contains some non-exempt sources, DAQ must assess the facility's emission rates from all sources to see whether they exceed TPERs. If so, the facility must submit plant-wide modeling to show that it will not violate the air toxics rules by exceeding AALs. DAQ should clarify and emphasize this point in the Air Toxics regulations.

6. The regulations must provide procedures for determining when an existing MACT-regulated facility presents an unacceptable risk to human health.

The amendments state that "[u]pon making a written finding that a source or facility presents...an unacceptable risk to human health," DENR must require the facility to eliminate

²⁷ See 15A NCAC 2D .1106(g).

²⁸ *Id.* 2D .1106(e).

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the risk. For new or modified sources, the Department can issue this finding after reviewing a permit application submitted by the source. But the law does not specify what might trigger DAQ's evaluation for an existing source that is not modified. Importantly, the law does not limit the situations under which DAQ can make a written finding, and therefore does not preclude DAQ from considering whether existing sources may present an unacceptable risk.

DAQ must clarify the circumstances under which it will review existing source emissions. This should include instances where DAQ lowers an AAL based on new evidence of a pollutant's impact on human health. If an existing facility exceeds the new AAL but did not exceed the previous AAL, DAQ must issue a written finding requiring the facility to eliminate this unacceptable risk. In addition, DAQ should review existing source emissions when a facility becomes subject to federal HAP regulations for the first time, but is not yet subject to TAPs regulations. DAQ should review the federal HAP permit application to determine whether the facility presents an unacceptable risk. Finally, an existing facility may also present an unacceptable risk if there is a change in weather patterns or any other change that influences the facility's emission, but would not be considered a "modification." DAQ should review all of these circumstances to determine whether existing facilities present an unacceptable risk.

7. DAQ should evaluate sources located near vulnerable populations with particular care.

The AALs are designed to protect sensitive sub-populations in North Carolina. To make certain that the program achieves this goal, DAQ should require facilities located in proximity to these groups to provide additional assurances that their emissions will not endanger public health. These vulnerable groups include children, senior citizens, pregnant women, and sick people. Therefore facilities located near schools, hospitals, nursing homes, and daycare facilities must take extra measures to prove that their emissions will not harm individuals that live or spend time in the area.

The USA Today newspaper published a study that compares health risks from exposure to toxic air pollutants outside schools across the country.²⁹ The study used a Risk Screening Environmental Indicators computer model, developed by the U.S. Environmental Protection Agency, to relatively rank 127,800 schools based on exposure to toxic chemicals. The report revealed that seven North Carolina schools were in the first percentile of schools in areas of highest modeled levels of toxic chemicals. These schools are located in Canton, Gastonia, Maxton, and Raleigh, and are exposed to dangerous levels of sulfuric acid, diisocyanates, aniline, and nitrobenzene, among other pollutants. As noted above, the air toxics program is the only set of regulations that even purports to protect the public from dangerous ambient concentrations of these pollutants. DAQ must subject facilities in these areas to heightened analysis, and ensure that these facilities are not granted a blanket exemption from the air toxics program.

²⁹ The Somekstack Effect – Toxic Air and America's Schools, USA TODAY (Dec. 8, 2008), *available at* <http://content.usatoday.com/news/nation/environment/smokestack/index>.

Section 3

8. It would be imprudent for DAQ to make sweeping changes to the air toxics program under Section 3 at this time.

DAQ is not required to make any additional changes to the air toxics regulations at this time beyond those required by Section 1(a)(5) of the amendments. Section 3 of the session law requires DAQ to determine whether changes could be made to the air toxics rules or their implementation to “reduce unnecessary regulatory burden and increase the efficient use of Division resources while maintaining protection of public health.” DAQ must “report the results of its review, including recommendations, if any, to the Environmental Review Commission.”

But DAQ cannot ensure that additional alterations under Section 3 would maintain protection of the public health, especially when the full impacts of the exemptions in Section 1 are unknown. As described above, many of the requirements in Section 1 remain undefined and unexplored, much less tested in practice. DAQ should not rush changes under Section 3 until after it has implemented Section 1 of the law and evaluated the effects of those changes on the efficacy of the program. Doing so would result in redundancies, as DAQ would likely have to revise the regulations again after the effects of the Section 1 changes become clear. This would violate one of the commandments of Section 3 by inefficiently wasting DAQ resources. Most importantly, DAQ would not be able to guarantee protection of public health if it further weakened the air toxics rules at this time. DAQ should therefore report to the ERC that it has no recommended changes at this time.

9. DAQ cannot raise the TPER thresholds and still maintain protection of public health. (Option 1)

As a preliminary matter, DAQ should make the current guidelines for setting toxic air pollutant permitting emission rates (“TPERs”) and the models used to develop TPERs available and easily accessible to the public. Only then will stakeholders be able to determine the full impact of the regulatory changes that DAQ is considering.

a. DAQ must set TPERs at the lowest level necessary to ensure that facilities will not violate AALs.

DAQ must ensure that no facility or combination of facilities exceed the AALs for any toxic pollutant.³⁰ To do so, DAQ first determines the minimum emissions level – called a TPER – at which a facility could possibly exceed an AAL.³¹ If a facility’s emission rates are above the TPER for one or more pollutants, the facility must demonstrate that it will not cause or

³⁰ 15A N.C.A.C. 2D .1104 (“A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health.”); *Id.* 2D .1107.

³¹ *Id.* 2Q .0711.

contribute to an exceedance of an AAL.³² If a facility's emission rates are below the TPER, no further effort is made to determine whether the emissions will violate an AAL. Because DAQ does not investigate facilities with emissions below the TPERs, DAQ must set the TPERs so low that it is impossible for any facility to exceed the AALs at those emission rates. This means DAQ must consider reasonable worst-case scenarios when setting TPERs. Here, the term "reasonable worst-case scenario" means the lowest emission level at which a facility could still, under certain circumstances, cause or contribute to an exceedance of an AAL.

To determine the worst-case scenario, DAQ must consider 1) the geographic and meteorological characteristics of the area surrounding the facility; 2) characteristics of the facility itself, such as the height of emission stacks or other release points, the exit temperature of the exhaust gases, and the exit velocity of pollutants, and 3) cumulative effects from multiple facilities or background levels of a pollutant. All of these factors affect a facility's potential to cause an exceedance of an AAL. DAQ must evaluate the greatest ambient concentration that a facility could produce taking into account all of these factors, plus a margin of safety, as discussed below.

- i. *TPERs must be low enough to account for weather conditions that result in the highest local concentrations of pollutants emitted by a facility.*

Meteorological and topographic conditions affect how pollutants from a facility will be distributed in the air and deposited. DAQ must therefore develop TPERs based on the meteorological conditions that will result in the greatest local concentrations of pollutants. The weather conditions that will satisfy this standard may differ based on the particular characteristics of each toxic pollutant. DAQ must use weather data that correspond to the health-risk averaging times for each pollutant. Thus, for instance, DAQ should use hourly weather data rather than monthly or yearly averages for pollutants that pose health risks based on peak short-term exposures. Moreover, DAQ must tailor its analysis for areas of the state with different weather patterns and topography.

- ii. *DAQ should consider facility characteristics that would result in the highest impact on ambient levels of pollution, rather than rely on assumptions that are favorable to facility owners.*

Many facility parameters affect pollutant dispersion, including 1) stack or release height, 2) exit velocity, 3) exit temperature, 4) stack diameter, and 5) proximity of the emission source to the property boundary.

DAQ proposes to raise the existing TPERs by using "conservative assumptions" about emission rates and facility parameters. But conservative assumptions may be less protective than

³² *Id.* 2Q .0709, .0711.

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reasonable worst-case scenario assumptions. As a result, a substantial number of facilities may exceed AALs, even though their emissions are below TPERs that are based on conservative assumptions. DAQ must ensure that its assumptions fully protect public health with a margin of error, and to do so it must set TPERs based on a reasonable worst-case scenario. In other words, the TPER should be the lowest emission rate that a facility can produce and still cause or contribute to an exceedance of AALs. This may include, for example, an assumption of ground level emissions and a low exit velocity, and an assumption that emission sources abut a facility's property boundary. DAQ should not use assumptions that distort the impact of emission rates on AALs in favor of polluters.

iii. *DAQ must set TPERs low enough to account for the potential effects of multiple facilities and background pollutant levels.*

Even if a facility could not exceed AALs in isolation, it may do so when its emissions combine with those from other facilities in the same area. DAQ must determine whether the impacts of two or more facilities contribute collectively to the exceedance of an AAL.³³ If so, the facilities must apply additional controls or “otherwise reduce emissions.”³⁴ TPERs must therefore be set at the lowest level necessary to capture cumulative effects from other facilities. If TPERs are set too high, DAQ and the public may never even be aware of situations in which many low-emitting facilities collectively cause a public health problem.

To determine which facilities may have additive impacts, DAQ must have access to adequate mapping of emission sources. The official air toxics program website currently displays a map of toxic air pollutant sources that does not appear to have been updated since 1993.³⁵ This map shows how many toxic air pollution facilities are located in each county, but does not provide any greater specificity. DAQ must utilize a more detailed, frequently updated map that shows the actual location of facilities and the pollutants emitted by each facility. If two or more facilities that emit the same pollutant are located in close enough proximity to each other to cause cumulative impacts, DAQ must require a modeling demonstration.

Furthermore, DAQ does not currently consider background levels of pollution when setting TPERs.³⁶ This raises the risk that a facility will exceed AALs, even if its emission rates are too low to cause an exceedance of an AAL independently. A comprehensive assessment of the background levels of toxic air pollution in North Carolina must be conducted in order to

³³ *Id.* 2D .1107(a), (c).

³⁴ *Id.* 2D .1107(a).

³⁵ See Division of Air Quality, Hazardous and Toxic Air Pollutants, *Number of Facilities, Number of Toxic Air Pollutants, and Pounds Emitted by County for 1993*, available at <http://daq.state.nc.us/toxics/hap/>, Attachment D.

³⁶ See Air Toxics Program, Acceptable Ambient Levels (AALs), daq.state.nc.us/toxics/aaldisc.pdf (“Since there is not enough monitoring information to be able to know the general ambient concentrations for each of the 97 TAPs, the North Carolina program focuses on what a facility adds to the existing environment.”)

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allow facilities and DAQ to analyze the emissions that each facility adds to these background levels. Until then, DAQ should set TPERs low with a wide margin of safety to ensure that a facility's emissions do not combine with background levels of a pollutant and exceed public health standards.

The factors in the paragraphs above show that in reality, two facilities with the same emission rates can result in very different ambient levels of a pollutant. DAQ proposes to raise TPERs based on its observation that many facilities that exceed TPERs do not come close to exceeding AALs. But this reasoning defies logic and the requirements of the air toxics program, which prohibit *any* facility from exceeding AALs. Due to the factors listed above, one facility might exceed the AALs, even if other facilities with the same emission rate do not. Therefore DAQ must base TPERs on a worst-case scenario to ensure that all facilities remain below AALs. DAQ's approach also ignores the purpose of a screening level review, which is to identify sources for more detailed study. It is natural and expected that many of the sources that trigger the requirement for a more comprehensive modeling demonstration would not violate the health-based standard. Moreover, DAQ's statement that many permitted facilities do not come close to exceeding AALs may be based on faulty modeling, as discussed below.

In sum, if DAQ uses anything other than reasonable worst-case scenarios, the modeling would not depict maximum pollutant concentrations that might result over time and from a full range of operating and meteorological conditions. As a result, one or more facilities may exceed AALs and endanger public health. Moreover, as noted above, facilities that are below TPER thresholds do not have to submit a permit application or model their emissions. As a result, DAQ and the public cannot readily determine whether a particular facility that is below the TPER threshold is contributing to an exceedance of AALs. Violations of AALs in these circumstances would go unchecked. DAQ must prevent this from occurring by setting TPERs based on a reasonable worst-case scenario with a margin of safety. It cannot allow a facility to evade permit and modeling requirements unless there is absolutely no reasonable chance that the facility, alone or in combination with other facilities, could exceed the AALs.

b. DAQ's observation that many facilities that exceed TPERs do not exceed AALs may be based on faulty modeling.

DAQ is considering raising TPERs because the agency observes many instances where a facility that exceeds TPERs does not come close to exceeding AALs. But evidence suggests that this observation is based on faulty modeling. The modeling and limits for the PCS Phosphate permit illustrate this point.³⁷ PCS Phosphate is the largest emitter of toxic air pollutants in the state. Yet DAQ concluded that the facility can emit 5,199 pounds of mercury each day and stay below the AAL for mercury. These permitted emissions amount to roughly 949 tons of mercury per year – over six times the amount of mercury that is emitted each year by all U.S.

³⁷ See Southern Environmental Law Center Comments on PCS Phosphate Title V Permit Renewal, Attachment E.

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anthropogenic sources.³⁸ These levels of mercury, a potent neurotoxin, cannot be protective of public health, and call into question DAQ's impression that many facilities do not exceed human health standards.

In addition, many of the modeling inputs for PCS phosphate are outdated; others are estimates rather than measurements.³⁹ DAQ cannot base its conclusions about facilities' contributions to AALs on such inadequate modeling data.

10. Exempting natural gas and propane combustion units would do little to increase efficiency, but may pose great risks to public health. (Option 2)

DAQ should not provide a blanket exemption for natural gas combustion units. If, as DAQ presumes, most of these units do not emit potentially dangerous levels of toxic air pollutants, then they will be below TPER thresholds and exempt from permitting requirements. If any of these units are above the TPER threshold, then they may potentially emit toxic pollutants at levels that harm human health, either alone or in combination with other facilities.

In the alternative, if DAQ pursues this as a possible exemption, DAQ must craft the exemption so that only smaller sources will be eligible. Sources with the potential to emit above a certain threshold, such as the proposed Sutton plant, must not be exempted.

11. DAQ should not exempt emergency engines. (Option 3)

Emergency engines may be small and numerous, but they are also dirty and inefficient. They often emit a lot of pollution in a very condensed timeframe. These types of units emit formaldehyde, acetaldehyde, methanol, benzene, toluene, 1,3-butadiene, 2,2,4-trimethylpentane, hexane, xylene, naphthalene, PAH, methylene chloride, and ethylbenzene and should not be completely unregulated. Moreover, although these units are expected to be used only in emergencies, facilities may rely on them more frequently if they are unregulated. Industries that cannot shut down for even short time periods, such as internet server facilities, may rely on large emergency generators more regularly.⁴⁰

DAQ must review emergency engines at a facility under the air toxics program. If the facility's combined emission exceed TPERs, DAQ must quantify and impose restrictions on the toxic air pollutants from these sources. In the alternative, DAQ must simplify the process for emergency generators, rather than completely exempting or ignoring them.

³⁸ Mercury Study, *surpa* note 14, at Vol. I, 0-1.

³⁹ See Comments on PCS Phosphate, *surpa* note 39.

⁴⁰ James Glanz, *Power, Pollution and the Internet*, N.Y. TIMES (Sept. 22, 2012), available at http://www.nytimes.com/2012/09/23/technology/data-centers-waste-vast-amounts-of-energy-belying-industry-image.html?pagewanted=all&_r=0.

12. Registering, rather than permitting, small sources would not increase efficiency or protect public health. (Option 4)

North Carolina's permitting process provides for full notice and comment by the public, including public hearings. This process is very important for the citizens of North Carolina, and should not be eliminated. With regard to the air toxics program specifically, a permit application and the attendant public process helps inform DAQ of other sources of TAPs emissions in the same geographic area, which is an important factor in the permitting of new or additional sources, no matter how small or seemingly insignificant.

While the "registration" process has not been fully described, it is likely that important information regarding air pollution could be overlooked if facilities only have to register and not apply for a permit. Neither the agency nor the people of North Carolina will be given adequate details of pollutants emitted, emission rates, hours of operation, and other information of great importance to the public such as: whether there are multiple sources of the same pollutant in close proximity to the new source; what types of other centers of human activity are nearby, such as hospitals, schools, parks and residential areas; and other information that would assist DAQ in determining on a case by case basis if a source creates an unacceptable risk to human health.

This would be a very dramatic change to the Air Toxics Program. Hundreds of sources are already being exempt from the program as a result of Session Law 2012-91. This is certainly not the time to reduce even further the amount of information regarding toxic air pollution that will be available to DAQ and the citizens of North Carolina. Emitters in North Carolina reported in the 2010 Toxic Release Inventory over 34 million pounds of toxics and 1.5 million pounds of carcinogens. Reducing "regulatory burden" and ensuring "efficient use of division resources" cannot override the ultimate purpose of the air toxics program which is the protection of public health. DAQ therefore cannot register small sources at this time.

13. DAQ should not dispose of SIC Calls, which allow the agency to gather industry-wide information. (Option 5)

- a. Removing SIC Calls would not reduce any burden on facilities, or increase efficient use of Division resources. In fact, it would reduce efficiency because DAQ would have to reach out to each source individually.**

DAQ proposes to delete regulations that allow the Director to require all facilities under the same four-digit Standard Industrial Classification ("SIC") to submit an application at one time to comply with the air toxics rules. Currently, the Director can make this call for any facilities in industry groups that are not subject to MACT or GACT, or are only subject to MACT or GACT for unadulterated fuel combustion.⁴¹ A facility subject to a SIC Call must submit an air toxics application for all of its sources, even if they are not in the same industrial

⁴¹ 15A N.C.A.C. 2Q .0705(c).

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classification.⁴² Facilities that do not exceed TPERs for any sources do not have to file a permit application, even if they would otherwise be subject to a SIC Call.⁴³ In short, the SIC Call provides an efficient, streamlined way for DAQ to require applications from a potentially large number of facilities that may be emitting hazardous concentrations of toxic air pollutants.

DAQ has used the SIC Call provisions effectively in the past. For example, DAQ issued a SIC Call for decorative chrome platers after conducting a risk assessment for that class of sources.

Removing this useful regulatory tool would not promote any of the criteria in Section 3. First, it would not reduce any burden on facilities. Facilities would still have to provide the same required information – the only difference is that they would provide the information pursuant to a Director’s Call rather than a SIC Call. Second, removing the SIC Call option would not increase efficient use of Division resources. In fact, it would do the opposite. The Division would no longer be able to swiftly gather applications from all sources in an industry; instead, it would have to make risk determinations and request applications for each individual facility. Finally, eliminating the SIC Call would not protect human health and could unnecessarily delay implementing health protection standards for numerous facilities within a source category. It would only delay DAQ’s implementation of calls for applications that become necessary across an entire industry group.

b. The Director’s Call is not an adequate substitute.

