

## 2. HEALTH EFFECTS

### 2.1 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.

### 2.2 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 (LOAEL) 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 2-1, 2-3, and 2-4 and Figures 2-1, 2-3, and 2-4. Because cancer effects could occur at lower exposure levels, Figure 2-3 also shows 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or 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 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.

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.

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***Chemical Forms of Concern.*** Analysis of the toxic effects of arsenic is complicated by the fact that arsenic can exist in several different valence 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 ( $\text{As}_2\text{O}_3$ ), while a variety of inorganic arsenates ( $\text{AsO}_4^{3-}$ ) or arsenites ( $\text{AsO}_2^-$ ) 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 5.3) and the body (see Section 2.3); 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.

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.,  $\text{As}_2\text{S}_3$ ), but these are expected to be of approximately equal or lesser toxicity than the oxycompounds, depending mainly on solubility (see Section 2.3).

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 concern. Chief among these are monomethyl arsonic acid (MMA) and its salts, (monosodium methane arsonate [MSMA] and disodium methane arsonate [DSMA]), dimethyl arsinic acid (DMA, also known as cacodylic acid) and its sodium salt (sodium dimethyl arsinite, or sodium cacodylate), and roxarsone (3-nitro-4-hydroxyphenylarsonic acid). As with the inorganic compounds, there are toxicological differences between these various organic derivatives, but for the purposes of this profile these

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differences have not been emphasized, because data are rarely adequate to permit rigorous quantitative comparisons between different chemicals, and most data are derived from studies in animals. 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. 1978a; Kaise et al. 1985; Luten et al. 1982; Siewicki 1981; Tam et al. 1982; Yamauchi et al. 1986a). Thus, these compounds are not considered further here.

Arsine ( $\text{AsH}_3$ ) 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.

***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 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 arsenic is carcinogenic in humans by both oral and inhalation routes, evidence of arsenic-induced carcinogenicity in animals is mostly negative. 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.

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**2.2.1 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 2-1 and Figure 2-1 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 organic arsenicals are shown in Table 2-2 and Figure 2-2. All exposure data are expressed as milligrams of arsenic (as the element) per cubic meter of air ( $\text{mg As/m}^3$ ). These studies and others that provide useful qualitative information on health effects of inorganic and organic arsenicals are discussed below.

**2.2.1.1 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 ( $1\text{--}100 \text{ mg As/m}^3$ ) found previously in the workplace (e.g., Enterline and Marsh 1982; Jarup 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 2.2.1.2 and 2.2.1.8, 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  $20 \text{ mg As/m}^3$  (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  $\$100 \text{ mg/m}^3$  ( $76 \text{ mg As/m}^3$ ).

***Organic Arsenicals.*** No studies were located regarding death in humans after inhalation exposure to organic arsenicals. A 2-hour  $\text{LC}_{50}$  of  $2,117 \text{ mg As/m}^3$  was calculated for DMA in female rats (Stevens et al. 1979). This  $\text{LC}_{50}$  is shown in Table 2-2 and Figure 2-2. Male rats and mice of both sexes were less

Table 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>ACUTE EXPOSURE</b>							
<b>Immunological/Lymphoreticular</b>							
1	Mouse (CD-1)	3 hr		0.123 F	0.271 F (decr pulmonary bactericidal activity and incr 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 (decr pulmonary bactericidal activity and incr susceptibility to streptococcal infection)		Aranyi et al. 1985 As(+3)
<b>Developmental</b>							
3	Mouse (CFLP)	Gd 9-12 4 hr/d		0.20	2.2 (10% decr avg fetal body wt)	21.6 (incr fetal deaths, skeletal malformations, and retarded growth)	Nagymajtenyi et al. 1985 As(+3)
<b>INTERMEDIATE EXPOSURE</b>							
<b>Death</b>							
4	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d				20 F (5/10 dams died)	Holson et al. 1999 As(+3)

Table 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>Systemic</b>							
5	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d	Resp  Bd Wt	2 F  2 F	8 F (rales, dried red material around nose)  8 F (decr body wt gain during gestation)		Holson et al. 1999 As(+3)
6	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d	Resp  Gastro  Bd Wt	0.9 F  8 F  8 F	8 F (rales)	20 F (labored breathing, gasping)  20 F (gross gastrointestinal lesions)  20 F (drastic decr body wt)	Holson et al. 1999 As(+3)
<b>Immunological/Lymphoreticular</b>							
7	Mouse (CD-1)	4 wk 5 d/wk 3 hr/d		0.126 F	0.245 F (decr pulmonary bactericidal activity)		Aranyi et al. 1985 As(+3)
<b>Reproductive</b>							
8	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		8 F			Holson et al. 1999 As(+3)
9	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		20 F			Holson et al. 1999 As(+3)

Table 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference Chemical Form
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
<b>Developmental</b>							
10	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		8			Holson et al. 1999 As(+3)
11	Rat (CD)	14 d pre-mating thru Gd 19 7 d/wk 6 hr/d		8		20 (marked incr in post-implantation loss and marked decr in viable fetuses)	Holson et al. 1999 As(+3)
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
12	Human	23 yr (avg)	Cardio			0.36 M (incr incidence of vasospasticity and clinical Raynaud's phenomenon)	Lagerkvist et al. 1986 As(+3)
13	Human	6-8 yr 8 hr/day	Dermal		0.007 M (dermatitis)		Mohamed 1998 As(+3)
14	Human	0.5-50 yr	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)	

Table 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure/duration/frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>Neurological</b>							
15	Human	28 yr (avg)			0.31 M (decr nerve conduction velocity)		Lagerkvist and Zetterlund 1994 As(+3)
<b>Developmental</b>							
16	Human	NS		5.5E-5		0.0007 (incr risk of stillbirth)	Ihrig et al. 1998 As(+3)
<b>Cancer</b>							
17	Human	1->30 yr				0.213 M (CEL: lung cancer)	Enterline et al. 1987a As(+3)
18	Human	19.5 yr (avg)				0.069 M (CEL: lung cancer)	Enterline et al. 1987b As(+3)
19	Human	3 mo->30 yr				0.2 M (CEL: lung cancer)	Jarup and Pershagen 1991 As(+3)
20	Human	3 mo->30 yr				0.05 M (CEL: lung cancer)	Jarup et al. 1989 As(+3)
21	Human	1->30 yr				0.38 M (CEL: lung cancer)	Lee-Feldstein 1986 As(+3)

Table 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
22	Human	14.8 yr (avg)				0.3 M (CEL: lung cancer)	Welch et al. 1982 As(+3)

<sup>a</sup>The number corresponds to entries in Figure 2-1.

avg = average; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; F = female; Gd = gestation day; hr = hour(s); incr = increased; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); wt = weight; yr = year(s)

Figure 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation  
Acute ( $\leq 14$  days)

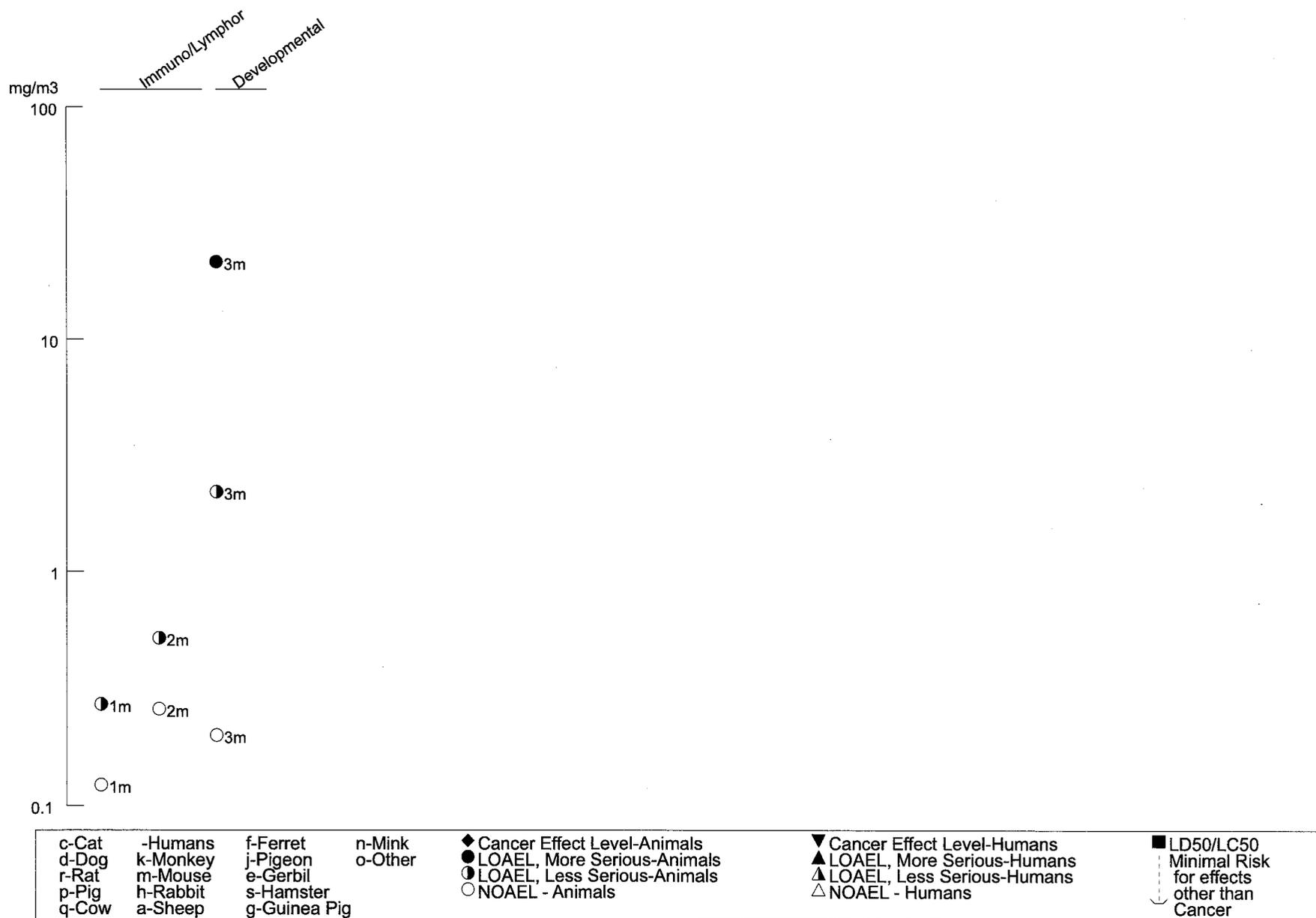


Figure 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Intermediate (15-364 days)

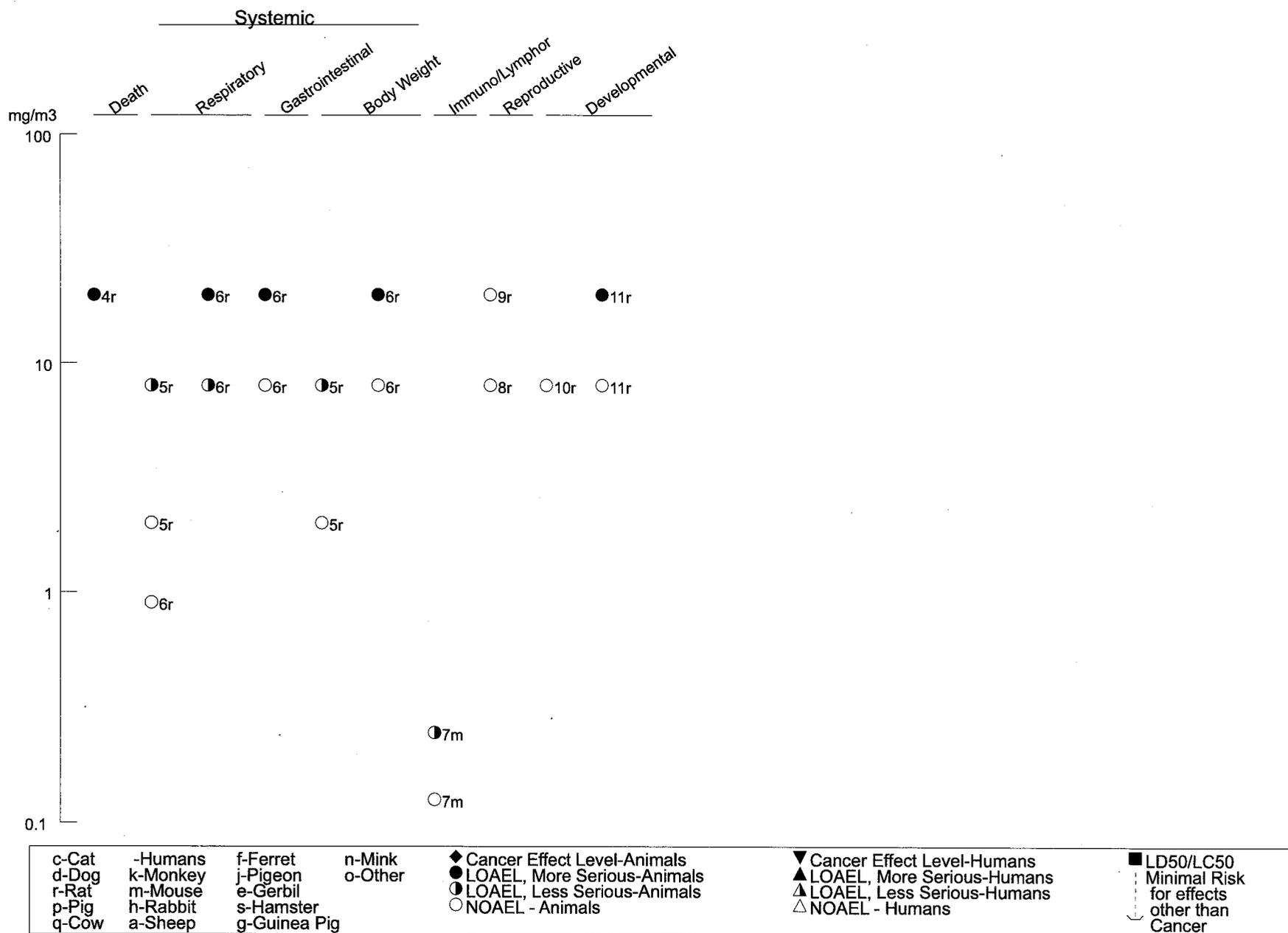


Figure 2-1. Levels of Significant Exposure to Inorganic Arsenic - Inhalation (continued)

Chronic (≥365 days)

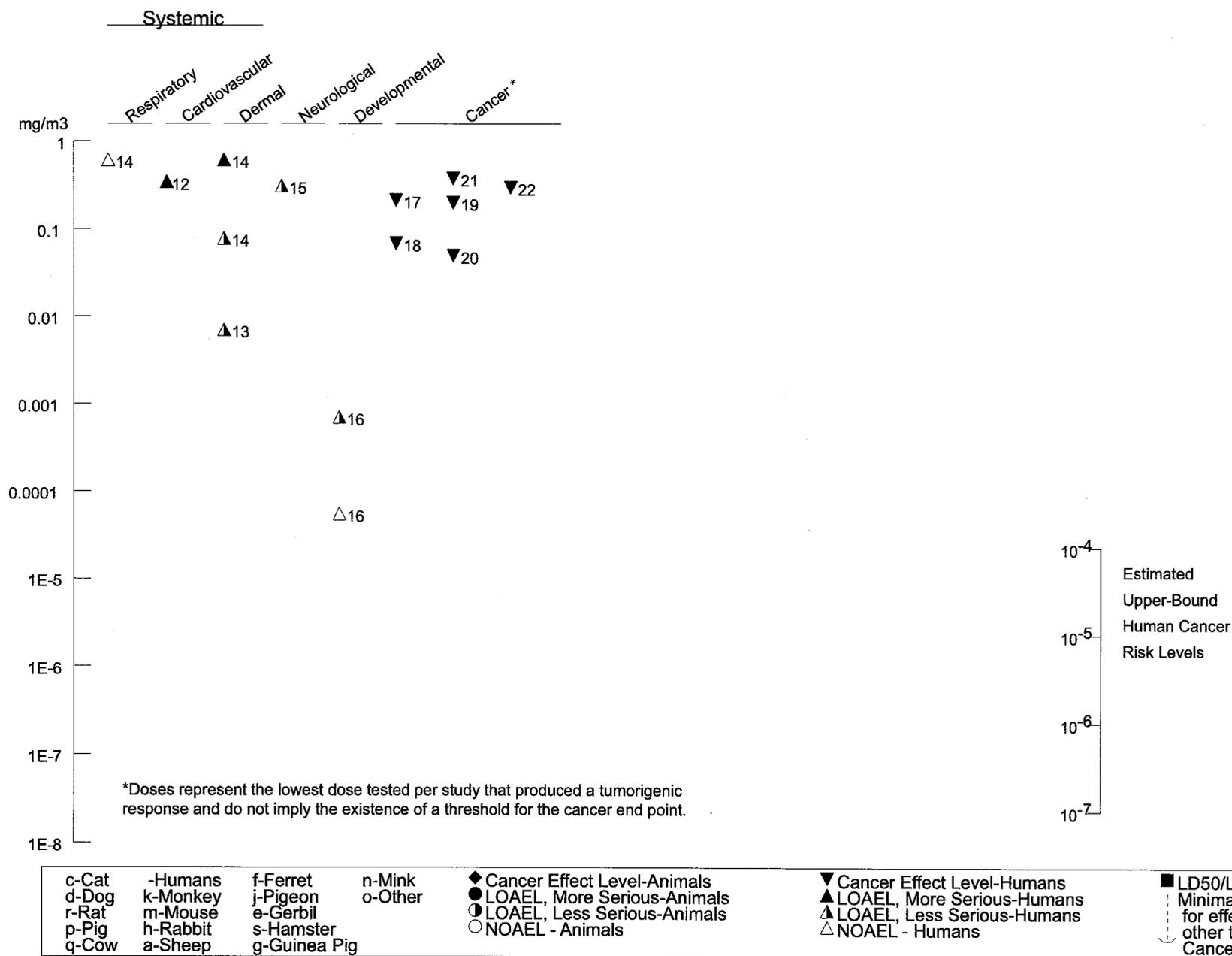


Table 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation

Key to figure	a Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (Sherman)	2 hr				2117 F (LC <sub>50</sub> )	Stevens et al. 1979 DMA
<b>Systemic</b>							
2	Rat (Sherman)	2 hr	Resp			2172 (respiratory distress)	Stevens et al. 1979 DMA
			Gastro		2172 (diarrhea)		
			Dermal	2226	3746 F (erythematous lesions of ears and feet)		
			Ocular		2172 (eye encrustation)		
			Bd Wt		2172 (unspecified decrease in body weight)		
3	Mouse (Swiss- Webster)	5 min	Resp		627 M (RD <sub>50</sub> )		Stevens et al. 1979 MMA
4	Mouse (Swiss- Webster)	5 min	Resp		1710 M (RD <sub>50</sub> )		Stevens et al. 1979 DMA

Table 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)	
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
5	Human	1.45-2.12 yr (group averages)	Hemato	0.13 M			Watrous and McCaughey 1945 AA

<sup>a</sup>The number corresponds to entries in Figure 2-2.

AA = arsanic acid; Bd Wt = body weight; DMA = dimethylarsinic acid; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); LC<sub>50</sub> = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MMA = monomethylarsenic acid; NOAEL = no-observable-adverse-effect level; RD<sub>50</sub> = concentration calculated to produce a 50% decrease in respiratory rate; Resp = respiratory; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation  
Acute (≤14 days)

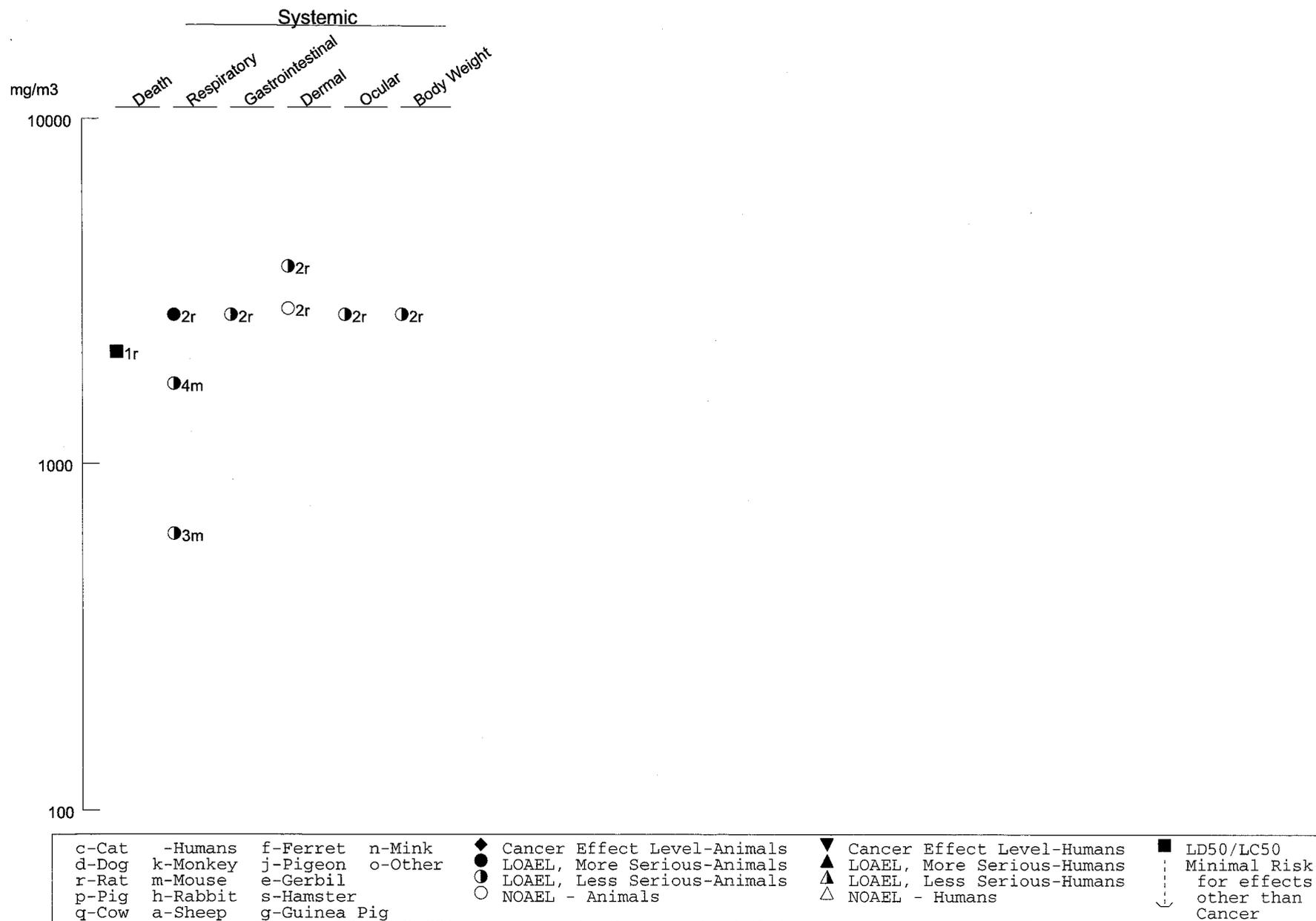
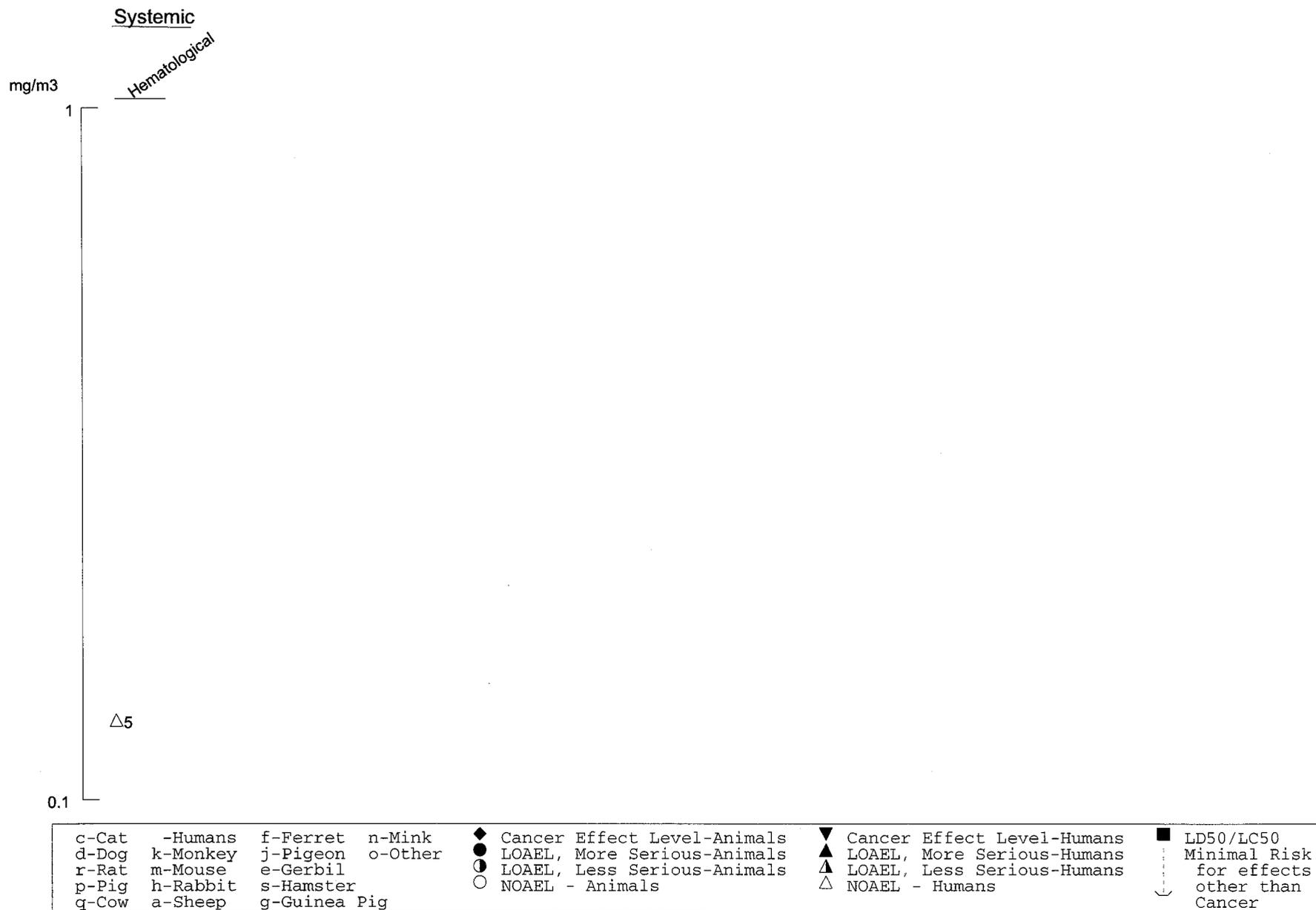


Figure 2-2. Levels of Significant Exposure to Organic Arsenic - Inhalation (continued)  
Chronic (≥365 days)



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susceptible, with only a few deaths after 2-hour exposures as high as 3,746 mg As/m<sup>3</sup> in rats and 3,474 mg As/m<sup>3</sup> in mice (Stevens et al. 1979). The cause of death was not specified, but was probably due to lung injury (see Section 2.2.1.2). No deaths were observed among rats and mice exposed to DSMA (the disodium salt of MMA) at concentrations up to 2,485 mg As/m<sup>3</sup> in rats and 2,811 mg As/m<sup>3</sup> 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.

### 2.2.1.2 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 2-1 and plotted in Figure 2-1, while the corresponding data for organic arsenicals are shown in Table 2-2 and Figure 2-2.

### 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; Lundgren 1954; 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/m<sup>3</sup> for respiratory effects in this study is shown in Table 2-1 and plotted in Figure 2-1.

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; 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

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arsenic exposure level did not show a clear dose-response. Similarly, Enterline et al. (1995) found a significant excess of non-malignant 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/m<sup>3</sup> and labored breathing and gasping at 20 mg As/m<sup>3</sup>, with no symptoms at 2 mg As/m<sup>3</sup> (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 (1.5–52 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 (2,172 mg As/m<sup>3</sup> or greater) 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 (2,485 mg As/m<sup>3</sup> or greater) 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 RD<sub>50</sub> (concentration calculated to produce a 50% decrease in respiration rate) values of 1,710 and 627 mg As/m<sup>3</sup>, respectively (Stevens et al. 1979). Based on these RD<sub>50</sub> values, neither DMA nor MMA is considered to be a potent respiratory irritant. Reliable LOAELs for respiratory effects of organic arsenic are shown in Table 2-2 and Figure 2-2.

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**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 2.2.2.2). A cross-sectional study of workers exposed to an estimated time-weighted average of 0.36 mg As/m<sup>3</sup> (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 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 (Jarup 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).

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The LOAEL for Raynaud's phenomenon and vasospasticity identified by Lagerkvist et al. (1986) is shown in Table 2-1 and Figure 2-1. 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 or animals after inhalation exposure to organic arsenicals.

### 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 2.2.2.2), 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/m<sup>3</sup> (Holson et al. 1999). These animals exhibited severe hyperemia and plasma discharge into the intestinal lumen at autopsy. Exposure to 8 mg As/m<sup>3</sup> 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 0.13 mg As/m<sup>3</sup> 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 2,000 mg As/m<sup>3</sup>) of MMA (disodium salt) or DMA experienced diarrhea (Stevens et al. 1979). The LOAEL for this effect is shown in Table 2-2 and Figure 2-2. 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).

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**Hematological Effects**

***Inorganic Arsenicals.*** Although anemia is a common feature of arsenic poisoning following oral exposure in humans (see Section 2.2.2.2), 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 0.13 mg As/m<sup>3</sup> in the workplace (Watrous and McCaughey 1945). Controls were an unspecified number of unexposed manufacturing workers with 221 complete blood counts. The NOAEL from this study is shown in Table 2-2 and Figure 2-2. No studies were located regarding hematological effects in animals after inhalation exposure to organic arsenicals.

**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;

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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 or animals after inhalation exposure to organic arsenicals.

### 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,  $\beta_2$ -microglobulin, brush-border antigen) used as markers of glomerular damage or tubular cell exfoliation (Foa et al. 1987). Routine 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 or animals after inhalation exposure to organic arsenicals.

### 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 (Dunlap 1921; Holmqvist 1951; Lagerkvist et al. 1986; Pinto and McGill 1953). Limited quantitative information is available regarding the exposure levels that produce dermatitis. 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/m<sup>3</sup> and estimated to average 0.613 mg As/m<sup>3</sup>) 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/m<sup>3</sup>) were much less affected, but still had a higher incidence of pigmentation keratosis than controls. Dermatitis characterized by hyperpigmentation, folliculitis, and superficial ulcerations was observed in 11 employees in one department of a Malaysian tin smelter (total of 500 employees in the plant) exposed to mean arsenic oxide concentrations ranging from 0.005 to

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0.014 mg As<sub>2</sub>O<sub>3</sub>/m<sup>3</sup> (estimated average exposure=0.007 mg As/m<sup>3</sup>) (Mohamed 1998). LOAEL values identified by Perry et al. (1948) and Mohamed (1998) are shown in Table 2-1 and Figure 2-1. 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 2.2.2.2). 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 two-fold higher than unexposed controls in female packaging workers exposed to arsanilic acid at an average concentration of 0.05 mg As/m<sup>3</sup> and in male manufacturing workers exposed to an average concentration of 0.13 mg As/m<sup>3</sup> in a chemical factory (Watrous and McCaughey 1945). This observation is consistent with the arsenic database as a whole, but 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 3,746 mg As/m<sup>3</sup> developed erythematous lesions on the feet and ears (Stevens et al. 1979); these lesions did not develop in females exposed at lower concentrations (2,226 mg As/m<sup>3</sup>) or males. The NOAEL and LOAEL values for dermal effects in female rats are shown in Table 2-2 and Figure 2-2. It seems likely these effects were due to direct irritation from dermal contact with the dust.

