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TOXICOLOGICAL PROFILE FOR ARSENIC

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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; 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.

Wulff et al. (1996) did not find an increase in the incidence of childhood cancer in children born to women living near a Swedish smelter plant, suggesting that maternal, perinatal, and childhood exposure to airborne arsenic does not increase the risk of cancer during childhood.

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 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 which 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

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Human	1 wk (W)				2 (death of 2/8)	Armstrong et al. 1984 NS
2	Human	once (IN)				121 M (death)	Civantos et al. 1995 As(+5)
3	Human	once (IN)				22 M (death)	Levin-Scherz et al. 1987 As(+3)
4	Human	once (IN)				93 M (1/1 died)	Quatrehomme et al. 1992 As(+3)
5	Rat (Sprague-Dawley)	2x (NS)				24 F (33% death)	Brown and Kitchin 1996 As(+3)
6	Rat	once (GW)				75 (LD50)	Dieke and Richter 1946 As(+3)
7	Rat (Sherman)	once (GW)				44 F (LD50)	Gaines 1960 As(+3)
8	Rat (Sherman)	once (GW)				112 F (LD50)	Gaines 1960 As(+5)

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
9	Rat (Sprague-Dawley)	once (GW)				15.1 M (LD50)	Harrisson et al. 1958 As(+3)
10	Mouse (Swiss-Webster)	once (GW)				39 M (LD50)	Harrisson et al. 1958 As(+3)
11	Mouse (NS)	once (GW)				26 M (LD50)	Kaise et al. 1985 As(+3)
	Systemic						
12	Human	1 wk (W)	Gastro		1 (throat irritation, nausea, vomiting, diarrhea, abdominal pain)	-	Armstrong et al. 1984 NS
			Hemato			1 (anemia, leukopenia)	
			Hepatic			1 (hepatitis, elevated serum transaminase levels)	
			Renal			1 (proteinuria, elevated serum creatine)	
			Ocular		1 (periorbital swelling)		
13	Human	once (IN)	Resp			121 M (respriatory distress, severe difussed bilateral alveolar hemmorhage and lung edema)	Civantos et al. 1995 As(+5)
			Cardio			121 M (cardiac arrest, hypotension, refractory ventricular fibrillation)	
			Gastro			121 M (ulceration of upper gastrointestinal tract, abdominal tenderness)	

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
14	Human	once (IN)	Cardio			~~0.02~~ 20 F (sinus tachycardia)	Cullen et al. 1995 As (+5)
			Gastro		~~0.02~~ 20 F (vomiting, diarrhea)		
			Hemato	0.02 F			
			Hepatic	0.02 F			
			Renal	0.02 F			
15	Human	once (NS)	Resp			8 M (hemorrhagic bronchitis)	Fincher and Koerker 1987 As(+3)
			Gastro			8 M (gastrointestinal bleeding)	
			Hemato			8 M (hemolysis)	
			Renal			8 M (acute renal failure)	
16	Human	once (IN)	Resp			93 M (pulmonary edema)	Quatrehomme et al. 1992 As(+3)
			Cardio		93M (wall of left ventricle slighly hypertrophic)		
			Gastro			93 M (ulcero-necrotico-hemorrhagic gastritis; pan-parietal necrosis in the stomach)	
			Hepatic			93 M (hepatic steatosis, hepatomegaly)	
			Renal			93 M (glomerular congestion in kidneys)	
			Dermal			93 M (dermoepidermic separation at autopsy)	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
17	Monkey (Rhesus)	13 d (IN)	Gastro	2.8	5.7 (vomiting, nausea)		Heywood and Sortwell 1979 As(+5)
			Hemato	5.7			
			Hepatic	2.8	5.7 (distinct vacuolation of the hepatocytes with decreased glycogen)		
			Renal	2.8	5.7 (dilation of proximal tubules)		
	Immunological/Lymphoreticular						
18	Human	once (IN)			93M (spleen congestion at autopsy)		Quatrehomme et al. 1992 As(+3)
	Neurological						
19	Human	1 wk (W)				1 (encephalopathy, peripheral neuropathy)	Armstrong et al. 1984 NS
20	Human	once (IN)				121 M (brain edema, confusion)	Civantos et al. 1995 As(+5)
21	Human	once (IN)			~~0.02~~ 20 F (lethargy)		Cullen et al. 1995 As (+5)
22	Human	once (NS)				8 M (encephalopathy)	Fincher and Koerker 1987 As(+3)
23	Human	once (IN)				93 M (encephalopathy)	Quatrehomme et al. 1992 As(+3)