DAQ reasons that the Director’s Call provides adequate protection in the absence of a SIC Call option. But the Director’s Call is less efficient in some situations, as described above, and insufficient for other reasons as well. Under the current regulations, DAQ can issue a SIC Call when it requires applications from many facilities in the same industry, and a Director’s Call when it needs more targeted information from a single facility. The Director’s Call forces DAQ to issue calls for one facility at a time, and is therefore not a good substitute. The proposed change also curtails the Director’s flexibility in requesting permit applications. DAQ can only issue a Director’s Call if a facility’s emissions present an unacceptable risk to human health based on the AALs or epidemiology studies. There are no such restrictions on DAQ’s ability to issue a SIC Call.⁴⁴ For example, DAQ could issue a SIC Call based on studies other than epidemiology studies, such as workplace studies, controlled human studies, laboratory animal bioassays or other laboratory studies.⁴⁵

⁴² *Id.*

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ Secretary’s Science Advisory Board on Toxic Air Pollutants, Internal Guidelines for Toxicological Evaluation of Chemicals Released to the Air, <http://daq.state.nc.us/toxics/risk/sab/sabtoxra.shtml>.

14. DAQ cannot allow facilities subject to MACT to simply comply with maximum feasible control, rather than eliminate their risk to human health. (Option 6)

If a source can show that it would be technically infeasible or cause serious economic hardship to comply with AALs, the source does not have to demonstrate that its emissions will remain below AALs.⁴⁶ In this case, the Director shall require the source to apply “maximum feasible control” instead.⁴⁷ Sources that could potentially apply for this exemption are sources constructed before May 1, 1990, certain perchloroethylene dry cleaning facilities, and combustion sources⁴⁸ permitted before July 10, 2010.⁴⁹ Maximum feasible control is defined as the maximum degree of reduction using the best technology that is available taking into account, on a case-by-case basis, human health, energy, environmental, and economic impacts and other costs.⁵⁰

Under DAQ’s proposed change, if a source is subject to MACT, then maximum feasible control would be defined as whatever federal MACT requirements apply to the source. DAQ would not make a case-by-case determination to see whether a facility could feasibly implement further controls or emission reductions. But this change would violate Section 1 of SL 2012-91 and create a loophole for sources subject to MACT when protections are needed the most, as described below.

a. If a MACT-regulated facility presents an unacceptable risk by exceeding an AAL, the facility must *eliminate* this risk.

Section 1 exempts all sources subject to MACT from the air toxics program, unless the Director determines that these sources present an “unacceptable risk to human health.” A facility that violates an AAL presents an unacceptable risk to human health.⁵¹ If a facility presents an unacceptable risk, the Director must require the facility to submit a permit application that *eliminates* the unacceptable risk.⁵² In other words, DAQ cannot simply require the facility to mitigate its violation of an AAL. The statutory requirement to eliminate the risk is absolute, and therefore a MACT-regulated source cannot evade this requirement in cases of technical infeasibility or economic hardship. There is no situation, then, where a MACT-regulated source would be able to apply maximum feasible control rather than comply with AAL requirements. As a result, DAQ’s proposal to set maximum feasible control equal to MACT is at best meaningless, and at worst contrary to the plain language of Section 1.

⁴⁶ 15A N.C.A.C. 2Q.0709(b).

⁴⁷ *Id.*

⁴⁸ Combustion sources include “boilers, space heaters, process heaters, internal combustion engines, and combustion turbines” that burn wood or fossil fuel. 15A N.C.A.C. 2Q. 0703. The term does not include incinerators, waste combustors, kilns, dryers, or direct heat exchange industrial processes. *Id.*

⁴⁹ 15A N.C.A.C. 2Q.0709(b).

⁵⁰ *Id.* 2Q .0703(13).

⁵¹ See discussion above in section 2.

⁵² See 2012 Sess. Laws 91 §1(a)(5)b.

b. Setting maximum feasible control equal to MACT deprives the public of protection when it is most needed.

Even if DAQ could allow a MACT-regulated source to apply maximum feasible control, it should not allow the source to satisfy the maximum feasible control requirement by complying with its existing MACT requirements. Instead, DAQ should analyze the source critically to ensure that emission controls are as stringent as possible. A source could also switch fuels or raw materials, or change its hours or methods of operations to ensure that it does not pose a threat to the public. DAQ must apply all of these potential options rather than allow a facility to simply comply with MACT requirements. DAQ has already determined that such a source presents a danger to public health, and therefore this is exactly where a rigorous analysis of possible controls is most critical.

15. DAQ should not use a facility's projected actual emissions to determine whether the facility is subject to and in compliance with the air toxics program. (Option 7)


DAQ proposes to use projected actual emissions to determine whether a facility exceeds TPERs and complies with AALs. But projected actual emissions do not represent the facility's maximum ability to pollute the environment and harm public health. Instead, DAQ should use the permitted emission rate, or in some cases the potential emission rate, to determine whether a facility will contribute to an exceedance of the acceptable ambient level or trigger TPERs. The emission limit contained in a facility's permit is the amount of pollution that a facility is legally allowed to emit. DAQ must therefore use this figure to determine whether a facility presents a risk to public health. If a facility's actual or projected actual emissions are lower than its permit limit, then the permit limit should be lowered to more accurately track these emissions. Without lowering the permit limits, there is no guarantee that a facility will keep its emissions low enough to prevent adverse health effects. In addition, DAQ should not rely on projected actual emissions in lieu of the "actual rate of emissions" as defined in 15A N.C.A.C. 2Q .0703.

Conclusion

DAQ must cease the unlawful implementation of Section 1 of Session Law 2012-91 and implement regulations that safeguard the public. DAQ should not impose any changes under Section 3 at this time because all of the contemplated amendments would fail to maintain protection of human health.

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Respectfully submitted,



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April 4, 2013

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VIA ELECTRONIC MAIL (daq.publiccomments@ncdenr.gov)

**Re: Comments on Proposed Amendments to the Air Toxics Rules
Pursuant to Section 1 and Section 3 of Session Law 2012-91.**

Dear Ms. Holman:

The Southern Environmental Law Center, on behalf of itself, Clean Air Carolina, and Medical Advocates for Healthy Air, respectfully submits the following comments on the proposed revisions to the North Carolina air toxics program. We also incorporate by reference and re-emphasize the comments we submitted to the Division of Air Quality (“DAQ”) on October 9, 2012 regarding potential amendments to the air toxics rules. *See* Comments on Potential Amendments to the Air Toxics Rules Pursuant to Section 1 and Section 3 of Session Law 2012-91 (Oct. 9, 2012), Attachment A (hereinafter the “2012 Comment Letter”).

On June 28, 2012, the North Carolina legislature enacted amendments to the air toxics program. *See* An Act to Exempt from State Air Toxics Emissions Controls Those Sources of Emissions That Are Subject to Certain Federal Emissions Requirements, 2012 N.C. Sess. Laws 91 (2012) (hereinafter the “session law”). On September 5, 2012, DAQ published notice of its review of the air toxics rules pursuant to sections 1 and 3 of the session law. On March 13, 2013, DAQ issued proposed revisions to the air toxics rules, and held a stakeholder meeting regarding these revisions on March 20, 2013. DAQ stated that it would accept written comments through April 4, 2013. These comments are therefore timely. The Southern Environmental Law Center reserves the right to provide additional comments throughout the rule revision process.

**ATTACHMENT 5 TO SELC'S COMMENTS ON AAL AND TPER FOR ARSENIC
JUNE 14, 2013**

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I. Background

The air toxics program was established in 1990 “to protect public health.” Control of Toxic Air Pollutants, 15A N.C. Admin. Code 02D .1101 (2012). The program fills gaps left by the federal hazardous air pollution program. As the North Carolina Department of Energy and Natural Resources (“DENR”) explains, “Federal programs [were] not intended to comprehensively address all air toxics emissions,” but were instead “designed in anticipation that state and local air toxics programs would address local issues and federal program limitations.” Control of Toxic Air Pollutants in North Carolina, DENR, Division of Air Quality, Environmental Review Commission Meeting at 12 (Sept. 28, 2011), *available at* http://www.wral.com/asset/news/state/nccapitol/2011/09/28/10196478/Holman_presentation.PDF.

The air toxics program supplements the federal hazardous air pollution regulations in a number of key respects. First, while the federal program imposes technology-based standards, the state program institutes health-based standards to prevent harmful levels of pollution in the ambient air. The use of health-based standards protects the public in situations where a facility uses state-of-the-art pollution controls, but still contributes to unacceptable concentrations of ambient pollutants. Second, the North Carolina program protects the public in situations where multiple facilities contribute to unsafe pollution levels, even though none of the facilities alone would exceed North Carolina’s health-based standards. Third, the air toxics program covers 21 pollutants that are not subject to federal hazardous air pollutant regulations. These pollutants include acetic acid, ammonia, bromine, fluoride, hydrogen sulfide, and nitric acid. The air toxics program is the only source of protection against emissions of these air pollutants for the people of North Carolina. Finally, the federal program applies on a source-by-source basis, so that some sources at a facility may not be subject to any limits. The air toxics program, on the other hand, applies to all sources at a regulated facility. In sum, the air toxics program safeguards public health where the federal program falls short.

The session law instructs the DENR to implement rules that exempt many sources from the protections provided by the air toxics program. If an exempt source presents an “unacceptable risk to human health,” however, the agency must require the facility to eliminate this unacceptable risk. The agency must make a written finding of unacceptable risk, which can be based on modeling, epidemiological studies, monitoring data, or other information. Section 3 of the session law requires DAQ to review the air toxics rules “to determine whether changes could be made to the rules or their implementation to reduce unnecessary regulatory burden and increase the efficient use of Division resources while maintaining protection of public health.” Any revision of the air toxics rules must ensure that DAQ’s implementation of the session law promotes the overarching purpose of the act: the protection of public health.

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II. Comments on DAQ's Proposed Revisions to the Air Toxics Rules

A. DAQ's Proposal to Create a More Lax Set of TPERs for Unobstructed, Vertically Oriented Sources Is Not Protective of Human Health.

DAQ proposes to create an additional set of toxic permitting emission rates ("TPERs") in 15A N.C. Admin. Code 02Q .0711 for facilities with non-obstructed, vertically oriented emission sources. TPERs are emission thresholds: if a facility's emissions are lower than the TPERs for each pollutant under the air toxics program, the facility does not have to obtain a permit or demonstrate that its emissions will not contribute to air toxics violations. It is therefore critical that TPERs are set at the appropriate level to capture all facilities that have the potential to violate the air toxics standards. The new set of TPERs proposed by DAQ would be based on less conservative assumptions, and would allow facilities to emit more carcinogens, chronic toxicants, acute systemic toxicants, and acute irritants without having to demonstrate that their emissions will not exceed the public health standards (also known as acceptable ambient levels ("AALs")). DAQ expects that at least one-third of all facilities subject to the air toxics rules would be able to rely on this new, less stringent set of TPERs. According to DAQ, the TPERs are conservatively set. But DAQ did not consider the effects of multiple sources or background pollution levels when establishing the TPERs, and therefore it is possible that a source's emissions might fall below the new, more permissive TPER thresholds and still contribute to an AAL violation.

If the combined emissions of two or more facilities exceed an AAL, DAQ must require facilities "to apply additional controls or to otherwise reduce emissions" in order to avoid adverse effects on human health. 15A N.C. Admin. Code 02D .1107. DAQ may not be aware that facilities' combined emissions exceed an AAL, however, if one or more of the facilities are exempted from the air toxics program because the emissions from each single facility fall below the TPERs. In order to assure compliance with the air toxics program, DAQ must set all TPERs at the lowest level necessary to capture the effects of multiple facilities' collective emissions. DAQ should therefore maintain the existing TPERs for all sources.

B. DAQ Should Incorporate and Clarify Section 1(A)(5)b. of the Session Law (the "Director's Call") in the Air Toxics Regulations.

In section 02Q .0702 of the air toxics rules, DAQ proposes to incorporate the exemption contained in the session law for sources that are also subject to the following federal standards: National Emission Standards for Hazardous Air Pollutants ("NESHAPs"), Maximum Achievable Control Technology ("MACT") standards, Generally Available Control Technology ("GACT") standards, or case-by-case MACTs.

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DAQ did not, however, include the human health protections that follow these exemptions in the session law.

The session law instructs the agency to review applications and determine whether a source's emissions "would present an unacceptable risk to human health." If so, the agency must require the owner or operator of the source to take action that "eliminates the unacceptable risk to human health." There is no logical reason to include the exemptions in the air toxics rules without also including the human health protections that accompany these exemptions in the session law. Doing so would generate questions and confusion about why the agency incorporated the exemption only. In addition, the session law instructs the agency to "implement *rules adopted* pursuant to this subsection." See Session Law 2012-91, Section 1(a)(5). The session law therefore requires the agency to adopt rules in order to implement the terms of the session law. To comply with the session law and avoid confusion, the air toxics rules should also include a description of DAQ's duty to examine the risks that exempt sources could present to human health.

DAQ should also clarify and memorialize its interpretation of potentially ambiguous terms in this provision. DAQ should define "unacceptable risk to human health" to mean, at a minimum, an exceedance of an AAL. In addition, DAQ should define "unacceptable risk" to include risks to vulnerable sub-populations, such as the young, elderly, and people with pre-existing medical conditions. Finally, the term should include risks that are based on all relevant transmission pathways, rather than inhalation only. For example, when determining whether emissions of mercury present an unacceptable risk, DAQ should consider the health risk posed by human consumption of fish contaminated with methylmercury.

DAQ should also describe the process it will follow when reviewing applications to determine whether emissions present an unacceptable risk. This process should include collection of sufficient and accurate data and model inputs, modeling that follows procedures at least as rigorous as those in 15A N.C. Admin. Code 02D .1106, pollutant-averaging times that correspond to the acute and long-term health risks for each pollutant, and consideration of the impacts of multiple facilities and background levels of pollutants.

C. DAQ Should Clarify that Any Existing Facility That Is Not Exempt Under Section 1 of the Session Law Is Still Subject to the Air Toxics Program.

DAQ proposes to repeal 15A N.C. Admin. Code 02Q .0705, which establishes requirements for existing sources under the air toxics program, in its entirety. DAQ should clarify that any existing facility that is not exempt must continue to comply with

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the air toxics rules, and must obtain a permit if its emissions exceed any of the TPERs listed in section 02Q .0711.

DAQ also proposes to repeal the provision relating to standard industrial classification ("SIC") calls in section 02Q .0705. As described in the 2012 Comment Letter, DAQ should not repeal the SIC call provision, which allows DAQ to efficiently require that all facilities in an industrial category submit air toxics applications at one time. If DAQ decides to repeal this provision, DAQ should also clarify that any facility that was required to apply for a permit pursuant to a SIC call in the past will remain subject to the air toxics program.

D. DAQ Should Not Exempt Emergency Engines. If It Does, However, DAQ Should Clarify that the Exemption Refers to Nameplate Capacity.

As described in more detail in the 2012 Comment Letter, DAQ should not exempt emergency engines under 02Q .0702(26). If DAQ decides to exempt these sources as it has proposed, however, it should clarify that only sources with a nameplate capacity of less than 4843 horsepower are exempt. As the exemption currently reads, there is a possibility that it could be misinterpreted to apply to actual usage, rather than nameplate capacity. Applying the exemption based on usage over a specific time frame would require additional monitoring and oversight by DAQ, and therefore would not satisfy the goal of increasing the efficient use of Division resources, as described in section 3 of the session law.

E. DAQ Should Not Eliminate Its Duty to Assess Risks from Exempt Combustion Sources.

DAQ proposes to eliminate its duty to (i) "assess all risks from existing exempt combustion sources using exposure and risk assessment methodologies and information," and (ii) determine whether amendments are necessary based on this assessment. *See* Toxic Air Pollutant Procedures, 15A N.C. Admin. Code 02Q .0701(b) (2012); 15A N.C. Admin. Code 02Q .0702(18). DAQ reasons that many combustion sources are also subject to federal hazardous air pollution rules, and are therefore exempt under section 1 of the session law. Yet it is still important to understand and address the risks posed by those combustion sources that are not exempt under the session law.

In addition, although section 1 of the session law exempts certain sources from the air toxics rules, the risk-assessment for combustion sources is a duty imposed on DAQ, rather than a requirement that the exempt sources themselves comply with a standard. Therefore the requirement for DAQ to perform a risk analysis does not conflict with the exemption provided by the session law.

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Finally, DAQ may still regulate exempt sources under section 1 if they pose an “unacceptable risk to human health,” and DAQ’s assessment will help reveal whether this is the case for combustion sources. Therefore DAQ should analyze the risks of combustion sources, as the air toxics rules currently require.

F. DAQ Should Not Exempt Combustion Sources That Burn Adulterated Wood.

The air toxics rules currently exempt combustion sources that burn unadulterated wood. DAQ proposes to expand this exemption to combustion sources that burn any type of wood. This could include wood that is painted, varnished, stained, oiled, waxed, or coated or treated with any chemical. DAQ should not further weaken the air toxics program by expanding exemptions at this time.

Conclusion

DAQ must ensure that any revisions to the air toxics rules protect public health, and must abandon proposed changes that fail to do so, as described above. We appreciate your consideration of these comments.

Respectfully submitted,



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MMA/MB/lap
Attachment: SELC Comments on Air Toxics Program (Oct. 9, 2012)

ATTACHMENT A

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October 9, 2012

Sheila Holman
Division of Air Quality
1641 Mail Service Center
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VIA ELECTRONIC MAIL (daq.publiccomments@ncdenr.gov)

**Re: Comments on Potential Amendments to the Air Toxics Rules Pursuant to
Section 1 and Section 3 of Session Law 2012-91**

Dear Ms. Holman:

The Southern Environmental Law Center, on behalf of itself, Clean Air Carolina, and Medical Advocates for Healthy Air, respectfully submits the following comments on potential changes to the North Carolina air toxics program. On September 5, 2012, the Division of Air Quality (“DAQ”) published notice of its review of the air toxics rules pursuant to Section 3 of Session Law 2012-91. DAQ also stated its intention to consider potential amendments to the air toxics rules pursuant to Section 1 of Session Law 2012-91 at this time. On September 25, 2012, DAQ held a stakeholder meeting and presented an overview of possible changes to the air toxics rules.