### Ocular Effects

**Inorganic Arsenicals.** Chemical conjunctivitis, characterized by redness, swelling, and pain, has been observed in workers exposed to arsenic dusts in air, usually in combination with 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 (2,172 mg As/m<sup>3</sup>) developed an encrustation around the eyes (Stevens et al. 1979). This LOAEL is shown in Table 2-2 and Figure 2-2. It seems likely that these effects were due to direct irritation from ocular contact with the dust.

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**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<sup>3</sup> (preliminary study) and a smaller decrease at 8 mg As/m<sup>3</sup> (definitive study), with no effect at 2 mg As/m<sup>3</sup> (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 (2,172 mg As/m<sup>3</sup>) for 2 hours had an unspecified decrease in body weight gain during the subsequent 14 days (Stevens et al. 1979). This LOAEL is shown in Table 2-2 and Figure 2-2.

**2.2.1.3 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 workers exposed to arsenic in a coal-burning power plant. However, the levels of arsenic were not measured and may have been too low for this to be a meaningful result. 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 2-1 and Figure 2-1.

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 2.2.1.2, above) is uncertain.

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

**2.2.1.4 Neurological Effects**

**Inorganic Arsenicals.** There is evidence from epidemiological studies that inhaled inorganic arsenic can produce neurological effects. Cross-sectional studies of copper smelter workers at the ASARCO smelter in Tacoma, Washington (Feldman et al. 1979) 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). 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<sup>3</sup> and lasted an average of 28 years in the exposed group, and this LOAEL is shown in Table 2-1 and Figure 2-1.

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 2.2.2.4).

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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 0.13 mg As/m<sup>3</sup> (Watrous and McCaughey 1945). Although peripheral nerve complaints were higher in arsenic packaging workers (mean exposure=0.05 mg As/m<sup>3</sup>) than in unexposed controls, this was not the case in manufacturing workers with higher arsenic exposure (mean=0.13 mg As/m<sup>3</sup>). 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.

### 2.2.1.5 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 0.08–20 mg As/m<sup>3</sup> (preliminary study) or 0.2–8 mg As/m<sup>3</sup> (definitive study) as As<sub>2</sub>O<sub>3</sub> 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 of matings resulting in pregnancy). The NOAEL values for this study are shown in Table 2-1 and Figure 2-1.

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

### 2.2.1.6 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 (Nordstrom et al. 1978a, 1978b, 1979a, 1979b). In comparison to a northern Swedish reference

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population, female employees of the smelter had a significantly increased incidence of spontaneous abortion (Nordstrom et al. 1979a), and their children had a significantly increased incidence of congenital malformations (Nordstrom et al. 1979b) and significantly decreased average birth weight (Nordstrom 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 (Nordstrom 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.

More recently, 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 featuring 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 ( $>100$  ng As/m<sup>3</sup>, midpoint=682 ng/m<sup>3</sup>). 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 22 mg As/m<sup>3</sup> (as As<sub>2</sub>O<sub>3</sub>) 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/m<sup>3</sup> had only a 10% decrease in average fetal body weight, and those exposed to 0.20 mg As/m<sup>3</sup> had no effects (Nagymajtenyi 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 birth weight occurred when rats were exposed to 0.2–8 mg As/m<sup>3</sup> (as As<sub>2</sub>O<sub>3</sub>), 6 hours daily from 14 days prior to mating through gestation day 19 (Holson et al. 1999). At the 8 mg/m<sup>3</sup> 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 post-implantation loss (primarily early

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resorptions) and consequent marked significant decrease in viable fetuses per litter at 20 mg As/m<sup>3</sup>, 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 Nagymajtenyi et al. (1985) and Holson et al. (1999) are shown in Table 2-1 and Figure 2-1.

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

### 2.2.1.7 Genotoxic Effects

**Inorganic Arsenicals.** 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/m<sup>3</sup> as arsenic trioxide on days 9–12 of gestation (Nagymajtenyi et al. 1985). Other genotoxicity studies on inorganic arsenicals are discussed in Section 2.5.

**Organic Arsenicals.** No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to organic arsenicals. Other genotoxicity studies on organic arsenicals are discussed in Section 2.5.

### 2.2.1.8 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 1983a, 1983b, 1983c; Enterline and Marsh 1982; Enterline et al. 1987a, 1987b, 1995; Ferreccio et al. 1996; Higgins et al. 1982; Jarup and Pershagen 1991; Jarup et al. 1989; Lee and Fraumeni 1969; Lee-Feldstein 1983, 1986; Mazumdar et al. 1989; Pinto et al. 1977, 1978; Sandstrom et al. 1989; 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

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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 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 (Jarup and Pershagen 1991; Jarup et al. 1989).

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/m<sup>3</sup>, 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/m<sup>3</sup>, 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 2-1 and Figure 2-1.

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

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increased in all groups hired between 1925 and 1947. Workers in the lowest cumulative exposure group ( $<10 \text{ mg}\cdot\text{mo}/\text{m}^3$ ) were reported to have had less than 2 years exposure at an average arsenic concentration of  $0.38 \text{ mg}/\text{m}^3$ . 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 ( $\text{SMR}=138$ ) exposed to  $0.05 \text{ mg}/\text{m}^3$  and significant increases in the medium ( $\text{SMR}=303$ ), high ( $\text{SMR}=375$ ), and very high ( $\text{SMR}=704$ ) groups exposed to 0.3, 2.75, and  $5.0 \text{ mg}/\text{m}^3$ , 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. The CELs from both analyses of the Anaconda cohort are presented in Table 2-1 and Figure 2-1.

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 ( $\text{SMR}=226.7$ ), which had the highest average arsenic exposure concentration ( $0.069 \text{ mg}/\text{m}^3$  vs.  $0.007\text{--}0.013 \text{ mg}/\text{m}^3$  in the other smelters) and also contributed the largest number of cohort members ( $n=2,288$  vs.  $189\text{--}965$  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 2-1 and Figure 2-1.

Jarup et al. (1989) reported significantly increased lung cancer mortality ( $\text{SMR}=372$ , 95% confidence interval  $[\text{CI}]=304\text{--}450$ ) based on 106 lung cancer deaths in a cohort of 3,916 male workers employed for  $\geq 3$  months between 1928 and 1967 at the Ronnskar smelter and followed for mortality through 1981. Workers were separated into low, medium, and high arsenic exposure groups with mean time-weighted average exposure estimates of 0.05, 0.2, and  $0.4 \text{ mg}/\text{m}^3$ , respectively. Lung cancer mortality was significantly increased in all three exposure groups in a concentration-related fashion ( $\text{SMR}=201, 353$ , 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

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smokers, and heavy smokers (Jarup 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 2-1 and Figure 2-1.

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  $1 \mu\text{g}/\text{m}^3$ ) of  $4.3 \times 10^{-3}$  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 1983a, 1983b, 1983c; Higgins et al. 1982; Lee-Feldstein 1983) and the ASARCO smelter in Tacoma, Washington (Enterline and Marsh 1982; EPA 1984a; IRIS 2000). In some cases, calculations of exposure, as well as the procedures for generating quantitative risk estimates, are quite complex and the

## 2. HEALTH EFFECTS

interested reader is referred to the EPA documents (EPA 1981c, 1984a, 1987e, 1996b; IRIS 2000) 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 (Jarup et al. 1989). Their analysis yielded a revised unit risk of  $1.28 \times 10^{-3}$  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  $1.43 \times 10^{-3}$  per ( $\mu\text{g}/\text{m}^3$ ). This unit risk estimate is a factor of 3 smaller than the EPA's current estimate of  $4.3 \times 10^{-3}$  per ( $\mu\text{g}/\text{m}^3$ ). Figure 2-1 shows the air concentrations that correspond to excess lifetime cancer risks of  $10^{-4}$  to  $10^{-7}$  based on the EPA unit risk estimate.

There have been occasional reports of other types of cancer (i.e., non-respiratory 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. 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 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. 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 (Col 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.

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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 Bjorklund 1985; Pershagen et al. 1984a; 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.

### 2.2.2 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 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 2-3 and Figure 2-3 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 organic arsenicals are listed in Table 2-4 and shown in Figure 2-4. 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.

#### 2.2.2.1 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). 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

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>						
<b>Death</b>						
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)				44 F (LD50)  Gaines 1960 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
8	Rat (Sherman)	once (G)				112 F (LD50) Gaines 1960 As(+5) calcium arsenate
9	Rat (Sherman)	once (G)				175 F (LD50) Gaines 1960 As(+5) lead arsenate
10	Rat (Sprague- Dawley)	once (GW)				15 M (LD50) Harrison et al. 1958 As(+3)
11	Rat (Sprague- Dawley)	once (F)				145 M (LD50) Harrison et al. 1958 As(+3)
12	Rat (CD)	once on Gd9 (GW)				23 F (7/25 dams died) Stump et al. 1999 As(+3)
13	Mouse (Swiss- Webster)	once (GW)				39 M (LD50) Harrison et al. 1958 As(+3)
14	Mouse (C57H46)	once (GW)				26 M (LD50) Harrison et al. 1958 As(+3)
15	Mouse (Db2)	once (GW)				32 M (LD50) Harrison et al. 1958 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
16	Mouse (C3H)	once (GW)				26 M (LD50)	Harrison 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 1x/d (GW)				1.49 F (7/20 dams died)	Nemec et al. 1998 As(+5)
<b>Systemic</b>							
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 (periobital 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 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	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	once or twice (W)	Gastro	0.05	(occasional nausea, diarrhea, and abdominal cramps)		Franzblau and Lilis 1989 As(+3) As(+5)
24	Human	once (W)	Gastro			120 M (vomiting and diarrhea)	Goebel et al. 1990 NS
			Renal			120 M (anuria)	
			Dermal		120 M (hyperkeratosis)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
25	Human	once (IN)	Gastro		2 F (vomiting)		Hantson et al. 1996 As(+3)
			Hepatic		2 F (slight incr 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 incr serum bilirubin, ALT, AST, LDH)	
			Dermal Ocular		13 M (erythematous eruption) 13 M (constricted vision)		
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 incr serum AST and LDH)	
			Renal			22 M (large incr serum creatinine and BUN indicating acute renal failure)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
28	Human	once at wk 30 of pregnancy (IN)	Cardio	0.05	6 F (high leukocyte count, low hematocrit)	6 F (hypotension, rapid pulse)	Lugo et al. 1969 As(+3)	
			Gastro			6 F (abdominal pain, vomiting)		
			Hemato			6 F (acute renal failure)		
29	Human	2-3 wk (F)	Resp	0.05	(sore throat, rhinorrhea, cough, sputum)	0.05 (abnormal electrocardiogram)	Mizuta et al. 1956 As(+5)	
			Cardio					
			Gastro					0.05 <sup>b</sup> (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 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					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. 1994 As(+3)
			Cardio	11 M		43 M (hypotension, asystolic cardiac arrest)	
			Gastro			11 M (profuse diarrhea and vomiting, severe abdominal pain)	
			Hemato Renal	43 M	11 M (incr 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)	
32	Monkey (Rhesus)	13 d 1x/d (IN)	Gastro	3		6 (vomiting, unformed stool, "loss of condition")	Heywood and Sortwell 1979 As(+5)
			Hepatic	3	6 (decr liver glycogen, vacuolation of hepatocytes)		
			Renal	3	6 (dilation of proximal tubules)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Rat (Wistar- Barby)	4-14 d 5 d/wk 1x/d (G)	Cardio	2 F	11 F (decr vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)
			Gastro	2 F		11 F (diarrhea, bloody stools)	
34	Rat (Sprague- Dawley)	2x (GW)	Resp	14 F			Brown and Kitchin 1996 As(+3)
			Hepatic		0.9 F (slight incr ornithine decarboxylase and heme oxygenase activity in liver)		
			Dermal	14 F			
35	Rat (Sprague- Dawley)	2x (GW)	Hepatic	8 F	24 F (incr heme oxygenase activity in liver)		Brown et al. 1997 As(+5)
36	Rat (CD)	once on Gd9 (GW)	Bd Wt	15 F	23 F (decr body wt gain)		Stump et al. 1999 As(+3)
37	Mouse (CD-1)	Gd 6-15 1x/d (GW)	Bd Wt	12 F	24 F (decr bd wt gain during gestation)		Nemec et al. 1998 As(+5)
38	Mouse (B6C3F1)	1 or 4 d 1x/d (GW)	Hemato	3 M	6 M (decr polychromatic erythrocytes in bone marrow)		Tice et al. 1997 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
39	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)	Bd Wt	0.37 F	1.49 F (loss of body weight during treatment during gestation)		Nemec et al. 1998 As(+5)
<b>Neurological</b>							
40	Human	1 wk (W)				2	(encephalopathy, peripheral neuropathy) Armstrong et al. 1984 NS
41	Human	once (IN)				121 M	(confusion, brain edema) Civantos et al. 1995 As(+5)
42	Human	once (IN)				19 F	(lethargy) Cullen et al. 1995 As (+5)
43	Human	once (NS)				8 M	(severe, persistent encephalopathy and peripheral neuropathy) Fincher and Koerker 1987 As(+3)
44	Human	once (W)				120 M	(severe polyneuropathy) Goebel et al. 1990 NS
45	Human	once (IN)				216 M	(peripheral neuropathy) Hanson et al. 1996 As(+3)
46	Human	once (IN)				13 M	(peripheral neuropathy) Kamijo et al. 1998 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
47	Human	once (IN)				22 M (agitation, disorientation, paranoia, violent reactions)	Levin-Scherz et al. 1987 As(+3)
48	Human	2-3 wk (F)				0.05 (hypesthesia in legs, abnormal patellar reflex)	Mizuta et al. 1956 As(+5)
49	Human	once (IN)		43 M			Moore et al. 1994 As(+3)
50	Human	once (IN)				93 M (encephalopathy)	Quatrehomme et al. 1992 As(+3)
51	Monkey (Rhesus)	13 d 1x/d (IN)		3		6 (marked salivation, uncontrolled head shaking)	Heywood and Sortwell 1979 As(+5)
52	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		0.37 F		1.49 F (prostration, ataxia)	Nemec et al. 1998 As(+5)
<b>Developmental</b>							
53	Human	once at wk 30 of pregnancy (IN)				6 (severe pulmonary hemorrhage that may have contributed to death in premature neonate)	Lugo et al. 1969 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
54	Rat (CD)	once on Gd9 (GW)		15		23 (incr post-implantation loss and decr viable fetuses) Stump et al. 1999 As(+3)
55	Mouse (CD-1)	once during Gd 8-15 (GW)		11		23 (incr fetal mortality, exencephaly) Baxley et al. 1981 As(+3)
56	Mouse (CD-1)	once during Gd 7-15 (GW)				48 (incr fetal death, decr fetal wt, gross and skeletal malformations) Hood et al. 1978 As(+5)
57	Mouse (CD-1)	Gd 6-15 1x/d (GW)		12		24 (incr resorptions per litter, decr live fetuses per litter, decr mean fetal wt) Nemec et al. 1998 As(+5)
58	Hamster (Lak:LVG [SYR])	once during Gd 8-12 (GW)		11		14 (incr fetal mortality, decr fetal wt) Hood and Harrison 1982 As(+3)
59	Rabbit (New Zealand)	Gd 6-18 1x/d (GW)		0.37		1.49 (incr resorptions per litter, decr live fetuses per litter) Nemec et al. 1998 As(+5)

**INTERMEDIATE EXPOSURE**

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
<b>Systemic</b>								
60	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 incr AST and ALT)	
			Dermal	0.1	(diffuse erythematous and scaly rash)			
			Ocular	0.1	(swelling and irritation of the eyes, impaired peripheral vision)			
61	Human	0.5-14 yr (W)	Dermal			0.05	(hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS
62	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 wt loss)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
63	Rat (Wistar- Barby)	4 wk 5 d/wk 1x/d (GW)	Cardio		11 F (decr vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)
64	Rat (Sprague- Dawley)	6 wk (W)	Renal		4.7 M (incr relative kidney wt, impaired renal mitochondrial respiration, ultrastructural changes in proximal tubule)		Brown et al. 1976 As(+5)
			Bd Wt	9.4 M	10.9 M (decr body wt gain)		
65	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 wt 28% lower than controls)	
66	Rat (CD)	14 d pre- mating thru Gd 19 1 x/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 (incr liver wt)		
			Renal	4 F	8 F (incr kidney wt)		
			Bd Wt	4 F	8 F (decr body wt gain)		
67	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 (decr body wt gain)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
68	Mouse (C57BL/6 B6)	14 wk (W)	Hepatic	25 M			Kerkvliet et al. 1980 As(+5)
			Renal	25 M			
69	Dog (Beagle)	26 wk ad lib (F)	Hemato	1.9 F			Neiger and Osweiler 1989 As(+3)
			Hepatic		0.8 F (mild incr serum ALT/AST)		
			Renal	1.9 F			
			Bd Wt	0.8 F	1.5 F (decr body wt gain)	1.9 F (25% decr in body wt)	
<b>Immunological/Lymphoreticular</b>							
70	Mouse (C57BL/6 B6)	14 wk (W)		25 M			Kerkvliet et al. 1980 As(+5)
<b>Neurological</b>							
71	Human	3 mo (W)				0.1 (paresthesia of hands and feet; confusion, disorientation and mental sluggishness)	Franzblau and Lilis 1989 As(+3) As(+5)
72	Human	4 mo (W)				0.06 F (weakness, paresthesia)	Wagner et al. 1979 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Reproductive</b>							
73	Rat (CD)	14 d pre- mating thru Gd 19 1 x/d (GW)		8 F			Holson et al. 2000 As(+3)
74	Mouse (CD)	3 gen (W)				1 (decr litter size)	Schroeder and Mitchener 1971 As(+3)
<b>Developmental</b>							
75	Rat (CD)	14 d pre- mating thru Gd 19 1 x/d (GW)		4	8 (decr fetal body wt, incr skeletal variations)		Holson et al. 2000 As(+3)
76	Mouse (CD)	3 gen (W)				1 (decr litter size)	Schroeder and Mitchener 1971 As(+3)
<b>CHRONIC EXPOSURE</b>							
<b>Death</b>							
77	Human	2-7 yr children (W)				0.05 (death)	Zaldivar and Guillier 1977 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
78	Human	22 yr (W)				0.014 M (death)	Zaldivar et al. 1981 NS
79	Monkey (Rhesus)	1 yr (IN)				3 (2/7 died)	Heywood and Sortwell 1979 As(+5)
80	Rat (Wistar)	27 mo (F)				30 (incr mortality)	Kroes et al. 1974 As(+5) lead arsenate
81	Mouse (CD)	2 yr (W)				1 (incr mortality, decr life span)	Schroeder and Balassa 1967 As(+3)
82	Dog (Beagle)	2 yr (F)				2.4 (6/6 died)	Byron et al. 1967 As(+3)
83	Dog (Beagle)	2 yr (F)				2.4 (1/6 died)	Byron et al. 1967 As(+5)
<b>Systemic</b>							
84	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)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL		LOAEL		Reference Chemical Form
				(mg/kg/day)	(mg/kg/day)	(mg/kg/day)	(mg/kg/day)	
85	Human	4 yr (IN)	Dermal				0.1 F (de-pigmentation with hyperkeratosis, possibly pre-cancerous)	Bickley and Papa 1989  As(+3)
86	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)	
87	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 hyperkeratosis, possibly pre-cancerous)	
88	Human	11-15 yr (W)	Dermal		0.01	(hypo- and hyperpigmentation)	Borgono et al. 1980 NS	
89	Human	continuous (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)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
90	Human	1-11 yr (W)	Hepatic	0.046	(hepatomegaly)		Chakraborty and Saha 1987 NS
			Dermal			0.046	
91	Human	continuous (W)	Cardio			0.064	(Blackfoot disease) Chen et al. 1988b NS
92	Human	>10 yr (W)	Cardio	0.0008		0.022	(increased risk of ischemic heart disease mortality) Chen et al. 1996 NS
93	Human	NS (W)	Cardio			0.002	(incr prevalence of cerebrovascular disease and cerebral infarction) Chiou et al. 1997 NS
94	Human	3-7 yr (W)	Cardio			0.05	(Blackfoot disease) Foy et al. 1992 NS
			Dermal			0.05	(melanosis with hyperkeratosis, possibly pre-cancerous)
95	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)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
96	Human	NS (W)	Hepatic	0.004		0.014 (hepatomegaly)	Guha Mazumder et al. 1988 NS
			Dermal	0.004		0.014 (pigmentation changes with hyperkeratosis, possibly pre-cancerous)	
97	Human	1-20 yr (W)					Guha Mazumder et al. 1988 NS
			Gastro		0.06 (abdominal pain)		
			Hemato		0.06 (anemia)		
			Hepatic			0.06 (hepatomegaly, fibrosis)	
			Dermal			0.06 (hyperpigmentation with hyperkeratosis, possibly pre-cancerous)	
98	Human	NS (W)	Dermal	0.0016		0.009 (hyperpigmentation with keratosis, possibly pre-cancerous)	Guha Mazumder et al. 1998a NS
99	Human	10 yr (W)	Gastro	0.00065			Harrington et al. 1978 NS
			Hemato	0.00065			
			Dermal	0.00065			

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
100	Human	NS (W)	Hepatic	0.0008	0.006 (incr serum alkaline phosphatase and bilirubin)		Hernandez-Zavala et al. 1998 NS
101	Human	NS (W)	Cardio			0.067 (ischemic heart disease)	Hsueh et al. 1998 NS
102	Human	0.5-14 yr (W)	Dermal			0.05 (hyperpigmentation with keratosis, possibly pre-cancerous)	Huang et al. 1985 NS
103	Human	15 yr (IN)	Gastro  Dermal			0.03 M (hematemesis, hemoperitoneum, melena)  0.03 M (hyperkeratosis - possibly pre-cancerous)	Lander et al. 1975 As(+3)
104	Human	NS (W)	Cardio  Dermal	0.004  0.004		0.005 (cyanosis of extremities, palpitations/chest discomfort)  0.005 (keratosis, hyperpigmentation, depigmentation)	Lianfang and Jianzhong 1994 NS
105	Human	3-22 yr (IN)	Gastro  Hepatic  Dermal			0.05 M (gastrointestinal hemorrhages)  0.05 M (vascular fibrosis, portal hypertension)  0.05 M (hyperpigmentation with keratoses, possibly pre-cancerous)	Morris et al. 1974 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
106	Human	15 yr (IN)	Hepatic			0.05 F (central fibrosis)	Piontek et al. 1989 As(+3)
			Dermal			0.05 F (hyperkeratosis, possibly pre-cancerous)	
107	Human	NS (W)	Endocr			0.11 (diabetes mellitus)	Rahman et al. 1998  NS
108	Human	NS (W)	Cardio	0.018		0.055 (hypertension)	Rahman et al. 1999  NS
109	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 Hepatic	0.06 F	0.06 F (hepatomegaly, fatty liver)		
			Renal Dermal	0.06 F		0.06 F (melanosis with hyperkeratosis, possibly pre-cancerous)	
			Ocular		0.06 F (conjunctival injection, periocular edema)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
110	Human	≥ 5 yr (W)	Hemato	0.006 M 0.007 F			Southwick et al. 1981 NS
			Dermal	0.0009 M 0.001 F			
111	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)	
112	Human	45 yr (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1977 NS
113	Human	NS (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1989 NS
114	Human	≥ 45 yr (W)	Dermal	0.0008 <sup>c</sup> M	0.014 M (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968 NS
115	Human	≥ 30 yr (W)	Cardio		0.064 M (deficits in cutaneous microcirculation of the toes)		Tseng et al. 1995 As(+3)
116	Human	52.6 yr (avg) (W)	Cardio	0.016		0.031 (peripheral vascular disease)	Tseng et al. 1996 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
117	Human	16 mo (IN)	Resp	0.1 M			Wade and Frazer 1953
			Cardio	0.1 M			As(+3)
			Hemato	0.1 M			
			Hepatic Dermal		0.1 M (liver enlargement)	0.1 M (hyperkeratosis, hyperpigmentation with hyperkeratosis, possibly pre-cancerous)	
118	Human	12 yr (W)	Resp		0.015 M (bronchitis, bronchiectasis)		Zaldivar 1974 NS
					0.018 F		
			Cardio			0.015 M (Raynaud's disease, thrombosis)	
						0.018 F	
			Gastro		0.015 M (diarrhea)		
					0.018 F		
Dermal		0.015 M (scaling of skin, hyperkeratosis, leukoderma, melanoderma)					
			0.018 F				
Bd Wt		0.015 M (unspecified decr body wt)					
			0.018 F				

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL		LOAEL		Reference Chemical Form
				(mg/kg/day)	Less Serious (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
119	Human	30-33 yr (W)	Dermal				0.015 M (hyperkeratosis of foot, possibly pre-cancerous)	Zaldivar 1974 NS
120	Human	NS (W)	Dermal				0.063 (hyperpigmentation with keratoses, possibly pre-cancerous)	Zaldivar 1977 NS
121	Human	1-39 yr (W)	Cardio				0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977 NS
122	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)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
123 Rat (Osborne- Mendel)		2 yr (F)	Resp	20			Byron et al. 1967 As(+3)
			Cardio	20			
			Gastro	20			
			Hemato	9	20	(slight transient decr in Hb and H values)	
			Hepatic	4		9 (enlarged bile duct, bile duct proliferation)	
			Renal	9	20	(pigmentation)	
			Bd Wt	2	4	(decr body wt gain)	
124 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	(decr body wt gain in females)	

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
125 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 (decr body wt gain)		
126 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 dilatation and inflammation)	
			Renal	30			
			Endocr	30			
			Bd Wt	7	30 (decr body wt gain)		

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
127 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				
128 Mouse (CD)		2 yr (W)	Bd Wt		1	(decr body wt gain after the first 6 mo of the study)	Schroeder and Balassa 1967 As(+3)	
129 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% wt loss)			

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
130	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 Bd Wt	2.4 1		2.4 (marked decr wt gain)	
<b>Neurological</b>							
131	Human	3-7 yr (W)				0.11 F (wrist weakness)	Foy et al. 1992 NS
132	Human	1-20 yr (W)			0.06	(tingling of hands and feet)	Guha Mazumder et al. 1988 NS
133	Human	10 yr (W)		0.00065			Harrington et al. 1978 NS
134	Human	continuous (W)		0.0014		0.04 (functional denervation)	Hindmarsh et al. 1977 NS

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
135	Human	NS (W)		0.004	0.005 (fatigue, headache, dizziness, insomnia, nightmare, numbness)		Lianfang and Jianzhong 1994 NS
136	Human	28 mo (IN)				0.06 F (paresthesia)	Silver and Wainman 1952 As(+3)
137	Human	≥ 5 yr (W)		0.006 M 0.007 F			Southwick et al. 1981 NS
138	Human	55 yr (IN)			0.03 M (absent ankle jerk reflex and vibration sense in legs)		Szuler et al. 1979 As(+3)
<b>Cancer</b>							
139	Human	continuous (W)				0.022 (CEL: skin cancer)	Cebrian et al. 1983 As(+5)
140	Human	continuous (W)				0.064 (CEL: bladder, lung and liver cancers)	Chen et al. 1986 NS
141	Human	continuous (W)				0.064 (CEL: malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b NS
142	Human	2 wk-12 yr (IN)				3.67 (CEL: bladder cancer risk)	Cuzick et al. 1992 As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
143	Human	NS (W)				0.0011 (CEL: lung cancer) Ferreccio et al. 1998 NS
144	Human	NS (W)				0.052 (CEL: incr incidence of transitional cell carcinomas of the bladder, kidney, & ureters and all urethral cancer) Guo et al. 1997 NS
145	Human	>1 yr (W)				0.0075 (CEL: basal or squamous skin carcinoma) Haupt et al. 1996 NS
146	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)
147	Human	60 yr continuous (W)				0.038 (CEL: intraepidermal carcinoma) Tseng 1977 NS
148	Human	≥ 45 yr (W)				0.014 (CEL: squamous cell carcinoma of the skin) Tseng et al. 1968 NS
149	Human	~5 yr (W)				0.033 (CEL: lung, urinary tract cancer) Tsuda et al. 1995a As(+3)

Table 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
150	Human	12 yr (W)				0.015 M (CEL: squamous cell carcinoma of the skin)  0.018 F (CEL: squamous cell carcinoma of the skin)	Zaldivar 1974 NS
151	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

<sup>a</sup>The number corresponds to entries in Figure 2-3.

<sup>b</sup>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).