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
24	Monkey (Rhesus)	13 d (IN)		2.8 M	7.5 M (uncontrolled head shaking, salivation) 2.8 F (unnatural posture of arm)		Heywood and Sortwell 1979 As(+5)
	Developmental						
25	Mouse (CD-1)	once (GW)		11		23 (teratogenicity, fetal mortality)	Baxley et al. 1981 As(+3)
26	Mouse (CD-1)	Gd 7, 8, 9, 10, 11, 12, 13, 14, or 15 (GW)			69 (decreased fetal body weights)		Hood et al. 1978 As(+3)
27	Hamster (Lak:LVG [SYR])	once (GW)				14 (prenatal mortality)	Hood and Harrison 1982 As(+3)
	Cancer						
28	Human	2 wk-12 yr (IN)				3.67 (CEL: bladder cancer risk)	Cuzick et al.1992 As(+3)
	INTERMEDIATE EXPOSURE						
	Systemic						
29	Human	and 1 time 1-2 mo (W)	Hemato			0.06 ~~0.29~~ (anemia, leukopenia)	Franzblau and Lilis 1989 NS
			Gastro		.06 ~~[illegible]~~ (0.04-~~[illegible]~~)	~~0.29~~ 0.06 (severe gastrointestinal irritation, diarrhea)	
			Dermal		~~0.29~~ (hyperkeratosis)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
30	Human	0.5-15 yr (W)	Gastro		0.05 (abdominal pain)		Huang et al. 1985 NS
			Hemato	0.05			
			Hepatic	0.05			
			Dermal		0.05 (pigmentation changes, hyperkeratosis)		
31	Human	2-3 wk (F)	Resp		0.05 (sore throat and upper respiratory symptoms)		Mizuta et al. 1956 NS
			Cardio			0.05 (abnormal electrocardiogram)	
			Gastro			0.05 (nausea, vomiting, diarrhea, gastrointestinal bleeding)	
			Hemato		0.05 (mild anemia)		
			Hepatic		0.05 (mild hepatomegaly)		
			Renal	0.05			
			Dermal		0.05 (itching, desquamation, exanthema)		
			Ocular		0.05 (conjunctivitis, edema of eyelids)		
			Metab		0.05 (fever, chills)		
32	Human	4 mo (W)	Gastro	0.06	~~0.045~~ F (nausea, vomiting, diarrhea)		~~Wagner et al. 1979 NS~~
			Hemato	0.06	~~0.045~~ F (erythroid hyperplasia of bone marrow; moderately hypochromic RBCs)		
			Dermal	0.06	~~0.045~~ F (hyperkeratosis of palms and soles)		
			Bd Wt			~~0.45~~ 0.06 F (31% decreased body weight)	
			Metab	0.06	~~0.45~~ F (increased body temperature)		

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
33	Monkey (Rhesus)	28 d (IN)	Resp			2.8 (*bronchopneumonia with* hemorrhagic edema and necrosis)	*Heywood and* Sortwell 1979 As(+5)
			Gastro	2.8	5.7 M (inflammation of small intestine)		
				2.8	5.7 F (moderate regression of thymus)		
34	Rat (Wistar-Barby)	2-4 wk 5 d/wk 1x/d (GW)	Cardio	2.3 F	11 F (decrease in vasoreactivity)		Bekemeier and Hirschelmann 1989 As(+3)
35	Rat (Sprague-Dawley)	6 wk (W)	Renal		4.7 M (increased organ weight, impaired mitochondrial respiration)		Brown et al. 1976 As(+5)
36	Mouse (B6C3F1)	32 or 91 d ad lib (W)	Resp	0.0065 M	0.75 M (11% increase lung weight after 32 d)		Healy et al. 1998 As(+3)
			Hepatic		0.0085 M (20% decreased liver weight after 91 d)		
			Renal		0.0085 M (13% decreased kidney weight after 91 d)		
			Bd Wt	0.87 M			
37	Dog (Beagle)	183 d ad lib (F)	Hepatic	0.03 F	1.73 F (increased aspartate aminotransferase and alanine aminotransferase)		Neiger and Osweiler 1989 As(+3)
			Other	0.03 F	1.04 F (decreased food consumption)		
	Immunological/Lymphoreticular						
38	Monkey (Rhesus)	28 d (IN)		2.8	5.7 F (moderate regression of thymus)		Heywood and Sortwell 1979 As(+5)