In the public notice, DAQ stated that it would accept written comments through October 9, 2012. These comments are therefore timely. DAQ also declared that it would accept supplemental comments during the pendency of its review process. The Southern Environmental Law Center therefore reserves the right to provide additional comments.

Background

The air toxics program was established in 1990 “to protect public health.”¹ The program fills gaps left by the federal hazardous air pollution program. As the North Carolina Department of Energy and Natural Resources (“DENR”) explains, “[f]ederal programs [were] not intended to comprehensively address all air toxics emissions”, but were instead “designed in anticipation that state and local air toxics programs would address local issues and federal program limitations.”²

¹ See Control of Toxic Air Pollutants, 15A N.C.A.C. 2D .1101 (2012).

² Control of Toxic Air Pollutants in North Carolina, DENR, Division of Air Quality, Environmental Review Commission Meeting at 12 (Sept. 28, 2011), *available at* http://www.wral.com/asset/news/state/nccapitol/2011/09/28/10196478/Holman_presentation.PDF, Attachment A.

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The air toxics program supplements the federal hazardous air pollution regulations in a number of key respects. First, the air toxics program covers 21 pollutants that are not subject to federal hazardous air pollutant regulations.³ These pollutants include acetic acid, ammonia, bromine, fluoride, hydrogen sulfide, and nitric acid.⁴ The air toxics program is the only source of protection against emissions of these air pollutants for the people of North Carolina. Second, while the federal program imposes technology-based standards, the state program institutes health-based standards to ensure that levels of pollution in the ambient air are safe. This protects the public in situations where a facility uses state-of-the-art pollution controls, but still contributes to unacceptable concentrations of ambient pollutants. Finally, the federal program applies on a source-by-source basis, so that some sources at a facility may not be subject to any limits. The air toxics program, on the other hand, applies to all sources at a regulated facility. In sum, the air toxics program safeguards public health where the federal program falls short.

Even so, only 75% of toxic air pollution is currently regulated under the state and federal rules combined.⁵ North Carolina is home to more hazardous air pollutant emissions than almost any other state, and ranks fourth in the nation according to the Toxics Release Inventory.⁶ Any attempts to weaken the North Carolina air toxics program would exacerbate this situation and the adverse health effects of toxic pollutants.

On June 28, 2012, the North Carolina legislature enacted amendments to the air toxics program.⁷ Section 1 of the amendments directs DENR to implement rules that exempt sources subject to federal hazardous air pollutant regulations from air toxics rules. But if an exempt source presents an “unacceptable risk to human health,” DENR must require the facility to eliminate this unacceptable risk. DENR must make a written finding of unacceptable risk, which can be based on modeling, epidemiological studies, monitoring data, or other information. Section 3 of the amendments requires DAQ to review the air toxics rules “to determine whether changes could be made to the rules or their implementation to reduce unnecessary regulatory burden and increase the efficient use of Division resources while maintaining protection of public health.” The amendments direct DAQ to “report the results of its review, including recommendations, if any, to the Environmental Review Commission”.

DAQ must take this opportunity to ensure that the new law is implemented in a way that promotes the overarching purpose of the act: the protection of public health.

³ See Toxic Air Pollutants Regulated by North Carolina, EPA and South Carolina 57-64, *available at* <http://www.ncleg.net/documentsites/committees/ERC/2011-2012%20ERC%20Documents/2%20-%20October%2012,%202011/Handouts%20and%20Presentations/2011-1012%20ERC%20Submittal%20-%20Attachments.pdf>, Attachment B.

⁴ *Id.*

⁵ Control of Toxic Air Pollutants in North Carolina, *supra* note 3, at 6.

⁶ *Id.* at 8.

⁷ See An Act to Exempt from State Air Toxics Emissions Controls Those Sources of Emissions That Are Subject to Certain Federal Emissions Requirements, 2012 N.C. Sess. Laws 91 (2012).

Section 1

1. DAQ's implementation of Section 1 is premature and unauthorized.

DAQ states that it has been implementing the session law since its effective date of June 28, 2012. As such, DAQ is currently exempting sources subject to the federal rules listed in section 1(a)(5)a, unless the agency determines that they present an unacceptable risk to human health.⁸

But DAQ's actions violate the plain language of the session law. If a statute is unambiguous, North Carolina courts will not defer to the interpretation of the agency charged with implementing the statute.⁹ Instead, the agency must apply the statute as written. Section 1(a)(5) states that the Department "shall implement *rules* adopted pursuant to this subsection as follows . . ." (emphasis added). DAQ has not adopted rules to exempt facilities that are subject to federal hazardous air pollutant regulations, and therefore it is prematurely granting exemptions without the regulatory framework mandated by the session law. This violates the plain language of the statute, and DAQ must cease implementing section 1(a)(5)a-b until it has adopted the legally required rules. Any exemptions that have been granted by DAQ so far are unauthorized and unlawful.

2. DAQ must define "unacceptable risk to human health."

Under the amendments to the air toxics program, the Department must determine whether increased toxic emissions from a new facility or a modification of a facility present an "unacceptable risk to human health."¹⁰ But "unacceptable risk" is not defined in the statute or in DAQ's regulations.

DAQ must provide a concrete, regulatory definition of "unacceptable risk" that protects the public from harmful levels of toxic air pollutants. This definition must be "commensurate with established air quality standards."¹¹ At the very least, any emission that causes or contributes to an exceedance of acceptable ambient levels ("AALs") should be defined as an "unacceptable risk." DAQ has indicated that an exceedance of an AAL would be considered an unacceptable risk, but it should codify this understanding to provide reassurance to the public and ensure that this interpretation is not abandoned in the future. Moreover, any exceedance of an AAL would endanger public health and contravene the purpose of the air toxics program. DAQ therefore cannot consider any AAL exceedance to be an acceptable risk. As explained in the following paragraphs, the regulations should also require DAQ to consider all potential exposure routes, impacts of multiple facilities and combinations of pollutants, and background pollution levels.

⁸ See 2012 N.C. Sess. Laws 91 § 1(a)(5)a.

⁹ See *Charlotte-Mecklenburg Hosp. Auth. v. N.C. HHS*, 201 N.C. App. 70, 72-73 (N.C. Ct. App. 2009).

¹⁰ 2012 N.C. Sess. Laws 91 § 1(a)(5)b.

¹¹ *Id.* § 1(a)(5).

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“Unacceptable risk” must be defined based on all relevant transmission pathways, not just inhalation. Human exposure to air pollutants occurs through multiple pathways, including water, soil, ingestion, and inhalation. For example, mercury that is emitted into the air eventually deposits into water bodies, where microbial action converts it into methylmercury. People are primarily exposed to methylmercury by eating fish¹² in which methylmercury accumulates and concentrates, rather than through inhalation of mercury.¹³ Mercury levels in the kinds of fish people eat can be hundreds of thousands to millions of times more concentrated than the water in which they swim.¹⁴ Mercury concerns are particularly salient in North Carolina, where all 13,123 water bodies in the state are listed as impaired for mercury.¹⁵ DAQ must therefore consider all exposure pathways to determine whether a facility’s emissions pose an unacceptable risk.

The current AALs fail to account for numerous exposure pathways, and therefore cannot alone be used to ensure that there is no unacceptable risk to human health. DENR relies on the North Carolina Scientific Advisory Board (“SAB”) to formulate recommendations for acceptable ambient concentrations for toxic air pollutants.¹⁶ The SAB conducts a number of assessments to determine the AALs, including an exposure assessment.¹⁷ According to SAB guidelines, exposure assessments “generally take into account potential inhalation exposures only.”¹⁸ The SAB *may* also consider dermal exposure and exposure due to deposition of airborne pollutants onto soil or water.¹⁹ But the SAB has not always done so when proposing AALs. For example, when the SAB conducted its latest review of mercury, it concluded that it was “unable to fulfill the request to develop an AAL based on indirect [i.e., non-inhalation] routes of exposure.”²⁰ The SAB explained that it lacked critical information on North Carolina freshwater systems, emission factors, and appropriate atmospheric models at that time.²¹ The current AALs therefore do not consider environmental fate and transport or likely routes of environmental exposure to mercury.²² DAQ must ensure that all exposure pathways are taken into account when determining whether the emission of any toxic air pollutant presents an unacceptable risk to human health, and cannot rely solely on AALs.

¹² EPA, Mercury Study Report to Congress, EPA-452/R-97-005 (Dec. 1997) (“Mercury Study”), Vol. 1, 0-2.

¹³ *Id.* at 2-5.

¹⁴ Environmental Protection Agency, Mercury, Human Exposure, <http://www.epa.gov/hg/exposure.htm#3> (last visited Oct. 9, 2012).

¹⁵ See North Carolina Mercury Total Maximum Daily Load (“TMDL”) at 4 (July 5, 2012).

¹⁶ Secretary’s Science Advisory Board on Toxic Air Pollutants, Internal Guidelines for Toxicological Evaluation of Chemicals Released to the Air, <http://daq.state.nc.us/toxics/risk/sab/sabtoxra.shtml>.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Id.*

²⁰ North Carolina Science Advisory Board, Mercury in the Environment at 3, 68 (Dec. 5, 2000), *available at* <http://daq.state.nc.us/toxics/risk/sab/>, Attachment C.

²¹ *Id.* at 3.

²² *Id.* at 14.

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DAQ must also take into account other sources of emissions and background levels of pollutants in its unacceptable risk analysis. If emissions of multiple facilities exceed the AALs, the air toxics program requires the facilities to “apply additional controls or to otherwise reduce emissions.”²³ DAQ should clarify that the same principle applies when multiple facilities emit toxic pollutants that present an unacceptable risk. The purpose of the air toxics program is to protect public health, and DAQ cannot achieve this goal if it allows unacceptable risks to occur simply because multiple facilities contribute to the problem. Similarly, DAQ must also consider background levels of pollutants in its analysis. Otherwise it cannot ensure that a facility’s emissions will not further exacerbate existing pollutant levels to the point that they present an unacceptable risk of harm. The regulations should therefore explain that DAQ will consider these aggravating factors in its risk analysis.

DAQ must also consider the cumulative impact of multiple pollutants. The current air toxics regulations acknowledge that the effects of multiple pollutants may be additive.²⁴ The regulations should clarify that DAQ will take this into account when considering whether a facility poses an unacceptable risk.

Finally, DAQ should not create an exemption for facilities that are located in remote areas. Under the current air toxics program, facilities do not have to show that their emissions are below acceptable ambient levels, as long as they are located in areas that are unoccupied or uninhabitable.²⁵ But “uninhabitable” and “unoccupied” are vague, undefined terms in the regulations. For example, a facility could emit dangerous levels of toxic pollutants, thereby making it unsafe for anyone to live in the surrounding area. Such an area might be considered “uninhabitable,” but it would be absurd to allow a facility to create its own loophole in this manner. Similarly, a facility could emit toxic levels of pollutants in a habitable but unoccupied area, thereby effectively prohibiting people from moving into the vicinity. Moreover, pollutants with acute health effects may harm people even in uninhabited locations. People may fish and recreate in these areas, and thereby be exposed to toxic pollutants. In sum, it would be contrary to the purpose of the air toxics program for DAQ to exempt facilities from the unacceptable risk analysis based on their location in an uninhabitable or unoccupied area.

3. The regulations must authorize DAQ to collect sufficient data from a facility to determine whether there is an unacceptable risk.

Section 1 requires DAQ to review a facility’s application and determine whether its emissions present an unacceptable risk to human health.²⁶ But the law does not specify what information a facility must provide to allow DAQ to conduct its determination. DAQ should promulgate regulations that clarify what information a facility must give in its permit application. At a minimum, this information must include actual, potential, and permitted emission rates for toxic emissions from each source at an existing facility, and projected actual and potential

²³ 15A N.C.A.C. 2D .1107(a).

²⁴ *See id.* 2D .1108.

²⁵ Toxic Air Pollutant Procedures, 15A NCAC 2Q .0709(a)(2)(A) (2012).

²⁶ 2012 N.C. Sess. Laws 91 § 1(a)(5)b.

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emission rates for each source at a new facility. Facilities must provide these emission rates using mass balancing analysis, source testing, or other methods approved by the Director that provide an equivalently accurate estimate of the emission rate.²⁷ Without this data, DAQ could do nothing more than guess whether a facility presents an unacceptable risk to human health.

4. DAQ must specify the models and averaging times that it will use in making its determination.

DAQ must create regulations that identify the models it will rely on when determining whether a facility presents an unacceptable risk. Regulations currently prescribe standards for the models that DAQ may use to see whether a facility will exceed AALs.²⁸ DAQ should follow this approach and use models that are at least as rigorous and accurate as the model described in 40 C.F.R. 51.166(l) or its equivalent.

In addition, DAQ must specify what time period it will use to evaluate a facility's impact on human health (i.e., a one-hour or 24-hour averaging period for emissions). DAQ should conduct its analysis and set emission limits based on averaging times that correspond to the health risks for each pollutant. Thus, for pollutants that present risks to people from short-term, higher-level exposures, DAQ should evaluate a facility's emissions and set limits for short-term peak emissions. Where chronic exposure to low-levels of pollutants pose a risk to people's health and welfare, DAQ should evaluate emissions and set limits on that basis. Notably, some pollutants may present risks at short-term, peak concentrations as well as from chronic exposure to lower concentrations. In such cases, the evaluation and resulting emission limits must address the full range of health risk scenarios.

5. DAQ should clarify that facilities with non-exempt sources must still comply with the air toxics program.

Under the amendments to the air toxics program, a source subject to federal hazardous air pollution regulations is no longer subject to the air toxics rules. But 15A N.C.A.C. 2Q .0711 states that an air toxic permit is required for any facility whose emissions from "all sources" are greater than any TPERs. Therefore, if a facility contains some non-exempt sources, DAQ must assess the facility's emission rates from all sources to see whether they exceed TPERs. If so, the facility must submit plant-wide modeling to show that it will not violate the air toxics rules by exceeding AALs. DAQ should clarify and emphasize this point in the Air Toxics regulations.

6. The regulations must provide procedures for determining when an existing MACT-regulated facility presents an unacceptable risk to human health.

The amendments state that "[u]pon making a written finding that a source or facility presents...an unacceptable risk to human health," DENR must require the facility to eliminate

²⁷ See 15A NCAC 2D .1106(g).

²⁸ *Id.* 2D .1106(e).

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the risk. For new or modified sources, the Department can issue this finding after reviewing a permit application submitted by the source. But the law does not specify what might trigger DAQ's evaluation for an existing source that is not modified. Importantly, the law does not limit the situations under which DAQ can make a written finding, and therefore does not preclude DAQ from considering whether existing sources may present an unacceptable risk.

DAQ must clarify the circumstances under which it will review existing source emissions. This should include instances where DAQ lowers an AAL based on new evidence of a pollutant's impact on human health. If an existing facility exceeds the new AAL but did not exceed the previous AAL, DAQ must issue a written finding requiring the facility to eliminate this unacceptable risk. In addition, DAQ should review existing source emissions when a facility becomes subject to federal HAP regulations for the first time, but is not yet subject to TAPs regulations. DAQ should review the federal HAP permit application to determine whether the facility presents an unacceptable risk. Finally, an existing facility may also present an unacceptable risk if there is a change in weather patterns or any other change that influences the facility's emission, but would not be considered a "modification." DAQ should review all of these circumstances to determine whether existing facilities present an unacceptable risk.

7. DAQ should evaluate sources located near vulnerable populations with particular care.

The AALs are designed to protect sensitive sub-populations in North Carolina. To make certain that the program achieves this goal, DAQ should require facilities located in proximity to these groups to provide additional assurances that their emissions will not endanger public health. These vulnerable groups include children, senior citizens, pregnant women, and sick people. Therefore facilities located near schools, hospitals, nursing homes, and daycare facilities must take extra measures to prove that their emissions will not harm individuals that live or spend time in the area.

The USA Today newspaper published a study that compares health risks from exposure to toxic air pollutants outside schools across the country.²⁹ The study used a Risk Screening Environmental Indicators computer model, developed by the U.S. Environmental Protection Agency, to relatively rank 127,800 schools based on exposure to toxic chemicals. The report revealed that seven North Carolina schools were in the first percentile of schools in areas of highest modeled levels of toxic chemicals. These schools are located in Canton, Gastonia, Maxton, and Raleigh, and are exposed to dangerous levels of sulfuric acid, diisocyanates, aniline, and nitrobenzene, among other pollutants. As noted above, the air toxics program is the only set of regulations that even purports to protect the public from dangerous ambient concentrations of these pollutants. DAQ must subject facilities in these areas to heightened analysis, and ensure that these facilities are not granted a blanket exemption from the air toxics program.

²⁹ The Somekstack Effect – Toxic Air and America's Schools, USA TODAY (Dec. 8, 2008), *available at* <http://content.usatoday.com/news/nation/environment/smokestack/index>.

Section 3

8. It would be imprudent for DAQ to make sweeping changes to the air toxics program under Section 3 at this time.

DAQ is not required to make any additional changes to the air toxics regulations at this time beyond those required by Section 1(a)(5) of the amendments. Section 3 of the session law requires DAQ to determine whether changes could be made to the air toxics rules or their implementation to “reduce unnecessary regulatory burden and increase the efficient use of Division resources while maintaining protection of public health.” DAQ must “report the results of its review, including recommendations, if any, to the Environmental Review Commission.”

But DAQ cannot ensure that additional alterations under Section 3 would maintain protection of the public health, especially when the full impacts of the exemptions in Section 1 are unknown. As described above, many of the requirements in Section 1 remain undefined and unexplored, much less tested in practice. DAQ should not rush changes under Section 3 until after it has implemented Section 1 of the law and evaluated the effects of those changes on the efficacy of the program. Doing so would result in redundancies, as DAQ would likely have to revise the regulations again after the effects of the Section 1 changes become clear. This would violate one of the commandments of Section 3 by inefficiently wasting DAQ resources. Most importantly, DAQ would not be able to guarantee protection of public health if it further weakened the air toxics rules at this time. DAQ should therefore report to the ERC that it has no recommended changes at this time.

9. DAQ cannot raise the TPER thresholds and still maintain protection of public health. (Option 1)

As a preliminary matter, DAQ should make the current guidelines for setting toxic air pollutant permitting emission rates (“TPERs”) and the models used to develop TPERs available and easily accessible to the public. Only then will stakeholders be able to determine the full impact of the regulatory changes that DAQ is considering.

a. DAQ must set TPERs at the lowest level necessary to ensure that facilities will not violate AALs.