<sup>c</sup>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; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); decr = decreased; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; GI = gastrointestinal; (GW) = gavage in water; gen = generation; Gd = gestation day; Gn pig = guinea pig; Hb = hemoglobin; Hct = hematocrit; Hemato = hematological; hr = hour(s); IN = ingestion; incr = increased; LD50 = lethal dose, 50% kill; LDH = lactate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; Metab = metabolic; mo = month(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; (W) = water; wk = week(s); wt = weight; yr = year(s)

Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral  
Acute (≤14 days)

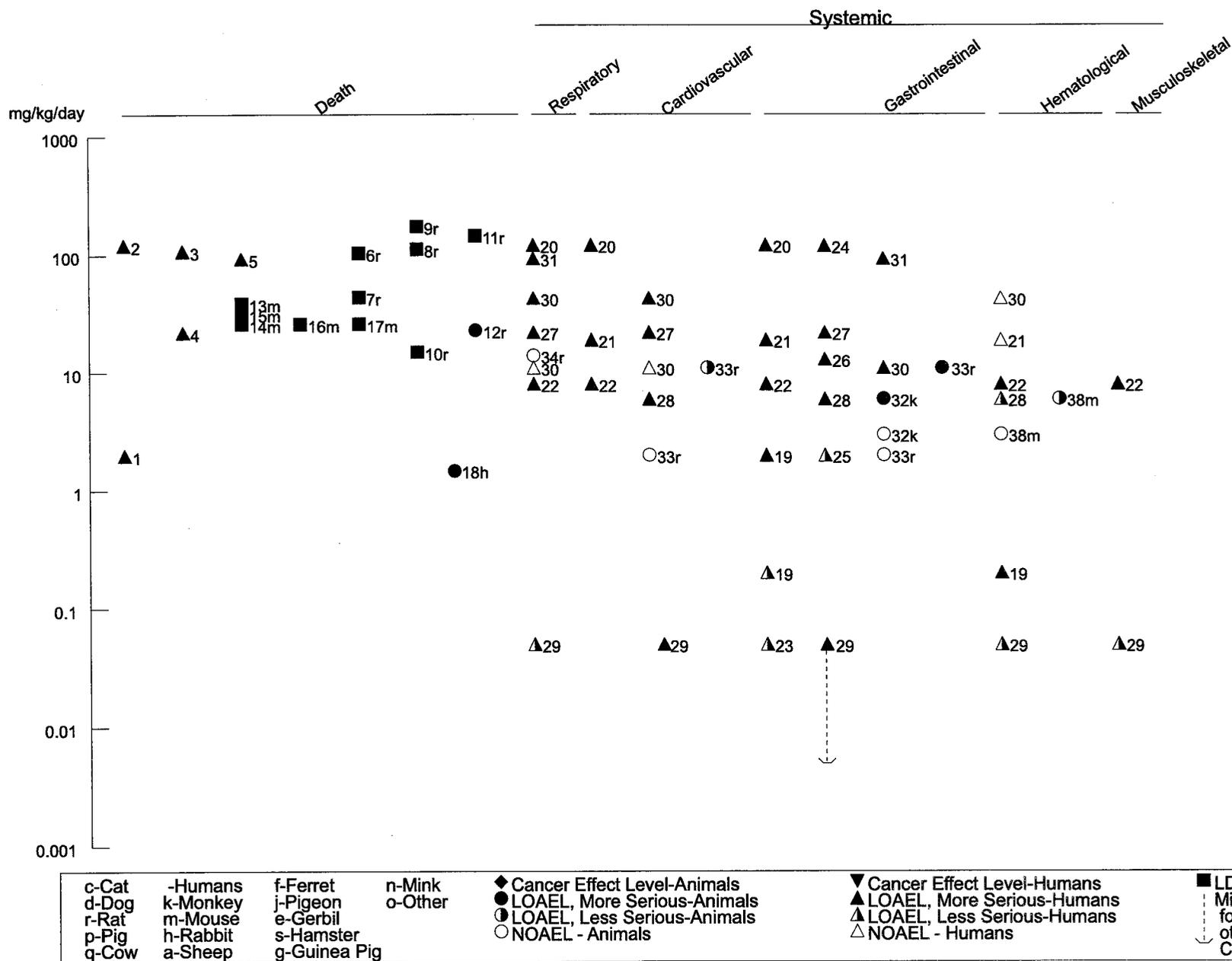


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)  
Acute (≤14 days)

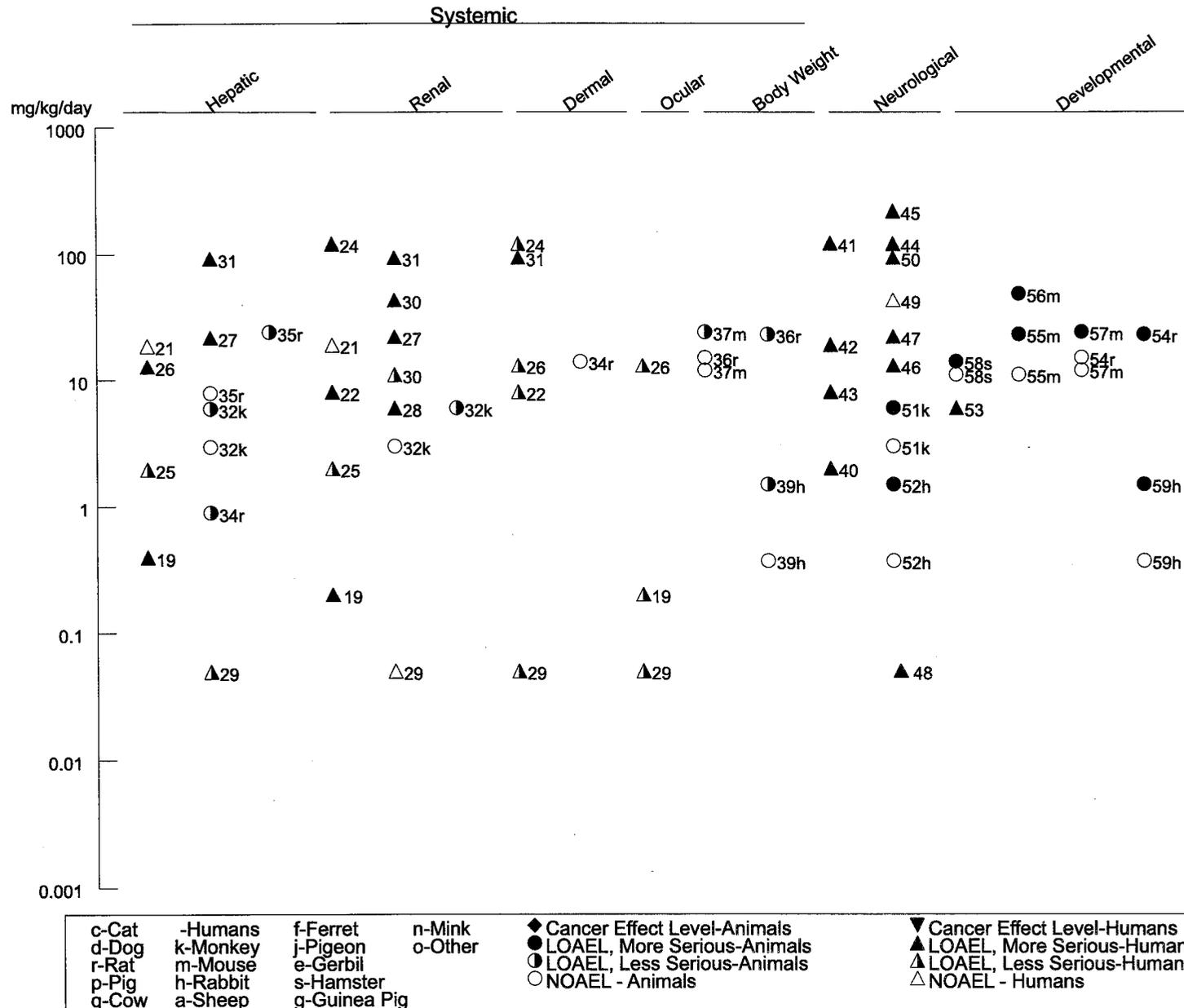




Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)  
Chronic (≥365 days)

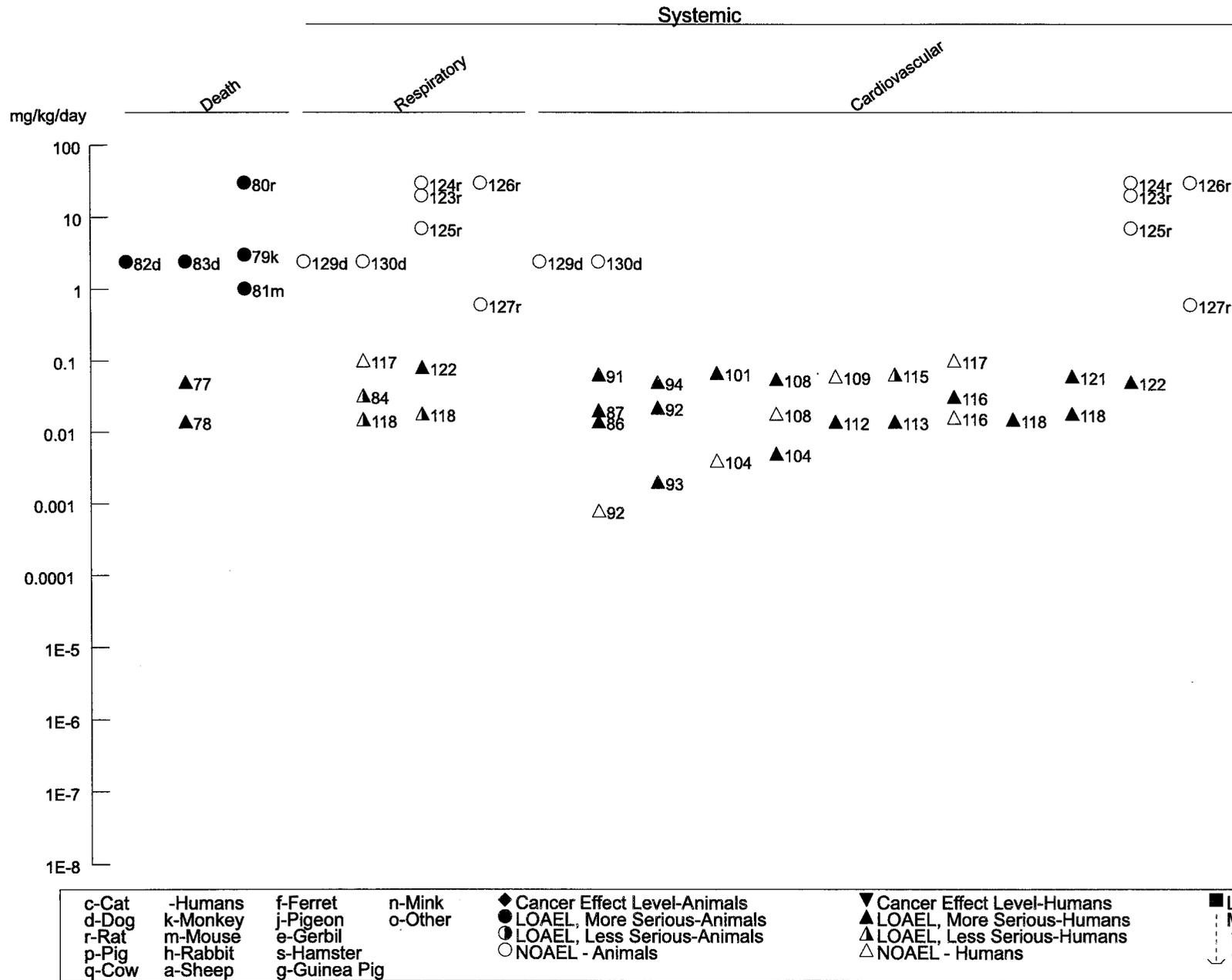


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (*continued*)

Chronic ( $\geq 365$  days)

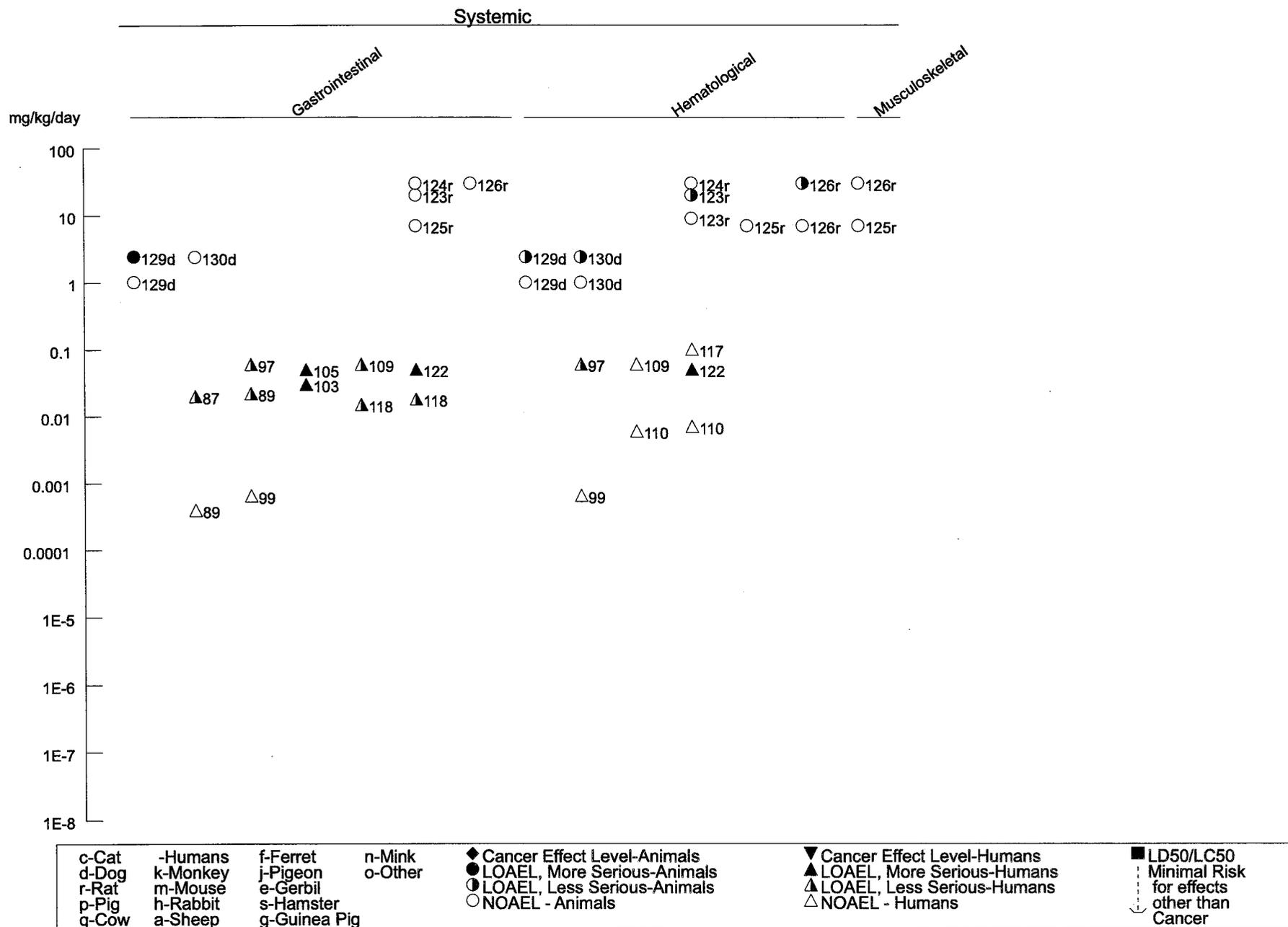


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)  
Chronic (≥365 days)

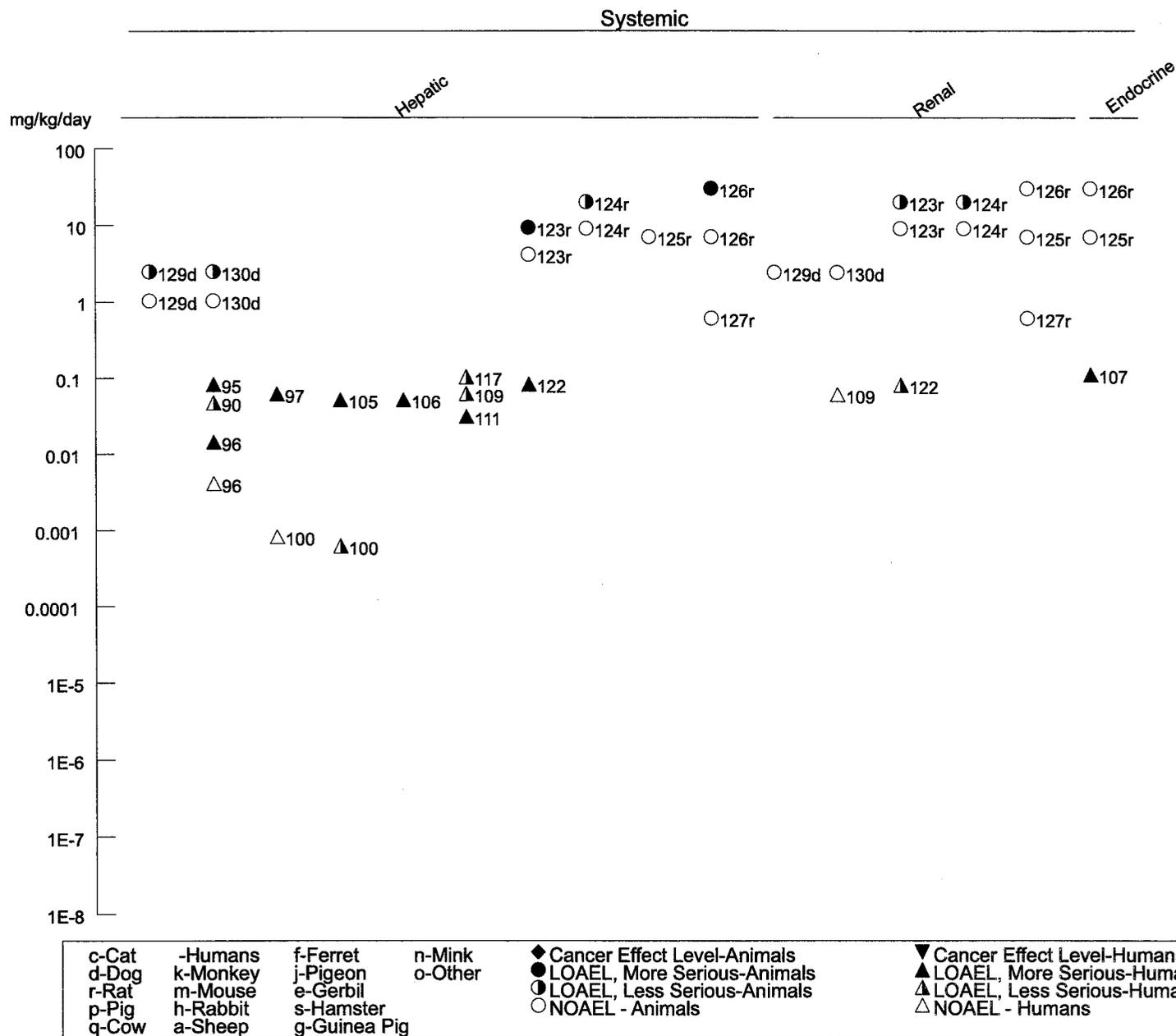


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)

Chronic (≥365 days)

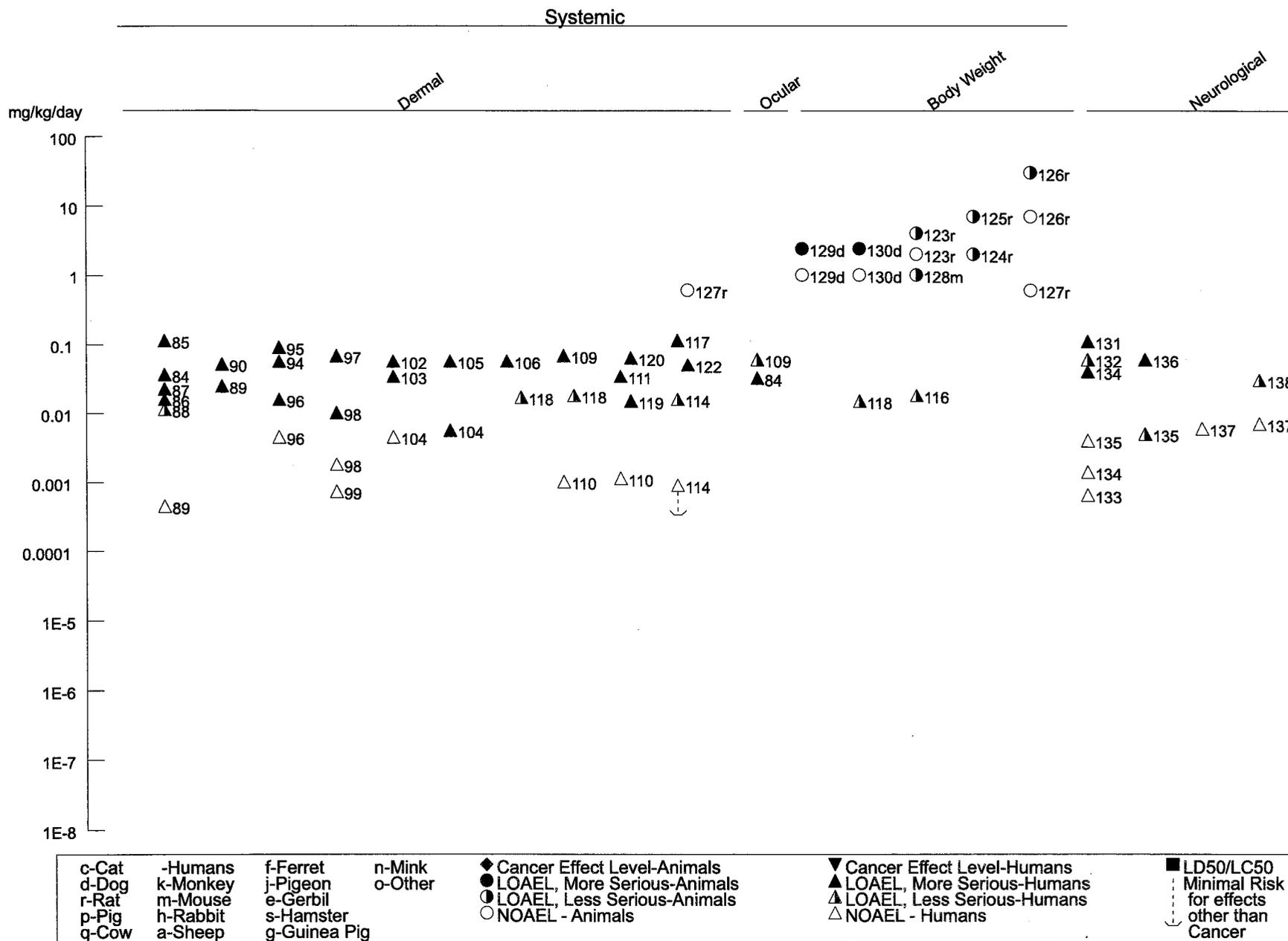


Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (continued)  
Chronic (≥365 days)

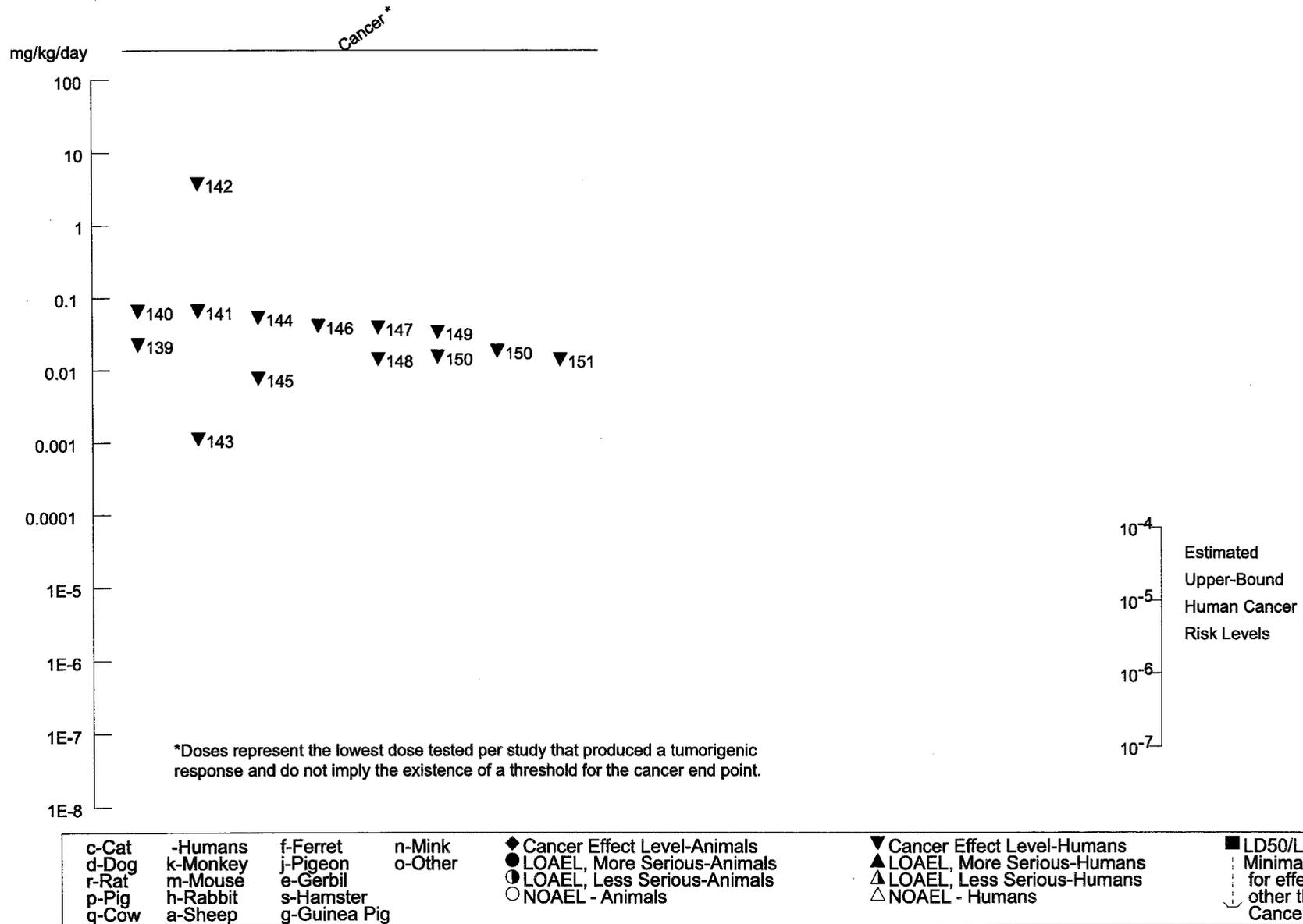


Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (Holtzman)	once (GW)				44 (LD50)	Kerr et al. 1963 ROX
2	Rat (Fischer- 344)	9d 1x/d (G)				61 (1/3 died)	Murai et al. 1993 DMA
3	Rat (Fischer- 344)	once (GO)				21.4 F (2/5 died; LD50=23.1 mg As/kg) 42.7 M (5/5 died)	NTP 1989b ROX
4	Rat (Fischer- 344)	14 d (F)				36.46 M (3/5 died) 41.02 F (5/5 died)	NTP 1989b ROX
5	Rat (CD)	10 d Gd 7-16 1x/d (GW)				21.7 F (4% mortality)	Rogers et al. 1981 DMA
6	Mouse (ddY)	once (GW)				652 M (LD50)	Kaise et al. 1989 DMA
7	Mouse (ddY)	once (GW)				963 M (LD50)	Kaise et al. 1989 MMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
8	Mouse (B6C3F1)	14 d (F)				48.4 (2/5 males died; 5/5 females died) NTP 1989b ROX
9	Mouse (B6C3F1)	once (GO)				69.5 F (LD50) 85.4 M (5/5 died) NTP 1989b ROX
10	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)				217 F (3% mortality) Rogers et al. 1981 DMA
11	Dog (Mongrel)	once (C)				14.2 (LD50) Kerr et al. 1963 ROX
12	Rabbit (New Zealand)	once (GW)				47 M (LD50) Jaghabir et al. 1988 MMA
<b>Systemic</b>						
13	Human	once (IN)	Cardio  Gastro  Hemato Hepatic		77.1 M (sinus tachycardia)  77.1 M (vomiting, abdominal pain, hyperactive bowel, watery garlic-smelling stools)	77.1 M 77.1 M Lee et al. 1995 DMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
14	Human	once (IN)	Resp	793 M			Shum et al. 1995 MSMA
			Cardio	793 M			
			Gastro		793 M (vomitin g)		
			Hepatic	793 M			
			Renal	793 M			
15	Rat (Fischer- 344)	14 d (F)	Hemato	18.23 M 20.51 F	36.46 M (cyanosis of the eye)		NTP 1989b ROX
			Bd Wt	4.56 M 41.02 F	9.11 M (22% reduced body weight)		
16	Rat (CD)	10 d Gd 7-16 1x/d (GW)	Bd Wt			21.7 F (27% decreased maternal weight gain)	Rogers et al. 1981 DMA
17	Mouse (B6C3F1)	24 hr 1 or 2x (GW)	Resp		391 F (decr lung ODC)		Ahmad et al. 1999 DMA
			Hepatic		391 F (decr liver GSH, GSSG, CYP-450 and ODC; incr serum ALT)		
18	Mouse (ddY)	once (GW)	Resp			489 M (respiratory arrest)	Kaise et al. 1989 DMA
			Gastro		954 M (diarrhea, slight congestion of the intestion)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
19	Mouse (ddY)	once (GW)	Resp			963 M (respiratory arrest)	Kaise et al. 1989 MMA
			Gastro		1177 M (diarrhea, slight congestion of the small intestine)		
20	Mouse (B6C3F1)	14 d (F)	Hemato	5.8	12.1 (pale skin)		NTP 1989b ROX
			Bd Wt	48.4			
21	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)	Bd Wt			109 F (26% decreased maternal weight gain)	Rogers et al. 1981 DMA
22	Dog (Mongrel)	once (C)	Resp			14.2 (localized hemorrhage in lung)	Kerr et al. 1963 ROX
			Gastro			14.2 (vomiting; hemorrhages in the pyloric portion of the stomach, colon and cecum)	
			Hepatic			14.2 (generalized icterus)	
			Renal			14.2 (hematuria, congested kidney)	
			Other	14.2 (bloody mucus in feces)			
23	Rabbit (New Zealand)	once (GW)	Gastro		28 M (constipation, diarrhea)		Jaghabir et al. 1988 MMA
			Renal		28 M (oliguri a)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Neurological</b>							
24	Rat (Fischer- 344)	14 d (F)		4.56	9.11 M (slight inactivity)		NTP 1989b ROX
				5.13	10.25 F		
25	Mouse (ddY)	once (GW)				954 M (increased startle reflex; ataxia)	Kaise et al. 1989 DMA
26	Mouse (B6C3F1)	14 d (F)		5.8	12.1 (slight inactivity; ruffled fur)		NTP 1989b ROX
27	Rabbit (New Zealand)	once (GW)			28 M (weakness, loss of appetite)		Jaghabir et al. 1988 MMA
<b>Developmental</b>							
28	Rat (CD)	10 d Gd 7-16 1x/d (GW)		8.1		16.3 (malformed palates in 15%)	Rogers et al. 1981 DMA
29	Mouse (CD-1)	10 d Gd 7-16 1x/d (GW)		109		217 (18% decrease in fetal weight, delayed ossification, cleft palate in 12/28; irregular palatine rugae in 4.8%)	Rogers et al. 1981 DMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>INTERMEDIATE EXPOSURE</b>							
<b>Death</b>							
30	Rat (Holtzman)	13 wk (F)				5.7 (10/12 died)	Kerr et al. 1963 ROX
31	Rat (Fischer- 344)	4 wk 5 d/wk 1x/d (G)				31 (50% survival in males; 20% survival in females)	Murai et al. 1993 DMA
32	Rat (Fischer- 344)	13 wk ad lib (F)				18.23 M (3/10 died) 20.51 F (2/10 died)	NTP 1989b ROX
33	Rat (Fischer- 344)	8 wk (W)				16 (10/10 died)	Wanibuchi et al. 1996 DMA
34	Mouse (B6C3F1)	13 wk ad lib (F)				13.4 (1/10 males died; 1/10 females died)	NTP 1989b ROX
35	Pig	28 d (F)				5.70 (death in 2/18)	Edmonds and Baker 1986 ROX
<b>Systemic</b>							
36	Rat (Fischer- 344)	4 wk 5 d/wk 1x/d (G)	Renal  Bd Wt			31 (papillary necrosis and hyperplasia; cortical degeneration and necrosis)	Murai et al. 1993 DMA
				31	(decreased body weight)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
37	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	18.33 M 20.51 F			NTP 1989b ROX
			Cardio	18.33 M 20.51 F			
			Gastro	18.33 M 20.51 F			
			Hemato	9.11 M 10.25 F	18.23 M (pale 20.51 F skin)		
			Musc/skel	18.33 M 20.51 F			
			Hepatic		1.14 M (incr relative liver wt.) 20.51 F		
			Renal	10.25	9.11 M (interstitial inflammation, focal regenerative hyperplasia of tubular cell epithelium and 10.25 F mineralization)	18.23 M (tubular necrosis)	
			Endocr	18.33 M 20.51 F		20.51 F	
			Dermal	18.33 M 20.51 F			
			Bd Wt	2.28 M 5.13 F	4.56 M (14% decreased body 10.25 F weight) (11% decreased body	9.11 M (26% decreased body 20.51 F weight) (33% decreased body	

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
38	Rat (Fischer- 344)	31 or 90 d ad lib (F)	Hemato	9.11 M			NTP 1989b ROX
				10.25 F			
			Hepatic	9.11 M			
				2.56 F	10.25 F (decrease relative liver weight)		
			Renal	2.28 M	9.11 M (increased relative kidney weight; mild tubular degeneration)		
			10.25 F				
39	Rat (Sprague- Dawley)	42 d (F)	Hemato	1.99 M			Siewicki 1981 DMA
			Hepatic	1.99 M			
			Renal	1.99 M			
			Bd Wt	1.99 M			
40	Mouse (B6C3F1)	13 wk ad lib (F)	Resp			38.7 (interstitial pneumonia)	NTP 1989b ROX
			Cardio	38.7			
			Gastro	38.7			
			Musc/skel	38.7			
			Hepatic	38.7			
			Renal	38.7			
			Endocr	38.7			
			Dermal	38.7			
			Bd Wt		38.7 (18% decreased body weight in males; 11% decreased body weight in females)		

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
41	Mouse (B6C3F1)	29 or 91 d ad lib (F)	Hemato	13.4			NTP 1989b ROX
			Hepatic	13.4			
			Renal	13.4			
42	Mouse (Swiss)	10 wk 1x/2d (GW)	Hemato	55			Prukop and Savage 1986 MMA
43	Rabbit (New Zealand)	40 d 1x/d (GW)	Gastro		2.3 M (intestinal hyperemia)		Jaghabir et al. 1989 MMA
			Hepatic		2.3 M (hepatocellular degeneration in 4/4)		
			Renal		2.3 M (interstitial nephritis in 2/4)		
<b>Neurological</b>							
44	Rat (Fischer- 344)	13 wk ad lib (F)		9.11 M		18.23 M (trembling, ataxia, hyperexcitability, slight inactivity, ruffled fur)	NTP 1989b ROX
				10.25 F		20.51 F	
45	Pig	28 d (F)		1.43		2.85 (muscle tremors)	Edmonds and Baker 1986 ROX
46	Pig	30 d (F)				0.87 (myelin degeneration)	Kennedy et al. 1986 ROX

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
47	Pig (Landrace)	30 d ad lib (F)				1.07 (seizures in 100%) Rice et al. 1985 ROX
<b>Reproductive</b>						
48	Mouse (Swiss)	19 d 3 d/wk (GW)		5 M		55 M (reduced fertility) Prukop and Savage 1986 MMA
<b>Cancer</b>						
49	Mouse A/J	50 wk ad lib (W)				5.5 M (CEL: lung tumors) Hayashi et al. 1998 DMA

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
50	Rat (Fischer- 344)	103 wk ad lib (F)	Resp	2.29 M			NTP 1989b ROX
				2.56 F			
			Cardio	2.29 M			
				2.56 F			
			Gastro	2.29 M			
				2.56 F			
			Musc/skel	2.29 M			
				2.56 F			
			Hepatic	2.29 M			
				2.56 F			
			Renal	2.29 M			
				2.56 F			
			Endocr	2.29 M			
				2.56 F			
Dermal	2.29 M						
	2.56 F						
Ocular	2.29 M						
	2.56 F						
Bd Wt	2.29 M						
	2.56 F						
Other	2.29 M						
	2.56 F						

Table 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
51	Mouse (Fischer- 344)	103 wk ad lib (F)	Resp	9.7			NTP 1989b ROX
			Cardio	9.7			
			Gastro	9.7			
			Musc/skel	9.7			
			Hepatic	9.7			
			Renal	9.7			
			Endocr	9.7			
			Dermal	9.7			
			Ocular	9.7			
			Bd Wt	9.7 M	4.8 F (6-11% decr. body wt.)		