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
39	Mouse	10-12 wk (W)		20 M			Kerkuleit et al. 1980 As(+5)
	Neurological						
40	Human	~~1-2 mo~~ 1-2 mo. + 1 time continuous (W)				~~0.29~~ 0.06 (0.04-0.08) (paresthesia of hands and feet; confusion, disorientation and mental sluggishness)	Franzblau and Lilis 1989 NS
41	Human	0.5-15 yr (W)				0.05 (amnesia, mild peripheral neuropathy)	Huang et al. 1985 NS
42	Human	2-3 wk (F)			0.05 (hypesthesia in legs)		Mizuta et al. 1956 NS
43	Human	4 mo (W)				~~0.045 F~~ (weakness, paresthesia)	~~Wagner et al. 1979~~ NS
	Reproductive						
44	Mouse (B6C3F1)	32 or 91 d ad lib (W)			0.0085 M (8% decreased testes weight)		Healy et al. 1998 As(+3)
45	Mouse (CD)	3 gen (W)		1.2			Schroeder and Mitchener 1971 As(+3)
	Developmental						
46	Mouse	3 gen (W)			1.2 (decreased pups per litter)		Schroeder and Mitchener 1971 As(+3)

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Cancer						
47	Human	1-3 mo (IN)				0.08 (CEL: skin, internal)	Reymann et al. 1978 As(+3)
48	Human	4 mo (W)				~~0.045 F~~ (CEL: squamous and basal cell carcinomas of the skin)	~~Wagner et al. 1979 NS~~
49	Rat	175 d (W)				8.5 M (CEL: renal tumors)	Shirachi et al. 1983 As(+3)
	CHRONIC EXPOSURE						
	Death						
50	Human	~5 yr (W)				1 (increased deaths)	Tsuda et al. 1995 As(+3)
51	Human	12 yr (W)				0.24 (males:4/208 died; females: 1/249 died)	Zaldivar 1974 NS
52	Human	1-39 yr (W)				0.13 (death in 5/337)	Zaldivar and Guillier 1977 NS
53	Monkey (Rhesus)	1 yr (IN)				2.8 (2/7 died)	Heywood and Sortwell 1979 As(+5)
54	Dog (Beagle)	2 yr (F)				3.1 (death in 6/6 given As+3; death in 1/6 given As+5)	Byron et al. 1967 As(+3) As(+5)

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
55	Human	4 yr (IN)	Dermal		0.1 F (hyperkeratosis)		Bickley and Papa 1989 As(+3)
56	Human	12 yr (W)	Cardio			0.02 (Raynaud's disease)	Borgono and Greiber 1972 NS
			Gastro		0.02 (diarrhea, abdominal pain)		
			Dermal		0.02 (abnormal pigmentation)		
57	Human	11-15 yr (W)	Dermal		0.01 (hypo- and hyperpigmentation hyperkeratosis)		Borgono et al. 1980 NS
58	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, hyperkeratosis)		
59	Human	1-11 yr (W)	Hepatic		0.02 (hepatomegaly)		Chakraborty and Saha 1987 NS
			Dermal		0.02 (melanosis, keratosis)		
60	Human	continuous (W)	Cardio			0.064 (Blackfoot disease)	Chen et al. 1988b NS
61	Human	3-7 yr (W)	Cardio			~~0.11~~ (Black~~foot~~ Disease)	Foy et al. 1992 NS
			Dermal		~~0.0008~~ (hyperkeratosis, hyperpigmentation)	0.11 hyperkeratosis hyperpigmentation	