DAQ must ensure that no facility or combination of facilities exceed the AALs for any toxic pollutant.³⁰ To do so, DAQ first determines the minimum emissions level – called a TPER – at which a facility could possibly exceed an AAL.³¹ If a facility’s emission rates are above the TPER for one or more pollutants, the facility must demonstrate that it will not cause or

³⁰ 15A N.C.A.C. 2D .1104 (“A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health.”); *Id.* 2D .1107.

³¹ *Id.* 2Q .0711.

contribute to an exceedance of an AAL.³² If a facility's emission rates are below the TPER, no further effort is made to determine whether the emissions will violate an AAL. Because DAQ does not investigate facilities with emissions below the TPERs, DAQ must set the TPERs so low that it is impossible for any facility to exceed the AALs at those emission rates. This means DAQ must consider reasonable worst-case scenarios when setting TPERs. Here, the term "reasonable worst-case scenario" means the lowest emission level at which a facility could still, under certain circumstances, cause or contribute to an exceedance of an AAL.

To determine the worst-case scenario, DAQ must consider 1) the geographic and meteorological characteristics of the area surrounding the facility; 2) characteristics of the facility itself, such as the height of emission stacks or other release points, the exit temperature of the exhaust gases, and the exit velocity of pollutants, and 3) cumulative effects from multiple facilities or background levels of a pollutant. All of these factors affect a facility's potential to cause an exceedance of an AAL. DAQ must evaluate the greatest ambient concentration that a facility could produce taking into account all of these factors, plus a margin of safety, as discussed below.

- i. *TPERs must be low enough to account for weather conditions that result in the highest local concentrations of pollutants emitted by a facility.*

Meteorological and topographic conditions affect how pollutants from a facility will be distributed in the air and deposited. DAQ must therefore develop TPERs based on the meteorological conditions that will result in the greatest local concentrations of pollutants. The weather conditions that will satisfy this standard may differ based on the particular characteristics of each toxic pollutant. DAQ must use weather data that correspond to the health-risk averaging times for each pollutant. Thus, for instance, DAQ should use hourly weather data rather than monthly or yearly averages for pollutants that pose health risks based on peak short-term exposures. Moreover, DAQ must tailor its analysis for areas of the state with different weather patterns and topography.

- ii. *DAQ should consider facility characteristics that would result in the highest impact on ambient levels of pollution, rather than rely on assumptions that are favorable to facility owners.*

Many facility parameters affect pollutant dispersion, including 1) stack or release height, 2) exit velocity, 3) exit temperature, 4) stack diameter, and 5) proximity of the emission source to the property boundary.

DAQ proposes to raise the existing TPERs by using "conservative assumptions" about emission rates and facility parameters. But conservative assumptions may be less protective than

³² *Id.* 2Q .0709, .0711.

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reasonable worst-case scenario assumptions. As a result, a substantial number of facilities may exceed AALs, even though their emissions are below TPERs that are based on conservative assumptions. DAQ must ensure that its assumptions fully protect public health with a margin of error, and to do so it must set TPERs based on a reasonable worst-case scenario. In other words, the TPER should be the lowest emission rate that a facility can produce and still cause or contribute to an exceedance of AALs. This may include, for example, an assumption of ground level emissions and a low exit velocity, and an assumption that emission sources abut a facility's property boundary. DAQ should not use assumptions that distort the impact of emission rates on AALs in favor of polluters.

iii. *DAQ must set TPERs low enough to account for the potential effects of multiple facilities and background pollutant levels.*

Even if a facility could not exceed AALs in isolation, it may do so when its emissions combine with those from other facilities in the same area. DAQ must determine whether the impacts of two or more facilities contribute collectively to the exceedance of an AAL.³³ If so, the facilities must apply additional controls or “otherwise reduce emissions.”³⁴ TPERs must therefore be set at the lowest level necessary to capture cumulative effects from other facilities. If TPERs are set too high, DAQ and the public may never even be aware of situations in which many low-emitting facilities collectively cause a public health problem.

To determine which facilities may have additive impacts, DAQ must have access to adequate mapping of emission sources. The official air toxics program website currently displays a map of toxic air pollutant sources that does not appear to have been updated since 1993.³⁵ This map shows how many toxic air pollution facilities are located in each county, but does not provide any greater specificity. DAQ must utilize a more detailed, frequently updated map that shows the actual location of facilities and the pollutants emitted by each facility. If two or more facilities that emit the same pollutant are located in close enough proximity to each other to cause cumulative impacts, DAQ must require a modeling demonstration.

Furthermore, DAQ does not currently consider background levels of pollution when setting TPERs.³⁶ This raises the risk that a facility will exceed AALs, even if its emission rates are too low to cause an exceedance of an AAL independently. A comprehensive assessment of the background levels of toxic air pollution in North Carolina must be conducted in order to

³³ *Id.* 2D .1107(a), (c).

³⁴ *Id.* 2D .1107(a).

³⁵ See Division of Air Quality, Hazardous and Toxic Air Pollutants, *Number of Facilities, Number of Toxic Air Pollutants, and Pounds Emitted by County for 1993*, available at <http://daq.state.nc.us/toxics/hap/>, Attachment D.

³⁶ See Air Toxics Program, Acceptable Ambient Levels (AALs), daq.state.nc.us/toxics/aaldisc.pdf (“Since there is not enough monitoring information to be able to know the general ambient concentrations for each of the 97 TAPs, the North Carolina program focuses on what a facility adds to the existing environment.”)

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allow facilities and DAQ to analyze the emissions that each facility adds to these background levels. Until then, DAQ should set TPERs low with a wide margin of safety to ensure that a facility's emissions do not combine with background levels of a pollutant and exceed public health standards.

The factors in the paragraphs above show that in reality, two facilities with the same emission rates can result in very different ambient levels of a pollutant. DAQ proposes to raise TPERs based on its observation that many facilities that exceed TPERs do not come close to exceeding AALs. But this reasoning defies logic and the requirements of the air toxics program, which prohibit *any* facility from exceeding AALs. Due to the factors listed above, one facility might exceed the AALs, even if other facilities with the same emission rate do not. Therefore DAQ must base TPERs on a worst-case scenario to ensure that all facilities remain below AALs. DAQ's approach also ignores the purpose of a screening level review, which is to identify sources for more detailed study. It is natural and expected that many of the sources that trigger the requirement for a more comprehensive modeling demonstration would not violate the health-based standard. Moreover, DAQ's statement that many permitted facilities do not come close to exceeding AALs may be based on faulty modeling, as discussed below.

In sum, if DAQ uses anything other than reasonable worst-case scenarios, the modeling would not depict maximum pollutant concentrations that might result over time and from a full range of operating and meteorological conditions. As a result, one or more facilities may exceed AALs and endanger public health. Moreover, as noted above, facilities that are below TPER thresholds do not have to submit a permit application or model their emissions. As a result, DAQ and the public cannot readily determine whether a particular facility that is below the TPER threshold is contributing to an exceedance of AALs. Violations of AALs in these circumstances would go unchecked. DAQ must prevent this from occurring by setting TPERs based on a reasonable worst-case scenario with a margin of safety. It cannot allow a facility to evade permit and modeling requirements unless there is absolutely no reasonable chance that the facility, alone or in combination with other facilities, could exceed the AALs.

b. DAQ's observation that many facilities that exceed TPERs do not exceed AALs may be based on faulty modeling.

DAQ is considering raising TPERs because the agency observes many instances where a facility that exceeds TPERs does not come close to exceeding AALs. But evidence suggests that this observation is based on faulty modeling. The modeling and limits for the PCS Phosphate permit illustrate this point.³⁷ PCS Phosphate is the largest emitter of toxic air pollutants in the state. Yet DAQ concluded that the facility can emit 5,199 pounds of mercury each day and stay below the AAL for mercury. These permitted emissions amount to roughly 949 tons of mercury per year – over six times the amount of mercury that is emitted each year by all U.S.

³⁷ See Southern Environmental Law Center Comments on PCS Phosphate Title V Permit Renewal, Attachment E.

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anthropogenic sources.³⁸ These levels of mercury, a potent neurotoxin, cannot be protective of public health, and call into question DAQ's impression that many facilities do not exceed human health standards.

In addition, many of the modeling inputs for PCS phosphate are outdated; others are estimates rather than measurements.³⁹ DAQ cannot base its conclusions about facilities' contributions to AALs on such inadequate modeling data.

10. Exempting natural gas and propane combustion units would do little to increase efficiency, but may pose great risks to public health. (Option 2)

DAQ should not provide a blanket exemption for natural gas combustion units. If, as DAQ presumes, most of these units do not emit potentially dangerous levels of toxic air pollutants, then they will be below TPER thresholds and exempt from permitting requirements. If any of these units are above the TPER threshold, then they may potentially emit toxic pollutants at levels that harm human health, either alone or in combination with other facilities.

In the alternative, if DAQ pursues this as a possible exemption, DAQ must craft the exemption so that only smaller sources will be eligible. Sources with the potential to emit above a certain threshold, such as the proposed Sutton plant, must not be exempted.

11. DAQ should not exempt emergency engines. (Option 3)

Emergency engines may be small and numerous, but they are also dirty and inefficient. They often emit a lot of pollution in a very condensed timeframe. These types of units emit formaldehyde, acetaldehyde, methanol, benzene, toluene, 1,3-butadiene, 2,2,4-trimethylpentane, hexane, xylene, naphthalene, PAH, methylene chloride, and ethylbenzene and should not be completely unregulated. Moreover, although these units are expected to be used only in emergencies, facilities may rely on them more frequently if they are unregulated. Industries that cannot shut down for even short time periods, such as internet server facilities, may rely on large emergency generators more regularly.⁴⁰

DAQ must review emergency engines at a facility under the air toxics program. If the facility's combined emission exceed TPERs, DAQ must quantify and impose restrictions on the toxic air pollutants from these sources. In the alternative, DAQ must simplify the process for emergency generators, rather than completely exempting or ignoring them.

³⁸ Mercury Study, *surpa* note 14, at Vol. I, 0-1.

³⁹ See Comments on PCS Phosphate, *surpa* note 39.

⁴⁰ James Glanz, *Power, Pollution and the Internet*, N.Y. TIMES (Sept. 22, 2012), available at http://www.nytimes.com/2012/09/23/technology/data-centers-waste-vast-amounts-of-energy-belying-industry-image.html?pagewanted=all&_r=0.

12. Registering, rather than permitting, small sources would not increase efficiency or protect public health. (Option 4)

North Carolina's permitting process provides for full notice and comment by the public, including public hearings. This process is very important for the citizens of North Carolina, and should not be eliminated. With regard to the air toxics program specifically, a permit application and the attendant public process helps inform DAQ of other sources of TAPs emissions in the same geographic area, which is an important factor in the permitting of new or additional sources, no matter how small or seemingly insignificant.

While the "registration" process has not been fully described, it is likely that important information regarding air pollution could be overlooked if facilities only have to register and not apply for a permit. Neither the agency nor the people of North Carolina will be given adequate details of pollutants emitted, emission rates, hours of operation, and other information of great importance to the public such as: whether there are multiple sources of the same pollutant in close proximity to the new source; what types of other centers of human activity are nearby, such as hospitals, schools, parks and residential areas; and other information that would assist DAQ in determining on a case by case basis if a source creates an unacceptable risk to human health.

This would be a very dramatic change to the Air Toxics Program. Hundreds of sources are already being exempt from the program as a result of Session Law 2012-91. This is certainly not the time to reduce even further the amount of information regarding toxic air pollution that will be available to DAQ and the citizens of North Carolina. Emitters in North Carolina reported in the 2010 Toxic Release Inventory over 34 million pounds of toxics and 1.5 million pounds of carcinogens. Reducing "regulatory burden" and ensuring "efficient use of division resources" cannot override the ultimate purpose of the air toxics program which is the protection of public health. DAQ therefore cannot register small sources at this time.

13. DAQ should not dispose of SIC Calls, which allow the agency to gather industry-wide information. (Option 5)

- a. Removing SIC Calls would not reduce any burden on facilities, or increase efficient use of Division resources. In fact, it would reduce efficiency because DAQ would have to reach out to each source individually.**

DAQ proposes to delete regulations that allow the Director to require all facilities under the same four-digit Standard Industrial Classification ("SIC") to submit an application at one time to comply with the air toxics rules. Currently, the Director can make this call for any facilities in industry groups that are not subject to MACT or GACT, or are only subject to MACT or GACT for unadulterated fuel combustion.⁴¹ A facility subject to a SIC Call must submit an air toxics application for all of its sources, even if they are not in the same industrial

⁴¹ 15A N.C.A.C. 2Q .0705(c).

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classification.⁴² Facilities that do not exceed TPERs for any sources do not have to file a permit application, even if they would otherwise be subject to a SIC Call.⁴³ In short, the SIC Call provides an efficient, streamlined way for DAQ to require applications from a potentially large number of facilities that may be emitting hazardous concentrations of toxic air pollutants.

DAQ has used the SIC Call provisions effectively in the past. For example, DAQ issued a SIC Call for decorative chrome platers after conducting a risk assessment for that class of sources.

Removing this useful regulatory tool would not promote any of the criteria in Section 3. First, it would not reduce any burden on facilities. Facilities would still have to provide the same required information – the only difference is that they would provide the information pursuant to a Director’s Call rather than a SIC Call. Second, removing the SIC Call option would not increase efficient use of Division resources. In fact, it would do the opposite. The Division would no longer be able to swiftly gather applications from all sources in an industry; instead, it would have to make risk determinations and request applications for each individual facility. Finally, eliminating the SIC Call would not protect human health and could unnecessarily delay implementing health protection standards for numerous facilities within a source category. It would only delay DAQ’s implementation of calls for applications that become necessary across an entire industry group.

b. The Director’s Call is not an adequate substitute.

DAQ reasons that the Director’s Call provides adequate protection in the absence of a SIC Call option. But the Director’s Call is less efficient in some situations, as described above, and insufficient for other reasons as well. Under the current regulations, DAQ can issue a SIC Call when it requires applications from many facilities in the same industry, and a Director’s Call when it needs more targeted information from a single facility. The Director’s Call forces DAQ to issue calls for one facility at a time, and is therefore not a good substitute. The proposed change also curtails the Director’s flexibility in requesting permit applications. DAQ can only issue a Director’s Call if a facility’s emissions present an unacceptable risk to human health based on the AALs or epidemiology studies. There are no such restrictions on DAQ’s ability to issue a SIC Call.⁴⁴ For example, DAQ could issue a SIC Call based on studies other than epidemiology studies, such as workplace studies, controlled human studies, laboratory animal bioassays or other laboratory studies.⁴⁵

⁴² *Id.*

⁴³ *Id.*

⁴⁴ *Id.*

⁴⁵ Secretary’s Science Advisory Board on Toxic Air Pollutants, Internal Guidelines for Toxicological Evaluation of Chemicals Released to the Air, <http://daq.state.nc.us/toxics/risk/sab/sabtoxra.shtml>.

14. DAQ cannot allow facilities subject to MACT to simply comply with maximum feasible control, rather than eliminate their risk to human health. (Option 6)

If a source can show that it would be technically infeasible or cause serious economic hardship to comply with AALs, the source does not have to demonstrate that its emissions will remain below AALs.⁴⁶ In this case, the Director shall require the source to apply “maximum feasible control” instead.⁴⁷ Sources that could potentially apply for this exemption are sources constructed before May 1, 1990, certain perchloroethylene dry cleaning facilities, and combustion sources⁴⁸ permitted before July 10, 2010.⁴⁹ Maximum feasible control is defined as the maximum degree of reduction using the best technology that is available taking into account, on a case-by-case basis, human health, energy, environmental, and economic impacts and other costs.⁵⁰

Under DAQ’s proposed change, if a source is subject to MACT, then maximum feasible control would be defined as whatever federal MACT requirements apply to the source. DAQ would not make a case-by-case determination to see whether a facility could feasibly implement further controls or emission reductions. But this change would violate Section 1 of SL 2012-91 and create a loophole for sources subject to MACT when protections are needed the most, as described below.

a. If a MACT-regulated facility presents an unacceptable risk by exceeding an AAL, the facility must *eliminate* this risk.

Section 1 exempts all sources subject to MACT from the air toxics program, unless the Director determines that these sources present an “unacceptable risk to human health.” A facility that violates an AAL presents an unacceptable risk to human health.⁵¹ If a facility presents an unacceptable risk, the Director must require the facility to submit a permit application that *eliminates* the unacceptable risk.⁵² In other words, DAQ cannot simply require the facility to mitigate its violation of an AAL. The statutory requirement to eliminate the risk is absolute, and therefore a MACT-regulated source cannot evade this requirement in cases of technical infeasibility or economic hardship. There is no situation, then, where a MACT-regulated source would be able to apply maximum feasible control rather than comply with AAL requirements. As a result, DAQ’s proposal to set maximum feasible control equal to MACT is at best meaningless, and at worst contrary to the plain language of Section 1.

⁴⁶ 15A N.C.A.C. 2Q.0709(b).

⁴⁷ *Id.*

⁴⁸ Combustion sources include “boilers, space heaters, process heaters, internal combustion engines, and combustion turbines” that burn wood or fossil fuel. 15A N.C.A.C. 2Q. 0703. The term does not include incinerators, waste combustors, kilns, dryers, or direct heat exchange industrial processes. *Id.*

⁴⁹ 15A N.C.A.C. 2Q.0709(b).

⁵⁰ *Id.* 2Q .0703(13).

⁵¹ See discussion above in section 2.

⁵² See 2012 Sess. Laws 91 §1(a)(5)b.

b. Setting maximum feasible control equal to MACT deprives the public of protection when it is most needed.

Even if DAQ could allow a MACT-regulated source to apply maximum feasible control, it should not allow the source to satisfy the maximum feasible control requirement by complying with its existing MACT requirements. Instead, DAQ should analyze the source critically to ensure that emission controls are as stringent as possible. A source could also switch fuels or raw materials, or change its hours or methods of operations to ensure that it does not pose a threat to the public. DAQ must apply all of these potential options rather than allow a facility to simply comply with MACT requirements. DAQ has already determined that such a source presents a danger to public health, and therefore this is exactly where a rigorous analysis of possible controls is most critical.