<sup>a</sup>The number corresponds to entries in Figure 2-4.

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); DMA = dimethyl arsenic acid or cacodylic acid; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; (GO) = gavage in oil; (GW) = gavage in water; Gd = gestation day; 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; ROX = roxarsone; wk = week(s); x = time(s).

Figure 2-4. Levels of Significant Exposure to Organic Arsenic - Oral  
Acute ( $\leq 14$  days)

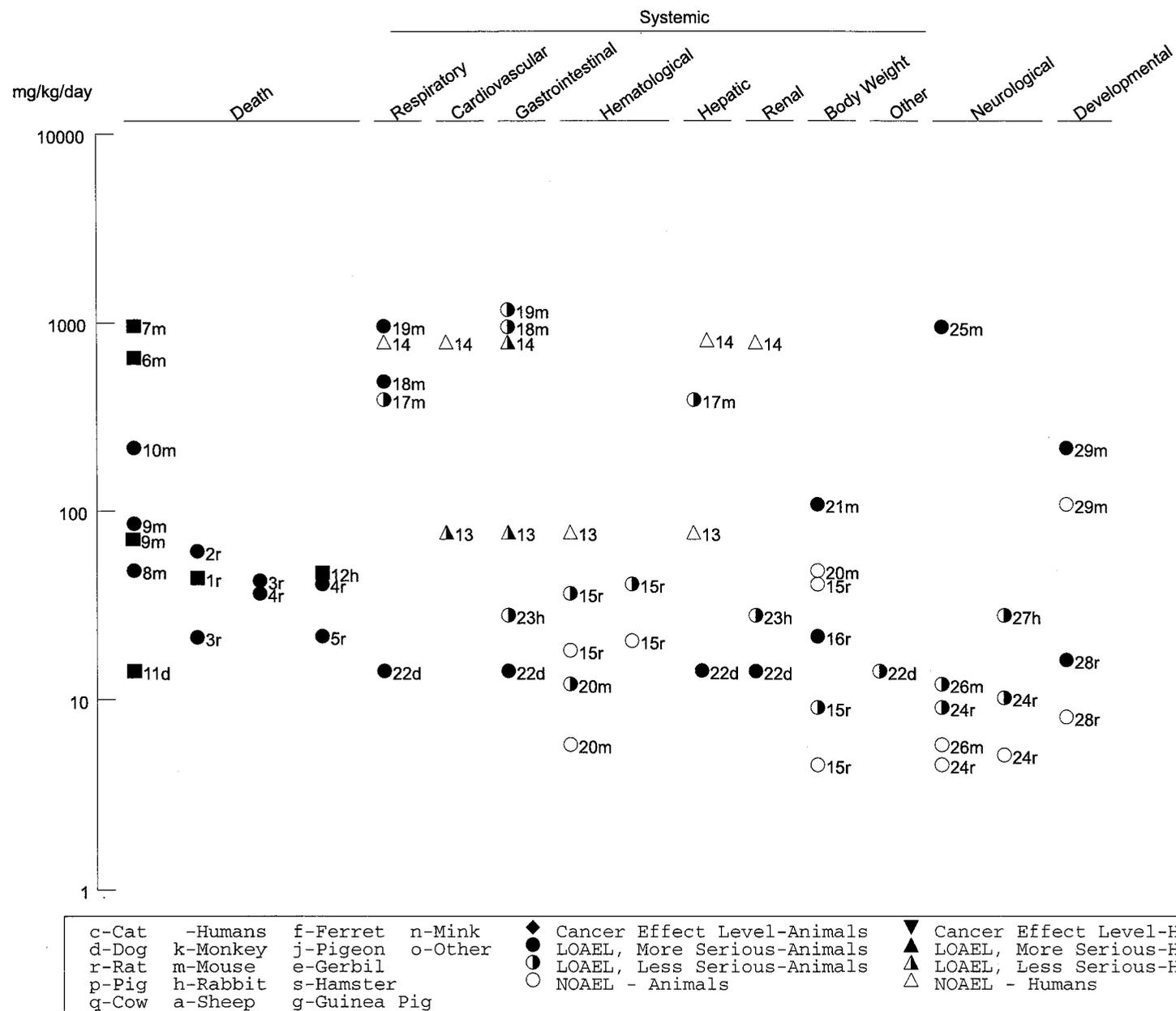
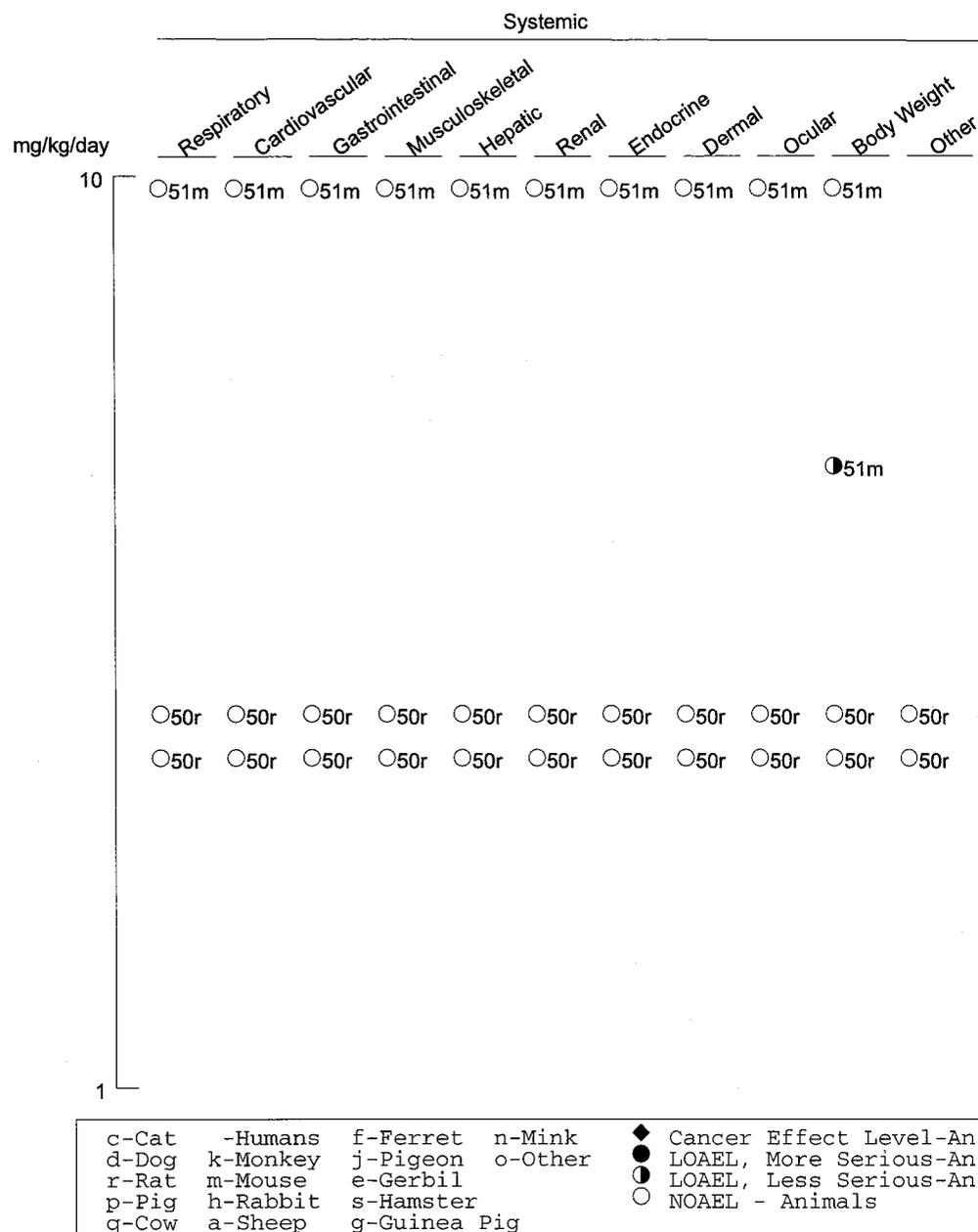




Figure 2-4. Levels of Significant Exposure to Organic Arsenic - Oral (continued)  
Chronic ( $\geq 365$  days)



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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 (Zaldivar 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 (Zaldivar et al. 1981). Systematic studies of lethality from chronic exposure attributable to increased risk of cardiovascular disease or cancer are discussed below in Sections 2.2.2.2 and 2.2.2.8, respectively.

Lethality studies in animals are consistent with the limited data in humans. Available LD<sub>50</sub> 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 LD<sub>50</sub> values for lethality from oral exposure to inorganic arsenicals in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

**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

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studies. As shown in Table 2-4 and Figure 2-4, most acute lethal values range from about 15 to 70 mg As/kg (Jaghabir et al. 1988; Kerr et al. 1963; NTP 1989b; Rogers et al. 1981), although one study (Kaise et al. 1989) reported somewhat higher values (650–970 mg As/kg) for MMA and DMA in mice. The cause of death was not investigated in any of these studies. Intermediate-duration exposure to roxarsone caused death in pigs and rats at exposure levels of 5.7–21.5 mg As/kg/day (Edmonds and Baker 1986; Kerr et al. 1963; NTP 1989b). No increase in mortality was seen after chronic exposure of rats (2.3–2.6 mg/kg/day) or mice (9.7 mg/kg/day) to roxarsone (NTP 1989b).

### 2.2.2.2 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 2-3 and plotted in Figure 2-3. Similar data for oral exposure to organic arsenicals are shown in Table 2-4 and plotted in Figure 2-4.

### 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. 1994; 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 at autopsy in some chronic poisoning cases (Rosenberg 1974; Zaldivar 1974; Zaldivar 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 (Zaldivar and Guillier 1977). 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. Chronic oral studies in

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dogs and rats treated with arsenate or arsenite also 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.

**Organic Arsenicals.** No respiratory effects were noted after acute human ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) (Shum et al. 1995). Mice exhibited respiratory arrest after a single oral dose of 489 mg/kg DMA or 963 mg/kg MMA (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. 1999). 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 (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to 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 Q-T interval, nonspecific S-T 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. 1994). Hypertrophy of the ventricular wall was observed at autopsy after acute exposure to 93 mg As (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 (Abernathy et al. 1989). 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; Chi 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

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levels indicates that arsenic is at least a contributing factor. Arsenic exposure in Taiwan has also been associated with an increased incidence of cerebrovascular disease (Chiou et al. 1997) and ischemic heart disease (Chen et al. 1996; Hsueh et al. 1998b). Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, increased arsenic exposure has been associated with an increase in hypertension in Bangladesh (Rahman et al. 1999). 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) increase the incidence of Raynaud's disease and of cyanosis of fingers and toes (Borgono and Greiber 1972; Zaldivar 1974, 1977; Zaldivar 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 (Zaldivar 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; Zaldivar and Guillier 1977). Some studies of chronic human arsenic exposure report no cardiovascular effects (Guha Mazumder et al. 1988; Silver and Wainman 1952; Valentine et al. 1992).

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).

**Organic Arsenicals.** No adverse cardiovascular effects were noted after acute human ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) (Shum et al. 1995). However, sinus tachycardia was noted after acute ingestion of 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). No cardiovascular effects were seen after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to 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 acute high-dose exposures to inorganic

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arsenic (e.g., Armstrong et al. 1984; Campbell and Alvarez 1989; 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. 1994). Similar signs are also frequently observed in groups or individuals with longer-term lower-dose exposures (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hauptert et al. 1996; Holland 1904; Huang et al. 1985; Mizuta et al. 1956; Nagai et al. 1956b; 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. Gastrointestinal irritation symptoms form the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 2-3. 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 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 one month was found to have acute inflammation and hemorrhage of the small intestine upon autopsy (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 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) induced vomiting, abdominal pain, hyperactive bowel, and diarrhea (Lee et al. 1995). Diarrhea and slight congestion of the intestines was observed in mice after a single dose of 954 mg/kg arsenic (as dimethylarsinic acid) or 1,177 mg/kg arsenic as MMA (Kaise et al. 1989).

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Vomiting and gastrointestinal hemorrhage was observed in dogs after a single capsulized dose of 14 mg arsenic as roxarone (Kerr et al. 1963), although slightly higher doses administered for 13 weeks to rats and mice had no effect (NTP 1989b). One study in rabbits indicates that the intestinal wall may be irritated and weakened by repeated intake of MMA (Jaghabir et al. 1989), but this one observation is not enough to support a firm conclusion. No gastrointestinal effects were seen after chronic exposure of rats (2–3 mg/kg/day) or mice (10 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; Westhoff et al. 1975), intermediate (Franzblau and Lilis 1989; Heyman et al. 1956; Nagai et al. 1956b; Wagner et al. 1979), and chronic oral exposures (Glazener et al. 1968; Guha Mazumder et al. 1988; Kyle and Pease 1965; Tay and Seah 1975) at doses of 0.05 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 Pease 1965; Lerman et al. 1980). However, hematological effects are not observed in all cases of arsenic exposure (Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952; Southwick et al. 1981) or even all acute poisoning cases (Cullen et al. 1995; Moore et al. 1994).

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 in dogs 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). Gallium arsenide also disrupts heme synthesis in rats, although the evidence suggests that this effect of this compound is due primarily to the gallium moiety (Flora et al. 1997a).

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**Organic Arsenicals.** No adverse hematological effects were noted for a man who ingested 77 mg/kg As (as dimethyl arsenic acid and dimethyl arsenate) (Lee et al. 1995). Several studies in rats and mice have not detected any significant hematological effects from repeated exposure (2–13 weeks) to MMA (Prukop and Savage 1986), DMA (Siewicki 1981), or roxarsone (NTP 1989b) at doses of 5–55 mg As/kg/day. These data suggest that oral exposure to organic arsenicals is unlikely to cause hematological effects, but this is not certain.

**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 (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 mg/kg/day, respectively) to 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; 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; Hernandez-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 be effective with chronic exposure (Hernandez-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), although acute exposure to 19 mg As/kg did not cause hepatic effects in an infant (Cullen et al. 1995). Histological examination of the livers of persons chronically exposed to similar doses has revealed a consistent finding of portal tract fibrosis (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

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bleeding from esophageal varices (Szuler et al. 1979). 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 liver of rats exposed to 12 mg As/kg/day as arsenate in the drinking water for 6 weeks (Fowler et al. 1977). 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). 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).

***Organic Arsenicals.*** No adverse hepatic effects were noted after ingestion of 793 mg/kg arsenic (as monosodium methanearsenate) or 77 mg/kg arsenic (as dimethyl arsenic acid and dimethyl arsenate) in a suicide attempt (Lee et al. 1995; Shum et al. 1995). 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).

Histological examination of liver from rabbits given repeated oral doses of MMA showed diffuse inflammation and hepatocellular degeneration (Jaghabir et al. 1989), but the lesions were not severe. 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. 1999). These data suggest that organic arsenicals may cause mild injury to the liver, but the data are too limited to draw firm conclusions.

### **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;

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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. 1994), 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. 1994) is probably a result of fluid imbalances or vascular injury (Rosenberg 1974; Zaldivar 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 mild histological changes in renal tubules of monkeys exposed to arsenate for 2 weeks was 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 (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 793 mg/kg arsenic (as monosodium methanearsenate) in a suicide attempt (Shum et al. 1995). Hematuria and congested kidneys have been observed in dogs after acute exposure, and tubular degeneration and necrosis have been noted in rats (but not mice) given repeated oral doses of roxarsone (up to 20 mg/kg/day As) (Abdo et al. 1989; Kerr et al. 1963; NTP 1989b). Oligouria was noted after acute exposure and interstitial nephritis and tubular nephrosis have been noted in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). However, no renal injury was observed in rats and mice chronically exposed to roxarsone at lower doses (2–10 mg/kg/day As) (NTP 1989b). These data suggest that organic arsenicals can lead to significant renal injury, although the minimal dose is not well defined.

**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 autopsy of five children who died in Chile after chronic exposure to arsenic in the drinking water, arterial thickening in pancreas was noted (Rosenberg 1974). An association has been demonstrated between exposure to arsenic in drinking water and increased incidence of diabetes

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mellitus in Bangladesh (Rahman et al. 1998). No studies in animals were found in which effects of oral exposure to inorganic arsenic on endocrine organs were described.

**Organic Arsenicals.** No studies of effects of organic arsenic compounds on human endocrine glands were found. No adverse effects were seen in the adrenal or pituitary glands, thyroid, or pancreas after intermediate or chronic exposure of rats (18–20 or 2–3 mg/kg/day, respectively) or mice (39 or 10 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; Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrian et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Franzblau and Lilis 1989; Guha Mazumder et al. 1988, 1998a, 1998c; Hauptert et al. 1996; Huang et al. 1985; Lander et al. 1975; Luchtrath 1983; Mizuta et al. 1956; Morris et al. 1974; Nagai et al. 1956b; 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; Zaldivar 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 effects) also appear to have similar thresholds. As shown in Table 2-3 and Figure 2-3, numerous studies in humans have reported dermal effects at chronic dose levels ranging from about 0.01 to 0.1 mg As/kg/day (Bickley and Papa 1989; Borgono and Greiber 1972; Borgono et al. 1980; Cebrian et al. 1983; Chakraborty and Saha 1987; Foy et al. 1992; Franklin et al. 1950; Guha Mazumder et al. 1988; Huang et al. 1985; Luchtrath 1983; Piontek et al. 1989; Silver and Wainman 1952; Tseng et al. 1968; Zaldivar 1974, 1977). 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 (Cebrian et al. 1983; Guha Mazumder et al. 1988; Harrington et al. 1978; Southwick et al. 1981; Valentine et al. 1985), and one very large study (based on 17,000 people) detected no effects in any person at an average total daily intake (from water plus food) of 0.0008 mg As/kg/day

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(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 2-3.

Another prominent dermal effect associated with chronic ingestion of inorganic arsenic is skin cancer. As discussed in greater detail in Section 2.2.2.8 (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 1988e).

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).

**Organic Arsenicals.** No studies were located regarding dermal effects in humans or animals after oral exposure to organic arsenicals.

### 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 provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic, as described in footnote b in Table 2-3. Nemeč 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.

### 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

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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 (Zaldivar 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). 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 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 DMA and roxarsone (Murai et al. 1993; NTP 1989b; Rogers et al. 1981; Siewicki 1981). The lowest dose to produce a decrease in growth was approximately 4 mg As/kg/day (NTP 1989b).

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**2.2.2.3 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 2-3 and Figure 2-3. 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.

**2.2.2.4 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; 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). Repeated exposures to lower levels (0.03–0.1 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Foy et al. 1992; Franzblau and Lilis 1989; Guha Mazumder et al. 1988; Hindmarsh et al. 1977; Huang et al. 1985; Mizuta et al. 1956; Silver and Wainman 1952; Szuler et al. 1979; Wagner et al. 1979). This neuropathy usually begins as a 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; LeQuesne 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; Fincher and Koerker 1987; Goebel et al. 1990; Hantson

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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 (Harrington et al. 1978; Hindmarsh et al. 1977; Southwick et al. 1981), 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). Among animals, neurological effects have been observed only in monkeys and rabbits. Heywood and Sortwell (1979) remarked 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. Nemeč 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.

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 2-3 and plotted in Figure 2-3.

**Organic Arsenicals.** One case report of the ingestion of organic arsenic was located. A 52-year-old Vietnamese woman ingested an unspecified amount of organic arsenic in the form of bird's nest soup, resulting in numbness and tingling of the fingertips, toes, and circumoral region. Discontinuation of exposure resulted in the disappearance of symptoms (Luong and Nguyen 1999). Several studies in pigs indicate that repeated oral doses of roxarsone (0.87–5.8 mg As/kg/day for 1 month) can cause significant neurotoxicity (Edmonds and Baker 1986; Rice et al. 1985). The main signs were muscle tremors, partial paralysis, and seizures. Histological examinations of the spinal cord revealed a time-dependent degeneration of myelin and axons (Kennedy et al. 1986). Such prominent signs of neurological effects were not detected in rats or mice exposed to roxarsone, although evidence of neurological effects (hyperexcitability, ataxia, trembling) was noted in rats at the highest dose (11.4 mg As/kg/day) (NTP 1989b). These data (shown in Table 2-4 and Figure 2-4) suggest that organic arsenicals (at least the phenyl arsenates) are neurotoxic at high doses.

### 2.2.2.5 Reproductive Effects

**Inorganic Arsenicals.** Only one study was located relevant to reproductive effects in humans after oral exposure to inorganic arsenicals. Lugo et al. (1969) reported a case of a 17-year-old mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison) at 30-week pregnancy. She was admitted for treatment of acute renal failure 24 hours after she ingested approximately 30 mL of arsenic trioxide (0.39 mg As/kg). She went into labor and delivered a live female infant weighing 2 pounds, 7 ounces

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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 As<sub>2</sub>O<sub>3</sub>) from 14 days prior to mating through gestation day 19 (Holson et al. 2000). Reproductive 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 decreased number of pups per litter in all three generations of the treated group (Schroeder and Mitchner 1971). This finding is consistent with the results of developmental toxicity studies reported in Section 2.2.2.6. NOAEL and LOAEL values from these studies are shown in Table 2-3 and Figure 2-3.

**Organic Arsenicals.** No studies were located regarding reproductive effects in humans after oral exposure to organic arsenicals. Male and female mice dosed with MMA (55 mg As/kg/day) prior to mating and during pregnancy produced fewer litters than normal, an effect that was attributable mainly to decreased fertility of the males (Prukop and Savage 1986). This observation (shown in Figure 2-4 and summarized in Table 2-4) suggests that spermatogenesis or sperm function might be impaired by organic arsenicals, but this was not studied directly.

### 2.2.2.6 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. 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.

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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 (odds ratio [OR]=3.4, 95% CI=1.3–8.9). Due to the small study size (a total of 270 cases with any congenital heart disease and 665 controls), this association could be due to random variation. In a similar case-control study, a marginal association (not statistically significant) was noted between detectable levels of arsenic in drinking water and the occurrence of spontaneous abortion (Aschengrau et al. 1989). Marginal positive associations were also noted for mercury, potassium, silica, and water hardness in this study, while a decreased incidence of abortion was associated with sulfate, nitrate, and alkalinity. This pattern of divergent associations for multiple contaminants suggests that at least some of the apparent associations may be random, or may be due to covariation with other risk factors. Thus, neither of these studies provides convincing evidence that ingestion of arsenic, at least at the levels usually encountered in drinking water, causes developmental toxicity in humans.

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 post-implantation 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. 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.

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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 effects (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Nemeč et al. 1998; Stump et al. 1999).

It is noteworthy that the effect in the 3-generation reproduction study in mice by Schroeder and Mitchner (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; Nemeč 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).

These studies (shown in Table 2-3 and Figure 2-3) indicate that the fetus may be affected by ingested arsenic, but suggest that the fetus is not more susceptible to arsenic than the mother.

**Organic Arsenicals.** No studies were located regarding developmental effects in humans after oral exposure to organic arsenicals. However, effects on fetal development (malformed palate, reduced fetal weight, delayed ossification, increased fetal mortality) have been observed in rats and mice given repeated oral doses of DMA during gestation (Rogers et al. 1981). These findings (summarized in Table 2-4 and shown Figure 2-4) suggest that high doses of organic arsenicals may have significant developmental toxicity, but the data are too limited to draw broad conclusions.

### 2.2.2.7 Genotoxic Effects

**Inorganic Arsenicals.** Investigations of genotoxic effects of ingested arsenic have yielded mixed results. 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). 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 exchange, 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 prevalence of micronucleated cells in a Chilean male population chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15 µg As/L, respectively), and suggested that chromosome breakage was the major cause of micronucleus (MN)

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formation. Vig et al. (1984) found no significant differences in the frequency of chromosomal aberrations or sister chromatid exchange 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. Other genotoxicity studies on inorganic arsenicals are discussed in Section 2.5.

**Organic Arsenicals.** No studies were located regarding genotoxic effects in humans after oral exposure to organic arsenicals. An increased number of DNA strand breaks were detected in lung and other tissues of mice and rats given oral doses of 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. Other genotoxicity studies on organic arsenicals are discussed in Section 2.5.

### 2.2.2.8 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; Bickley and Papa 1989; Cebrian et al. 1983; Hauptert et al. 1996; Hsueh et al. 1995; Luchtrath 1983; Morris et al. 1974; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; Tsai et al. 1998a; Tseng 1977; Tseng et al. 1968; Zaldivar 1974; Zaldivar et al. 1981). Lesions commonly observed are multiple squamous cell carcinomas, which appear to develop from some of the hyperkeratotic warts or corns described in Section 2.2.2.2. 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 several studies have reported skin cancer in people exposed for less than 1 year (Reymann et al. 1978; Wagner et al. 1979). 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 2-3 and shown in Figure 2-3. The EPA reviewed the studies that provided dose-response data on the risk of skin cancer

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(EPA 1988e) 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 1988e). 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 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  $5 \times 10^{-5}$  (IRIS 1999). The average daily doses (expressed as mg As/kg/day) that correspond to excess cancer risks of  $1 \times 10^{-4}$  to  $1 \times 10^{-7}$  are shown in Figure 2-3.

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. A number of concerns have been raised 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 that might increase cancer risk in Taiwan (Beck et al. 1995); the possibility that arsenic is an essential nutrient at lower doses (EPA 1988e; NRC 1999); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997). These factors, many of which were recognized by EPA (1988e) at the time of the assessment, all contribute to uncertainty in the risk assessment.

Several epidemiological studies performed in the United States have not detected an increased frequency of skin cancer in small populations consuming water containing arsenic at levels of around 0.1–0.2 ppm (Goldsmith et al. 1972; Harrington et al. 1978; Morton et al. 1976; Southwick et al. 1981). These data suggest 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).

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Wong et al. (1992) also report no evidence of skin cancer in a U.S. cohort. An ecologic study of skin cancer incidence rates was conducted from January 1980 through June 1986 in residents of four counties in Montana. The two counties considered to be exposed to arsenic were Deer Lodge, containing the former Anaconda copper smelter, and Silver Bow, containing an open pit copper mine. Residents in these counties had potential exposure to arsenic and other heavy metals. Gallatin and Park counties served as controls. Data were collected from pathology services and dermatologists in these four counties. In addition, all skin cancer cases from four dermatologists practicing in urban referral areas outside the counties were reviewed. The age-adjusted annual skin cancer rates were higher for the two control counties as compared to either the county with the former smelter, Deer Lodge, or the county with the mine, Silver Bow. The clinical features of the skin cancers in the exposed counties were not similar to those described for arsenic-related skin cancer. One of the common types of skin cancer associated with arsenic exposure (squamous cell carcinoma) was only observed in two cases in the unexposed population. The overall skin cancer incidence rates for the exposed counties were well within the range of skin cancer rates observed for other locations in the United States. The results could not be explained by differences in ascertainment, latitude, or altitude. A partial explanation could be the difference in outdoor employment. There was a higher percentage of "outside" occupations in the two nonexposed counties (9 and 15%) compared to the two exposed counties (both at 1%). The authors state that the power of the study was adequate to detect a relatively small increase in skin cancer, if one existed.

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; Zaldivar 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; Rivara et al. 1997; Smith et al. 1998a; 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.

Chen et al. (1992) compared risk of various internal organ cancers induced by ingested inorganic arsenic and assessed the differences in risk between males and females. Cancer potency indices were calculated using mortality rates among residents in an endemic area of chronic arsenicism on the southwest coast of Taiwan, and with the use of the Armitage-Doll multistage model. Based on a total of 898,806 person-

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years, a significant dose-response relationship was observed between arsenic level in drinking water and mortality from the cancers. Elevated mortality rates were associated with a variety of cancers including 202 liver cancers (140M, 62F), 304 lung cancers (169M, 135F), 202 bladder cancers (97M, 105F), and 64 kidney cancers (30M, 34F). The potency index of developing cancer of the liver, lung, bladder, and kidney due to an intake of 10  $\mu\text{g}/\text{kg}/\text{day}$  of arsenic was estimated as  $4.3 \times 10^{-3}$ ,  $1.2 \times 10^{-2}$ ,  $1.2 \times 10^{-2}$ , and  $4.2 \times 10^{-3}$ , respectively, for males; and  $3.6 \times 10^{-3}$ ,  $1.3 \times 10^{-2}$ ,  $1.7 \times 10^{-2}$ , and  $4.8 \times 10^{-3}$ , respectively, for females in the study area. Based on the results reported by Tseng et al. (1968), the prevalence rate of skin hyperpigmentation, hyperkeratosis, or both lesions in this population were approximately 18, 7, and 6%, respectively. Thus, a substantial number of the cancer cases reported in Chen et al. (1992) may have been preceded by pre-cancerous skin lesions related to arsenic exposure.

Chiou et al. (1995) conducted a 7-year prospective cohort study in four townships in Taiwan to monitor the occurrence of internal cancers and ingested inorganic arsenic in drinking water (0–1.14 mg/L or 0–1.14 ppm). A dose-response relationship was also observed 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. Blackfoot patients had a significantly increased cancer incidence after adjustment for cumulative arsenic exposure.

Chow et al. (1997) compared the histopathological characteristics of As-associated (n=49) and other bladder cancers (n=64). A higher histological grading was observed for the As-exposed tumors (p=0.04), but no other difference in pathological features or prognosis was found between the two groups.

Smith et al. (1992) used the large Taiwan population and high arsenic levels in well water (170–800  $\mu\text{g}/\text{L}$ ) to establish dose-response relationships between cancer risks and the concentration of inorganic arsenic naturally present in water supplies. It was estimated that at the current EPA standard of 50  $\mu\text{g}/\text{L}$ , the lifetime risk of dying from cancer of the liver, lung, kidney, or bladder from drinking 1 L/day of water could be as high as 13 per 1,000 persons. It has been estimated that more than 350,000 people in the United States may be supplied with water containing more than 50  $\mu\text{g}/\text{L}$  arsenic, and more than 2.5 million people may be supplied with water with levels above 25  $\mu\text{g}/\text{L}$ . For average arsenic levels and water consumption patterns in the United States, the risk estimate was around 1/1,000. Ingestion of arsenic, both from water supplies and medicinal preparations, is known to cause skin cancer. The authors state that the evidence assessed here indicates that arsenic can also cause liver, lung, kidney, and bladder cancer and that the population cancer risks due to arsenic in U.S. water supplies may be comparable to those from environmental tobacco smoke and radon in homes. Although further research

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is needed to validate these findings, the authors believed that measures to reduce arsenic levels in water supplies should be considered.