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
62	Human	2-6 yr (IN)	Hepatic			0.08 M (cirrhosis, ascites)	Franklin et al. 1950 As(+3)
			Dermal		0.08 M (hyperpigmentation, hyperkeratosis)		
63	Human	10 yr (W)	Gastro	0.003			Harrington et al. 1978 NS
			Hemato	0.003			
			Dermal	0.003			
64	Human	0.5-15 yr (W)	Gastro		0.05 (abdominal pain)		Huang et al. 1985 NS
			Hemato	0.05			
			Hepatic	0.05			
			Dermal		0.05 (pigmentation changes, hyperkeratosis)		
65	Human	15 yr (IN)	Gastro			0.030 M (hematemesis, hemoperitoneum, melena)	Lander et al. 1975 As(+3)
			Dermal		0.03 M (hyperkeratosis)		
66	Human	once (IN)	Gastro		0.39 F (abdominal pain, vomiting)		Lugo et al. 1969 As(+3)
			Hemato	0.39 F			
			Renal		0.39 F (elevated BUN, diminished urine output)	0.39 F (acute renal failure)	
			Other		0.39 F (dehydration)		
67	Human	NS (W)	Hepatic		0.006 (hepatomegaly)		Mazumder et al. 1988 NS
			Dermal	0.0009	0.006 (pigmentation changes, hyperkeratosis)		

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
68	Human	1-20 yr (W)	Cardio	0.06			Mazumder et al. 1988 NS
			Gastro		0.007 M (abdominal pain) 0.03 F		
			Hemato		0.007 M (anemia) 0.03 F		
			Hepatic		0.007 M (hepatomegaly, fibrosis) 0.03 F		
			Dermal		0.007 M (hyperpigmentation, 0.03 F hyperkeratosis)		
69	Human	3-22 yr (IN)	Gastro			0.05 M (gastrointestinal hemorrhages)	Morris et al. 1974 As(+3)
			Hepatic			0.05 M (vascular fibrosis, portal hypertension)	
			Dermal		0.05 M (hyperpigmentation, keratoses)		
70	Human	15 yr (IN)	Hepatic			0.05 F (central fibrosis)	Piontek et al. 1989 As(+3)
			Dermal		0.05 F (hyperkeratosis)		

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
71	Human	12 yr (W)	Resp			0.02 (arterial thickening; interstitial fibrosis; bronchitis with slight bronchiectasis; desquamative interstitial pneumonia)	Rosenberg 1974 NS
			Cardio			0.02 (arterial thickening; increased heart weight)	
			Gastro			0.02 (arterial thickening in stomach and intestines)	
			Hepatic			0.02 (arterial thickening; cirrhotic changes in 1/5; incr. liver wt. in 2/5)	
			Renal			0.02 (arterial thickening)	
			Endocr			0.02 (arterial thickening in pancreas)	
			Dermal		0.02 (pigment derangements, hyperkeratosis and adnexal changes)		
72	Human	2-3 yr (IN)	Cardio	0.086 F			Silver and Wainman 1952 As(+3)
			Gastro		0.086 F (nausea, cramps, diarrhea)		
			Hemato	0.086 F			
			Hepatic		0.086 F (hepatomegaly, fatty liver)		
			Renal	0.086 F			
			Dermal		0.086 F (hyperkeratosis, hyperpigmentation, melanosis)		
			Ocular		0.086 F (conjunctival injection, periocular edema)		

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
73	Human	≥ 5 yr (W)	Hemato	0.006 M 0.007 F			Southwick et al. 1981 NS
			Dermal	0.0009 M 0.001 F			
74	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 (hyperkeratosis, hyperpigmentation, hypopigmentation, warts)		
75	Human	45 yr (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1977 NS
76	Human	NS (W)	Cardio			0.014 (Blackfoot disease)	Tseng 1989 NS
77	Human	≥ 45 yr (W)	Dermal	0.0008[b] M	0.014 M (hyperkeratosis and hyperpigmentation)		Tseng et al. 1968 NS
78	Human	≥ 30 yr (W)	Cardio		0.024 M (deficits in cutaneous microcirculation of the toes)		Tseng et al. 1995 As(+3)
79	Human	NS (W)	Gastro	0.01			Valentine et al. 1985 NS
			Dermal	0.01			