15. DAQ should not use a facility's projected actual emissions to determine whether the facility is subject to and in compliance with the air toxics program. (Option 7)

DAQ proposes to use projected actual emissions to determine whether a facility exceeds TPERs and complies with AALs. But projected actual emissions do not represent the facility's maximum ability to pollute the environment and harm public health. Instead, DAQ should use the permitted emission rate, or in some cases the potential emission rate, to determine whether a facility will contribute to an exceedance of the acceptable ambient level or trigger TPERs. The emission limit contained in a facility's permit is the amount of pollution that a facility is legally allowed to emit. DAQ must therefore use this figure to determine whether a facility presents a risk to public health. If a facility's actual or projected actual emissions are lower than its permit limit, then the permit limit should be lowered to more accurately track these emissions. Without lowering the permit limits, there is no guarantee that a facility will keep its emissions low enough to prevent adverse health effects. In addition, DAQ should not rely on projected actual emissions in lieu of the "actual rate of emissions" as defined in 15A N.C.A.C. 2Q .0703.

Conclusion

DAQ must cease the unlawful implementation of Section 1 of Session Law 2012-91 and implement regulations that safeguard the public. DAQ should not impose any changes under Section 3 at this time because all of the contemplated amendments would fail to maintain protection of human health.

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CHAPTER VI

INDEX OF ATTACHMENTS

ATTACHMENTSPAGE

Economic Analysis for Amendment to Acceptable Ambient Level for Arsenic

VI-2

ECONOMIC ANALYSIS

Rule Citation Number: 15A NCAC 02D .1104 *Toxic Air Pollutant Guidelines*, and 02Q .0711 *Emission Rates Requiring a Permit* (TPER)

Rule Topic: Amendments to Acceptable Ambient Level for Arsenic (514)

DENR Division: Division of Air Quality

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Impact Summary:

State government:	Yes
Local government:	No
Substantial impact:	Yes
Federal government:	Yes
Private Industry:	Yes

Authority: G.S. 143 215.3(a)(1); 143 215.107(a)(4); 143 215.108

Necessity: In response to a request made by the North Carolina Division of Air Quality (DAQ), the Secretary's Science Advisory Board for Toxic Air Pollutants (NCSAB) has reassessed arsenic and arsenic-containing inorganic compounds (AsC) and recommends an update to the Acceptable Ambient Level (AAL) for these compounds. It is in the public interest to adopt these amendments because it may reduce regulatory burden without compromising health benefits.

I. Executive Summary

This document evaluates the costs and benefits associated with a revision to the acceptable ambient level (AAL) for Arsenic Compounds (AsC). This change involves amending two rules: 15A NCAC 02D .1104, Toxic Air Pollutant Guidelines and 02Q .0711, Emission Rates Requiring a Permit, which is commonly referred to as the "toxics permit emission rate" (TPER). See Appendix for proposed rule text. These state air toxics program rules establish the value against which a facility's emissions and resulting modeled ambient concentrations are compared in the permitting process. DAQ staff and the North Carolina Science Advisory Board (NCSAB) support the amendment.

The current AAL for AsC is 2.3×10^{-7} milligrams per cubic meter (mg/m^3). The proposed amendment would change the annual AAL for Arsenic Compounds to $2.1 \times 10^{-6} \text{ mg}/\text{m}^3$. The proposed standard would be less stringent than the one currently utilized. Amending the annual AAL would require changing the corresponding emission rate requiring a permit (TPER). The

amendment replaces the current annual TPER of 0.016 pounds per year with an annual TPER of 0.053 pounds per year. These amendments may represent a potential cost savings for operations when any modification is evaluated against a related existing permit restriction at a facility.

Arsenic is a known human carcinogen. The NCSAB recommendation to revise the AAL for AsC is based upon current scientific studies and widely accepted risk assessment methods. The NCSAB establishes the AAL based on inhalation exposure limits to ambient arsenic concentrations. The board's final recommendation, referred to as the "central estimate" or "central AAL" in this analysis, is $2.1 \times 10^{-6} \text{ mg/m}^3$. This recommendation is within an exposure range from a statistical lower bound of $1.6 \times 10^{-6} \text{ mg/m}^3$ to an upper bound of $3.0 \times 10^{-6} \text{ mg/m}^3$. Public health would not be impacted by the proposed relaxation of the AsC standard. The change in the standard is possible due to better data quality that shows a higher arsenic AAL would not increase the public health risk.

In November 2012, The Division of Air Quality reviewed its emission inventory of North Carolina facilities that emit arsenic compounds to determine if any economic impacts are likely to occur from the proposed rule change. Accordingly, there were 450 facilities out of 686 with actual arsenic emissions that were greater than the current TPER of 0.016 pounds per year. Under existing rules, all of these 450 facilities are required to demonstrate compliance with the NC Air Toxics Program when their permit modification triggers review. After the amendment becomes effective, only 313 emitting facilities will exceed the proposed annual TPER of 0.053 pounds per year. Therefore, the impact of this proposed rule change is that 137 fewer facilities would exceed the proposed annual TPER limit. For approximately 80 percent of these permitted facilities, this proposed AAL will have no impact with respect to toxic air pollutant compliance and demonstration modeling. Occasionally, some of the 137 facilities that previously limited production to remain below the existing annual AAL limit may get some regulatory relief, but only if a previously required permit restriction can be modified.

Table 1, Avoided Cost Summary, estimates substantial economic impacts in the form of regulatory relief that results in avoided cost impacts from adoption of these rule amendments. The relief may affect government owned state or federal facilities. There are avoided costs for the Division of Air Quality. Local governments did not own any of the facilities that are expected to receive regulatory relief due to the rule amendments associated with the central AAL. There are no impacts on any of the three local air programs in North Carolina. There may be related small business impacts due to the regulatory relief that are similar to typical facilities. The five-year net present value of the proposed rule is \$2.4 million in savings.

Table 1. Avoided Cost Summary

	FY 13-14	FY 14-15	FY 15-16	FY 16-17	FY 17-18
Local Government Impact	\$0	\$0	\$0	\$0	\$0
State Government Impact	\$14,700	\$14,700	\$14,700	\$14,700	\$14,700
Federal Government Impact	\$5,600	\$11,200	\$16,800	\$22,400	\$28,000
Private Sector Impact	\$190,400	\$380,800	\$571,200	\$761,600	\$952,000
Total Impact	\$210,700	\$406,700	\$602,700	\$798,700	\$994,700

Depending on the type of compliance actions facilities currently perform, savings can either be one-time modeling cost avoidance or recurring add-on control cost avoidance. The analysis

assumed that approximately \$211,000 in annual avoided costs begins to occur the first year. The portion of the cost representing cost savings from annualized add-on control cost grows each year using an assumption that two percent more of the potentially affect parties experience these same cost savings. The total annual avoided cost may grow to \$994,700 within the five year period of this analysis. It also is possible that none of these facilities will need to make a modification that would result in an increase in their arsenic limit and trigger a permit review. In such a case, the proposed rule change would result in no cost savings.

Due to regulatory relief, these rule amendments are estimated to cause substantial economic impacts as defined in the Administrative Procedures Act in N.C.G.S. *150B-21.4*.

Proposed Effectiveness Date is August 1, 2013.

II. Background

The state air toxics rules administered by the Division of Air Quality (DAQ) were established in the early 1990s in the absence of an effective federal program to protect citizens from adverse health effects from exposure to toxic air pollutants. North Carolina's health risk-based air toxics rules provide for local scale evaluation of the maximum impact of air toxic emissions from a facility at or beyond its property boundary through site-specific emissions estimates and modeling.

The rules set Acceptable Ambient Level (AAL), where "acceptable" means "below the concentration that would produce adverse health effects in sensitive subgroups of the general population."¹ The rules require the regulated community to reduce emissions of toxic air pollutants below those levels that are predicted to exceed the AAL beyond their property line. The DAQ air toxics program uses computer-based air dispersion models to compare toxic air pollutant emissions to AALs.

Currently, the Secretary of Environment and Natural Resources maintains a scientific body of experts known as the Science Advisory Board (NCSAB),² whose job it is to continually review the scientific information that forms the basis of the AALs. As this information changes, the NCSAB recommends updates to the AALs. The NCSAB reviews are focused on recommending safe exposure concentrations for toxic air pollutants that allow an ample margin of safety for people with potential exposures. NCSAB's final recommendations are considered by DAQ in drafting rules for AAL concentrations; however, any changes to the AALs go through the normal rulemaking process, with the Environmental Management Commission making the final decision.

Determining what exposure level to a toxic air pollutant is acceptable is challenging. First, health assessment professionals carefully study what is known about a pollutant to determine

¹ North Carolina Academy of Sciences (1986). Report and Recommendations of the Air and Toxics Panel of the North Carolina Academy of Sciences. <http://daq.state.nc.us/toxics/riskintro.pdf>

² The NCSAB is composed of eight individuals, appointed to four-year terms, having expertise in environmental health, occupational and pediatric medicine, toxicology, risk assessment, exposure assessment, epidemiology and biostatistics. The NCSAB meets regularly to perform risk assessments on toxic air pollutants emitted in North Carolina.

if it is a carcinogen or not. Next, they identify the lowest level known to harm people or the highest level at which health effects are not observed. Then, from one of these starting points, several safety factors may be used to reduce that level in order to protect sensitive people, such as children or asthmatics, or to account for other possible adverse health effects that have not been fully studied. In general, larger safety factors are used when less is known about the health impacts of a chemical. For example, if an adverse health effect is observed in a study of human adult males, then to protect children, the level that caused harm in the adults is reduced using safety factors that address differences in body mass or gender. In the some cases, evidence of toxic effects in animals can be extrapolated to humans after making adjustments for differences in physiology, breathing patterns or other factors. The use of safety factors is a standard approach employed by health professionals in federal, state and academic institutions when determining safe exposure levels. It is especially valuable when there are gaps in scientific data.

For toxic air pollutants that are known to cause cancer, especially for those known to cause cancer in humans such as arsenic, risk assessment methods assume by default that any exposure contains some risk. (double negative). In these cases, the conventional scientific approach used by academia and state and federal health protection programs is to set extremely low risk exposure guidelines, usually based on a concept of additional cancers not to exceed “one in a million.” Meaning, if one million people were exposed to this pollutant level continuously, then statistically one additional person would be expected to develop cancer from this exposure over and above the “usual” cancer rate expected in a population. (Similarly, the excess cancer risk is less restrictive for those chemicals that are known to cause cancer in animals, but evidence in humans is incomplete.)

The North Carolina air toxics rules approach protection of public health differently than the United States Environmental Protection Agency’s (USEPA) regulations for toxic air pollution. In the 1990 Clean Air Act Amendments, Congress directed USEPA to use a technology-based approach to significantly reduce emissions of air toxics from major stationary sources of air pollution, followed by a risk-based approach to address any remaining, or residual risks. Under the technology-based approach, USEPA develops standards for controlling the emissions of air toxics from each major type of source within an industry group. These standards, known as Maximum Achievable Control Technology (MACT) and Generally Available Control Technology (GACT), are based on emission levels that are already being achieved by the better-controlled and lower-emitting sources in an industry. The USEPA has issued all of the technology based standards (although a few are being reconsidered), and is in the process of addressing residual risks from each of the source categories. To date, USEPA has issued 40 percent of the residual risk regulations.

A new provision in Session Law 2012-91 specifies that sources subject to the federal air toxics requirement for MACT and GACT equipment installation would not have to demonstrate compliance with the state rules, unless the DAQ director determined that the source emissions posed unacceptable health risks. DAQ makes this determination by performing demonstration modeling. Often times, installing the technologies required under the federal rules allows a facility to also meet the state health-based standard, which evaluates emissions at a facility’s property boundaries, so no further action is required. If the emissions however still exceed the public health guideline at the property boundary, the state program works with the facility to identify other measures the facility can implement to lower the level of toxic air pollutants.

The session law also requires DAQ to review all permit applications for new sources or for modifications to existing facilities in which there are toxics emissions increases to ensure the protection of public health. This is performed through demonstration modeling.

III. Necessity for Rule Change

The proposed amendments are necessary to revise the AAL for Arsenic Compounds (AsC) as a result of the agency identifying a possible burden reduction that would not affect health standards. This reduction is possible due to new data showing the health standard of no more than one additional cancer case in a million can be achieved with a less stringent emission rate. The amendments are being proposed based on recommendation of the North Carolina Science Advisory Board (NCSAB). This change involves amending two rules: 15A NCAC 02D .1104, Toxic Air Pollutant Guidelines and 02Q .0711, The Emission Rates Requiring a Permit (also referred to as the “toxics permit emission rate” - TPER).

The NCSAB recommendation to revise the AAL for AsC is based upon current scientific studies and widely accepted risk assessment methods. The final recommendation from NCSAB is $2.1 \times 10^{-6} \text{ mg/m}^3$, the central estimate, within an exposure range from a statistical lower bound of $1.6 \times 10^{-6} \text{ mg/m}^3$ to an upper bound of $3.0 \times 10^{-6} \text{ mg/m}^3$.

Health benefits remain unchanged from adoption of the proposed AAL. The change in the standard is possible due to better data quality that shows a higher AsC AAL would not increase the public health risk. These amendments, however, may reduce the financial burden of these rules since in certain circumstances they could present cost savings for public and private operations when an existing permit restriction is modified at a facility.

These amendments also are consistent with the General Assembly mandated review of the state air toxics rules in Session Law 2012-91. The law requires the state Division of Air Quality, or DAQ, to review the state air toxics rules and determine whether changes could be made to reduce unnecessary regulatory burden and increase efficient use of DAQ resources while maintaining protection of public health.

IV. Description of the Current Rules and Proposed Changes

15A NCAC 02D .1104, *Toxic Air Pollutant Guidelines*. The table included in the rule establishes Acceptable Ambient Level (AAL) concentrations expressed in milligrams per cubic meter for each toxic air pollutant. Depending on the health effect toxicology, there may be a one-hour AAL established for acute systemic or irritant toxicants or a 24-hour AAL established in consideration of chronic effects. In the case of arsenic, the existing annual AAL was established for carcinogens.

15A NCAC 02Q .0711, *Emission Rates Requiring a Permit* (TPER). The table included in this rule contains toxic permit emission rates with annual, daily or hourly periods associated with their corresponding AALs. A facility must demonstrate through modeling that predicted maximum concentrations at and beyond the property boundary line are below AALs as defined in Toxic Air Pollutant Guidelines.

The NCSAB recommends amending the current annual AAL of $2.3 \times 10^{-7} \text{ mg/m}^3$ for Arsenic Compounds to $2.1 \times 10^{-6} \text{ mg/m}^3$, their central estimate. Modification of any AAL requires

changing the corresponding emission rate requiring a permit (TPER) for that averaging period. These amendments will replace the current TPER of 0.016 pounds per year with the “central estimate” TPER of 0.053 pound per year. The recommended AAL range corresponds to a low TPER of 0.041 to a high TPER of 0.076 pound per year.

V. Establishment of the Regulatory Baseline

To understand what the impact of the proposed rule would be, it is important to establish a baseline for comparison. Table 2 below shows the current number of arsenic-emitting facilities by industry. Total annual arsenic compound emissions from these 686 facilities summed to 3,740 pounds emitted in North Carolina. Based on small fluctuations in recent trends, this analysis assumes that the number of facilities and emissions remain constant over the next five years.

Table 2. Summary of Facility Counts ranked by percentage of total Annual Arsenic Compound Emissions, by North American Industry Classification System (NAICS)

NAICS DESCRIPTIONS	Facility Count	Arsenic (lb/yr)	% of Total Arsenic
Fossil Fuel Electric Power Generation	26	2,377	63.5%
Paper (except Newsprint) Mills	4	551	14.7%
National Security	6	277	7.4%
Glass Container Manufacturing	3	86	2.3%
Sawmills	15	55	1.5%
Noncellulosic Organic Fiber Manufacturing	5	48	1.3%
Other Electric Power Generation	3	36	1.0%
Cut Stock, Resawing Lumber, and Planing	13	28	0.8%
Broadwoven Fabric Mills	4	28	0.7%
Nonupholstered Wood Household Furniture Manufacturing	28	25	0.7%
Tobacco Stemming and Redrying	2	25	0.7%
Brick and Structural Clay Tile Manufacturing	11	25	0.7%
Phosphatic Fertilizer Manufacturing	1	20	0.5%
Steam and Air-Conditioning Supply	2	19	0.5%
Softwood Veneer and Plywood Manufacturing	3	12	0.3%
Ready-Mix Concrete Manufacturing	181	12	0.3%
All Other Miscellaneous Wood Product Manufacturing	8	12	0.3%
Solid Waste Combustors and Incinerators	4	9	0.2%
Flat Glass Manufacturing	2	8	0.2%
Hardwood Veneer and Plywood Manufacturing	8	8	0.2%
Reconstituted Wood Product Manufacturing	5	7	0.2%
Asphalt Paving Mixture and Block Manufacturing	87	7	0.2%
Textile and Fabric Finishing (except Broadwoven Fabric) Mills	8	7	0.2%
Other Animal Food Manufacturing	13	6	0.2%
Iron and Steel Mills	1	4	0.1%
Rendering and Meat Byproduct Processing	3	4	0.1%
Corrugated and Solid Fiber Box Manufacturing	4	4	0.1%
106 Additional NAICS CODES Combined	<u>236</u>	<u>40</u>	<u>1.1%</u>
Total	686	3,740	100.0%

Facilities with emissions greater than the current TPER face three different tiers of compliance costs: simple modeling, complex modeling, and add-on controls. Both simple and complex modeling costs are generally born by DAQ. This is a result of the session law 2012-91 that requires DAQ to review all permit applications for new sources or for modifications to existing facilities that would result in toxics emission increases, including those exempt by virtue of complying with MACT and GACT federal requirements, in order to ensure the protection of public health at the facility boundary and beyond. This review includes demonstration modeling, which requires inputs that represent the maximum average emission rate associated with annual averaging periods and the emission profile represents a temporal distribution of emissions. Annual arsenic concentrations determine compliance with the AAL and the TPER is based on threshold levels measures in pound of AsC per year.

The regulatory baseline assumes that if a facility has annual AsC emissions above the TPER but less than ten times the TPER, then the first level of regulatory burden results in average opportunity costs by DAQ for simple modeling of \$2,000 per facility. The required air dispersion models use simple site-specific parameters including: stack height and location, property boundary distance, plus exit gas temperature and velocity. Quite often this simple modeling process is able to demonstrate compliance with the AAL without add-on controls or the addition of enforceable permit restrictions. The modeling cost estimates contained in this analysis were validated by DAQ permitting staff.