In a similar vein, Moore et al. (1997a) report the results from a cross-sectional biomarker study in a Chilean male population chronically exposed to high and low arsenic levels in their drinking water (average concentrations, 600 and 15  $\mu\text{g As/L}$ , respectively). A fluorescent version of the exfoliated bladder cell MN assay was used employing fluorescence *in situ* hybridization with a centromeric probe to identify the presence (MN+) or absence (MN-) of whole chromosomes within micronuclei to investigate the mechanism of arsenic-induced genotoxicity *in vivo*. The results showed an exposure-dependent increase in prevalence of micronucleated cells and suggested that chromosome breakage was the major cause of MN formation. Prevalence of total MN, MN+, and MN- returned to baseline levels for urinary arsenic in the highest group (729–1,894  $\mu\text{g/L}$ ), perhaps due to cytostasis or cytotoxicity. Inorganic arsenic is an established cause of lung and skin cancer. These results add additional weight to the hypothesis that ingesting arsenic-contaminated water enhances bladder cancer risk and suggest that arsenic induces genetic damage to bladder cells at drinking water levels close to the current U.S. Maximum Contaminant Level (MCL) of 50  $\mu\text{g/L}$  for arsenic.

Yu et al. (1992) report the effects of arsenic on the mitogenic responses of mononuclear cells (MNC) derived from patients with arsenical skin cancers from an arsenic endemic area on the southwest coast of Taiwan. The subjects enrolled in this study included patients with Bowen's disease, arsenical skin cancers (basal cell carcinoma and squamous cell carcinoma), non-arsenical skin cancers (basal cell carcinoma and squamous cell carcinoma), nasopharyngeal cancer, and healthy controls from endemic and non-endemic areas. Phytohemagglutinin (PHA) stimulated [ $^3\text{H}$ ]thymidine incorporation in MNC in all groups except the arsenical skin cancer group. However, when a low concentration of  $\text{As}_2\text{O}_3$  ( $2.5 \times 10^{-7}$  M) was added to PHA-stimulated MNC, a tremendous amplification of the uptake of [ $^3\text{H}$ ]thymidine was noticed in patients with arsenical skin cancer. In this study, this phenomenon did not occur in cancers not related to arsenic. This result suggests that arsenical carcinomas are hyperreactive to arsenic. Arsenic seems to play a role as a co-stimulant of PHA similar to interleukin-1.

Hsueh et al. (1995) conducted a cross-sectional study to evaluate the prevalence of arsenic-induced skin cancer among residents in Taiwanese villages exposed to inorganic arsenic in drinking water (0–0.93 ppm). A dose-response increase in skin cancer was associated with arsenic. There was also an increase in skin cancers associated with carriers of hepatitis B surface antigen with liver dysfunction, and

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undernourishment. This study supports concerns about the differences between the Taiwanese and U.S. populations.

Hopenhayn-Rich et al. (1996a) investigated bladder cancer mortality for the years 1986–1991 in the 26 counties of Cordoba, Argentina. Rates for all of Argentina were used as the standard for comparison. Several areas of Argentina have had high exposures to arsenic from naturally contaminated drinking water, particularly the eastern region of the province of Cordoba. Bladder cancer SMRs were consistently higher in counties with documented arsenic exposure. The clear trends found in this Argentina population with different genetic composition and a high-protein diet support the findings in Taiwan of dose-response relation between ingestion of inorganic arsenic from drinking water and bladder cancer.

Cuzick et al. (1992) evaluated a cohort treated with Fowler's solution (potassium arsenite) in Lancashire, England, during the period 1945–1969. These results add 11 years to the initial study results that followed the cohort until January 1, 1980. The cohort of 478 patients showed a significant excess of bladder cancer mortality (observed/expected ratio=5/1.6;  $p=0.05$ ). No excess was found for other causes of death. Of a subcohort of 142 patients examined for signs of arsenicism around 1970, all 11 subsequent cancer deaths occurred in those with signs of arsenicism ( $p=0.0009$ ).

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, sulfur dioxide, and possibly other emissions such as nickel and selenium. 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 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.

Studies in U.S. populations exposed to arsenic in drinking water (Morton et al. 1976; Southwick et al. 1981; 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

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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 2.3). Chan and Huff (1997) argue that a carefully controlled long-term carcinogenesis bioassay (i.e., using the National Toxicology Program protocol) has not been conducted for either arsenic trioxide by inhalation exposure or for sodium arsenite by drinking water. Thus, statements as to the paradoxical nature of arsenic as a human carcinogen are premature.

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 incidence of skin papillomas when compared to transgenic mice receiving only TPA treatment or only arsenic or to wild-type mice receiving both TPA and arsenic (Germolec et al. 1998). Increases in mRNA transcripts for the growth factors transforming growth factor- $\alpha$  (TGF- $\alpha$ ) 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. 1976), and tumors resulting from injection of mouse sarcoma cells (Kerkvliet et al. 1980). However, arsenic also increased the growth rate of the tumors which 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). However, these data do not suggest that arsenic should be viewed as having any net therapeutic “anti-cancer” effect.

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**Organic Arsenicals.** No studies were located regarding cancer in humans after oral exposure to organic arsenicals. In an early 2-year study of roxarsone toxicity in animals, no increase in tumor frequency was detected in dogs given 1.5 mg As/kg/day, rats given 2.9 mg As/kg/day, or mice given 3.8 mg As/kg/day (Prier et al. 1963). More recently, lifetime studies of roxarsone at doses up to 1.4 mg As/kg/day yielded no evidence of carcinogenicity in male or female mice or female rats, but a slight increase in pancreatic tumors was noted in male rats (NTP 1989b). This was considered to constitute equivocal evidence of carcinogenicity. The incidence of basophilic foci (believed to be a precancerous lesion) in liver of rats initiated with diethylnitrosamine was increased by subsequent exposure to DMA, suggesting that this compound could act as a cancer promoter (Johansen et al. 1984).

Yamamoto et al. (1995) also evaluated the carcinogenic effects of DMA in rats in a multiorgan carcinogenesis bioassay. Male F344/DuCrj rats were treated sequentially with diethylnitrosamine (DEN) and N-methyl-N-nitrosamine (MNU), then 1,2-dimethylhydrazine (DMH). The animals were then sequentially administered N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) in drinking water in weeks 1 and 2 and N-bis(2-hydroxypropyl)nitrosamine (DHPN) in drinking water during weeks 3 and 4. This is referred to as the DMBDD treatment. After a 2-week interval, rats were given 50, 100, 200, or 400 ppm DMA in drinking water. DMA significantly enhanced the tumor induction in the urinary bladder, kidney, liver, and thyroid gland in DMBDD-treated groups. Induction of preneoplastic lesions (glutathione S-transferase placental form-positive foci in the liver and atypical tubules in the kidney) was also significantly increased in DMA-treated groups. DMA thus acted as a promoter of urinary bladder, kidney, liver, and thyroid gland carcinogenesis in rats.

A study by Li et al. (1998b) further evaluating the promotional effects of DMA on bladder cancer exposed NBR rats (which do not synthesize  $\alpha_{2u}$ -globulin) to BBN in drinking water for 4 weeks, followed by 100 ppm DMA in drinking water for 32 weeks. A statistically significant increase in simple hyperplasia and papillary or nodular hyperplasia of the bladder and a non-statistically significant increase in papilloma carcinoma was observed.

Wanibuchi et al. (1996) evaluated the promoting and carcinogenic effects of DMA in a male F344/DuCrj rat urinary bladder carcinogenicity model. Rats were administered BBN in drinking water during weeks 1–4, then received 0, 2, 10, 25, 50, or 100 ppm DMA in drinking water for an additional 32 weeks. For 100 ppm of DMA with no BBN pretreatment, there were no urinary bladder papillomas or carcinomas observed. DMA with BBN pretreatment resulted in a dose-dependent increase in both the incidence and multiplicity of tumors, clearly demonstrating the promoting effects of DMA in this model.

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Yamamoto et al. (1997) evaluated the promoting and carcinogenic effects of DMA in a medium-term, two-step, rat hepatocarcinogenesis model. Male F344/DuCrj rats were treated with a single intraperitoneal dose of DEN, then 2 weeks later with either 0, 25, 50, or 100 ppm DMA in drinking water. Animals in all groups were subjected to a two-thirds partial hepatectomy at week 3 to maximize any interaction between proliferations and the effects of DMA. The number and areas of glutathione S-transferase placental form (GST-P) positive foci per unit of liver sections increased in the DMA-treated groups with significant enhancement of hepatocarcinogenesis observed with 50 ppm DMA and above.

Hayashi et al. (1998) evaluated the effects of DMA on lung tumorigenesis. Small (not statistically significant) increases in percent tumor-bearing mice and number of tumors per mouse in mice receiving 50 or 200 ppm DMA in drinking water for 50 weeks were observed. Mice receiving 400 ppm DMA showed significant increases in number of tumors per mouse.

The above studies with DMA are limited, but they do provide some evidence that organic arsenicals can promote carcinogenicity and may act as weak carcinogens.

These data are too limited to draw firm conclusions, but it appears that organic arsenicals might possess weak carcinogenic potential.

### 2.2.3 Dermal Exposure

Adverse effects from dermal exposure to inorganic or organic arsenicals have not been extensively investigated. Table 2-5 summarizes studies in animals and humans which 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.

#### 2.2.3.1 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.

Table 2-5. Levels of Significant Exposure to Inorganic Arsenic, - Dermal

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
					Less Serious	Serious	
<b>ACUTE EXPOSURE</b>							
<b>Immunological/Lymphoreticular</b>							
	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)
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
	Mouse (Rockland)	30 wk 11x/wk	Dermal		6 F (gross hyperplasia, ulceration)		Boutwell 1963 As(+3)

F = female; Gn pig = guinea pig; wk = week(s); x = time(s).

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**Organic Arsenicals.** No studies were located regarding death in humans or animals after dermal exposure to organic arsenicals.

### 2.2.3.2 Systemic Effects

No studies were located that have associated respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals to dermal exposure to inorganic or organic arsenicals.

### 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 2.2.3.3 below.

**Organic Arsenicals.** Application of MMA to the skin of rabbits was reported to result in mild dermal irritation (Jaghabir et al. 1988), but too few details on dose, duration, or degree of irritation were provided to draw firm conclusions regarding the dermal irritancy of organic arsenicals.

### Ocular Effects

**Inorganic Arsenicals.** No studies were located regarding ocular effects in humans or animals after dermal exposure to inorganic arsenicals.

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**Organic Arsenicals.** Application of MMA to the skin of rabbits was reported to result in mild dermal irritation (Jaghabir et al. 1988), but too few details on dose, duration, or degree of irritation were provided to draw firm conclusions regarding the ocular irritancy of organic arsenicals.

### 2.2.3.3 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 a more recent 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/m<sup>3</sup>. 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 control study 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 to dermal exposure to inorganic or organic arsenicals:

#### 2.2.3.4 Neurological Effects

#### 2.2.3.5 Reproductive Effects

#### 2.2.3.6 Developmental Effects

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**2.2.3.7 Genotoxic Effects**

Genotoxicity studies are discussed in Section 2.5.

**2.2.3.8 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 dimethylbenzanthracene 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.

**2.3 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:

- C 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.
- C 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.
- C Once absorbed, arsenites are partially oxidized to arsenates and arsenates are partially reduced to arsenites, yielding a mixture of As(+3) and As(+5) in the blood.
- C 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.

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- C 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 may also vary among tissues.
  
- C Most arsenic is promptly excreted in the urine as a mixture of As(+3), As(+5), MMA, and DMA. 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 which supports these conclusions is presented below.

### 2.3.1 Absorption

#### 2.3.1.1 Inhalation Exposure

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 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 2.3.4) 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),

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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.

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. 1977b). This indicates that organic arsenicals are likely to be well absorbed by the inhalation route.

### 2.3.1.2 Oral Exposure

Several studies in humans indicate that arsenates and arsenites are well absorbed across the gastrointestinal tract. The most direct evidence is from measurement of fecal excretion in humans given oral doses of arsenite, where less than 5% was recovered in the feces (Bettley and O'Shea 1975). This indicates absorption was at least 95%. This is supported by studies in which urinary excretion in humans was found to account for 55–80% of daily oral intakes of arsenate or arsenite (Buchet et al. 1981b; Crecelius 1977; Mappes 1977; Tam et al. 1979b). In contrast, ingestion of arsenic triselenide ( $\text{As}_2\text{Se}_3$ ) did not lead to a measurable increase in urinary excretion (Mappes 1977), indicating that 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. 1978a; Vahter 1981; Vahter and Norin 1980). Oral absorption of [ $^{73}\text{As}$ ] 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  $\mu\text{g}$ , 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).

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Bioavailability of arsenic was measured in rabbits ingesting doses of smelting soils which 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; 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  $67.6\pm 2.6\%$  (gavage),  $19.2\pm 1.5\%$  (oral dust), and  $13.8\pm 3.3\%$  (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels was reported at  $91.3\pm 12.4\%$  (gavage),  $9.8\pm 4.3\%$  (oral dust), and  $10.9\pm 5.2\%$  (oral soil). The arsenic in the dust and soil was approximately 3.5–5-fold (based on urine) and 8–9-fold (based on blood) less bioavailable than arsenic in solution. A study in beagle dogs fed with soil containing  $\text{As}_2\text{O}_5$  or treated with intravenous soluble arsenic found that compared to injection the bioavailability of arsenic from ingested soil was  $8.3\pm 2.0\%$  (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  $\mu\text{g/g}$ , lead at concentrations of 3,000–14,000  $\mu\text{g/g}$ . The arsenic doses ranged from 1 to 65.4  $\mu\text{g/kg/day}$ . 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 $\pm$ SD,  $45\%\pm 32$ ). Estimates for relative bioavailability of arsenic in samples of smelter slag and mine tailings ranged from 7 to 51% (mean $\pm$ SD,  $35\%\pm 27$ ). 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  $\mu\text{g/g}$ . Relative bioavailability (waste:sodium arsenate) ranged from 3 to 43%

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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; 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 (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).

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. 1977b; Yamauchi and Yamamura 1984) and MMA (Yamauchi et al. 1988).

### 2.3.1.3 Dermal Exposure

No quantitative studies were located on absorption of inorganic arsenicals in humans after dermal exposure. Percutaneous absorption of [<sup>73</sup>As] as arsenic acid (H<sub>3</sub>AsO<sub>4</sub>) 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 [<sup>73</sup>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 (Wester et al. 1993). After 24 hours, 6.4% of [<sup>73</sup>As] as arsenic acid was absorbed systemically, as was 4.5% of [<sup>73</sup>As] mixed with soil. 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 µg/cm<sup>2</sup>/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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No studies were located on absorption of organic arsenicals in humans or animals after dermal exposure.

### 2.3.2 Distribution

#### 2.3.2.1 Inhalation Exposure

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.

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. 1977b), suggesting that inhalation of organic arsenicals would also lead to widespread distribution.

#### 2.3.2.2 Oral Exposure

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. 1999). 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 2.7, 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 30-week pregnancy (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 (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  $^{74}\text{As}$  was widely distributed to all tissues, with the highest levels in kidney and liver. No obvious differences between  $\text{As}(+3)$  and  $\text{As}(+5)$  were found, although residual levels after 24 hours tended to be higher for  $\text{As}(+3)$  than  $\text{As}(+5)$  (Vahter and Norin 1980). In hamsters, increases in tissue levels were noted after oral treatment with  $\text{As}(+3)$  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).

No studies were located on the distribution of organic arsenicals in people following oral exposure, but MMA and DMA formed *in vivo* by methylation of inorganic arsenic in hamsters appears to be distributed to all tissues (Takahashi et al. 1988; Yamauchi and Yamamura 1985). This is supported by studies in animals, in which MMA and DMA were found in all tissues after acute oral doses (Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

### 2.3.2.3 Dermal Exposure

No studies were located regarding distribution of inorganic or organic arsenicals in humans or animals after dermal exposure.

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**2.3.2.4 Other Routes of Exposure**

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 (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 in dogs, mice, guinea pigs, rabbits, and chicks found very little uptake of arsenic into the blood in these species (cats gave intermediate results).

**2.3.3 Metabolism**

The metabolism of inorganic arsenic has been extensively studied in humans and animals. Two processes are involved: (1) reduction/oxidation reactions that interconvert arsenate and arsenite, and (2) methylation reactions, which convert arsenite to MMA and DMA. 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 less toxic 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, more than 75% of the absorbed arsenic dose is excreted in the urine (Marcus and Rispin 1988). Long-term accommodation to arsenic exposure is also possible in which methylation and excretion become more efficient with several months of exposure. 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. 1999). 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 basic type of evidence that supports these conclusions is derived from analysis of urinary excretion products. Exposure of humans to either arsenates or arsenites results in increased levels of inorganic

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As(+3), inorganic As(+5), MMA, and DMA in urine (Buchet et al. 1981a, 1981b; Concha et al. 1998a, 1998b; Crecelius 1977; Kurttio et al. 1998; Lovell and Farmer 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).

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, with lower levels of inorganic arsenic [As(+3) and As(+5)] and MMA. In humans, the relative proportions are usually about 40–60% DMA, 20–25% inorganic arsenic, and 15–25% MMA (Buchet et al. 1981a; Smith et al. 1977; Tam et al. 1979b; Vahter 1986). 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 the best animal model for toxicokinetics in humans. In contrast, the guinea pig and the marmoset and tamarin monkeys do not methylate inorganic arsenic (Healy et al. 1998; Vahter and Marafante 1985; Vahter et al. 1982; Zakharyan et al. 1996), and so 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 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) and Rhesus monkey liver (Zakharyan et al. 1996). It

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appears that a single protein (MW 60,000) 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  $\mu\text{M}$ , for MMA methyltransferase it is 1,000  $\mu\text{M}$ . The purified activity is specific for arsenite and MMA; selenite, selenate, selenide, and catechols do not serve as substrates.

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. Distribution of activity was reported in this study. 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.

Since the methyl derivatives of arsenic appear to be less toxic than inorganic arsenic (see Section 2.2), and 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. 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(+3) in tissues. 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 people, 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 appear to undergo little metabolism. Humans who ingested a dose of MMA converted a small amount (about 13%) to DMA (Buchet et al. 1981a), and several studies in hamsters have noted the formation of low levels of the trimethyl derivative (trimethylarsine oxide,  $(\text{CH}_3)_3\text{AsO}$ ) (Yamauchi and Yamamura 1984; Yamauchi et al. 1988). However, the methylarsenates are not demethylated to

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inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 1977b; Yamauchi and Yamamura 1984).

### 2.3.4 Elimination and Excretion

#### 2.3.4.1 Inhalation Exposure

As noted previously (see Section 2.3.1.1), 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, small amounts of arsenic may remain bound in the lung, and only be cleared with a half-time of several months (Rhoads and Sanders 1985).

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 excreted about 60% in the urine and about 8% in the feces within 24 hours (Stevens et al. 1977b). This indicates that organic arsenicals are likely to be promptly excreted after inhalation exposure.

#### 2.3.4.2 Oral Exposure

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 (Buchet et al. 1981a; Crecelius 1977; Mappes 1977; Tam et al. 1979b). 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). Accordingly, whole body clearance is fairly rapid, with half-times of 40–60 hours in humans (Buchet et al. 1981b; Mappes 1977).

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Clearance is even more rapid in mice and hamsters, with 90% removed in 2 days (Marafante and Vahter 1987; Vahter 1981; Vahter and Norin 1980).

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 and hamsters, although in animals excretion is more evenly distributed between urine and feces (Marafante et al. 1987b; Stevens et al. 1977b; Yamauchi and Yamamura 1984; Yamauchi et al. 1988).

### 2.3.4.3 Dermal Exposure

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).

No studies were located regarding excretion of organic arsenicals in humans or animals following dermal exposure.

### 2.3.4.4 Other Routes of Exposure

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).

## 2.3.5 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

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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 (Clewell 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 et al. 1987; Andersen and Krishnan 1994). 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 parametrization, (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) is 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).

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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 2-5 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.

PBPK models for arsenic are discussed below.

### **2.3.5.1 Summary of PBPK Models.**

The Mann model (Mann et al. 1996a, 1996b), Yu model (Yu 1998a, 1998b), 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 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 and rats. 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.

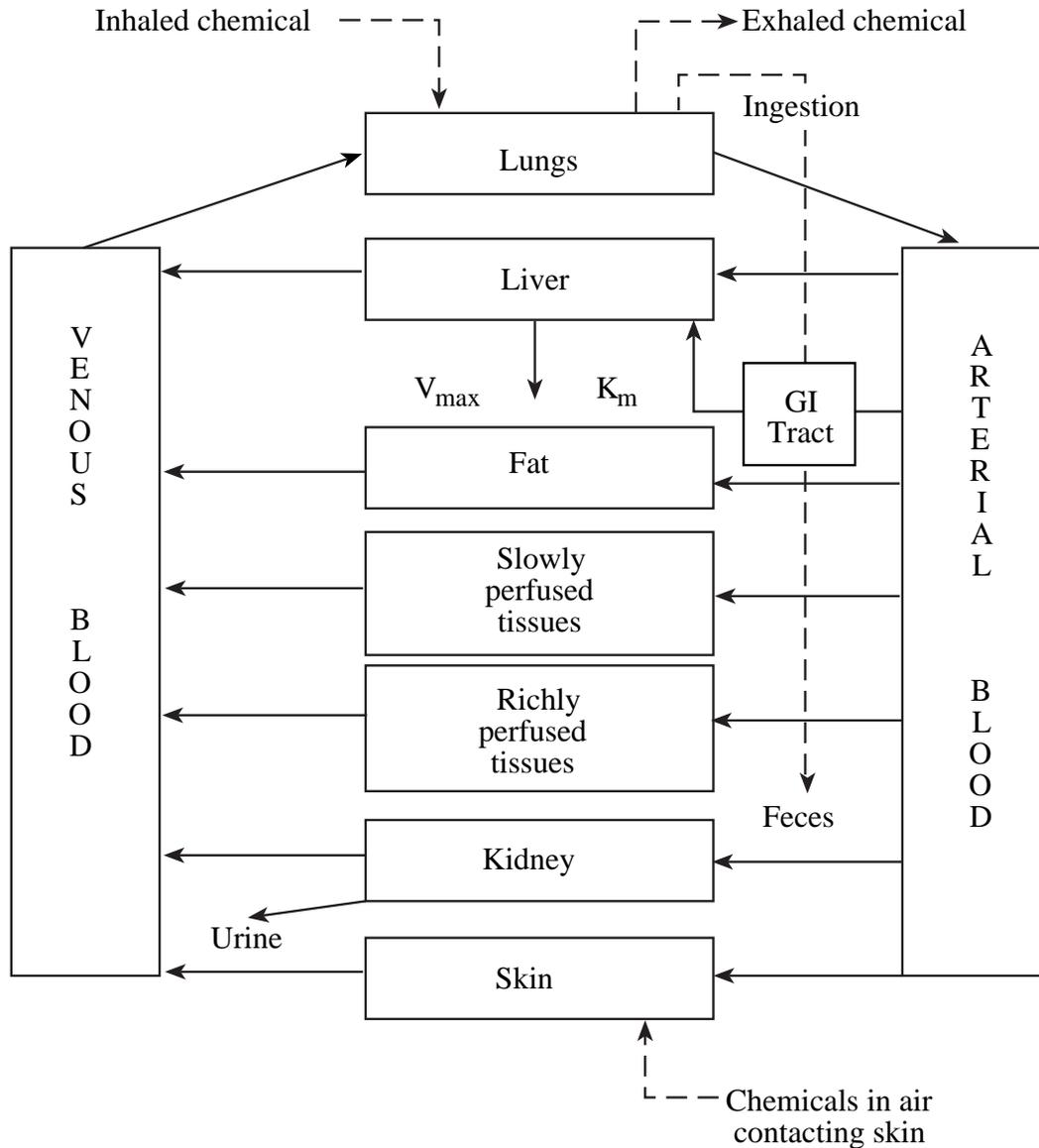
### **2.3.5.2 Arsenic PBPK Model Comparison.**

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.

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**Figure 2-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**

Source: adapted from Krishnan et al. 1994



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.

## 2. HEALTH EFFECTS

**2.3.5.3 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).

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 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 (Lindstedt 1992). 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 2-6 shows the animal model and Tables 2-6, 2-7, 2-8, and 2-9 provide the parameters used in the animal model.

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**Table 2-6. Parameters Used in the Mann PBPK Model for Animals**

Physiological parameter	Rabbit (bw = 3.5 kg)	Hamster (bw = 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/min)		
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 <sup>2</sup> )	93,835	2,681.0

Source: Mann et al. 1996a

bw = body weight; PBPK = physiologically based pharmacokinetic

## 2. HEALTH EFFECTS

**Table 2-7. 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

Source: Mann et al. 1996a

DMA = dimethyl arsenic acid; MMA = monomethyl arsonic acid; PBPK = physiologically based pharmacokinetic

## 2. HEALTH EFFECTS

**Table 2-8. 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)	3000.00	100.00
Oxidation	(1/hour)	6000.00	400.00
Kidney reduction	(1/hour)	30.00	1.00
Methylation	Michaelis–Menten		
1st step	$K_{M_{MMA}}$ ( $\mu\text{mol/mL}$ )	0.05	0.12
	$V_{MAX_{MMA}}$ ( $\mu\text{mol/mL@hour}$ )	4.00	0.12
2nd step	$K_{M_{DMA}}$ ( $\mu\text{mol/mL}$ )	0.90	0.08
	$V_{MAX_{DMA}}$ ( $\mu\text{mol/mL@hour}$ )	1.50	0.12

Source: Mann et al. 1996a

PBPK = physiologically based pharmacokinetic

## 2. HEALTH EFFECTS

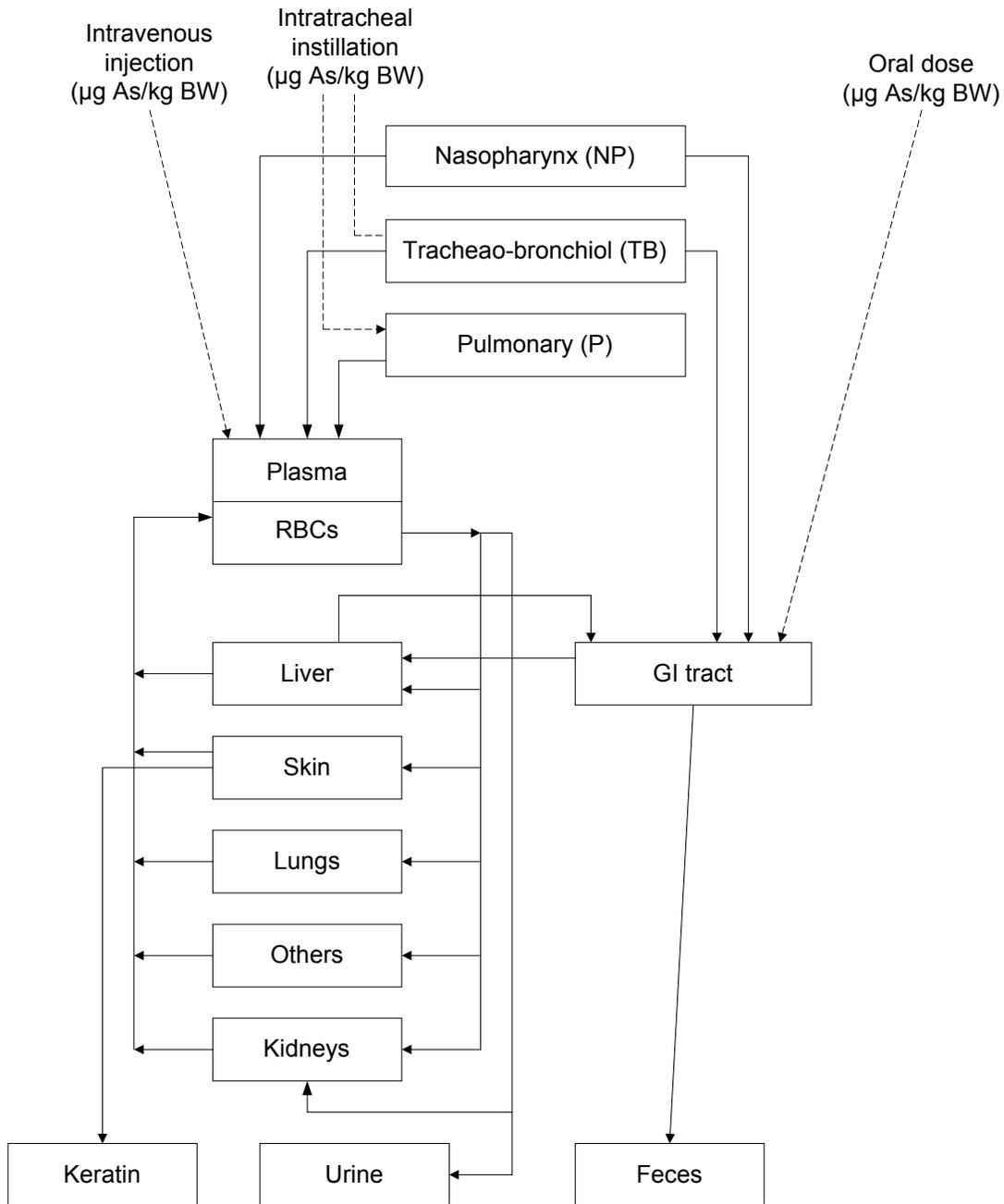
**Table 2-9. Fitted Gastrointestinal Tract and Lung Absorption Half-time for the Hamster for the Mann PBPK Model**

Exposure As compound	Absorption, half-time (hour)	
	Gastrointestinal tract	Lung
As(V)		
$\text{Na}_3(\text{AsO}_4)$	0.08	12
$\text{Pb}_3(\text{AsO}_4)$	0.39	690
$\text{As}_2\text{O}_5$	0.28	-
As(III)		
$\text{NaAsO}_2$	0.08	12
$\text{As}_2\text{S}_3$	0.48	12
$\text{As}_2\text{O}_3$	0.02	-
DMA	0.09	-

Source: Mann et al. 1996a

DMA = dimethyl arsenic acid; PBPK = physiologically based pharmacokinetic

## 2. HEALTH EFFECTS

**Figure 2-6. Parameters Used in the Mann PBPK Model for Animals**

Source: Mann et al. 1996b

## 2. HEALTH EFFECTS

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 2-7 shows the human model, and Tables 2-10 and 2-11 provide the data and constants used in the human model.

**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.

**Target tissues.** Levels in skin were not well predicted by this model in animals; results for the lung were not presented. 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.