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
80	Human	16 mo (IN)	Resp	0.1 M			Wade and Frazer 1953 As(+3)
			Cardio	0.1 M			
			Hemato	0.1 M			
			Hepatic		0.1 M (hepatomegaly)		
			Dermal		0.1 M (hyperkeratosis, hyperpigmentation)		
81	Human	12 yr (W)	Resp		0.019 M (bronchitis; bronchiectasis) 0.022 F		Zaldivar 1974 NS
			Cardio			0.019 M (Raynaud's disease, thrombosis) 0.022 F	
			Gastro		0.019 M (diarrhea) 0.022 F		
			Dermal		0.019 M (scaling of skin, hyperkeratosis, leukoderma, melanoderma) 0.022 F		
			Bd Wt		0.019 M (unspecified decreased body weight) 0.022 F		
82	Human	30-33 yr (W)	Dermal		0.019 M (hyperkeratosis of the sole)		Zaldivar 1974 NS

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
83	Human	2-7 yr (W)	Resp			0.024 (inflammation of bronchi and larynx)	Zaldivar 1974 NS
			Cardio			0.024 M (cardiac failure, arterial hypotension, ischemia, vascular spasms, myocardial necrosis, thrombosis)	
			Gastro		0.024 M (chronic diarrhea)		
			Hepatic			0.024 M (cirrhosis, hepatomegaly)	
			Renal		0.024 M (occlusive arterial lesions in kidney, cloudy swelling in kidneys)		
			Dermal		0.024 M (hyperkeratosis of palms and soles, melanoderma, leukoderma)		
84	Human	NS (W)	Dermal		0.0633 (hyperpigmentation, keratoses in children)		Zaldivar 1977 NS
85	Human	1-39 yr (W)	Cardio			0.06 (arterial thickening, Raynaud's disease)	Zaldivar and Guillier 1977 NS

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
86	Rat (Osborne-Mendel)	2 yr (F)	Resp	12.5			Byron et al. 1967 As(+3) As(+5)
			Cardio	12.5			
			Gastro	12.5			
			Hemato	12.5 M 6.3 F	20 M (slight incr. in leucoyte) 12.5 F (slight decr. in Hgb and HCT values)		
			Hepatic	3.1	6.3 (enlargement of the bile duct)		
			Renal	12.5			
			Bd Wt	6.3 M 3.1 F	12.5 M (14.9% decreased mean body weights in arsenate) 6.3 F (18.8% decreased mean body weights in arsenite)	12.5 M (41% decreased mean body weight in arsenite)	
87	Rat	1 yr (F)	Hemato	20 F			Kroes et al. 1974 As(+5)
88	Rat (Long- Evans)	approx. 3-3.4 yr (W)	Cardio	0.07 F	0.6 M (15% decr. relative heart weight)		Schroeder et al. 1968 As(+3)
			Hemato		0.06 (incr. mean serum cholesterol in males; decr. fasting serum glucose in males and females)		
			Renal	0.7			
			Bd Wt	0.7			
89	Mouse	2 yr (W)	Resp	1			Schroeder and Balassa 1967 As(+3)
			Cardio	1			
			Hepatic	1			
			Renal	1			