If annual arsenic emissions at a facility are between ten-times and one hundred times the TPER, then this regulatory burden results in an average modeling cost of \$8,000 per facility. This stage utilizes more complex dispersion models and additional detailed site-specific parameters including building dimensions and terrain geography. For this analysis, expenses incurred for the complex modeling process are assumed to result in an adequate compliance demonstration with the AAL without add-on controls or enforceable permit restrictions.

The final level of baseline regulatory impact assumes that facilities with annual arsenic emissions that are one-hundred times above the TPER are going to incur expenditures related to purchase and operate pollution abatement controls or enforceable permit restrictions. A previous study, performed by the DAQ modeling staff, revealed that 76% of compliance demonstrations required permit restrictions. These restrictions included permit limits on emissions (47%), operating hours (38%), and/or limits on fuel usage (21%), in various combinations. Additional permit restrictions involve physical modification (add-on controls) at the facility and include control devices (43%), stack modifications (11%), source relocation (2%), source design (6%) and/or reformulation (4%).

There are a wide range of reasonably available add-on controls based on the emission profile of different industry groups and processes. Previous 2008 analysis prepared for the Director's Call and cost estimates for particulate controls on the combustion source exemption rules for the air toxics program assumed an average annualized cost of \$280,000 for such add-on controls (this includes both capital costs and operation and maintenance costs).³ This estimate represents an average composite cost of add-on controls, usually these are some combination

³ North Carolina Office of State Budget and Management. Regulatory Analysis. "Economic Analysis: Address Combustion Source Exemption in North Carolina Air Toxics Rules (472)" approved by OSBM on 9/8/2008. http://www.osbm.state.nc.us/files/pdf_files/DENR09082008.pdf

of filter baghouses or electro static precipitators. The range of controls is selected to represent the variability expected between the extremes of these cost savings.

As mentioned above, besides installing emission reducing add-on controls this impact category accounts for various alternative methods of demonstrating compliance with the AAL such as: fuel-switching, stack modification, process reformulation, or binding permit condition. The suitability of these options is site and source dependent. Due to this uncertainty, the average add-on control is used as a proxy for these generalized other compliance costs, which a presumably lower, so the 2008 cost estimate of \$280,000 is not adjusted for inflation. Note that while the facility bears the cost of add-on controls, complex modeling analysis is done by DAQ to determine compliance through permit conditions.

In summary, there are several options responses that a facility may use to demonstrate compliance with the current AAL for AsC. For the purpose of this fiscal analysis the Division of Air Quality assumed that under the current rules if a facility's annual emissions exceed the TPER, but are less than ten-times the TPER, then simple dispersion modeling, at an average cost of \$2,000 is assumed to be conducted by the DAQ. Complex modeling, also performed by DAQ and which costs \$8,000, is assumed when emissions are greater than ten-times. If annual emissions are greater than one hundred-times the TPER, then add-on controls with average annualized costs of \$280,000 are assumed to be required or permit conditions that demonstrate compliance which is determined through DAQ modeling efforts.

VI. Changes from the Baseline

All facilities in North Carolina with any Arsenic Compound (AsC) emissions that are currently subject to property boundary air toxic concentration limits or whose operations have been constrained by these binding permit restrictions may potentially be affected by the proposed AAL increase (i.e. relaxation of the standard). For such facilities, the baseline has required expenditures that could be reduced or eliminated with the proposed less stringent AAL.

There are a total of 686 facilities in the state that emit AsC. Figure 1 below shows a graphical representation of how many of these facilities emit at or above certain levels of AsC (in pounds per year). Facilities are ranked in descending order by annual Arsenic Compounds (AsC) emissions, expressed in pounds per year and shown on the vertical axis, according to DAQ's most 2011 annual emission inventory. The horizontal axis shows the number of facilities above the current, 0.016 lbs/year, and the proposed, 0.053 lbs/year, toxics permit emission rates (TPER). The figure also presents the statistical range from a "Low TPER" of 0.041 pounds per year to a "High TPER" of 0.076 pounds per year. Approximately, 450 facilities exceed the current annual TPER and 313 would exceed the proposed TPER, which means about 137 facilities would be impacted by this rule change.

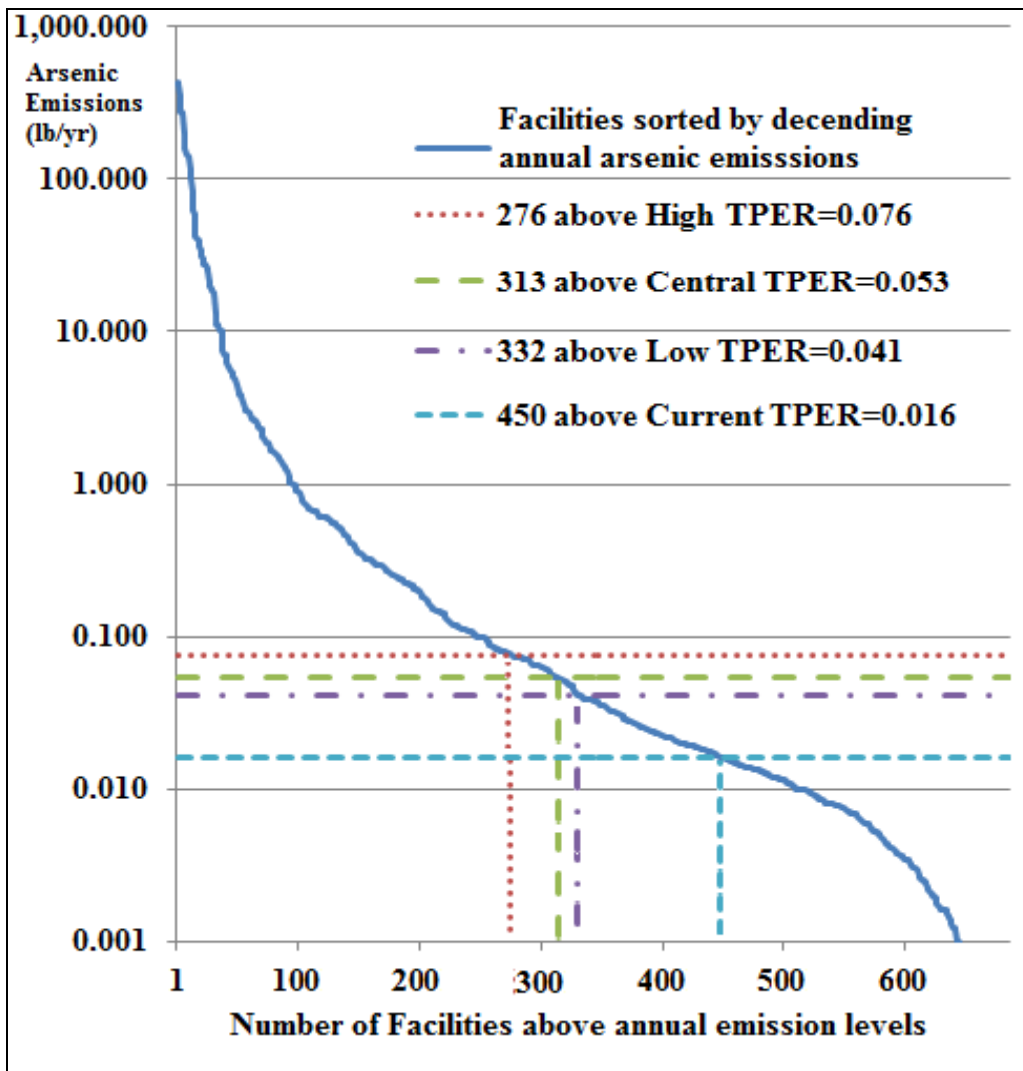


Figure 1. Number of Facilities with Arsenic Compounds (AsC) emissions in pounds per year, with the current toxic permit emission rate (TPER) compared to high, low and central estimate.

Figure 2 shows a detailed graphic illustration of the rank ordered facilities that have annual arsenic emissions greater than ten times (10x) the TPER. Two hundred and nine facilities are over ten times the current TPER, which mean that under the current rules a maximum of 241 facilities can be subject to simple modeling (= 450 facilities operating over current TPER as seen in Figure 1 less 209). Under the proposed rule, 132 facilities would emit over ten times the proposed TPER, which means a maximum of 181 facilities could be subject to simple modeling (= 313 facilities operating over proposed TPER as seen in Figure 1 less 132). As a result of the rule change, a maximum of 60 fewer facilities (=241-181) could be subject to simple modeling.

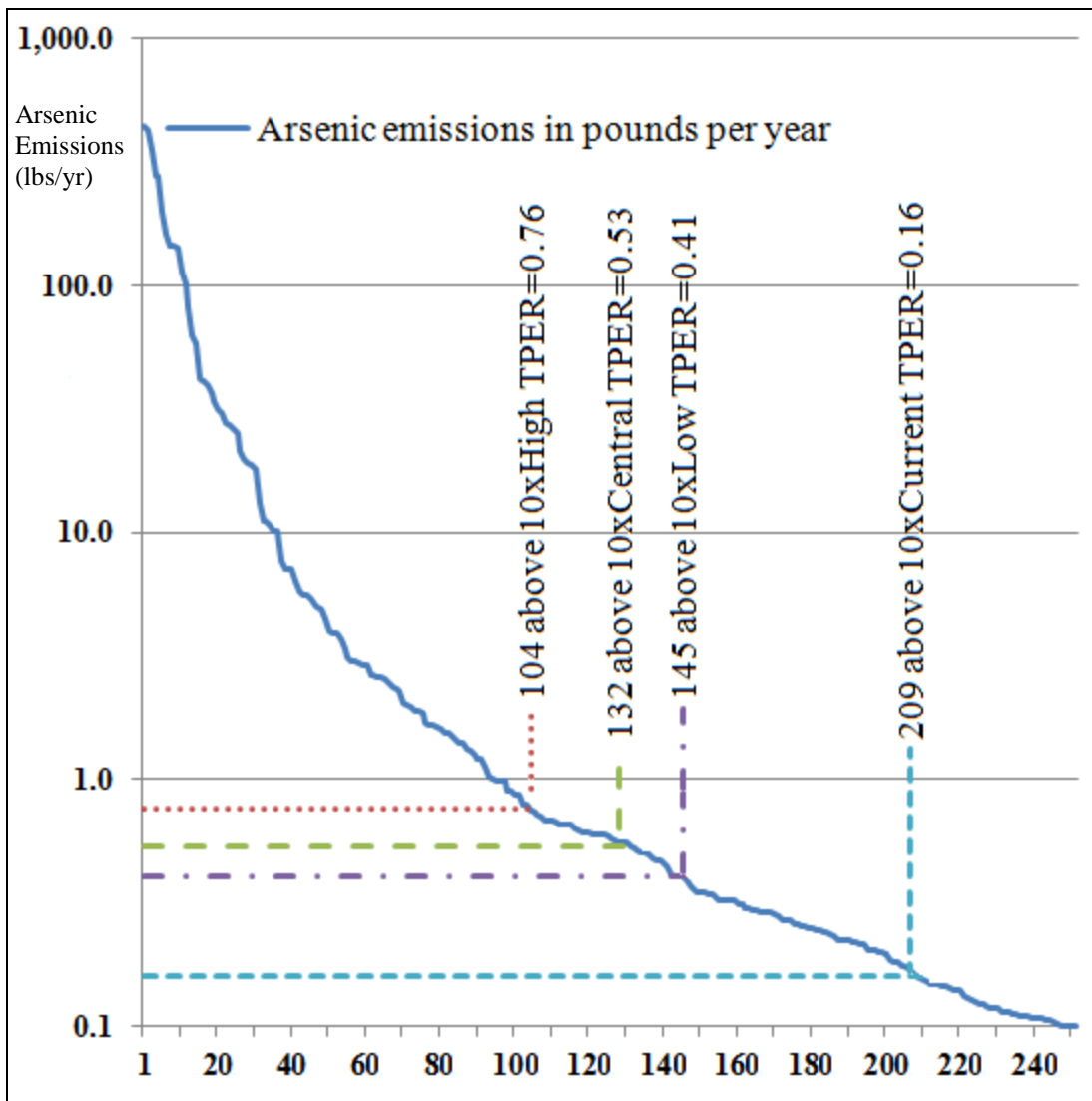


Figure 2. Facilities with annual emissions greater than 10x the proposed TPER.

Figure 3 shows similar detailed view of the rank ordered facilities having emissions greater than one hundred times (100x) the TPER. This provides the basis for comparison of the various TPER alternatives and a method to estimate the marginal cost avoided impacts. Eighty-one facilities operate over a hundred times the current TPER, which mean that under the current rules a maximum of 128 facilities can be subject to complex modeling without add-on controls (= 209 facilities operating over 10x current TPER as seen in Figure 2 less 81). Under the proposed rule, 46 facilities would emit over a hundred times the proposed TPER, which means a maximum of 86 facilities could be subject to simple modeling (= 132 facilities operating over 10x proposed TPER as seen in Figure 2 less 46). As a result of the rule change, a maximum of 42 fewer facilities (=128-86) could be subject to complex modeling without additional add-ons and 35 fewer facilities (=81-46) could be subject to complex modeling plus add-on controls.

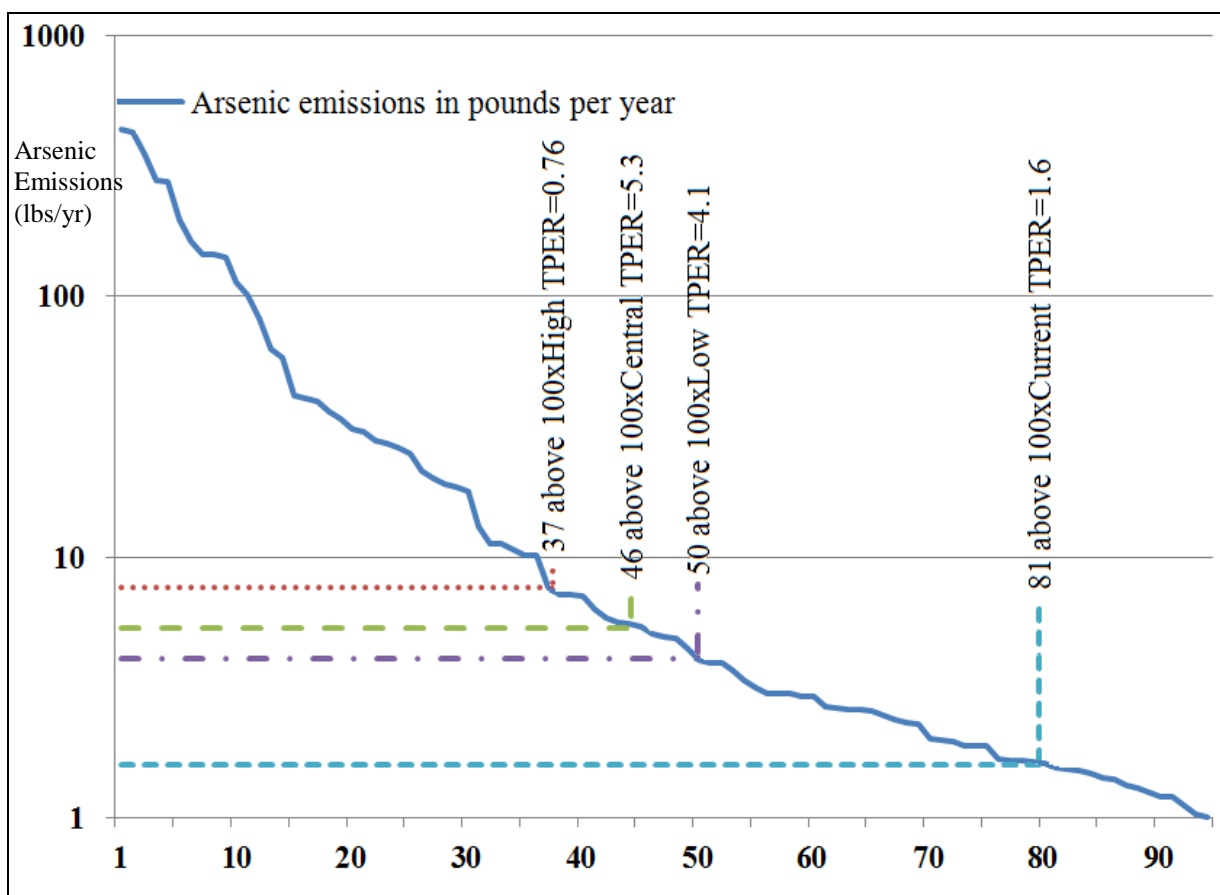


Figure 3. Facilities with annual emissions greater than 100x the proposed TPER.

Table 3 below summarizes the information discussed above and shows the assumed maximum number of facilities subject to different types of compliance options the existing TPER and under the proposed TPER associated with the NCSAB recommendation for the Arsenic AAL, as well as the difference between the two situations. The last column of the table present the amount of savings a facility could incur depending on the type of compliance option.

Table 3. Model baseline and the maximum number of facilities that may be impacted by the change in recommended Central AAL

Compliance Options	Baseline	Proposed Central AAL	Net Change from Baseline	Savings per facility
Simple Model	241	181	-60	\$2,000
Complex Model	128	86	-42	\$8,000
Add-on Controls Plus Complex Model	<u>81</u>	<u>46</u>	<u>-35</u>	\$8,000 for modeling + reoccurring \$280,000/yr
Facilities above TPER	450	313	-137	

Note that the maximum of 137 facilities shown above includes those that are exempt from the state air toxics permit because they comply with federal MACT or GACT requirements. The reason for this is that DAQ still has to perform modeling for these facilities under recent legislation and may incur some cost savings as a result of the relaxation in the AAL. Also, the

proposed rule change could positively impact the very small number of these facilities qualifying for exemptions that still need to implement add-on controls due to a DAQ determination that their emissions at the property boundary pose an unacceptable health risk. For these calculations, 33 percent of the facilities with arsenic emission were assumed to qualify for that categorical exemption. The assumption is based on a matched query of facilities with arsenic emissions and also subject to federal MACT or GACT.

Table 4 below shows a summary, by industry type, of the maximum pool of 137 facilities that could be impacted, as well as their current AsC emissions in pounds per year. The total arsenic compound emissions from these marginally affected parties were below four pounds per year, a very small fraction of the 3,740 total pounds per year emitted in North Carolina.