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**Table 2-10. Physiological Data Used in the Mann PBPK Model for Humans**

Physiological parameter	Organ	Units	Human (bw = 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 <sup>2</sup>	177
Tracheobronchial area		cm <sup>2</sup>	5,036
Pulmonary area		cm <sup>2</sup>	712,471
Total capillary surface area		cm <sup>2</sup>	1,877x10 <sup>6</sup>

Source: Mann et al. 1996b

bw = body weight; PBPK = physiologically based pharmacokinetic

## 2. HEALTH EFFECTS

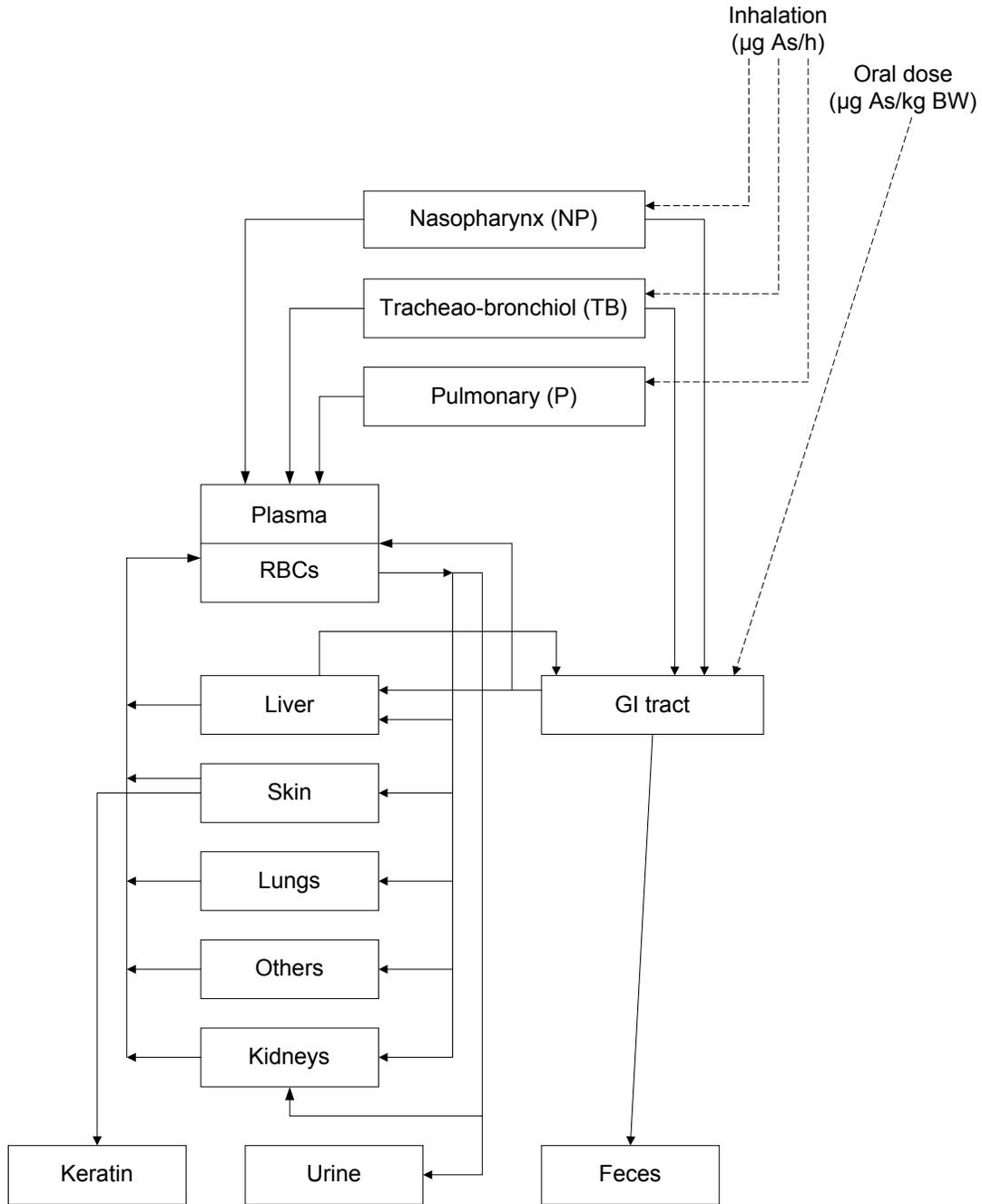
**Table 2-11. Tissue Affinity Constants ( $K_{ij}$ ) Obtained by Fitting the Mann PBPK Animal Model for Use with Humans**

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
Red blood cells	0.2	1.5	0.2	0.2
Others	10	40	1	1

Source: Mann et al. 1996b

DMA = dimethyl arsenic acid; MMA = monomethyl arsonic acid; PBPK = physiologically based pharmacokinetic

## 2. HEALTH EFFECTS

**Figure 2-7. Parameters Used in the Mann PBPK Model for Humans**

Source: Mann et al. 1996b

## 2. HEALTH EFFECTS

**The Menzel Model.**

**Risk assessment.** The Menzel model was not used for risk assessment.

**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 Anderson and coworkers (Anderson et al. 1987; Ramsey and Anderson 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.

**Interroute extrapolation.** Interroute extrapolation was not attempted in this model.

**The Yu Model.**

**Risk assessment.** The Yu model was not used for risk assessment.

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**Description of the model.** The Yu model was developed to simulate oral exposure to arsenic in mice and rats (Yu 1998a, 1998b, 1999). 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.

The model consists of eight tissue compartments: intestine, skin, muscle, fat, kidney, liver, lung, and vessel-rich group (VRG, e.g., brain). 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 1988f; 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 2-8 shows the model and Table 2-12 provide 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 0.85 to 0.93 for the rat. However, the model overpredicted the amount of inorganic arsenic found in the feces of both 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 ability of the model to predict tissue burdens was not compared to actual data.

**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 and mice.

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**Table 2-12. Parameters Used in the Yu PBPK Model**

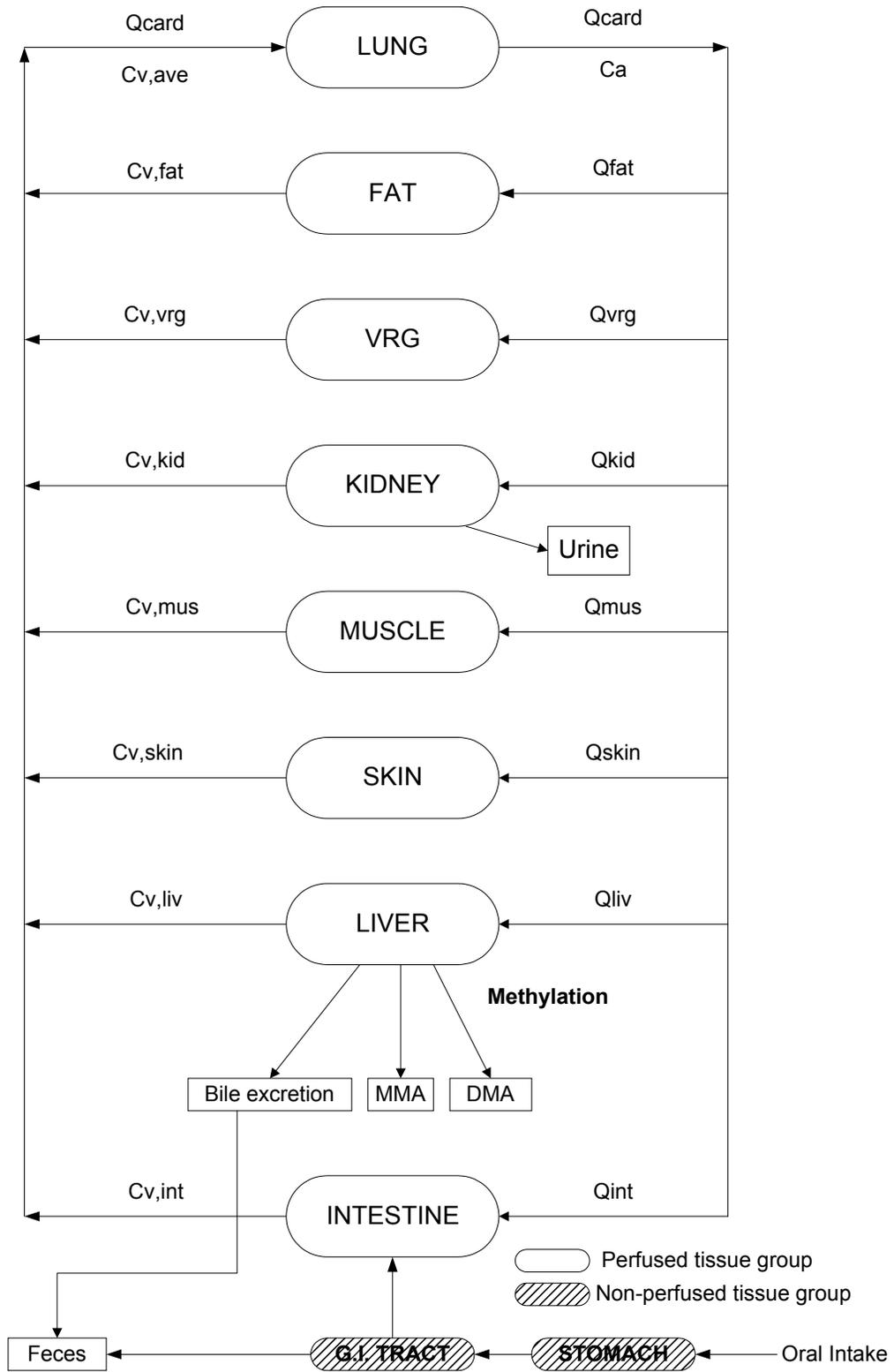
	Mouse	Rat
<b>Partition coefficients</b>		
Intestine	6.0	6.0
Skin	5.0	5.0
VRG	6.0	6.0
Muscle	5.0	10.0
Fat	-	0.5
Kidney	8.5	7.5
Liver	10.0	10.0
Lung	4.0	4.0
<b>Blood flow rate (mL/hour)</b>		
Intestine	100	528
Skin	7.68	37.8
VRG	157	960
Muscle	153	1260
Fat	-	253.2
Kidney	255	255
Liver	255	1260
<b>Tissue volume (mL)</b>		
Intestine	1.94	6.9
Skin	1.83	15.4
VRG	0.81	23.0
Muscle	19.9	162
Fat	-	14.5
Kidney	0.484	1.63
Liver	1.67	5.82
Lung	0.124	1.0
<b>Metabolism constants</b>		
$V_{max_{(MMA)}} (\mu\text{mol/hour})$	0.45	0.15
$V_{max_{(DMA)}} (\mu\text{mol/hour})$	0.375	0.06
$K_{m_{(MMA)}} (\mu\text{mol/hour})$	1.0	0.2
$K_{m_{(DMA)}} (\mu\text{mol/hour})$	0.2	0.2
<b>First-order rate constants</b>		
$K_{Sj} (\text{hour}^{-1})$	0.3	0.3
$K_{Ai} (\text{hour}^{-1})$	1.5	3.6
$K_{\text{fecal}} (\text{hour}^{-1})$	0.33	0.048
$K_{\text{urinary}} (\text{hour}^{-1})$	1.32	0.9
$K_{\text{biliary}} (\text{hour}^{-1})$	0.33	0.3

Values taken from Yu 1998a, 1998b.

PBPK = physiologically based pharmacokinetic

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Figure 2-8. Parameters Used in the Yu PBPK Model for Animals



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**Species extrapolation.** Species extrapolation beyond rats and mice was not attempted using this model.

**Interroute extrapolation.** Interroute extrapolation was not attempted using this model.

## 2.4 MECHANISMS OF ACTION

### 2.4.1 Pharmacokinetic Mechanisms

Arsenic absorption depends on its chemical form. In humans, As(+3), As(+5), MMA, and DMA are orally absorbed 80%. Arsenic is also easily absorbed via inhalation. Absorption appears to be by passive diffusion in humans and mice, although there is evidence for a saturable carrier-mediated transport process for arsenate in rats (Gonzalez et al. 1995). 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 detoxification 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.

The manifestation of arsenic toxicity depends on dose and duration of exposure. Single oral doses in the range of 20 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

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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/m<sup>3</sup>. 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 metal 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).

### 2.4.2 Mechanisms of Toxicity

***Effect of Metabolism on Toxicity.*** The effect of metabolism on toxicity appears to depend on dose. In relatively high oral exposures (0.05 mg/kg/day), it is likely that methylation capacity is not adequate to prevent cytotoxic levels of As(+3) from reaching tissues. At lower long-term doses, which have been associated with cancer, the relationship between metabolism and toxicity is the object of debate. The demand of arsenic on cellular methylating capacity (particularly the co-factor S-adenosylmethionine) may lower the efficiency of other cellular methyltransferases. These effects on DNA methylating activity are discussed below.

***Target Organ Toxicity.*** Relatively high-dose acute- and intermediate-duration toxicity appears to be the result of arsenic cytotoxicity. Reduced inorganic arsenic [As(+3)] reacts strongly with sulfhydryl groups in proteins and inactivates many enzymes. A particular target in the cell is the mitochondria, which accumulates arsenic (Goyer 1991). Arsenic inhibits succinic dehydrogenase activity and can uncouple oxidative phosphorylation; the resulting fall in ATP levels affects virtually all cellular functions (Na<sup>+</sup>/K<sup>+</sup> balance, protein synthesis, etc.).

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***Carcinogenesis.*** The EPA and the International Agency for Research on Cancer (IARC) classify arsenic as a carcinogen for which there is sufficient epidemiological evidence to support a causal relationship between exposure to arsenic and skin cancer. Unlike the large majority of substances considered as human carcinogens based on epidemiological evidence, arsenic alone will not induce cancer in rodent models. The genotoxicity database for arsenic indicates that it does not induce point mutations or DNA adducts, but chromosomal aberrations and sister chromatid exchanges have been reported. Arsenic can also potentiate mutagenicity observed with other chemicals. This potentiation may be the result of direct interference by arsenic with DNA repair processes, perhaps by inhibiting DNA ligase (Li and Rossman 1989). Finally, arsenic can also induce DNA amplification (Lee et al. 1988).

It has been hypothesized that methylation changes in genes or their control regions can lead to altered gene expression, and potentially, carcinogenesis (Baylin et al. 1998; Costa 1995). Effects of arsenic on DNA methylation have been studied in two model systems. In the first, arsenite exposure in the human lung adenocarcinoma cell line A549 resulted in hypermethylation of cytosine in the promoter region of the tumor suppressor gene p53 (Mass and Wang 1997). In the second, hypomethylation throughout the genome was found in a rat liver cell line (TRL 1215) that had been exposed to submicromolar sodium arsenite for 18 weeks; these cells exhibited aberrant gene expression and had undergone malignant transformation, as demonstrated by the induction of tumors when injected into Nude mice (Zhao et al. 1997).

The tissue-specificity of arsenic carcinogenicity in humans is being studied in primary human epidermal keratinocytes (Germolec et al. 1997a). Low micromolar concentrations of sodium arsenite resulted in neoplasia accompanied by increased mRNA transcripts and secretion of growth factors including granulocyte macrophage-colony stimulating factor (GM-CSF), transforming growth factor alpha (TGF- $\alpha$ ), and the cytokine tumor necrosis factor alpha (TNF- $\alpha$ ). Arsenic in drinking water also increased the number of skin papillomas in transgenic mice in which dermal application of phorbol esters induces papillomas (genetically initiated mice). These results support a hypothesis that chronic low-level exposure to arsenic stimulates keratinocyte secretion of growth factors, the resulting increased cellular division (and concomitant DNA replication) allows greater opportunities for genetic damage to occur.

### **2.4.3 Animal-to-Human Extrapolations**

The usefulness of animal models for toxicity studies with arsenic is limited by two major factors. First and most importantly, no animal model exists for the health effect of greatest concern for human

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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 most other mammalian species (the rabbit may be an exception). 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.

### 2.5 RELEVANCE TO PUBLIC HEALTH

#### Overview.

Arsenic is a potent toxicant that may exist in several valence 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 and are not focused on in this profile.

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. By the inhalation route, the effect of greatest public health concern is increased risk of lung cancer, although respiratory irritation, nausea, and skin effects may also occur. As summarized in Table 2-1 and Figure 2-1 in Section 2.2.1, there are only a few quantitative data on noncancer effects in humans exposed to inorganic arsenic by the inhalation route. However, it appears that such effects are unlikely below a concentration of about 0.1–1.0 mg As/m<sup>3</sup>.

The diet is usually the predominant source of exposure for the general population. The effects most likely to be of human health concern from ingestion of arsenic are gastrointestinal irritation, peripheral neuropathy, vascular lesions, anemia, a group of skin diseases, including skin cancer, and other cancers of the internal organs including bladder, kidney, liver, and lung cancer. As summarized in Table 2-3 and Figure 2-3 in Section 2.2.2, most of the noncancer effects tend to occur at similar oral exposure levels, indicating that the dose-response curves for these effects are similar. For acute and intermediate exposures, most reported LOAEL values are 0.05 mg As/kg/day or higher (see Figure 2-3). However, these data are mainly from case reports of poisoning episodes, so it is likely that lower doses could also produce the characteristic signs of acute arsenic toxicity. Chronic LOAELs are as low as 0.001 mg

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As/kg/day and chronic NOAEL values are as low as 0.0004 mg As/kg/day (see Figure 2-3). Based on these data, the calculated provisional acute oral MRL is 0.005 mg/kg/day and the calculated chronic oral MRL is 0.0003 mg As/kg/day.

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

Humans may also be exposed to a variety of organic arsenicals (mainly methyl and phenyl derivatives of arsenic acid), since these are widely used in agriculture. Although human health effects data are sparse, it is generally considered that organic arsenicals are substantially less toxic than the inorganic forms. However, available data (mainly from animal studies) make clear that adequate doses of the methyl and phenyl arsenates can produce adverse health effects that resemble those of the inorganic arsenicals, and so the possibility of health risks from the organic arsenicals should not be disregarded.

Presented below are more detailed descriptions and discussions of the characteristic adverse effects of the inorganic and organic arsenicals most likely to be of concern to humans. These evaluations focus on human health effects data wherever possible, since most studies in animals suggest that animals are less sensitive to arsenic than humans. Animal data are presented when human data are lacking, but these data should be extrapolated to humans only with caution.

Issues relevant to children are explicitly discussed in Sections 2.7 Children's Susceptibility and Section 5.6 Exposures of Children.

### **Minimal Risk Levels for Arsenic.**

#### ***Inhalation MRLs.***

No inhalation MRLs were derived for arsenic.

#### ***Oral MRLs.***

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

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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 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 provisional 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 provisional MRL of 0.005 mg As/kg/day was calculated by applying an uncertainty factor of 10 (10 for use of a LOAEL and 1 for intrahuman variability) to the LOAEL of 0.05 mg As/kg/day (see Appendix A for MRL worksheets). The MRL is considered provisional because the gastrointestinal effects (nausea, vomiting, diarrhea, and occult blood in feces and gastric and duodenal juice) are serious and because serious neurological (hypesthesia in legs, abnormal patellar reflex) and cardiovascular (abnormal electrocardiogram) effects also occurred at the same dose. Although it is not customary to base an MRL on a serious LOAEL, public health concerns regarding arsenic suggested that a provisional value derived from these data would be useful for the general public.

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

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NOAEL identified by Tseng (1977) (0.0008 mg As/kg/day) was limited by the fact that the majority of the population was less than 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 (0.016 mg/kg/day) (see Appendix A for MRL worksheets).

No intermediate-duration MRL was derived due to lack of suitable studies.

**Death.** There have been many reported cases of death in humans due to ingestion of inorganic arsenicals. Acute lethality is usually attributable to cardiopulmonary collapse (Levin-Scherz et al. 1987; Saady et al. 1989), while delayed lethality results from failure of one or more of the many tissues injured by arsenic (Campbell and Alvarez 1989). Estimates of the minimum lethal oral dose in humans range from 1 to 3 mg As/kg/day (Armstrong et al. 1984; Holland 1904; Vallee et al. 1960), although there may be considerable variation between individuals. The lowest lethal level in an animal study was 1.5 mg As/kg/day in pregnant rabbits dosed repeatedly throughout gestation. No cases were located regarding death in humans from inhalation exposure to inorganic arsenicals. The reason for this apparent route specificity is not clear, but might simply be due to lower exposure levels, or perhaps to toxicokinetic differences in exposure rate or arsenic metabolism. Dermal exposure to inorganic arsenicals has not caused lethality in humans, presumably because dermal absorption is very limited.

No cases of death in humans were located that are attributable to exposure to organic arsenicals, but studies in animals show that ingestion or inhalation of organic arsenicals (DMA, MMA, roxarsone) may be lethal. Fatal doses by the inhalation route are so high (above 2,000 mg As/m<sup>3</sup>) (Stevens et al. 1979) as to be of no practical concern, while most oral and parenteral lethal doses range from 15 to 960 mg As/kg/day, depending on the compound and the animal species (Jaghabir et al. 1988; Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979).

### **Systemic Effects**

**Respiratory Effects.** Inhalation of inorganic arsenic dusts (usually containing mainly arsenic trioxide) is irritating to the nose, throat, and lungs, and can lead to laryngitis, bronchitis, and rhinitis (Dunlap 1921; Lundgren 1954; Morton and Caron 1989; Pinto and McGill 1953). However, chronic functional

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impairment of respiration is not usually observed even in workers exposed to high levels of arsenic trioxide in air (Perry et al. 1948). Effects on the lung may actually be more pronounced following high-dose (i.e., near-lethal) oral exposure, where edema and hemorrhagic lesions have been noted (Campbell and Alvarez 1989; Civantos et al. 1995; Fincher and Koerker 1987; Levin-Scherz et al. 1987; Moore et al. 1994; Quatrehomme et al. 1992). It seems possible that this is due mainly to an effect of ingested arsenic on pulmonary blood vessels rather than on alveolar cells, but this is not known with certainty. In general, 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).

The effects of organic arsenicals on the respiratory tract have not been well studied. There are no data by any route from human studies, but acute respiratory distress and lung injury have been reported in mice that inhaled very high levels of DMA (Stevens et al. 1979). Since only high exposures were investigated, it is not possible to compare the relative irritancy and respiratory toxicity of the organic and inorganic arsenicals.

***Cardiovascular Effects.*** Several studies of smelter workers have reported that chronic exposure to arsenic trioxide may increase the risk of dying from cardiovascular disease (Axelson et al. 1978; Jensen and Hansen 1998; Lee-Feldstein 1983; Wall 1980). However, other confounding factors may have predisposed these workers to cardiovascular disease (i.e., lead, cigarette smoking). High oral doses of inorganic arsenic can lead to marked cardiac arrhythmias and altered electrocardiograms in humans (e.g., Glazener et al. 1968; Little et al. 1990). In severe cases, this can lead to premature ventricular contractions and ventricular tachycardia that require medical intervention (Goldsmith and From 1986) or may even result in death (Hall and Harruff 1989).

Chronic oral exposure to lower levels of inorganic arsenic can also result in serious damage to the vascular system. The most extreme manifestation of this is "Blackfoot disease," a progressive loss of circulation in the fingers and toes that ultimately leads to gangrene (Chen et al. 1988b; Chi and Blackwell 1968; Tseng et al. 1968, 1995). This disease has only been reported in one area of Taiwan, and it seems likely that other factors (e.g., fluorescent humic substances in the water) may contribute to the severity of the effect besides the elevated level of arsenic intake (Ko 1986; Lu et al. 1990; Yu et al. 1984).

Symptoms of peripheral vascular disease, including Raynaud's disease, and cyanosis and gangrene of the fingers and toes, which may represent less severe manifestations of what has become known as Blackfoot

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disease, have been reported in other populations. These include populations in Bangladesh (Biswas et al. 1998), Mexico (Cebrian et al. 1983), and Chile (Borgono and Greiber 1972; Zaldivar 1977) that were exposed to high concentrations of arsenic in drinking water; wine vinters in Germany who ingested grape beverages that had a high concentration of arsenic (Roth 1957); and workers who were exposed to arsenic by the inhalation route (Lagerkvist et al. 1986, 1988).

Possible myocardial or vascular effects have not been investigated for the organic arsenicals, either in humans or animals.

***Gastrointestinal Effects.*** Nausea, vomiting, and diarrhea are very common symptoms in humans following oral exposure to inorganic arsenicals, both after acute high-dose exposure (e.g., Fincher and Koerker 1987; Levin-Scherz et al. 1987; Lugo et al. 1969; Moore et al. 1994) and after repeated exposure to lower doses (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Franzblau and Lilis 1989; Mizuta et al. 1956). These effects are likely due mainly to a direct irritation of the gastrointestinal mucosa. Similar effects have also been observed following intermediate- or chronic-duration inhalation exposure (Beckett et al. 1986; Ide and Bullough 1988; Morton and Caron 1989), presumably because of the transfer of inhaled particulates from the respiratory tree to the stomach via mucociliary clearance. By either route, gastrointestinal symptoms usually wane within several days after exposure ceases (Mizuta et al. 1956). The provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic was based in part on gastrointestinal irritation symptoms in people exposed by consumption of tainted soy sauce (Mizuta et al. 1956).

The effects of organic arsenicals on the gastrointestinal tract have not been as thoroughly investigated. No reports were located of gastrointestinal complaints in humans exposed to organic arsenicals, but inhalation exposure of rats to high doses of DMA can cause diarrhea (Stevens et al. 1979), and oral exposure of rabbits to MMA can cause intestinal irritation and weakening of the intestinal wall (Jaghabir et al. 1989). These data suggest that the organic arsenicals are capable of producing gastrointestinal effects similar to the inorganic arsenicals, but the data are too sparse to make quantitative comparisons.

***Hematological Effects.*** Anemia is often observed in humans exposed to arsenic by the oral route (e.g., Armstrong et al. 1984; Glazener et al. 1968; Mizuta et al. 1956; Westhoff et al. 1975). This is probably due mainly to a toxic effect on the erythropoietic cells of bone marrow (Franzblau and Lilis 1989; Lerman et al. 1980; Westhoff et al. 1975), although increased hemolysis may also contribute (Goldsmith and From 1986; Kyle and Pease 1965). Leukopenia is also common in cases of oral exposure to inorganic

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arsenicals (e.g., Armstrong et al. 1984; Franzblau and Lilis 1989; Kyle and Pease 1965). Similar depression of red or white blood cells has not been reported in workers exposed by the inhalation route (e.g., Beckett et al. 1986; Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988; Morton and Caron 1989). As discussed above, the reason for this is not clear but may be simply a function of dose.

Information on possible hematological effects of organic arsenicals is sparse. No effects were observed in humans exposed to arsanilic acid (Watrous and McCaughey 1945), and no effects were detected in animals exposed to MMA, DMA, or roxarsone (NTP 1989b; Prukop and Savage 1986; Siewicki 1981). These data suggest that the organic arsenicals have low hematotoxicity, but the data are too limited to draw firm conclusions, particularly for humans.

***Hepatic Effects.*** Oral exposure of humans to inorganic arsenicals often produce a swollen and tender liver (e.g., Chakraborty and Saha 1987; Guha Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953). Although large serum enzyme changes indicating hepatotoxicity have been found in some acute poisoning cases (Armstrong et al. 1984; Hantson et al. 1996; Kamijo et al. 1998; Levin-Scherz et al. 1987; Quatrehomme et al. 1992), there is usually only marginal evidence of hepatic cell injury with longer-term exposure to lower doses (Franzblau and Lilis 1989; Hernandez-Zavala et al. 1998). Histological examination suggests that the principal lesion is a portal tract fibrosis and cirrhosis that results in portal hypertension (Franklin et al. 1950; Guha Mazumder et al. 1988; Morris et al. 1974; Szuler et al. 1979). Thus, the hepatic effects may be largely vascular in origin. Similar hepatic effects have not been noted in workers exposed to inorganic arsenic by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). However, too few human subjects have been studied to draw firm conclusions.

No information was located on hepatotoxic effects of organic arsenicals in humans, although some mild effects on liver weight and histological appearance have been detected in rats and mice given repeated oral doses of roxarsone (NTP 1989b) and rabbits given MMA (Jaghabir et al. 1989). These data are too limited to judge whether the organic arsenicals act on the liver similarly to inorganic arsenic.

***Renal Effects.*** Signs of renal injury are usually mild or absent in cases of humans exposed to inorganic arsenic either by the oral route (Franzblau and Lilis 1989; Jenkins 1966; Kersjes et al. 1987; Mizuta et al. 1956; Silver and Wainman 1952) or by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). 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. 1994) is probably a result of

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fluid imbalances or vascular injury (Rosenberg 1974; Zaldivar 1974). These observations suggest that the kidney is relatively less sensitive to inorganic arsenic than other systemic target tissues, and that renal effects are unlikely to be of major human health concern.

No information was located on renal effects of organic arsenicals in humans, but histological signs of tubular damage have been noted in rats given repeated oral doses of roxarsone (NTP 1989b) and in rabbits given repeated oral doses of MMA (Jaghabir et al. 1989). This suggests that the organic arsenicals may have limited nephrotoxicity, but it is difficult to judge the significance of these observation for humans exposed to organic arsenicals.

***Dermal Effects.*** Perhaps the single most common and characteristic sign of exposure to inorganic arsenic is a triad of dermatological manifestations, including 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. One or more of these effects have been noted in numerous studies of intermediate or chronic oral exposure to inorganic arsenic (e.g., Borgono and Greiber 1972; Cebrian et al. 1983; Chakraborty and Saha 1987; Guha Mazumder et al. 1988; Nagai et al. 1956b; Tay and Seah 1975; Tseng et al. 1968; Zaldivar 1977), and similar effects have also been noted only rarely in workers exposed to inorganic arsenic primarily by the inhalation route (Perry et al. 1948). A small fraction of the hyperkeratinized corns may ultimately progress to squamous cell carcinoma of the skin (see below).

Since these skin lesions appear to be the earliest observable sign of chronic exposure, this end point is considered to be the most appropriate for derivation of a chronic-duration MRL. Oral exposure data from studies in humans (Cebrian et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; Tseng 1977; Tseng et al. 1968) identify a chronic average daily intake of about 0.01–0.02 mg As/kg/day as the approximate LOAEL for skin lesions, and indicate the NOAEL is between 0.0004 and 0.0009 mg As/kg/day. The NOAEL of 0.0008 mg As/kg/day identified by Tseng et al. (1968) and Tseng (1977) has been selected as the most appropriate basis for calculation of a chronic oral MRL for inorganic arsenic because of the large number of people in the study. However, because the population in the no-effect group were relatively young (only 38% older than 20 and 17% older than 40), there is some chance that dermal effects might not have had time to occur and might become manifest as the population ages. For this reason, the MRL is derived from the NOAEL by an uncertainty factor of three. Chronic inhalation data suggest that exposure of workers to about 0.1–1.0 mg As/m<sup>3</sup> may lead to hyperkeratinization and hyperpigmentation

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(Perry et al. 1948), but in the absence of other studies to support this, and without identification of a reliable NOAEL, these data are not considered sufficient for derivation of a chronic inhalation MRL.

Direct dermal contact 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 (Holmqvist 1951). These conditions tend to heal without treatment if exposure ceases. Effects of this sort have only been observed in workplace environments where there are high levels of arsenic dusts (Holmqvist 1951; Pinto and McGill 1953), and have not been noted in people exposed to arsenic in water or soil (presumably because the concentrations of arsenic that contact the skin from water or soil are too low to cause significant irritation).

Little information was located on dermal effects of organic arsenicals. Workers exposed to arsanilic acid did not complain of dermal problems (Watrous and McCaughey 1945), but no direct examination or comparison of dermal appearance of the workers with a control group was performed. Rats exposed to very high concentrations of DMA developed erythema on the ears and feet along with encrustations around the eyes (Stevens et al. 1979). These effects were presumably due to direct irritation from dermal contact, suggesting that at least some of the organic arsenicals may be able to cause contact dermatitis. However, these data are too limited to draw firm conclusions.

***Ocular Effects.*** Chemical conjunctivitis, characterized by redness, swelling, and pain, usually in combination with facial dermatitis, has been observed in workers exposed to arsenic dusts in air (Dunlap 1921; Pinto and McGill 1953). Facial edema, generally involving the eyelids, was a prominent feature of inorganic arsenic poisoning among 220 cases associated with an episode of arsenic contamination of soy sauce in Japan (Mizuta et al. 1956) and has also been reported in poisoning cases in the United States (Armstrong et al. 1984). The edema developed soon after the initial exposure and then subsided. This effect forms the basis (in part) for the provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic.

Little information was located on ocular effects of organic arsenicals.

**Immunological and Lymphoreticular Effects.** No studies were located on immune and lymphoreticular effects in humans after oral exposure to inorganic arsenicals, but workers exposed to arsenic dusts in air did not have altered levels of antibodies in their blood (Bencko et al. 1988). Mice exposed to arsenate in drinking water did not display any signs of immunotoxicity (Kerkvliet et al. 1980),

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and mice given intratracheal doses of sodium arsenite had decreased humoral responsiveness to antigens but no measurable decrease in resistance to bacterial or cellular pathogens (Sikorski et al. 1989). However, mice exposed to arsenic trioxide aerosol for 3 hours had 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 (Aranyi et al. 1985). Reports that gallium arsenide suppresses immune function and increases the co-stimulatory activity of macrophages in rodents treated orally or by intraperitoneal injection (Caffrey-Nolan and McCoy 1998; Flora et al. 1998; Lewis et al. 1998a, 1998b) are confounded by the use of gallium nitrate as an immuno-suppressing drug (Makkonen et al. 1995; Orosz et al. 1997). Repeated dermal contact with arsenic dusts in the workplace may lead to dermal sensitization (Holmqvist 1951), but sensitization appears to be very rare in the general population (Wahlberg and Boman 1986). Overall, these data suggest that the immune and lymphoreticular systems are probably not a major target of arsenic, but the data are too sparse to draw firm conclusions.