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
90	Dog (Beagle)	2 yr (F)	Resp	1.25			Byron et al. 1967 As(+3) As(+5)
			Cardio	1.25			
			Gastro	1.25			
			Hemato	1.25			
			Hepatic	1.25			
			Renal	1.25			
			Bd Wt	1.25			
	Immunological/Lymphoreticular						
91	Human	1-11 yr (W)			0.020 (spleen palpable in 3%)		Chakraborty and Saha 1987 NS
92	Human	12 yr (W)				0.02 (arterial thickening in spleen)	Rosenberg 1974 NS
93	Human	2-7 yr (W)			0.024 M (splenomegaly)		Zaldivar 1974 NS
	Neurological						
94	Human	3-7 yr (W)		0.0008		0.11 F (weakness, learning impairment, anorexia)	Foy et al. 1992 NS
95	Human	10 yr (W)		0.003			Harrington et al. 1978 NS
96	Human	continuous (W)		0.0007	0.019 (electromyographic abnormalities)	0.04 (functional denervation)	Hindmarsh et al. 1977 NS

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
97	Human	0.5-15 yr (W)				0.05 (amnesia, mild peripheral neuropathy)	Huang et al. 1985 NS
98	Human	1-20 yr (W)			0.007 M 0.03 F (Tingling of hands and feet)		Mazumder et al. 1988 NS
99	Human	2-3 yr (IN)				0.086 F (paresthesia)	Silver and Wainman 1952 As(+3)
100	Human	≥ 5 yr (W)		0.006 M 0.007 F			Southwick et al. 1981 NS
101	Human	55 yr (IN)			0.03 M (absent ankle jerk reflex and vibration sense in legs)		Szuler et al. 1979 As(+3)
102	Human	NS (W)		0.01			Valentine et al. 1985 NS
103	Human	12 yr (W)			0.019 M 0.022 F (anorexia, general debility)		Zaldivar 1974 NS
104	Human	2-7 yr (W)			0.024 F (thrombosis of brain arteries)		Zaldivar 1974 NS
105	Monkey (Rhesus)	1 yr (IN)		2.8			Heywood and Sortwell 1979 As(+5)
106	Dog (Beagle)	2 yr (F)		1.25	3.1 (listlessness, anorexia)		Byron et al. 1967 As(+3) As(+5)

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

Key to[a] figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
Developmental							
107	Human	once (IN)				0.39 F (immaturity, generalized petechial hemorrhages, hyaline membrane disease; death)	Lugo et al. 1969 As(+3) ✓
Cancer							
108	Human	1-11 yr (W)				0.02 (CEL: squamous cells carcinoma of the skin)	Chakraborty and Saha 1987 NS
109	Human	continuous (W)				0.064 (CEL: bladder, lung and liver cancers)	Chen et al. 1986 NS
110	Human	continuous (W)				0.064 (CEL: malignant neoplasms of the bladder, skin, lung and liver)	Chen et al. 1988b NS
111	Human	>10 yr (W)				0.001 (CEL: liver, lung, bladder and kidney cancer risk)	Chen et al. 1992 NS ✓
112	Human	2 wk-12 yr (IN)				3.67 (CEL: bladder cancer risk)	Cuzick et al.1992 As(+3)
113	Human	NS (W)				0.0192 (CEL: increased incidence of transitional cell carcinomas of the bladder, kidney, & ureters and all urethral cancer)	Guo et al. 1997 NS
114	Human	>1 yr (W)				0.0014 (CEL: basal or squamous skin carcinoma, breast cancer)	Haupert et al. 1996 NS ✓

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
123	Human	14-23 yr (W)				0.009 M (CEL: basal cell and squamous cell carcinomas of the skin)	Zaldivar et al. 1981 NS

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

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
115	Human	15 yr (IN)				0.030 M (CEL: hepatic angiosarcoma, angiosarcoma of the skin)	Lander et al. 1975 As(+3)
116	Human	16 yr (ave) (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)
117	Human	3-22 yr (IN)				0.05 M (CEL: skin tumors, carcinomal of the larynx, bronchialcarcinoma)	Morris et al. 1974 As(+3)
118	Human	60 yr continuous (W)				0.038 (CEL: intraepidermal carcinoma)	Tseng 1977 NS
119	Human	≥ 45 yr (W)				0.014 (CEL: squamous cell carcinoma of the skin)	Tseng et al. 1968 NS
120	Human	~5 yr (W)				1 (CEL: lung, urinary cancer)	Tsuda et al. 1995 As(+3)
121	Human	12 yr (W)				0.019 M (CEL: squamous cell carcinoma of the skin) 0.022 F (CEL: squamous cell carcinoma of the skin)	Zaldivar 1974 NS
122	Human	30-33 yr (W)				0.019 M (CEL: squamous cell carcinoma)	Zaldivar 1974 NS