Table 4. Summary of Affected Facilities and Arsenic Compound Emissions, by North American Industry Classification System (NAICS) Codes

NAICS CODE	NAICS Description	Facility Count	Sum Arsenic (lb/yr)
32732	Ready-Mix Concrete Manufacturing	50	1.243
324121	Asphalt Paving Mixture and Block Manufacturing	27	0.876
62211	General Medical and Surgical Hospitals	6	0.154
313312	Textile and Fabric Finishing (except Broadwoven Fabric) Mills	4	0.141
327331	Concrete Block and Brick Manufacturing	3	0.060
32739	Other Concrete Product Manufacturing	3	0.077
334413	Semiconductor and Related Device Manufacturing	3	0.090
92811	National Security	2	0.067
313311	Broadwoven Fabric Finishing Mills	2	0.035
337211	Wood Office Furniture Manufacturing	2	0.063
325199	All Other Basic Organic Chemical Manufacturing	2	0.073
33612	Heavy Duty Truck Manufacturing	2	0.067
Multiple	Group of 31 NAICS Descriptions with a single facility count*	<u>31</u>	<u>0.995</u>
TOTAL	Affected NAICS Industry Codes with ASC greater than current TPER (0.016 lb /yr), but less than proposed TPER (0.053 lb/yr)	137	3.941

* Group of 31 NAICS Descriptions based on single facility count includes: All Other Basic Inorganic Chemical Manufacturing; All Other Nonmetallic Mineral Mining; Ball and Roller Bearing Manufacturing; Biological Product (except Diagnostic) Manufacturing; Cigarette Manufacturing; Colleges, Universities, and Professional Schools; Commercial, Industrial, and Institutional Electric Lighting Fixture Manufacturing; Concrete Pipe Manufacturing; Correctional Institutions; Corrugated and Solid Fiber Box Manufacturing; Cut Stock, Resawing Lumber, and Planing; Dog and Cat Food Manufacturing; Electric Power Distribution; Fossil Fuel Electric Power Generation; Glass Container Manufacturing; Glass Product Manufacturing Made of Purchased Glass; Hardwood Veneer and Plywood Manufacturing; Motor Vehicle Body Manufacturing; Nonupholstered Wood Household Furniture Manufacturing; Other Hosiery and Sock Mills; Other Major Household Appliance Manufacturing; Other Millwork (including Flooring); Paint and Coating Manufacturing; Petroleum Bulk Stations and Terminals; Plastics Material and Resin Manufacturing; Residential Mental Retardation Facilities; Sawmills; Soybean Processing; Steam and Air-Conditioning Supply; Toilet Preparation Manufacturing; Yarn Spinning Mills.

This maximum number of 137 potentially affected facilities assumes that all facilities chose to make a modification resulting in an increase in their AsC emission level. Such a scenario is not realistic. It is possible that some of these facilities are operating below their current limit, so an increase in the TPER would not provide them with any regulatory relief. Also, 77 (more than 50 percent) of the 137 facilities are asphalt or concrete batch plants, and for these small sources

there is currently an ongoing modeling review because they require DAQ assistance with modeling. Aside from DAQ incurring some savings from needing to perform less modeling for them, it is unlikely that these sources would be impacted by the proposed change.

Moreover, some benefits derived from the relaxation of the AAL may be delayed due to a current provision in 15A NCAC 02Q .0709(e), *Demonstrations*, which explicitly addresses any previous permit conditions and sets forth options that an affected facility may select regarding changes in any Acceptable Ambient Level. That existing rule states that:

“When an acceptable ambient level for a toxic air pollutant in 15A NCAC 02D .1104 is changed, any condition that has previously been put in a permit to protect the previous acceptable ambient level for that toxic air pollutant shall not be changed until:

(1) The permit is renewed, at which time the owner or operator of the facility shall submit an air toxic evaluation showing that the new acceptable ambient level will not be exceeded. If additional time is needed to bring the facility into compliance with the new acceptable ambient level, the owner or operator shall negotiate a compliance schedule with the Director. The compliance schedule shall be written into the facility's permit and final compliance shall not exceed two years from the effective date of the change in the acceptable ambient level.); or

(2) The owner or operator of the facility requests that the condition be changed and submits along with that request an air toxic evaluation showing that the new acceptable ambient level shall not be exceeded.”

Due to this provision, the rule change may create an additional cost to DAQ for preparing the evaluation to show the new AAL will not be exceeded at the time of permit renewal: however, this cost is expected to be minimal.

The division does not expect all 137 facilities to incur a benefit due to the reasons mentioned above. It is challenging to determine how many and which specific facilities out of the maximum total would experience lower costs as a result of the increase to the AAL propose in this rulemaking. There is little readily available information upon which to base impact estimates of the proposed change to the AAL. Without reviewing each and every permit there is no practical way to ascertain which facilities are operating at their permit limit, and would therefore be impacted by the rule. Therefore, this analysis assumes, based on staff's knowledge and best judgment, that only ten percent of the entire population of facilities would make a modification sometime within the next five-year period. A simplifying assumption is also made that these modifications would be evenly distributed among the five years (i.e. 2% of facilities would request a permit modification each year).

VII. Estimating the Cost Impacts to Affected Sources

As described in the section above, there are potential cost-savings to private sector sources due to these rule amendments. Compared to the current TPER, the proposed “central estimate” AAL may provide different degrees of regulatory relief for 137 facilities. If a facility doesn't wish to expand, then relaxing a non-binding permit restriction may not result in actual emissions increases. Such changes may provide only an extra compliance assurance margin, the value of which is not possible to estimate and is not presented in this analysis.

If facilities have been restricting operation due to the current annual AAL, they may request to modify those permit restrictions in response to these proposed amendments. The potential cost savings of this regulatory relief is uncertain due to limited knowledge of the site specific emission profiles and resulting regulatory responses of the facilities. For these reasons, the potential cost savings estimates included in the final cost summation of this economic analysis contain uncertainty.

Table 5 shows the type of compliance options and each one's potential costs impacts. The DAQ Permit Section provided the following cost estimates of the compliance cost options.

Table 5. Cost Estimated of various Compliance Options

Simple Modeling by DAQ	Complex Modeling by DAQ	Complex Modeling by DAQ plus Annualized Add-on Controls or Permit Conditions on Facilities
\$2,000	\$8,000	\$8,000+\$280,000= \$288,000

A. Summary of Costs/Savings Incurred by DAQ:

Calculations in the first part of Table 6 below assume that the maximum number of facilities, as presented in Table 3, has modifications resulting in net increase in arsenic emissions, and is therefore required to perform simple or complex modeling (see estimate cost of each option in Table 5 above). Note, facilities that have to install add-on controls still have to undergo demonstration modeling, so there could be 77 fewer facilities undergoing complex (= 42 less facilities face complex modeling plus 35 less face add-on controls and complex modeling, as shown in Table 3). As mentioned in the section above, the maximum impact estimates, however, is not very likely to occur, so for the purposes of this analysis, DAQ assumes only a fraction of the total impact is likely to occur. The second part of Table 6 presents the annual cost savings DAQ would incur from the rule change, assuming that two percent of that maximum impact is the "annual" avoided cost for DAQ over the five year period of this analysis. Therefore, the proposed AAL change would provide about \$14,700 in annual avoid cost for the implementing agency each year.

Table 6. Maximum and annual avoided costs by DAQ demonstration modeling

DAQ Modeling Impacts	Average Cost	#	Baseline	#	Central AAL	#	Change from Baseline
Simple Model	\$2,000	241	\$482,000	181	\$362,000	-60	-\$120,000
Complex Model	\$8,000	<u>209</u>	<u>\$1,672,000</u>	<u>132</u>	<u>\$1,056,000</u>	<u>-77</u>	<u>-\$616,000</u>
Maximum Impact on DAQ		450	\$2,154,000	313	\$1,418,000	-137	-\$736,000
Annual Impact on DAQ	2% of total	9	\$43,100	6	\$28,400	-3	-\$14,700

B. Summary of Costs/Savings Incurred by Facilities:

As noted at the beginning of this section, facilities may incur some benefits from being able to expand their operations and having extra compliance margin that are not included in this analysis due to lack of data and wide range of possibilities. However, a limited number of facilities will incur cost savings from not needing to install add-on controls.

Table 7 shows the additional annual impact to facilities assuming that only 2% of the maximum number of impacted facilities is expected to trigger a compliance demonstration due to a net increase in toxic emissions of arsenic each year.

Table 7. Maximum and annual avoided cost estimates

Facility Impacts	Average Cost	# Baseline	# Central AAL	# Change from Baseline
Add-on Controls	\$280,000	81 \$22,680,000	46 \$12,880,000	-35 -\$9,800,000
Additional Annual impact (2%/yr)	\$280,000	2 \$453,600	1 \$257,600	-1 -\$196,000

These impacts are further assumed to grow cumulatively. These add-on control costs are reoccurring, so the annual impact estimate above is assumed to grow cumulatively by adding another two percent more of the maximum impacts each year during the five year period of this analysis. Therefore, the cost saving amount will increase each year as more facilities experience relief until these annual savings reach the avoided costs of \$980,000 during the fifth year of this analysis.

C. Impact on Units of Local Government:

There are four facilities owned by a unit of local government among the maximum potentially affected facilities, however this analysis assumes only 10% of these would request modification in the next 5 years. Table 9 estimates the number of local government owned facilities that may be impacted by the baseline and proposed central AAL. There are no changes from the baseline, therefore none of these facilities are expected to experience economic relief due to adoption of the proposed central AAL.

Table 8. Maximum number of facilities owned by units of local Government potentially affected

Local Govt. Owned Facilities	Baseline	Central AAL	Change from Baseline
Simple Model	2	2	0
Complex Model	1	1	0
Add-on Controls	<u>1</u>	<u>1</u>	<u>0</u>
Local Govt. Owned above TPER	4	4	0

When compared with the baseline, the three local air programs in North Carolina incur no cost impacts. These local government agencies are responsible for adopting federally enforceable rules that are nearly identical to state rules and subsequent amendments. These local air quality programs may do that either “by reference”, or they can adopt an equally stringent local version of these regulations. Impacts from these locally mirrored regulations are expected to change relative to the baseline similar to the regulatory relief DAQ will experience.

D. Impact on Units of Federal Government:

There may be federally owned government facilities that are among the potentially affected community. The proposed amendments may be expected to generate additional cost savings to federal government facilities as a result of Arsenic emissions at these locations. Of the eleven federally owned facilities, Table 9 shows the maximum number impacted for the baseline and central AAL and may experience similar proportion of economic burden relief. The savings for demonstration modeling that DAQ could incur if indeed one federal facility would not require simple modeling and one would not require complex modeling are already included in the DAQ estimated savings in table 6.

Table 9. Maximum number of facilities owned by Federal government affected by the existing baseline and central AAL.

Federal Owned Facilities	Baseline	Central AAL	Change from baseline
Simple Model	3	2	-1
Complex Model	0	0	0
Add-on Controls	<u>4</u>	<u>3</u>	<u>-1</u>
Federal Owned above TPER	7	5	-2

Table 10 shows the cost saving one federal facilities may incur if it no longer would need add-on controls to meet the AAL requirements. Note this annual estimate represents an expected value – if one facility would actually be impacted by the proposed rule change, the cost saving would be of \$280,000 per year. Also, this savings would be reoccurring on a yearly basis, as in the case of private facilities, and would increase to \$28,000 over the 5-year period considered by this analysis. Note the avoided cost of this one federal facility that would not require add-on controls has already been included in the estimated savings in table 7.

Table 10. Maximum and annual avoided cost estimates for federal facilities

Federal Facilities	Average Cost	# Baseline	# Central AAL	# Change from Baseline
Add-on Controls	\$280,000	77 \$1,120,000	43 \$840,000	-1 -280,000
Additional annual impact (2%/yr)	\$280,000	22,400	16,800	-\$5,600

E. Impact on State Government:

Permitting Authority or Implementing Agency – The proposed amendments improve regulatory flexibility at sources that are already regulated by the Division of Air Quality, which is the primary implementing agency responsible for enforcing these rule amendments. The Central AAL may result in annual avoided costs of \$14,700 per year during the five year period of this analysis, because fewer facilities will exceed the TPER which will reduce the burden on DAQ modeling staff. Calculations of these impacts are included in Table 6 found in an earlier section of this analysis.

State Facilities – Fifteen state owned facilities were identified as having arsenic emissions. Some of these facilities may experience related economic relief relative to existing baseline requirements. Table 11 shows the initial step in determining the number within each compliance impact option. Only a maximum of three state facilities could be impacted and not required to participate in simple modeling demonstrations. The cost savings from this would be incurred by DAQ and it is already reflected in the savings to the division presented in Table 6.

Table 11. Maximum number of State Owned Facilities impacted by compliance impact option

State Owned Facilities	Baseline	Central AAL	Change from Baseline
Simple Model	4	1	-3
Complex Model	2	2	0
Add-on Controls	<u>0</u>	<u>0</u>	<u>0</u>
State Owned above TPER	6	3	-3

F. Impact on Private Facilities

The cost savings some private facilities would incur from no longer needing to install add-on controls are include in Table 7, alongside the impact to federal facilities. Given the expected probability of the impact on the federal facility (shown in Table 10), the expected probability of the annual impact on privately owned facilities is presented in Table 12 below. This annual savings would be cumulative and would increase to \$952,000 by year 5.

Table 12. Maximum and annual avoided cost estimates for private facilities

Private Facilities	Average Cost	# Baseline	# Central AAL	# Change from Baseline
Add-on Controls	\$280,000	77 \$21,560,000	43 \$12,040,000	-34 -\$9,520,000
Additional annual impact (2%/yr)	\$280,000	\$431,200	\$240,800	-\$190,400

G. Public Benefit:

The NCSAB reviewed the human health exposure risks associated with arsenic emissions. NCSAB's "Recommendation for the Revision of the AAL for Arsenic" as the result of a thorough discussion of the most recent studies and evaluation by Department of Environment and Natural Resources' panel of scientific experts. The central estimate or "Central AAL" provides the greatest amount of confidence toward the public health goal of providing the one in a million level of protection against an excess lung cancer death. The level of protection is established by the NCSAB risk assessment criteria and their scientific methodology. As mentioned in previous sections, public health would not be impacted by the proposed relaxation of the AsC standard. The change in the standard is possible due to better data quality that shows a higher AsC AAL would not increase the public health risk.

Table 13 shows a summary of avoided cost impacts associated with the proposed Central AAL over a 5 year period. Net Present Value calculation uses statutorily mandated 7% discount rate.

Table 13. Summary of avoided cost impacts associated with the proposed Central AAL

Impact from Central AAL	FY 13-14	FY 14-15	FY 15-16	FY 16-17	FY 17-18
Local Government Impact	\$0	\$0	\$0	\$0	\$0
State Government Impact	\$14,700	\$14,700	\$14,700	\$14,700	\$14,700
Federal Government Impact	\$5,600	\$11,200	\$16,800	\$22,400	\$28,000
Private Sector Impact	<u>\$190,400</u>	<u>\$380,800</u>	<u>\$571,200</u>	<u>\$761,600</u>	<u>\$952,000</u>
Total Impact	\$210,700	\$406,700	\$602,700	\$798,700	\$994,700
5-year Net Present Value	\$2,362,740				

VIII. Consideration of Alternatives

This economic analysis considered two alternatives relative to the proposed Central AAL and their corresponding TPER. The NCSAB's "Central AAL" recommendation identified the statistical bounds of the range of their recommendation for setting the AAL at a level that it is protective against one in one million excess risk of lung cancer. In proposing the rule change, DAQ considered both the lower and higher AALs that represent the statistical bounds.

Marginal changes in avoided cost impacts have been estimated in Table 14 for the low AAL alternative and in Table 15 for the high AAL, along with change from the baseline. Over the five-year period of this analysis, the low AAL alternative could result in \$273,000 fewer savings in net present value terms than the Central AAL. The High AAL alternative could result in \$612,000 more savings in net present value terms than the Central AAL.

Table 14. Avoided cost estimates of the Low AAL alternative

DAQ Modeling Impacts	Average Cost	# Baseline		# Low AAL		Change from Baseline	
Simple Model	\$2,000	241	\$482,000	187	\$374,000	-54	-\$108,000
Complex Model	\$8,000	209	<u>\$1,672,000</u>	145	<u>\$1,160,000</u>	-64	<u>-\$512,000</u>
Total Impact on DAQ	-	450	\$2,154,000	332	\$1,534,000	-118	-\$620,000
Annual Impact on DAQ (2% per year)		9	\$43,080	7	\$30,680	-2	-\$12,400

Facility Impacts	Average Cost	# Baseline		# Low AAL		Change from Baseline	
Add-on Controls*	\$280,000	81	\$22,680,000	50	\$14,000,000	0-31	-\$8,680,000
Annual impacts (2%/yr)	\$280,000	2	\$453,600	1	\$280,000	-0.62	-\$173,600

Impact - Low AAL	FY 13-14	FY 14-15	FY 15-16	FY 16-17	FY 17-18
Total Impact	\$186,000	\$359,600	\$533,200	\$706,800	\$880,400
5-year NPV	\$2,090,098				

Table 15. Avoided cost estimates of the High AAL alternative

DAQ Modeling Impacts	Average Cost	#	Baseline	#	High AAL	#	Change from Baseline
Simple Model	\$2,000	241	\$482,000	172	\$344,000	-69	-\$138,000
Complex Model	\$8,000	209	\$1,672,000	104	\$832,000	-105	-\$840,000
Total Impact on DAQ	-	450	\$2,154,000	276	\$1,176,000	-174	-\$978,000
Annual Impact on DAQ	-	9	\$43,080	6	\$23,520	-3	-\$19,560

Facility Impacts	Average Cost	#	Baseline	#	High AAL	#	Change from Baseline
Add-on Controls	\$280,000	81	\$22,680,000	37	\$10,360,000	-44	-\$12,320,000
Annualized (2%/yr)	\$280,000	2	\$453,600	1	\$207,200	-0.88	-\$246,400

Impact - High AAL	FY 13-14	FY 14-15	FY 15-16	FY 16-17	FY 17-18
Total Impact	\$265,960	\$512,360	\$758,760	\$1,005,160	\$1,251,560
5-year NPV	\$2,974,627				

The NCSAB recommendation was based on determining an acceptable risk over a statistical confidence range. When compared to the proposed Central AAL, Table 15 shows that the High AAL alternative is less costly. Due to uncertainties in the impact assumptions, the precision of these avoided cost estimates may not be statistically different from the avoided costs of the central AAL. From a statistical standpoint, the Department's NCSAB has the greatest confidence in the Central AAL value with regard to acceptable health risks. The mathematical methodology used to derive this range of risk is designed to provide public health protection benefits against one in a million additional lung cancer deaths. There is insufficient data to estimate and consider any possible health risk trade-off of this potentially less costly alternative. Therefore, since valid cost effectiveness comparisons cannot be calculated, there is no justification to stray from the NCSAB recommendation of the proposed Central AAL.