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

**Neurological Effects.** Signs of peripheral and/or central neuropathy are common in humans exposed to inorganic arsenicals by the oral route and have also been observed in some workers exposed by the inhalation route. Acute, high-dose exposure can lead to encephalopathy, with clinical signs such as confusion, hallucinations, impaired memory, and emotional lability (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989). In fatal or near-fatal cases, this may progress to seizures and coma (Armstrong et al. 1984; Fincher and Koerker 1987), while lower-level exposure can lead to significant peripheral neuropathy (e.g., Feldman et al. 1979; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This neuropathy is usually first detected as a numbness in the hands and feet, but may progress to a painful "pins and needles" sensation (Franzblau and Lilis 1989; Jenkins 1966; Le Quesne and McLeod 1977). Both sensory and motor neurons are affected, with distal axon degeneration and demyelination (Goebel et al. 1990; Hindmarsh and McCurdy 1986). More advanced symptoms include weakness, loss of reflexes, and wrist-drop or ankle-drop (Chhuttani et al. 1967; Heyman et al. 1956). These effects may diminish after exposure ceases, but recovery is slow and usually is not complete (Beckett et al. 1986; Fincher and Koerker 1987; Le Quesne and McLeod 1977; Morton and Caron 1989; Murphy et al. 1981).

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No studies were located regarding neurological effects in humans after exposure to organic arsenicals, but pigs given repeated oral doses of roxarsone developed muscle tremor, paralysis, and seizures (Edmonds and Baker 1986; Rice et al. 1985), along with a degeneration of myelinated axons in the spinal cord (Kennedy et al. 1986). These findings indicate that neurotoxicity may be an effect of concern for organic as well as inorganic arsenicals, but it is not possible to estimate human NOAEL or LOAEL values from the existing data.

**Reproductive Effects.** Limited information exists on the reproductive effects of inorganic arsenic. Only one human study was located (Lugo et al. 1969), in which a 30-week gestation live infant was delivered after maternal ingestion of 0.39 mg/kg As, and died 11 days later. In addition, few studies have been performed in animals. Reproductive performance was not affected in female rats that received inhalation exposures to concentrations as high as 20 mg As/m<sup>3</sup> or gavage doses as high as 8 mg As/kg/day from 14 days prior to mating through gestation day 19 (Holson et al. 1999, 2000). Schroeder and Mitchner (1971) found a significant increase in the incidence of small litters and a trend toward decreased number of pups per litter in all generations of a 3-generation drinking water study in mice. This finding is consistent with embryoletality produced by inorganic arsenic in developmental toxicity studies (see Developmental Effects, below) and may be due to a lethal effect on the developing organism rather than an effect on the reproductive organs of the parental animals.

Data are also very limited on the reproductive effects of organic arsenicals. No studies were located on effects in humans, but oral exposure of male mice to MMA resulted in a clear decrease in the number of females producing litters (Prukop and Savage 1986). This suggests that MMA might interfere with sperm production, but the effects could also be due to reduced mating as a consequence of illness from nonreproductive effects. Thus, in the absence of additional information, the reproductive toxicity of organic arsenicals cannot be evaluated.

**Developmental Effects.** There are several epidemiological studies that have reported an association between exposure to inorganic arsenic and increased risk of adverse developmental effects (congenital malformations, low birth weight, spontaneous abortion), both by the inhalation route (Nordstrom et al. 1978a, 1978b, 1979a, 1979b) and the oral route (Aschengrau et al. 1989; Zierler et al. 1988). However, in all of these studies, the populations were exposed to a number of other chemicals and risk factors, which may have contributed to the observed effects, and these studies provide only suggestive evidence that arsenic was a causative agent. Additional suggestive evidence comes from the case of a premature neonate that was born at 30 weeks gestation after maternal ingestion of 0.39 mg As/kg, and died 11 days

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later (Lugo et al. 1969). Although most of the findings in the neonate were attributable to immaturity, one remarkable finding at autopsy was severe pulmonary hemorrhage, which the authors suggested may have been due to arsenic. Studies in animals support the view that arsenic is a developmental toxicant, causing reduced birth weight, a variety of fetal malformations (both skeletal and soft tissue), and increased fetal mortality. These effects have been noted following inhalation exposure of mice and rats (Holson et al. 1999; Nagymajtenyi et al. 1985), oral exposure of mice, rats, hamsters, and rabbits (Baxley et al. 1981; Holson et al. 2000; Hood and Harrison 1982; Hood et al. 1978; Nemeč et al. 1998; Stump et al. 1999), and intraperitoneal or intravenous injection of rats, mice, and hamsters (Beaudoin 1974; Carpenter 1987; Ferm and Carpenter 1968; Ferm et al. 1971; Hanlon and Ferm 1986c; Hood 1998; Hood and Bishop 1972; Mason et al. 1989; Willhite 1981). However, in all cases, the doses required to cause these effects resulted in significant maternal toxicity or even lethality. Recent studies in mice, rats, and rabbits found no evidence of developmental effects at exposure levels that did not produce maternal toxicity (Holson et al. 1999, 2000; Nemeč et al. 1998; Stump et al. 1999). These data suggest that although inorganic arsenic is a developmental toxicant, the developing fetus is not especially susceptible, and teratogenicity or fetotoxicity are unlikely to be of concern except at doses that are also toxic to the pregnant female.

*In vitro* studies of inorganic arsenic have shown that arsenic is embryotoxic and teratogenic. Arsenic significantly impairs preimplantation mouse blastocyst development at concentrations of 1.1 mg/L, and decreased final cell number in preimplantation embryos in culture at 0.0075 mg/L (Hanna et al. 1997). Studies using mouse whole embryo culture indicate that arsenic causes nonclosure of the cranial neural tube, disruption of optic and otic development, and forebrain growth disruption, which is dependent on gestational age (Tabacova et al. 1996). In addition, postimplantation mouse embryos exposed *in vivo* and then grown *in vitro* exhibited altered neural tube cell cycles (Włodarczyk et al. 1996).

No studies were located regarding developmental effects in humans after exposure to organic arsenicals. Oral exposure of mice and rats to DMA during gestation resulted in minor fetal effects (malformed palates, decreased weight gain, delayed ossification), although doses that were maternally toxic also caused increased fetal death (Rogers et al. 1981). Intraperitoneal injection of hamsters with MMA or DMA caused no obvious teratogenic or fetotoxic effects at a dose of 54 mg As/kg (Willhite 1981), although very high doses (420–460 mg As/kg/day) caused stunted growth, malformations, and both fetal and maternal deaths (Hood et al. 1982). These studies suggest that the organic arsenicals are significantly less fetotoxic than the inorganic arsenicals, and are not likely to cause developmental effects in humans except at very high exposure levels.

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**Genotoxic Effects.** There have been a large number of studies of the genotoxic effects of arsenic. Tables 2-13 and 2-14 summarize a number of reports on the *in vivo* and *in vitro* genotoxicity of inorganic arsenicals, respectively. The results are mixed, but in general, it appears that the inorganic arsenicals are either inactive or weak mutagens (Jacobson-Kram and Montalbano 1985), but are able to produce chromosomal effects (aberrations, sister chromatid exchange) in most systems. Studies of humans have detected 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). However, the *in vivo* findings are strongly supported by *in vitro* studies using eukaryotic cells (e.g., Lee et al. 1985; Nakamuro and Sayato 1981; Zanzoni and Jung 1980) (see Table 2-14).

The genotoxicity of the organic arsenicals has not been as thoroughly studied, but several tests indicate that DMA and roxarsone may be able to cause mitotic arrest, chromosome aberrations, mutations, and DNA strand breaks (see Table 2-15).

**Cancer.** There is clear evidence from studies in humans that exposure to inorganic arsenic may increase the risk of cancer. In workers exposed by the inhalation route, the predominant carcinogenic effect is increased risk of lung cancer (e.g., Enterline et al. 1987a, 1987b; Jarup and Pershagen 1991; Jarup et al. 1989; Lee-Feldstein 1986; Welch et al. 1982), although a few reports have noted increased incidence of tumors at other sites (e.g., Lee-Feldstein 1983; Pinto et al. 1977; Tsuda et al. 1987). Based on the risk of lung cancer, EPA has assigned inorganic arsenic to Group A (known human carcinogen) by the inhalation route (IRIS 2000). This is supported by the U.S. Public Health Service, which has also classified inorganic arsenic as a known human carcinogen (NTP 1994, 2000). In general, most researchers observe that risk increases as a function of exposure level and duration (Axelson et al. 1978; Jarup et al. 1989; Lee-Feldstein 1983; Mabuchi et al. 1979; Pinto et al. 1978). Most cases are seen in workers with chronic exposures, although several studies suggest that even short (1 year) exposures may also increase risk (Lee-Feldstein 1986; Sobel et al. 1988). Computer modeling of available epidemiological data suggests that arsenic acts mainly as a promoter, increasing lung cancer by increasing the rate of a late stage in the carcinogenic sequence, although it may also act at an early stage (Brown and Chu 1983c; Enterline and Marsh 1982; Mazumdar et al. 1989).

When exposure occurs by the oral route, the main carcinogenic effect is increased risk of skin cancer. This conclusion is based on a number of epidemiological studies of populations exposed to elevated

Table 2-13. Genotoxicity of Inorganic Arsenic *In Vivo*

Valence	Exposure route	Species (test system)	End point	Results	Reference
Non-mammalian					
As <sup>+3</sup> As <sup>+5</sup>	Injection	<i>Drosophila melanogaster</i>	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As <sup>+3</sup> As <sup>+5</sup>	Larval feeding	<i>D. melanogaster</i>	Somatic mutations and mitotic recombination	+	Ramos-Morales and Rodriguez-Arnaiz 1995
As <sup>+5</sup>	Larvae	<i>D. melanogaster</i>	Mitotic recombinations	+	de la Rosa et al. 1994
Mammalian					
As <sup>+3</sup>	Inhalation	Human (lymphocytes)	Chromosomal aberrations	–	Beckman et al. 1977
As <sup>+3</sup>	Inhalation	Human (lymphocytes)	Chromosomal aberrations	+	Nordenson et al. 1978
As <sup>+3</sup>	Oral	Human (lymphocytes)	Chromosomal aberrations	–	Burgdorf et al. 1977
No data	Oral	Human (lymphocytes)	Chromosomal aberrations	–	Vig et al. 1984
As <sup>+3</sup>	Oral	Human (lymphocytes)	Sister chromatid exchange	–	Burgdorf et al. 1977
As <sup>+3</sup>	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Hsu et al. 1997
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Lerda 1994
As <sup>+3</sup>	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 <sup>+3</sup>	Oral	Exfoliated human epithelial cells	Micronuclei	+	Moore et al. 1996
No data	Oral	Human (bladder cells)	Micronuclei	+	Moore et al. 1995
As <sup>+3</sup>	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Hsu et al. 1997
No data	Oral	Human (lymphocytes)	Sister chromatid exchange	+	Lerda 1994
As <sup>+5</sup>	Oral	Rat (bone marrow cells)	Chromosomal aberrations	+	Datta et al. 1986
As <sup>+3</sup>	Inhalation	Mouse (fetal liver)	Chromosomal aberrations	(+)	Nagymajtenyi et al. 1985
As <sup>+3</sup>	Oral	Mouse (bone marrow cells)	Chromosomal aberrations	+	Das et al. 1993

**Table 2-13. Genotoxicity of Inorganic Arsenic *In Vivo* (continued)**

Valence	Exposure route	Species (test system)	End point	Results	Reference
As <sup>+3</sup>	Oral	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1981
As <sup>+3</sup>	Oral	Mouse (spermatogonia)	Chromosomal aberrations	–	Poma et al. 1981
As <sup>+3</sup>	Intraperitoneal	Mouse (bone marrow cells)	Chromosomal breaks, exchanges	–	Poma et al. 1981
As <sup>+3</sup>	Intraperitoneal	Mouse (bone marrow cells)	Micronuclei	+	DeKnudt et al. 1986
As <sup>+3</sup>	Intraperitoneal	Mouse (spermatogonia)	Spermatogonia	–	Poma et al. 1981
As <sup>+3</sup>	Intraperitoneal	Mouse (spermatogonia)	Sperm morphology	–	DeKnudt et al. 1986
As <sup>+3</sup>	Intraperitoneal	Mouse (spermatogenesis)	Dominant lethal mutations	–	DeKnudt et al. 1986

– = negative results; + = positive results; (+) = weakly positive result

Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro*

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
As <sup>+3</sup>	<i>Escherichia coli</i>	Reveres mutation	No data	+	Nishioka 1975
As <sup>+3</sup>	<i>E. coli</i> PQ37	Gene mutation	No data	–	Lantzsch and Gebel 1997
As <sup>+3</sup>	<i>E. coli</i> (6 strains)	Reverse mutation	No data	–	Rossmann et al. 1980
As <sup>+3</sup>	<i>Salmonella typhimurium</i>	Gene mutation	No data	–	Lofroth and Ames 1978
As <sup>+3</sup>	<i>Photobacterium fischeri</i>	Gene mutation	No data	–	Ulitzur and Barak 1988
As <sup>+5</sup>	<i>S. typhimurium</i>	Gene mutation	No data	–	Lofroth and Ames 1978
As <sup>+5</sup>	<i>P. fischeri</i>	Gene mutation	No data	+	Ulitzur and Barak 1988
Eukaryotic organisms:					
Fungi:					
As <sup>+3</sup> As <sup>+5</sup>	<i>Saccharomyces cerevisiae</i>	Gene mutation	No data	–	Singh 1983
Mammalian cells:					
As <sup>+3</sup>	Human fibroblasts	DNA repair inhibition	No data	+	Okui and Fujiwara 1986
As <sup>+3</sup>	Human fibroblasts	DNA repair and mutant frequencies	+	+	Wiencke et al. 1997
As <sup>+3</sup>	Human fibroblasts	DNA repair inhibition	+	+	Hartwig et al. 1997
As <sup>+3</sup>	Human fibroblasts (MRC5CV1)	DNA migration	No data	+	Hartmann and Speit 1996
As <sup>+3</sup>	Human fibroblasts (HFW cells)	Cytotoxicity	No data	+	Lee and Ho 1994
As <sup>+3</sup>	Human skin fibroblasts (HFW)	Chromosome endoreduplication	No data	+	Huang et al. 1995
As <sup>+3</sup>	Human skin fibroblasts	Chromosomal aberrations	No data	+	Yih et al. 1997

**Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro* (continued)**

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Mammalian cells (continued):					
As <sup>+3</sup>	Human fetal lung fibroblasts	DNA strand breaks	No data	+	Dong and Luo 1993
As <sup>+3</sup>	Human fetal lung fibroblasts (2BS cells)	DNA damage and repair	No data	+	Dong and Luo 1994
As <sup>+3</sup> As <sup>+5</sup>	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
As <sup>+3</sup>	Diploid human fibroblasts	Morphological transformation	No data	+	Landolph 1994
As <sup>+3</sup>	Human leukocytes	Chromosomal aberration	No data	+	Nakamuro and Sayato 1981
As <sup>+3</sup>	Human lymphocytes	DNA protein cross-links	–	–	Costa et al. 1997
As <sup>+3</sup> As <sup>+5</sup>	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993a
As <sup>+3</sup> As <sup>+5</sup>	Human lymphocytes	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1993b
As <sup>+3</sup> As <sup>+5</sup>	Human lymphocyte	Enhancement or inhibition on DNA synthesis	No data	+	Meng 1994
As <sup>+3</sup>	Human lymphocytes	Hyperdiploidy and chromosomal breakage	No data	(+)	Rupa et al. 1997
As <sup>+3</sup>	Human lymphocytes	Hyperdiploid nuclei	No data	+	Ramirez et al. 1997
As <sup>+3</sup>	Human lymphocytes	Chromosomal aberration	No data	+	Beckman and Nordenson 1986
As <sup>+3</sup>	Human lymphocyte	Chromosomal aberrations and sister chromatid exchange	No data	+	Nordenson et al. 1981
As <sup>+3</sup>	Human lymphocytes	Chromosomal aberration	No data	+	Sweins 1983
As <sup>+3</sup>	Human lymphocytes	Chromosomal aberrations	No data	+	Yager and Wiencke 1993
As <sup>+3</sup>	Human lymphocytes	Chromosomal aberrations	No data	+	Vega et al. 1995
As <sup>+3</sup>	Human lymphocytes	Chromosomal aberrations	No data	+	Wan et al. 1982

**Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro* (continued)**

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Mammalian cells (continued):					
As <sup>+3</sup>	Human lymphocytes	Chromosomal aberrations and sister chromatic exchange	No data	+	Wiencke and Yager 1992
As <sup>+3</sup>	Human lymphocyte	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As <sup>+3</sup> As <sup>+5</sup>	Human lymphocytes	Sister chromatid exchange	No data	+	Gebel et al. 1997
	Human lymphocytes	Sister chromatid exchange	No data	-	
As <sup>+3</sup>	Human lymphocytes	Sister chromatid exchange	No data	+	Hartmann and Speit 1994
As <sup>+3</sup>	Human lymphocytes	Sister chromatid exchange	No data	+	Jha et al. 1992
As <sup>+3</sup>	Human lymphocytes	Sister chromatid exchange	No data	+	Rasmussen and Menzel 1997
As <sup>+3</sup> As <sup>+5</sup>	Human T-cell lymphoma-derived cell line (Molt-3)	PARP activity inhibition	No data	+	Yager and Wiencke 1997
As <sup>+3</sup>	Human cervix carcinoma HeLa and cisplatin-resistant HeLa/CPR variant cells	DNA repair modification	+	+	Chao 1996
As <sup>+3</sup>	Human cervix carcinoma cells (HeLa)	DNA damage recognition	No data	-	Hartwig et al. 1998
As <sup>+3</sup>	Human osteosarcoma cells (HOS)	DNA repair	No data	+	Hu et al. 1998
As <sup>+3</sup>	Mouse lymphoma cells	Enhanced viral forward mutation		(+)	Oberly et al. 1982
As <sup>+3</sup> As <sup>+5</sup>	Mouse lymphoma cells (L5178Y/TK <sup>+/+</sup> -3.7.2C)	Chromosomal mutations	No data	+	Moore et al. 1997a
As <sup>+3</sup>	Mouse lymphoma cells [L5178Y tk <sup>+/+</sup> (3.7.sc)]	Mutagenicity	No data	+	Oberly et al. 1996
As <sup>+3</sup> As <sup>+5</sup>	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Moore et al. 1994

**Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro* (continued)**

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As <sup>+3</sup>	Mouse lymphoma cells	Chromosomal aberrations	No data	+	Sofuni et al. 1996
	Mammalian cells (continued):				
As <sup>+3</sup>	Mouse 3T6 cells	Gene amplification	No data	+	Lee et al. 1988
As <sup>+3</sup>	Mouse embryo fibroblasts (C3H/10T/2 Cl8)	Morphological transformation	No data	+	Landolph 1994
As <sup>+3</sup>	Chinese hamster V79 cells	Gene mutation	No data	–	Li and Rossman 1991
As <sup>+3</sup>	Chinese hamster V79 cells	Gene mutation	No data	–	Rossman et al. 1980
As <sup>+3</sup>	Chinese hamster V79 cells	DNA damage, DNA-protein cross-linking, micronucleus induction	No data	+	Gebel et al. 1998a
As <sup>+3</sup>	Chinese hamster V79 cells	DNA repair and mutant frequencies	No data	+	Li and Rossman 1991
As <sup>+3</sup>	Chinese hamster ovary cells (CHO-A <sub>L</sub> )	Gene mutation	No data	+	Hei et al. 1998
As <sup>+3</sup>	Chinese hamster ovary cells (CHO-AS <sub>52</sub> )	Mutagenicity	No data	+	Meng and Hsieh 1996
As <sup>+3</sup>	Chinese hamster ovary cells	Gene mutation	No data	+	Yang et al. 1992
As <sup>+3</sup>	Chinese hamster ovary cells	DNA repair inhibition	No data	+	Lee-Chen et al. 1993
As <sup>+3</sup>	Chinese hamster ovary cells	DNA repair inhibition	No data	–	Lee-Chen et al. 1992
As <sup>+3</sup>	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	+	+	Lee-Chen et al. 1994
As <sup>+3</sup>	Chinese hamster ovary cells (CHO-K1)	DNA strand breaks	No data	+	Lynn et al. 1997
As <sup>+3</sup>	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Jan et al. 1986
As <sup>+3</sup>	Chinese hamster ovary cells	Aberrant metaphases	No data	+	Lee et al. 1986b

**Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro* (continued)**

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As <sup>+3</sup>	Chinese hamster ovary cells	Chromosomal aberrations	+	+	Huang et al. 1992
As <sup>+3</sup>	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations	No data	+	Huang et al. 1993
Mammalian cells (continued):					
As <sup>+3</sup> As <sup>+5</sup>	Chinese hamster ovary cells (CHO-K1)	Chromosomal aberrations and sister chromatid exchange	No data	+	Kochhar et al. 1996
As <sup>+3</sup>	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	+	+	Lin and Tseng 1992
As <sup>+3</sup>	Chinese hamster ovary cells	Chromosomal aberrations and sister chromatid exchange	No data	+	Wan et al. 1982
As <sup>+3</sup>	Chinese hamster ovary cells	Sister chromatid exchange and micronucleus induction	No data	+	Fan et al. 1996
As <sup>+3</sup>	Chinese hamster ovary cells	Cell-killing and micronucleus induction	No data	+	Wang and Huang 1994
As <sup>+3</sup>	Chinese hamster ovary cells	Micronuclei	No data	+	Liu and Huang 1997
As <sup>+3</sup>	Chinese hamster ovary cells	Micronuclei formation	No data	+	Yee-Chien and Haimei 1996
As <sup>+3</sup>	Chinese hamster ovary cells	Micronuclei induction	No data	+	Wang et al. 1997a
As <sup>+3</sup>	Chinese hamster ovary cells	Cytotoxicity	No data	–	Lee and Ho 1994
As <sup>+3</sup>	Syrian hamster embryo cells	Gene mutation	No data	–	Lee et al. 1985
As <sup>+3</sup>	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981

**Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro* (continued)**

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As <sup>+3</sup>	Syrian hamster embryo cells	Chromosomal aberration	No data	+	Lee et al. 1985
As <sup>+3</sup>	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As <sup>+3</sup>	Syrian hamster embryo (SHE) cells	Micronuclei induction	No data	–	Gibson et al. 1997
As <sup>+3</sup>	Syrian hamster embryo (SHE) cells	Micronuclei induction	No data	–	Gibson et al. 1997
As <sup>+3</sup>	Syrian hamster embryo cells	Morphological transformation	No data	+	Kerckaert et al. 1996
As <sup>+3</sup>	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As <sup>+3</sup>	Syrian hamster embryo cells	Morphological transformation	No data	+	Casto et al. 1979
Mammalian cells (continued):					
As <sup>+5</sup>	Human fibroblasts	DNA repair inhibition	No data	–	Okui and Fujiwara 1986
As <sup>+5</sup>	Human leukocyte	Chromosomal aberrations	No data	(+)	Nakamuro and Sayato 1981
As <sup>+5</sup>	Human lymphocyte	Chromosomal aberrations	No data	–	Nordenson et al. 1981
As <sup>+5</sup>	Human lymphocyte	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As <sup>+5</sup>	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
As <sup>+5</sup>	Human peripheral lymphocytes	Sister chromatid exchange	No data	+	Zanzoni and Jung 1980
As <sup>+5</sup>	Human keratinocyte line SCC-9 cells	Keratinocyte programming and transcriptional activity	No data	+	Kachinskas et al. 1997
As <sup>+5</sup>	Mouse lymphoma cells	Gene mutation	No data	–	Amacher and Paillet 1980
As <sup>+5</sup>	Mouse lymphoma cells	Gene mutation	No data	–	Amacher and Paillet 1980

**Table 2-14. Genotoxicity of Inorganic Arsenic *In Vitro* (continued)**

Valence	Species (test system)	End point	Results		Reference
			With activation	Without activation	
As <sup>+5</sup>	Chinese hamster ovary cells	Chromosomal aberrations	No data	+	Wan et al. 1982
As <sup>+5</sup>	Syrian hamster embryo cells	Gene mutation	No data	-	Lee et al. 1985
As <sup>+5</sup>	Syrian hamster embryo cells	Chromosome aberrations and sister chromatid exchanges	No data	+	Larramendy et al. 1981
As <sup>+5</sup>	Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Lee et al. 1985
As <sup>+5</sup>	Syrian hamster embryo cells	Sister chromatid exchange	No data	+	Lee et al. 1985
As <sup>+5</sup>	Syrian hamster embryo cells	Morphological transformation	No data	+	Lee et al. 1985
As <sup>+5</sup>	Syrian hamster embryo cells	Morphological transformation	No data	+	DiPaolo and Casto 1979

(+) = weakly positive or marginal result; - = negative result; + = positive result

Table 2-15. Genotoxicity of Organic Arsenic

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms ( <i>in vitro</i> ):					
Dimethylarsenic acid	<i>Escherichia coli</i>	Gene mutation	No data	%	Yamanaka et al. 1989b
Roxarsone	<i>Salmonella typhimurium</i>	Gene mutation	–	–	NTP 1989b
Eukaryotic organisms ( <i>in vitro</i> ):					
Arsenobetaine	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
Arsenobetaine	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	–	Eguchi et al. 1997
Dimethylarsenic acid	Human peripheral lymphocytes	Mitogenesis inhibited	No data	–	Endo et al. 1992
Dimethylarsenic acid	Human lymphocytes	Sister chromatid exchange	No data	–	Rasmussen and Menzel 1997
Dimethylarsenic acid	Human alveolar (L-132) cells	Lung-specific DNA damage	No data	+	Kata et al. 1993
Dimethylarsenic acid	Human alveolar type II (L-132) cells	DNA single-strand breaks	+	+	Kawaguchi et al. 1996
Dimethylarsenic acid	Human diploid L-132 epithelial cells	DNA single-strand breaks	No data	+	Rin et al. 1995
Dimethylarsenic acid	Human alveolar type II (L-132) cells	DNA strand breaks	No data	+	Tezuka et al. 1993
Dimethylarsenic acid	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
Dimethylarsenic acid	Human alveolar epithelial (L-132) cells	DNA single-strand breaks and DNA-protein crosslinks	No data	+	Yamanaka et al. 1995
Dimethylarsenic acid	Human pulmonary epithelial (L-132) cells	DNA single-strand breaks	No data	+	Yamanaka et al. 1997
Dimethylarsenic acid	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996
Dimethylarsenic acid	Mouse lymphoma cells (L5178Y/TK <sup>+</sup> -3.7.2C)	Chromosomal mutations	No data	+	Moore et al. 1997a
Dimethylarsenic acid	Chinese hamster lung and diploid cells (V79)	Mitotic arrest and tetraploid formation	No data	+	Endo et al. 1992
Dimethylarsenic acid	Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Ueda et al. 1997
Dimethylarsenic acid	Chinese hamster V79 cells	Tetraploids and mitotic arrest	No data	+	Eguchi et al. 1997
Methylarsonic acid	Human umbilical cord fibroblasts	Chromosomal aberrations	No data	+	Oya-Ohta et al. 1996

**Table 2-15. Genotoxicity of Organic Arsenic (continued)**

Chemical form	Species (test system)	End point	Results		Reference
			With activation	Without activation	
Eukaryotic organisms ( <i>in vitro</i> ): (continued)					
Monomethylarsonic acid	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> ):					
Dimethylarsenic acid	Rat (oral exposure)	DNA single-stand breaks in lung	No data	%	Yamanaka and Okada 1994
Dimethylarsenic acid	Mouse (oral exposure)	DNA strand breaks in tissues	No data	%	Yamanaka et al. 1989b
Dimethylarsenic acid	Mouse (oral exposure)	DNA single-stand breaks in lung	No data	+	Yamanaka et al. 1993
Dimethylarsenic acid	Mouse (oral exposure)	DNA single-strand breaks in lung	No data	–	Yamanaka et al. 1989a
Dimethylarsenic acid	Mouse (injection)	Aneuploidy in bone marrow cells	No data	+	Kashiwada et al. 1998

– = negative result; + = positive result

## 2. HEALTH EFFECTS

levels of arsenic in drinking water (e.g., Chakraborty and Saha 1987; Hauptert et al. 1996; Luchtrath 1983; Tseng 1977; Tseng et al. 1968; Zaldivar 1974), and on numerous case reports of people exposed to Fowler's solution (Bickley and Papa 1989; Piontek et al. 1989; Sommers and McManus 1953). Based on these findings, the EPA has placed inorganic arsenic in Group A (known human carcinogen) for exposure by the oral route. In addition to skin cancer, there are a number of case reports (Kasper et al. 1984; Lander et al. 1975; Regelson et al. 1968; Roth 1957; Sommers and McManus 1953) and epidemiological studies (Chen et al. 1986, 1988b, 1992; Cuzick et al. 1992; Guo et al. 1997; Kurttio et al. 1999; Lewis et al. 1999; Tsuda et al. 1995a) that indicate ingestion of arsenic also increases the risk of internal tumors (mainly of liver, bladder, kidney, and lung).

As discussed previously (see Section 2.2.2.8), EPA has calculated an oral cancer slope factor for inorganic arsenic based on the dose-response data obtained by Tseng et al. (1968) in Taiwan (IRIS 1999). The Tseng et al. (1968) study has considerable strengths for risk assessment, including a very large sample size, excellent case ascertainment (physical examination), inclusion of both males and females, and lifetime exposure duration. Uncertainties in the assessment 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) (IRIS 1999).

The biochemical mechanism of arsenic-induced carcinogenicity is not known. As discussed previously, arsenic does not appear to damage DNA by a direct mechanism, but several studies support the concept that arsenic inhibits one or more of the enzymes involved in DNA replication or repair (Li and Rossman 1989; Nordberg and Anderson 1981; Okui and Fujiwara 1986; Rossman 1981). Another possible mechanism of arsenic-induced carcinogenicity is incorporation of arsenate into DNA in place of phosphate (Nordberg and Anderson 1981). This concept is consistent with observations that arsenate must be present during DNA synthesis in order to be effective, and would explain why arsenic is clastogenic (the arsenate-phosphate bond would be weaker than the normal phosphodiester) but does not cause gene mutations (Jacobson-Kram and Montalbano 1985).

**Beneficial Effects.** There are several studies in animals that suggest that low levels of arsenic in the diet are beneficial or essential. Rats fed a low-arsenic diet (<0.05 ppm of arsenic in food, corresponding to about 0.0025 mg As/kg/day) did not gain weight normally (Schwartz 1977; Uthus et al. 1983), and arsenic deprivation has been noted to decrease the growth of offspring from rats, goats, and minipigs

## 2. HEALTH EFFECTS

(Anke et al. 1976, 1978; Uthus et al. 1983). Decreased reproductive success and increased postnatal mortality has also been noted in goats, minipigs, and rats maintained on low-arsenic diets (Anke et al. 1976, 1978; Uthus et al. 1983). No specific biochemical mechanism is known by which arsenic could be exerting a beneficial effect, but Nielsen et al. (1980) and Uthus et al. (1983) have proposed that arsenic plays a role in arginine and/or zinc metabolism.

While these observations suggest that low levels of arsenic may be essential or beneficial to animals, several researchers consider the weight of evidence inadequate to conclude this with certainty (Hindmarsh and McCurdy 1986; Solomons 1984). EPA (1988e) performed a detailed review of the evidence, and concluded that essentiality, although not rigorously established, is plausible. NRC (1999) also reviewed the evidence for arsenic as an essential element and concluded that the available studies did not provide evidence that arsenic is an essential element in humans, although arsenic supplementation at high doses (concentrations of 350–4,500 ng/g in the diet) does appear to stimulate growth in minipigs, chicks, goats, and rats. If arsenic is essential or beneficial to humans the daily requirement for humans probably lies somewhere between 10 and 50  $\mu\text{g/day}$  (0.0001–0.0007 mg As/kg/day) (EPA 1988e; NAS 1977b). This level of arsenic intake is usually provided in a normal diet (about 50  $\mu\text{g/day}$ ; see Section 5.5), and no cases of arsenic deficiency in humans have ever been reported.