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

Acute (≤14 days)

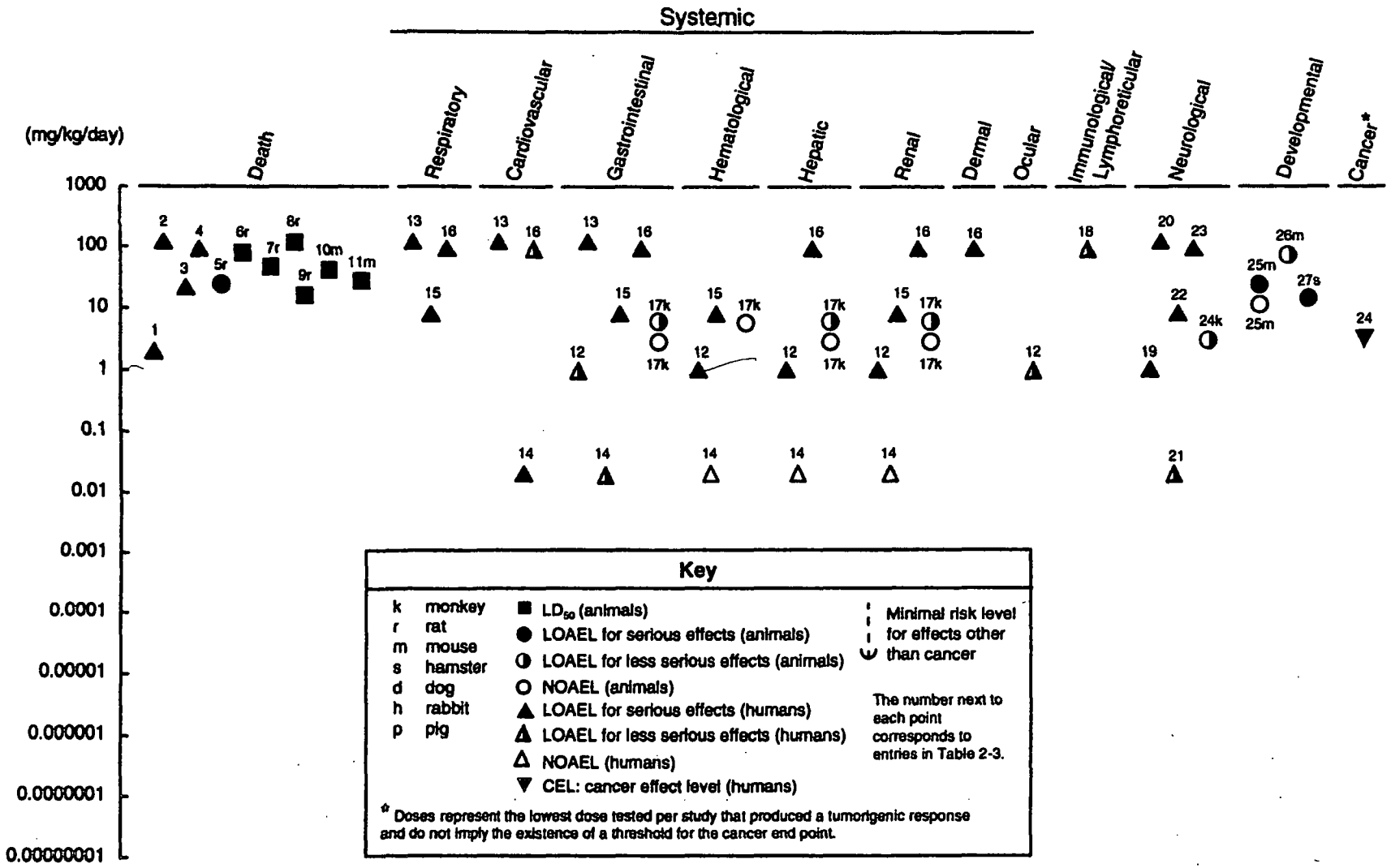

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Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (cont.)