IX. Risk Analysis

The estimates contained in this fiscal note rely on multiple assumptions to simplify these calculations. This was necessary because the compliance cost scenario model that was developed is very general and based on rules of thumb to characterize individual decisions by hundreds of facilities. There is not adequate information available to find out if, when and which of these facilities may benefit from the burden relief offered by these proposed changes.

Possibly the greatest contributor to the uncertainty in these estimates is the baseline assumption that ten percent of the facilities would have triggered an air toxics review due to modification resulting in net increases in arsenic emissions or concentrations over the next 5 years, at a rate of two percent per year. The assumption that two percent of the facilities are impacted each year simplifies and allows for calculations, but it may very well not reflect the reality that eventually occurs. Given this assumption, the calculated net present value (NPV) over the five year period of this analysis of these annual cost savings from adoption of the "central AAL" is \$2.4 million.

The period of analysis was chosen as being likely to hold within the five year period which corresponds to the five year permit renewal cycle. As such, that assumption places an upper

limit on the cost savings estimate. Shortening or lengthening the period of analysis causes the result to vary according to the time value of money principle using a statutorily fixed discount rate of seven percent for NPV calculations. Also, if a smaller number or size of the facilities ever triggered review, then these estimated, cumulative impacts would be reduced proportionately.

Recent changes to state law also will affect this estimate. Some regulatory baseline requirements have been modified due to recent legislative action by the North Carolina General Assembly that became effective July 3, 2012. The DAQ will immediately implement provisions that accept compliance with federal MACT as being sufficient to demonstrate compliance to the NC Air Toxics Program, unless the Director's Call provision is warranted.

X. Conclusion

After these amendments become effective, facilities whose annual arsenic emissions are less than the revised TPER may no longer be required to demonstrate compliance with the AAL during an air toxics review. Such a review is normally triggered when a modification results in net increase in arsenic emissions. All facilities with a modeled concentration of arsenic that is numerically near the existing annual AAL will have the potential for some regulatory relief.

There may be substantial economic impacts in terms of avoided cost that result from these rule amendments, estimated at \$2.4 million over five years in net present value terms. There is considerable uncertainty, however, related to individual responses to the amended AAL and resultant TPER. The general method applied throughout this analysis was to statistically distribute maximum cost impacts at a chance rate of two percent per year.

Most of the 137 facilities that are potentially impacted are privately owned (and some may be small businesses), and the regulatory relief comes from not having an otherwise restrictive permit condition or the need to install add-on controls. Due to the proposed rule amendments, owners of regulated facilities may incur impacts in the form of avoided costs of almost one million dollars by the fifth year of this analysis.

No local government owned facilities will be affected by the proposed change. There could be some unquantified savings incurred by state and federal facilities, as well as add-on controls cost avoidance from a single federal owned facility assumed to be impacted at that level. The Division of Air Quality may experience a reduction in annual modeling efforts for an estimated \$14,700 in administrative cost savings relative to the baseline when compared to the proposed central AAL. There are no changes from the baseline to the three local air programs in North Carolina, which are units of local government that implement their own equally stringent version of these rules.

As shown in Table 13, within the five year period of this analysis, the total potential annual avoided costs would grow to almost \$1 million by adopting the NCSAB's recommended Central AAL for arsenic compounds. The five year net present value (NPV) of the impacts reaches \$2.36 million. In conclusion, the impacts may potentially represent avoided cost and as such these rule amendments are expected to cause substantial economic impacts as defined in Administrative Procedures Act in N.C.G.S. 150B-21.4, *Fiscal notes on rules*. The term "substantial economic impact" means an aggregate financial impact on all persons affected of at least one-half million dollars (\$500,000) in any 12-month period.

APPENDIX

15A NCAC 02D .1104 is proposed for amendment as follows:

15A NCAC 02D .1104 TOXIC AIR POLLUTANT GUIDELINES

A facility shall not emit any of the following toxic air pollutants in such quantities that may cause or contribute beyond the premises (adjacent property boundary) to any significant ambient air concentration that may adversely affect human health. In determining these significant ambient air concentrations, the Division shall be guided by the following list of acceptable ambient levels in milligrams per cubic meter at 77° F (25° C) and 29.92 inches (760 mm) of mercury pressure (except for asbestos):

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
acetaldehyde (75-07-0)				27
acetic acid (64-19-7)				3.7
acrolein (107-02-8)				0.08
acrylonitrile (107-13-1)		0.03	1	
ammonia (7664-41-7)				2.7
aniline (62-53-3)			1	
arsenic and inorganic arsenic compounds	2.3×10^{-7} 2.1×10^{-6}			
asbestos (1332-21-4)	2.8×10^{-11} fibers/ml			
aziridine (151-56-4)		0.006		
benzene (71-43-2)	1.2×10^{-4}			
benzidine and salts (92-87-5)	1.5×10^{-8}			
benzo(a)pyrene (50-32-8)	3.3×10^{-5}			
benzyl chloride (100-44-7)			0.5	
beryllium (7440-41-7)	4.1×10^{-6}			
beryllium chloride (7787-47-5)	4.1×10^{-6}			
beryllium fluoride (7787-49-7)	4.1×10^{-6}			
beryllium nitrate (13597-99-4)	4.1×10^{-6}			
bioavailable chromate pigments, as chromium (VI) equivalent	8.3×10^{-8}			
bis-chloromethyl ether (542-88-1)	3.7×10^{-7}			
bromine (7726-95-6)				0.2

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
1,3-butadiene (106-99-0)	4.4×10^{-4}			
cadmium (7440-43-9)	5.5×10^{-6}			
cadmium acetate (543-90-8)	5.5×10^{-6}			
cadmium bromide (7789-42-6)	5.5×10^{-6}			
carbon disulfide (75-15-0)		0.186		
carbon tetrachloride (56-23-5)	6.7×10^{-3}			
chlorine (7782-50-5)		0.0375		0.9
chlorobenzene (108-90-7)		2.2		
chloroform (67-66-3)	4.3×10^{-3}			
chloroprene (126-99-8)		0.44	3.5	
cresol (1319-77-3)			2.2	
p-dichlorobenzene (106-46-7)				66
dichlorodifluoromethane (75-71-8)		248		
dichlorofluoromethane (75-43-4)		0.5		
di(2-ethylhexyl)phthalate (117-81-7)		0.03		
dimethyl sulfate (77-78-1)		0.003		
1,4-dioxane (123-91-1)		0.56		
epichlorohydrin (106-89-8)	8.3×10^{-2}			
ethyl acetate (141-78-6)			140	
ethylenediamine (107-15-3)		0.3	2.5	
ethylene dibromide (106-93-4)	4.0×10^{-4}			
ethylene dichloride (107-06-2)	3.8×10^{-3}			
ethylene glycol monoethyl ether (110-80-5)		0.12	1.9	
ethylene oxide (75-21-8)	2.7×10^{-5}			
ethyl mercaptan (75-08-1)			0.1	
fluorides		0.016	0.25	
formaldehyde (50-00-0)				0.15
hexachlorocyclopentadiene (77-47-4)		0.0006	0.01	
hexachlorodibenzo-p-dioxin (57653-85-7)	7.6×10^{-8}			
n-hexane (110-54-3)		1.1		

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
hexane isomers except n-hexane				360
hydrazine (302-01-2)		0.0006		
hydrogen chloride (7647-01-0)				0.7
hydrogen cyanide (74-90-8)		0.14	1.1	
hydrogen fluoride (7664-39-3)		0.03		0.25
hydrogen sulfide (7783-06-4)		0.12		
maleic anhydride (108-31-6)		0.012	0.1	
manganese and compounds		0.031		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.0006		
manganese tetroxide (1317-35-7)		0.0062		
mercury, alkyl		0.00006		
mercury, aryl and inorganic compounds		0.0006		
mercury, vapor (7439-97-6)		0.0006		
methyl chloroform (71-55-6)		12		245
methylene chloride (75-09-2)	2.4×10^{-2}		1.7	
methyl ethyl ketone (78-93-3)		3.7		88.5
methyl isobutyl ketone (108-10-1)		2.56		30
methyl mercaptan (74-93-1)			0.05	
nickel carbonyl (13463-39-3)		0.0006		
nickel metal (7440-02-0)		0.006		
nickel, soluble compounds, as nickel		0.0006		
nickel subsulfide (12035-72-2)	2.1×10^{-6}			
nitric acid (7697-37-2)				1
nitrobenzene (98-95-3)		0.06	0.5	
n-nitrosodimethylamine (62-75-9)	5.0×10^{-5}			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	8.3×10^{-8}			
pentachlorophenol (87-86-5)		0.003	0.025	
perchloroethylene (127-18-4)	1.9×10^{-1}			

Pollutant (CAS Number)	Annual (Carcinogens)	24-hour (Chronic Toxicants)	1-hour (Acute Systemic Toxicants)	1-hour (Acute Irritants)
phenol (108-95-2)			0.95	
phosgene (75-44-5)		0.0025		
phosphine (7803-51-2)				0.13
polychlorinated biphenyls (1336-36-3)	8.3×10^{-5}			
soluble chromate compounds, as chromium (VI) equivalent		6.2×10^{-4}		
styrene (100-42-5)			10.6	
sulfuric acid (7664-93-9)		0.012	0.1	
tetrachlorodibenzo-p-dioxin (1746-01-6)	3.0×10^{-9}			
1,1,1,2-tetrachloro-2,2,-difluoroethane (76-11-9)		52		
1,1,2,2-tetrachloro-1,2,-difluoroethane (76-12-0)		52		
1,1,2,2-tetrachloroethane (79-34-5)	6.3×10^{-3}			
toluene (108-88-3)		4.7		56
toluene diisocyanate, 2,4- (584-84-9) and 2,6- (91-08-7) isomers		0.0002		
trichloroethylene (79-01-6)	5.9×10^{-2}			
trichlorofluoromethane (75-69-4)			560	
1,1,2-trichloro-1,2,2- trifluoroethane (76-13-1)				950
vinyl chloride (75-01-4)	3.8×10^{-4}			
vinylidene chloride (75-35-4)		0.12		
xylene (1330-20-7)		2.7		65

History Note: Authority G.S. 143-215.3(a)(1); 143-215.107(a)(3),(4),(5); 143B-282; S.L. 1989, c. 168, s. 45; Eff. May 1, 1990; Amended Eff. September 1, 1992; March 1, 1992; Temporary Amendment Eff. July 20, 1997; Amended Eff. _____; March 1, 2010; June 1, 2008; April 1, 2005; April 1, 2001; July 1, 1998.

15A NCAC 02Q .0711 is proposed for amendment as follows:

15A NCAC 02Q .0711 EMISSION RATES REQUIRING A PERMIT

(a) A permit to emit toxic air pollutants is required for any facility whose actual (or permitted if higher) rate of emissions from all sources are greater than any one of the following toxic air pollutant permitting emissions rates:

Pollutant (CAS Number)	Carcinogens lb/yr	Chronic Toxicants lb/day	Acute Systemic Toxicants lb/hr	Acute Irritants lb/hr
acetaldehyde (75-07-0)				6.8
acetic acid (64-19-7)				0.96
acrolein (107-02-8)				0.02
acrylonitrile (107-13-1)		0.4	0.22	
ammonia (7664-41-7)				0.68
aniline (62-53-3)			0.25	
arsenic and inorganic arsenic compounds	0.016 0.053			
asbestos (1332-21-4)	1.9 X 10 ⁻⁶			
aziridine (151-56-4)		0.13		
benzene (71-43-2)	8.1			
benzidine and salts (92-87-5)	0.0010			
benzo(a)pyrene (50-32-8)	2.2			
benzyl chloride (100-44-7)			0.13	
beryllium (7440-41-7)	0.28			
beryllium chloride (7787-47-5)	0.28			
beryllium fluoride (7787-49-7)	0.28			
beryllium nitrate (13597-99-4)	0.28			
bioavailable chromate pigments, as chromium (VI) equivalent	0.0056			
bis-chloromethyl ether (542-88-1)	0.025			
bromine (7726-95-6)				0.052
1,3-butadiene (106-99-0)	11			
cadmium (7440-43-9)	0.37			
cadmium acetate (543-90-8)	0.37			
cadmium bromide (7789-42-6)	0.37			
carbon disulfide (75-15-0)		3.9		
carbon tetrachloride (56-23-5)	460			

chlorine (7782-50-5)		0.79		0.23
chlorobenzene (108-90-7)		46		
chloroform (67-66-3)	290			
chloroprene (126-99-8)		9.2	0.89	
cresol (1319-77-3)			0.56	
p-dichlorobenzene (106-46-7)				16.8
dichlorodifluoromethane (75-71-8)		5200		
dichlorofluoromethane (75-43-4)		10		
di(2-ethylhexyl)phthalate (117-81-7)		0.63		
dimethyl sulfate (77-78-1)		0.063		
1,4-dioxane (123-91-1)		12		
epichlorohydrin (106-89-8)	5600			
ethyl acetate (141-78-6)			36	
ethylenediamine (107-15-3)		6.3	0.64	
ethylene dibromide (106-93-4)	27			
ethylene dichloride (107-06-2)	260			
ethylene glycol monoethyl ether (110-80-5)		2.5	0.48	
ethylene oxide (75-21-8)	1.8			
ethyl mercaptan (75-08-1)			0.025	
fluorides		0.34	0.064	
formaldehyde (50-00-0)				0.04
hexachlorocyclopentadiene (77-47-4)		0.013	0.0025	
hexachlorodibenzo-p-dioxin (57653- 85-7)	0.0051			
n-hexane (110-54-3)		23		
hexane isomers except n-hexane				92
hydrazine (302-01-2)		0.013		
hydrogen chloride (7647-01-0)				0.18
hydrogen cyanide (74-90-8)		2.9	0.28	
hydrogen fluoride (7664-39-3)		0.63		0.064
hydrogen sulfide (7783-06-4)		1.7		
maleic anhydride (108-31-6)		0.25	0.025	
manganese and compounds		0.63		
manganese cyclopentadienyl tricarbonyl (12079-65-1)		0.013		
manganese tetroxide (1317-35-7)		0.13		
mercury, alkyl		0.0013		
mercury, aryl and inorganic compounds		0.013		

mercury, vapor (7439-97-6)		0.013		
methyl chloroform (71-55-6)		250		64
methylene chloride (75-09-2)	1600		0.39	
methyl ethyl ketone (78-93-3)		78		22.4
methyl isobutyl ketone (108-10-1)		52		7.6
methyl mercaptan (74-93-1)			0.013	
nickel carbonyl (13463-39-3)		0.013		
nickel metal (7440-02-0)		0.13		
nickel, soluble compounds, as nickel		0.013		
nickel subsulfide (12035-72-2)	0.14			
nitric acid (7697-37-2)				0.256
nitrobenzene (98-95-3)		1.3	0.13	
n-nitrosodimethylamine (62-75-9)	3.4			
non-specific chromium (VI) compounds, as chromium (VI) equivalent	0.0056			
pentachlorophenol (87-86-5)		0.063	0.0064	
perchloroethylene (127-18-4)	13000			
phenol (108-95-2)			0.24	
phosgene (75-44-5)		0.052		
phosphine (7803-51-2)				0.032
polychlorinated biphenyls (1336-36-3)	5.6			
soluble chromate compounds, as chromium (VI) equivalent		0.013		
styrene (100-42-5)			2.7	
sulfuric acid (7664-93-9)		0.25	0.025	
tetrachlorodibenzo-p-dioxin (1746-01-6)	0.00020			
1,1,1,2-tetrachloro-2,2-difluoroethane (76-11-9)		1100		
1,1,2,2-tetrachloro-1,2-difluoroethane (76-12-0)		1100		
1,1,2,2-tetrachloroethane (79-34-5)	430			
toluene (108-88-3)		98		14.4
toluene diisocyanate, 2,4-(584-84-9) and 2,6-(91-08-7) isomers		0.003		
trichloroethylene (79-01-6)	4000			
trichlorofluoromethane (75-69-4)			140	

1,1,2-trichloro-1,2,2-trifluoroethane (76-13-1)				240
vinyl chloride (75-01-4)	26			
vinylidene chloride (75-35-4)		2.5		
xylene (1330-20-7)		57		16.4

(b) For the following pollutants, the highest emissions occurring for any 15-minute period shall be multiplied by four and the product shall be compared to the value in Paragraph (a). These pollutants are:

- (1) acetaldehyde (75-07-0);
- (2) acetic acid (64-19-7);
- (3) acrolein (107-02-8);
- (4) ammonia (7664-41-7);
- (5) bromine (7726-95-6);
- (6) chlorine (7782-50-5);
- (7) formaldehyde (50-00-0);
- (8) hydrogen chloride (7647-01-0);
- (9) hydrogen fluoride (7664-39-3); and
- (10) nitric acid (7697-37-2).

History Note: Authority G.S. 143-215.3(a)(1); 143-215.108; 143B-282; S.L. 1989, c. 168, s. 45;
Rule originally codified as part of 15A NCAC 02H .0610;
Eff. July 1, 1998;
Amended Eff. _____; January 1, 2010; June 1, 2008; April 1, 2005; February 1, 2005;
April 1, 2001.

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Chapter VII

The following documentation of filing and notification is incorporated as part of this hearing record and is maintained on file:

1. ENR 101 Internal Approval Form.
2. Submission for Notice Form and material submitted to the Office of Administrative Hearings.
3. The public notice as it appears in *The North Carolina Register* Volume 27, Issue 20, pages 1903-1908.
4. Memorandum transmitting hearing notice and proposal to regional offices for public inspection.
5. Memorandum transmitting hearing notice and proposal to local programs.
6. Submission of Filing Forms and material filed with Office of Administrative Hearings.
7. Executive Order No. 70 Certification Form

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