Arsenic has long been used for medicinal purposes. As Fowler's solution (1% arsenic trioxide), it was used in the 19th and early 20th century to treat a wide variety of ailments, particularly skin diseases, asthma, fevers, and pain (NRC 1999). Organic arsenic antibiotics were used extensively in the early 20th century to treat protozoal and spirochetal diseases, such as syphilis, but these compounds were largely replaced by penicillin in the 1940s and 1950s. Recent studies have described the use of inorganic arsenic to treat acute promyelocytic leukemia. Intravenous injection with 10 mg/day or 0.5 mg/kg/day of arsenic trioxide has been reported to induce remission in patients suffering this disease (Bergstrom et al. 1998; Huang et al. 1998; Shen et al. 1997; Soignet et al. 1998). Arsenic trioxide appears to selectively induce apoptosis in leukemia cells (Akao et al. 1998; Bazarbachi et al. 1999; Chen et al. 1997a; Lu et al. 1999; Rousselot et al. 1999; Zhu et al. 1997). A number of different mechanisms by which arsenic trioxide may trigger apoptosis have been proposed. These include down regulation of Bcl-2 (Akao et al. 1998), direct interaction with tubulin (Li and Broome 1999), degradation of the leukemia specific protein PML/RAR $\alpha$  (Zhu et al. 1997), and opening the mitochondrial permeability transition pore allowing the release of an apoptosis-inducing factor (Larochette et al. 1999). It has also been suggested that cells with lower levels of GSH have greater sensitivity to the effects of arsenic trioxide (Dai et al. 1999) and that combining

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arsenic trioxide treatment with interferon can produce a synergistic improvement in the effectiveness of therapy.

### 2.6 ENDOCRINE DISRUPTION

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, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997h). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of 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. Rahman et al. (1998) reported a correlation between exposure to arsenic in the drinking water and increased incidence of diabetes mellitus in residents of Bangladesh, but no other relevant data were located in humans or animals.

### 2.7 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.

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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 5.6 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 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 while 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

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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 (Borgono et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldivar 1974; Zaldivar and Gullier 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 (Blackfoot disease) 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 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  $\mu\text{g}/\text{mL}$  and the arsenic level in hair ranged from 14.4 to 20  $\mu\text{g}/\text{g}$ . 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.

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 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.

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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; Willite 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 only at maternally toxic doses (Baxley et al. 1981; Holson et al. 1999, 2000; Hood and Harrison 1982; Hood et al. 1978; Nemeč et al. 1998; Stump et al. 1999). In humans, acute prenatal exposure to high doses of inorganic arsenic can result in miscarriage and early neonatal death (Bollinger 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 (Aschengrau et al. 1989; Nordstrom et al. 1978a, 1979b; Zierler et al. 1988), none of these studies have provided convincing evidence for such effects.

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 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

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children exposed to arsenic. In addition, no unique interactions of arsenic with other chemicals have been identified in children.

The mechanism of action of arsenic in the mammalian cell involves inhibition of proliferation of cells (Dong and Luo 1993; Jha et al. 1992; Petres et al. 1977). In addition, arsenic impairs assembly and disassembly of microtubules, thus interfering with mitotic spindle formation and embryonal cell division (Leonard and Lauwerys 1980; Li and Chou 1992; Mottet and Ferm 1983). Arsenic compounds also cause chromosomal aberrations (Jha et al. 1992; Leonard and Lauwerys 1980), which disrupt cell cycling. The direct toxic effects 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 Beliveau 1992; Edelman 1992; Gunn et al. 1992; Li and Chou 1992; Moriss-Kay et al. 1994; Scheonwolf 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 especially sensitive to this manifestation of arsenic toxicity.

### 2.8 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 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 or 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

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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 2.8.1.

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 2.8.2.

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 2.10, "Populations That Are Unusually Susceptible".

### **2.8.1 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 less than 1  $\mu\text{g/L}$  (Heydorn 1970; Hindmarsh and McCurdy 1986; Valentine et al. 1979). Consumption of medicines containing arsenic is associated with blood values of 100–250  $\mu\text{g/L}$ , while blood levels in acutely toxic and fatal cases may be 1,000  $\mu\text{g/L}$  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  $\mu\text{g/L}$  (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.

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As discussed in Section 2.3.4, 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 ( $C_{\text{air}}$ ,  $\mu\text{g}/\text{m}^3$ ) and the concentration in the urine ( $C_{\text{urine}}$ ,  $\mu\text{g}/\text{L}$ ) of exposed workers. For example, Pinto et al. (1976) found a linear relationship for exposures ranging up to  $150 \mu\text{g}/\text{m}^3$ , given by the following equation:

$$C_{\text{air}} = 0.3 C_{\text{urine}}$$

More recently, Enterline et al. (1987a) reinvestigated this relationship over a wider range of exposures (up to  $3,500 \mu\text{g}/\text{m}^3$ ), 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  $100 \mu\text{g}/\text{L}$ ) as evidence of recent arsenic ingestion (e.g., Borgono et al. 1980; Fincher and Koerker 1987; Franzblau and Lilis 1989; Goldsmith and From 1986; Kyle and Pease 1965; Valentine et al. 1981), but a quantitative relation between ingested arsenic and urinary excretion levels has only recently been reported. Calderon et al. (1999) found a quantitative correlation between the log of the mean total urinary arsenic concentration/creatinine (TAs/c,  $\mu\text{g}/\text{mg}$ ) of people living in areas with arsenic-contaminated drinking water sources and the log of the inorganic arsenic concentration in the drinking water (InAs,  $\mu\text{g}/\text{L}$ ). The equation for the regression line is:

$$\text{TAs/c} = 10^{-2.57} \times (\text{InAs})^{0.63}$$

where  $-2.57$  and  $0.63$  are the intercept and slope, respectively, for the regression of the log<sub>10</sub>-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).

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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 6.1, 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 et al. 1986; de Peyster and Silvers 1995; Karagas et al. 1996; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; 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). 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 recently been evaluated by MacIntosh et al. (1997) using standard multivariate regression models. This approach does not appear to be highly

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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 ( $\mu\text{g/L}$ ), arsenic concentration in drinking water ( $\mu\text{g/L}$ ) or daily intake of arsenic ( $\mu\text{g/day}$ ). A 10  $\mu\text{g/L}$  increase in the drinking water concentration or a 10–20  $\mu\text{g/day}$  increase in daily arsenic intake corresponded to a 0.1 mg/kg increase in the arsenic concentration in hair.

### 2.8.2 Biomarkers Used to Characterize Effects Caused by Arsenic

As discussed in Section 2.2, 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 (Hindmarsh et al. 1977; Landau et al. 1977; Valentine et al. 1981) or undetectable (Kreiss et al. 1983; Southwick et al. 1981) 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.

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

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humans (Garcia-Vargas and Hernandez-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 (1990) and for information on biomarkers for neurological effects, see OTA (1990).

### 2.9 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; 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), cytotoxicity (Babich et al. 1989; Rossner et al. 1977), 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 complex that is excreted more rapidly than either arsenic or selenium alone (Cikrt et al. 1988; Hill 1975; Levander 1977; Levander and Baumann 1966). 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 (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.

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). 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. 1984a).

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

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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 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 Marfante 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.

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**2.10 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 5.7, Populations With Potentially High Exposures.

No studies were located regarding unusual susceptibility of any human subpopulation to arsenic. However, since the degree of arsenic toxicity may be influenced by the rate and extent of its methylation in the liver (see Section 2.3.3), it seems likely that some members of the population might be especially susceptible because of lower than normal methylating capacity. 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. While there is some evidence that methylation capacity does vary among individuals (e.g., Buchet et al. 1981a; Foa et al. 1984; Tam et al. 1979b), the basis of this variation and its impact on human susceptibility have not been established. One report did describe severe arsenic toxicity, including 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).

**2.11 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 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:

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Tintinalli JE, Ruiz E, Krone RL, eds. 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4<sup>th</sup> ed. The McGraw-Hill Companies, Inc.

Goldfrank RL, et al. 1994. Goldfrank's toxicologic emergencies. 5<sup>th</sup> ed. Appleton and Lange 5th Edition.

Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology: Diagnosis and treatment of human poisoning. New York, NY: Elsevier Science Publishing Company, Inc.

### **2.11.1 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 consumption of large volumes of water, gastric lavage, stomach intubation, induced emesis, or use of cathartics (saline, sorbitol) within a few hours after ingestion (Aposhian and Aposhian 1989; ATSDR 1990; 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). 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, 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 is

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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).

### 2.11.2 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 (ATSDR 1990; Kajimo 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 (Aposhian and Aposhian 1989; Aposhian et al. 1997; ATSDR 1990; 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. 1998b). 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).

As discussed in Section 2.3.3, 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

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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.

### 2.11.3 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.

## 2.12 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 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

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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.

**2.12.1 Existing Information on Health Effects of Arsenic**

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to arsenic are summarized in Figures 2-9 and 2-10. 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* (ATSDR 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 2-9, 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.

As shown in Figure 2-10, 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.

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**Figure 2-9. 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 2-10. Existing Information on Health Effects of Organic Arsenic**

	Death	Acute	Intermediate	Chronic	Systemic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		•		•		•					
Oral		•				•					
Dermal						•					

**Human**

	Death	Acute	Intermediate	Chronic	Systemic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	•	•									
Oral	•	•	•	•	•	•	•	•	•	•	•
Dermal		•									

**Animal**

- Existing Studies

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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.

### 2.12.2 Identification of Data Needs

**Acute-Duration Exposure.** 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). A provisional 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.

No information was located on the acute toxicity of organic arsenicals in humans. Acute lethality and systemic toxicity data exist for several compounds by both oral and inhalation exposure of animals, and these data suggest that the organic derivatives of arsenic may cause effects similar to the inorganic forms, but only at higher doses (Kaise et al. 1989; NTP 1989b; Rogers et al. 1981; Stevens et al. 1979). Even though these compounds appear to be less toxic than inorganic arsenic, additional studies (especially in humans) would be valuable, since acute oral, inhalation, or dermal exposures may occur during manufacture or use of agricultural organic arsenicals, or at waste sites where organic arsenicals have been

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deposited. Derivation would be useful, but not critical, since those coming into contact with organic arsenic compounds are regulated under OSHA and/or wear protective clothing as recommended by manufacturers.

**Intermediate-Duration Exposure.** 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 studies are probably not essential.

No information was located on the intermediate-duration toxicity of organic arsenicals in humans. The intermediate-duration oral toxicities of roxarsone, MMA, and DMA have been investigated in animals (Edmonds and Baker 1986; Jaghabir et al. 1989; Kerr et al. 1963; NTP 1989b; Prukop and Savage 1986; Siewicki 1981), but data are lacking for any compound by the inhalation route. Further studies on the intermediate-duration oral, 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.** 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/m<sup>3</sup> as the LOAEL for skin changes (Perry et al. 1948), but because there are no additional supporting studies and a

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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) (Cebrian et al. 1983; Hindmarsh et al. 1977; Southwick et al. 1981; 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). For this reason, further epidemiological studies to 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; Jarup and Pershagen 1991; Jarup 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; Luchtrath 1983; Smith et al. 1992; Tseng 1977; Tseng et al. 1968; Yu et al. 1992; Zaldivar 1974; Zaldivar 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. 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).

There is very little information on the chronic toxicity of organic arsenicals. 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). A chronic-duration

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study in rats and mice given roxarsone in the diet did not reveal any obvious clinical effects (Prier et al. 1963). These data suggest that the organic arsenicals have low chronic toxicity, but further studies (especially of humans exposed during manufacture or use of organic arsenicals) would be valuable in deriving estimates of safe exposure limits.

No information was located on carcinogenic effects of organic arsenicals in humans. The carcinogenic potential of roxarsone has been investigated in rats and mice (NTP 1989b); this study detected only equivocal evidence of carcinogenicity in male rats, with no evidence of carcinogenicity in female rats or in male or female mice. However, the cancer potential for other organic arsenic compounds has not been studied in chronic bioassays. Since MMA and DMA are formed from inorganic arsenic *in vivo* by methylation in the liver, chronic studies of the carcinogenic potential of these compounds would be valuable. Studies of humans exposed in the workplace would probably be preferable to studies in animals, since animals appear to be less susceptible to the carcinogenic effects of arsenic than humans. Studies on cancer risk following chronic dermal exposure to organic arsenicals are probably not essential.

**Genotoxicity.** 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; Nagymajtenyi et al. 1985) and cultured cells (Beckman and Nordenson 1986; Casto et al. 1979; DiPaulo and Casto 1979; Lee et al. 1985; Nakamuro and Sayato 1981; Nishioka 1975; Oberly et al. 1982; Okui and Fujiwara 1986; Sweins 1983; Ulitzer and Barak 1988; Zanzoni and Jung 1980). The mechanism of genotoxicity is not known, but may be due to the ability of arsenite to inhibit DNA replicating or repair enzymes (Li and Rossman 1989) 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.

**Reproductive Toxicity.** No information was located regarding the effect of inorganic arsenic on gametogenesis or reproductive organ pathology in humans, and few reproduction studies were located in animals. 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 Mitchner 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

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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.

No information was located on reproductive effects of organic arsenicals in humans, but one study in animals indicated that oral exposure of male mice to MMA could result in a marked decrease in litter production in untreated females (Prukop and Savage 1986). This suggests that spermatogenesis or mating behavior may have been adversely affected, and further studies would be valuable to investigate the mechanism of this effect and whether other organic arsenicals produce similar effects.

**Developmental Toxicity.** There are several epidemiological studies that suggest that inhalation (Nordstrom et al. 1978a, 1978b, 1979a, 1979b) or oral (Aschengrau et al. 1989; Zierler et al. 1988) 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 parameters in humans exposed to arsenic would be valuable in determining whether this is an effect of concern. 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 1986c; Holson et al. 1999, 2000; Hood and Bishop 1972; Hood and Harrison 1982; Hood et al. 1978; Mason et al. 1989; Nagymajtenyi et al. 1985; Nemeč et al. 1998; Stump et al. 1999; Willhite 1981). 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.

No information was located regarding developmental effects in humans after oral or inhalation exposure to organic arsenicals. One oral study and two intraperitoneal ingestion studies in animals indicate that MMA and DMA can produce developmental effects, but only at levels that cause maternal toxicity (Hood et al. 1982; Rogers et al. 1981; Willhite 1981). However, 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.

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**Immunotoxicity.** No studies were located on immunotoxic effects in humans after oral exposure to inorganic arsenic. One inhalation study in humans (Bencko et al. 1988), 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 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.

No information was located on the immunotoxicity of organic arsenicals in humans or animals. 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.** There is convincing evidence from studies in humans that inorganic arsenic can cause serious neurological effects, both after inhalation (Beckett et al. 1986; Danan et al. 1984; Morton and Caron 1989) and oral exposure (Armstrong et al. 1984; Feldman et al. 1979; Fincher and Koerker 1987; Huang et al. 1985; Landau et al. 1977; Mizuta et al. 1956; Silver and Wainman 1952). This is based mainly on clinical observations and neurological examinations of exposed persons and is confirmed by histological examination of nerve biopsy specimens. 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. Animals appear to be much less susceptible than humans to the neurological effects of inorganic arsenic, so studies in animals would probably not help in estimation of a safe exposure limit.

No information was located on neurological effects of organic arsenicals in humans, but clear clinical and histological signs of neurotoxicity have been noted in pigs given repeated oral doses of roxarsone (Edmonds and Baker 1986; Kennedy et al. 1986; Rice et al. 1985). These findings suggest that more extensive investigations of the neurotoxic potential of roxarsone and other organic arsenicals would be

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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.

### **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; Landau et al. 1977; Milham and Strong 1974; Southwick et al. 1981; Valentine et al. 1979; Yamauchi et al. 1989), although care must be

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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.

**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

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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 models for humans and could ultimately lead to development of a physiologically based pharmacokinetic 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 (Aposhian and Aposhian 1989; ATSDR 1990; Campbell and Alvarez 1989; Driesback 1980; Ellenhorn and Barceloux 1988; EPA 1989e; Haddad and Winchester 1990; 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 which 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

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(ATSDR 1990; Ellenhorn and Barceloux 1988). 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 in treatment of chronic arsenic exposure would also be helpful. Trivalent arsenic is generally believed to exert toxic effects by binding to the 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.

**Children's Susceptibility** 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 (Borgono et al. 1980; Foy et al. 1992; Kersjes et al. 1987; Rosenberg 1974; Zaldivar 1974; Zaldivar 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.

### 2.12.3 Ongoing Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of arsenic. Table 2-16 summarizes studies being sponsored by agencies of the U.S. federal government. Additional research is being sponsored by industry groups and other agencies, and research is also ongoing in a number of foreign countries. Some of these studies are listed in Table 2-17.

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**Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded**

Investigator	Affiliation	Title	Sponsor
Aposhian, H Vasken	University of Arizona, Tucson, Arizona	Detoxification of metals— <i>in vitro</i> and <i>in vivo</i> studies	NIEHS
Bayse, Gladys S	Spelman College, Atlanta, Georgia	Biotransformation of the feed additives roxarsone and arsanilic acid	National Institute of General Medical Sciences
Benjamin, Stephen A	Colorado State University, Fort Collins, Colorado	Chemical mixtures as promoters of hepatocarcinogenesis	NIEHS
Billings, Ruth E	Colorado State University, Fort Collins, Colorado	Mechanisms of toxic chemical interaction in the liver—hepatotoxicity	NIEHS
Block, Gladys	University of California, Berkeley, California	Nutrition, environment interactions	NIEHS
Capra, J Donald	Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma	Immunoglobulin V region structures—genetic implications	National Institute of Allergy and Infectious Diseases
Carter, Dean E	University of Arizona College of Pharmacy, Tucson, Arizona	Arsine metabolism and mechanism of toxicity	NIEHS
Checkoway, Harvey	University of Washington, Seattle, Washington	Environmental and biochemical risk factors for Parkinson's disease	NIEHS
Chou, Billy J	Battelle Pacific Northwest Laboratories	Isoprene, indium phosphide, gallium arsenide	NIEHS
Finnell, Richard H	Texas A & M University College Station, Texas	Folate receptor knockouts, arsenate and birth defects	National Institute of Child Health and Human Development
Gandolfi, A Jay	University of Arizona, Tucson, Arizona	Metal-metal interactions in the kidney	NIEHS
Germolec, D R	NIEHS, NIH	Effects of environmental pollutants and therapeutics on the immune	NIEHS
Hall, Eric H	Columbia University, New York, New York	Quantitative studies of oncogenic transfection	National Cancer Institute
Hamilton, Joshua W	Dartmouth College, Hanover, New Hampshire	Molecular basis for effects of carcinogenic metals on inducible gene expression	NIEHS
Holbrook, N J	NIA, NIH	Regulation and function of the putative transcription factor GADD153	National Institute on Aging

## 2. HEALTH EFFECTS

**Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded (continued)**

Investigator	Affiliation	Title	Sponsor
Howell, Stephen B	University of California San Diego, California	Molecular pharmacology of platinum drug resistance	National Cancer Institute
Hunter, David	Harvard School of Public Health, Boston, Massachusetts	Arsenic exposure and skin and bladder cancer	NIEHS
Karagas, M	Dartmouth College, Hanover, New Hampshire	Epidemiology of arsenic and other toxic metals	NIEHS
Kochhar, TS	Kentucky State University, Frankfort, Kentucky	Induction of chromosome changes in mammalian cells	National Institute of General Medical Sciences
McCoy, Kathleen L	Virginia Commonwealth University, Richmond, Virginia	Gallium arsenide suppression of antigen processing	NIEHS
Nielsen FH, Hunt CD, Uthus EO	Agricultural Research Service, Grand Forks, North Dakota	Biochemical, physiological, and nutritional roles of certain ultratrace elements	USDA, Agricultural Research Service
Nielsen FH, Uthus EO, Hunt CD	Agricultural Research Service, Grand Forks, North Dakota	Biochemistry and metabolism of certain ultratrace elements	USDA, Agricultural Research Service
Pott, Wendy A	Colorado State University, Foothills Campus, Fort Collins, Colorado	Arsenic containing mixtures in angiosarcoma induction	National Cancer Institute
Pritsos CA	University of Nevada, Reno, Nevada	Environmental transformation, exposure and effects of pesticide residues	USDA, Cooperative State Research Svc
Ron, David	New York University Medical Center Skirball Institute Lab 9 New York, New York	Cellular response to nonmutagenic carcinogens	NIEHS
Shelburne, John D, M.D., Ph.D.	Department of Veterans Affairs, Medical Center, Durham, North Carolina	<i>In vitro</i> and <i>in vivo</i> effects of sodium arsenite and sodium arsenate on organelle function, and element composition of proximal tubules	Department of Veterans Affairs, Research and Development

## 2. HEALTH EFFECTS

**Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded (continued)**

Investigator	Affiliation	Title	Sponsor
Silver, S	University of Illinois at Chicago, Department of Microbiology and Immunology	Oxidation and reduction of arsenic oxyanions: a molecular genetics, biochemistry, and microbiological approach	USDOE Energy Research
Smith, Allan	University of California, Berkeley, California	Mutagenesis and carcinogenesis	NIEHS
Smith, Allan H	University of California, Berkeley, California	Bladder cancer case control study of arsenic in water	NIEHS
Smith, Allan H	University of California, Berkeley, California	Arsenic biomarker epidemiology	NIEHS
Smith, Allan H	University of California, Berkeley, California	A dose-response and susceptibility investigation of skin keratoses and hyperpigmentation due to ingestion of arsenic in drinking water	EPA
Smith, Karol R	Dartmouth College, Hanover, New Hampshire	As(iii) enhances AP 1 activity via c jun phosphorylation	NIEHS
Snow, Elizabeth T	New York University Medical Center, New York, New York	Arsenic-glutathione interactions and skin cancer	EPA
Styblo, Miroslav	University of North Carolina, Chapel Hill, North Carolina	Arsenicals, glutathione reductase and cellular redox status	EPA
Tannenbaum, Steven R	Massachusetts Institute of Technology, Cambridge, Massachusetts	Proteins and DNA—new methods of adduct detection	NIEHS
Taylor, PR	NCI, NIH	Biologic specimen bank for early lung cancer markers in Chinese tin miners	Division of Cancer Prevention and Control
Thilly, William G	Massachusetts Institute of Technology, Cambridge, Massachusetts	Human peripheral blood studies of mutations in the Aberjona region	NIEHS
Thilly, William G	Massachusetts Institute of Technology, Cambridge, Massachusetts	Human cell culture studies of mutagens in the Aberjona Basin	NIEHS

## 2. HEALTH EFFECTS

**Table 2-16. Ongoing Studies on Health Effects of Arsenic, Federally Funded (continued)**

Investigator	Affiliation	Title	Sponsor
Warrell, Raymond P, Jr	Sloan Kettering Institute Cancer Research, New York, New York	Arsenic trioxide in acute promyelocytic leukemia	National Cancer Institute
Yang, Raymond SH	Colorado State University, Fort Collins, Colorado	Toxicological interaction studies in chemical mixtures—pharmacokinetics	NIEHS

EPA = Environmental Protection Agency; NCI = National Cancer Institute; NIA = National Institute on Aging; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health; USDA = U.S. Department of Agriculture; USDOE = U.S. Department of Energy

## 2. HEALTH EFFECTS

**Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign, and Other Agency Funding\***

Investigator	Research description
Aposhian et al. 1989	Biodiversity of organic arsenite methyltransferases
Ayala-Fierro and Carter 1998	Arsenic vs arsenite toxicity in different cell types
Bajenova et al. 1998	Effects of the heavy metals chromium and arsenic on hormone-inducible expression of PEPCK/luciferase genetic constructs
Beck and Slayton 1998	Impact of arsenic (As <sub>3</sub> ) metabolism on human populations: Dose response relationships in arsenic-induced cancers
Bencko 1997	Contribution to neurotoxicity of arsenic in environmental settings
Brown and Kitchin 1998	Arsenic carcinogenesis: dimethylarsinic acid causes rat pulmonary DNA damage
Calleha et al. 1997	Arsenic trioxide induces apoptosis in K562 chronic myelogenous leukemia (CML) cells
Dai et al. 1997	Induction of apoptosis by the combined activity of arsenic trioxide (As <sub>2</sub> O <sub>3</sub> ) and ascorbic acid (AA) in (14;18) B-cell lymphoma
Das et al. 1997	Bio-anticlastogenic effects of mustard oil and garlic in the first-generation offspring of sodium arsenite treated mice
Del Razo et al. 1998	Impact of arsenic metabolism on human populations: Metabolism of arsenic and sensitivity to carcinogenesis in humans
Di Noto et al. 1997	<i>In vitro</i> treatment of APL cells with arsenic trioxide (As <sub>2</sub> O <sub>3</sub> ) results in a highly specific induction of solitary CD66c display
Fortoul et al. 1998	Ultrastructural changes in human lymphocytes challenged with sodium arsenite
Gabrilove et al. 1997	Effects of arsenicals in chronic leukemias
Gailer and Aposhian 1998	The detection of a novel arsenic-selenium compound
Gilani 1997	Teratogenicity of metals to chick embryos
Gonsebatt et al. 1996	Genotoxicity of arsenic exposure
Hamadeh et al. 1998	Arsenic species and gene activation in human lymphoblastoid cells
Harrington-Brock et al. 1998	Biological effects of arsenic exposure: <i>in vitro</i> and <i>in vivo</i>
He et al. 1997	Therapeutic trials with retinoic acid and arsenic trioxide (As <sub>2</sub> O <sub>3</sub> ) in PML-RAR $\alpha$ and ZF-RAR $\alpha$ transgenic mice as models of APL
Hu Yu and Snow 1998a	Effect of arsenic on DNA ligase activity in human cells in culture
Hu Yu and Snow 1998b	Arsenic-GSE interactions: modulation of cellular redox levels and signal transduction pathways
Huang et al. 1997	Potential of arsenic trioxide (As <sub>2</sub> O <sub>3</sub> ) induced apoptosis by retinoic acid (RA) in RA-sensitive (S) and RA-resistant (R) HL-60 myeloid leukemia cells

## 2. HEALTH EFFECTS

**Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign and Other Agency Funding\* (continued)**

Investigator	Research description
Hueges de Thé et al. 1997	Arsenic and retinoic acid: towards rational treatments of acute promyelocytic leukemia
Hunter and Dix 1996	Antisense oligonucleotides against <i>Hsp70-1</i> and <i>70-3</i> increase mouse embryonic sensitivity to arsenite-induced dysmorphogenesis <i>in vitro</i>
Ishitsuka et al. 1997	Arsenic acid as well as retinoic acids have therapeutic potential to adult T-cell leukemia
Kaltreider et al. 1998	Effects of the heavy metals arsenic and chromium on transcription factor binding and gene expression
Kato et al. 1997	Modulation of the stress-induced synthesis of stress proteins by reducing reagents: stimulation and suppression
Kinjo et al. 1997	Establishment of a retinoic acid resistant human APL model in hGM-CSF transgenic SCID mice and their application to the <i>in vivo</i> study of arsenic trioxide ( $As_2O_3$ )
Lehmann et al. 1997	Arsenic trioxide ( $As_2O_3$ ) induces apoptosis and cytotoxic effects in blast cells from patients with non-M3 AML
Li and Broome 1997a	Differential cytotoxicity of $As_2O_3$ and arsenic azoproteins on leukemic cells
Li and Broome 1997b	Apoptosis induced in promyelocytic leukemia cells by arsenic and proteasome inhibitors
Ma Jun et al. 1997	Clinical observation on arsenic trioxide in the treatment of acute promyelocytic leukemia
Mass 1998	Mechanisms of arsenic induced cancer: A role for hypermethylation
McDorman et al. 1998	Micronucleus analysis in mice chronically exposed to arsenic in drinking water
Menendez et al. 1998	Induction of p53 protein expression by sodium arsenite
Ostrosky-Wegman et al. 1998	Modulation of p53 function by arsenic and its role in cell cycle impairment
Peraza et al. 1998	Lack of dimethyl arsenic hepatotoxicity to 6-week old male Fischer 344 rats
Peters et al. 1998	Application of <i>in vitro</i> bioaccessibility test data to a public health risk assessment of arsenic-contaminated soils
Pott et al. 1998	Inhibitory effects of arsenic-containing mixtures in a multiple organ carcinogenicity bioassay
Rousselot et al. 1997	Arsenic trioxide ( $As_2O_3$ ) and Melarsoprol induce myeloma cell apoptosis <i>in vitro</i> with a preferential effect on tumoral cells in patients' bone marrow
Schoof and Evans 1998	Use of background arsenic exposure data to assess health significance of exposures to arsenic in soil
Shao et al. 1997	An APL subclone with a dominant negative PML/RARA mutation that resists retinoid degradation undergoes loss of PML-RARA protein and apoptosis in response to arsenic

## 2. HEALTH EFFECTS

**Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign and Other Agency Funding\* (continued)**

Investigator	Research description
Shipp et al. 1998	Application of the risk assessment approaches in EPA proposed cancer guidelines to arsenic
Smith et al. 1998	Evaluation of carcinogenic potential of chemical mixtures containing arsenic and volatile organics in SHE cells
Steinberg et al. 1997	Low dose chronic treatment of human keratinocytes with inorganic arsenic causes hyperproliferation and altered protein phosphorylation
Su et al. 1997	Arsenic is cytotoxic at micromolar concentration, but does not inhibit purified human DNA repair enzymes at less than millimolar concentrations
Susten et al. 1998	An integrated approach to estimating total arsenic exposure in humans
Swanson and Angle 1998	Increased cellular homocysteine (Hcy) as a mechanism for the proliferative responses of cobalamin (B12) dependent human fibroblasts to arsenic (As <sup>3+</sup> )
Thomas and Herbin-Davis 1998	Characteristics of the accumulation of arsenic (As) by arsenate (As <sup>v</sup> )-exposed rabbit erythrocytes
Tong and Xu 1998	Peripheral neuropathy, skin damage and liver abnormalities in miners with long-term exposure to arsenic
Trouba et al. 1998	Long-term modulation of mitogen activated protein kinase following sodium arsenite exposure
Turck et al. 1998	Assessment of the developmental toxicity of sodium monofluoroacetate (1080) in rats
Vargas et al. 1998	Activation of transcription factors by sodium arsenite in human lymphocytes
Vega 1996	Sodium arsenite effects on interleukin 2 secretion
Waalkes and Zhao 1998	The association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression
Wang et al. 1997	Arsenic trioxide and melarsoprol induce programmed cell death in myeloid leukemia cell lines and function in a PML and PML/RAR $\alpha$ independent manner
Westervelt et al. 1997	Response and toxicity associated with dose escalation of arsenic trioxide in the treatment of resistant acute promyelocytic leukemia
Wildfang et al. 1998	Hamster and rabbit arsenite and MMA methyltransferase kinetics: comparisons of <i>in vitro</i> properties
Xie et al. 1997	Melarsoprol and arsenic trioxide increase cell death on doxorubicin-resistant human leukemia and myeloma cells by regulating expression of BCL-2 apoptosis regulatory family
Yamauchi et al. 1998	Metabolism and biological monitoring of arsenic poisoning following chronic arsenic exposure in Inner Mongolia, China

## 2. HEALTH EFFECTS

**Table 2-17. Ongoing Studies on Health Effects of Arsenic with Industry, Foreign and Other Agency Funding\* (*continued*)**

Investigator	Research description
Zakharyan et al. 1998	Purification and properties of the arsenite methylating isoenzymes of rabbit liver
Zhao et al. 1998	Role of c-myc overexpression in arsenic-induced malignant transformation
Zheng et al. 1998	Molecular alterations in renal cortical slices following exposure to sub-toxic levels of arsenite

\* Research found in the open literature, not identified in the Federal Research in Progress database