Intermediate (15-364 days)

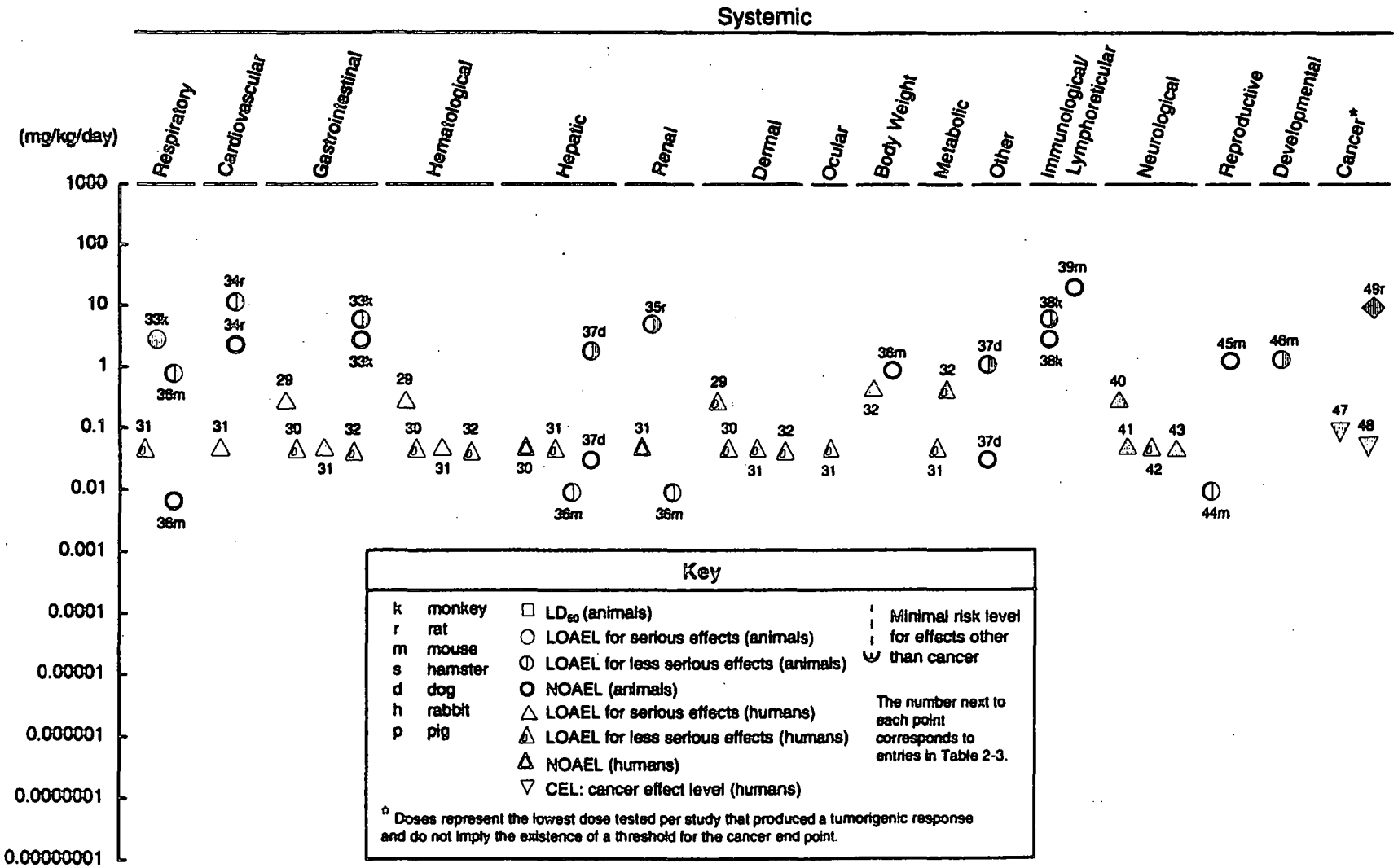

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Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (cont.)

Chronic (≥365 days)

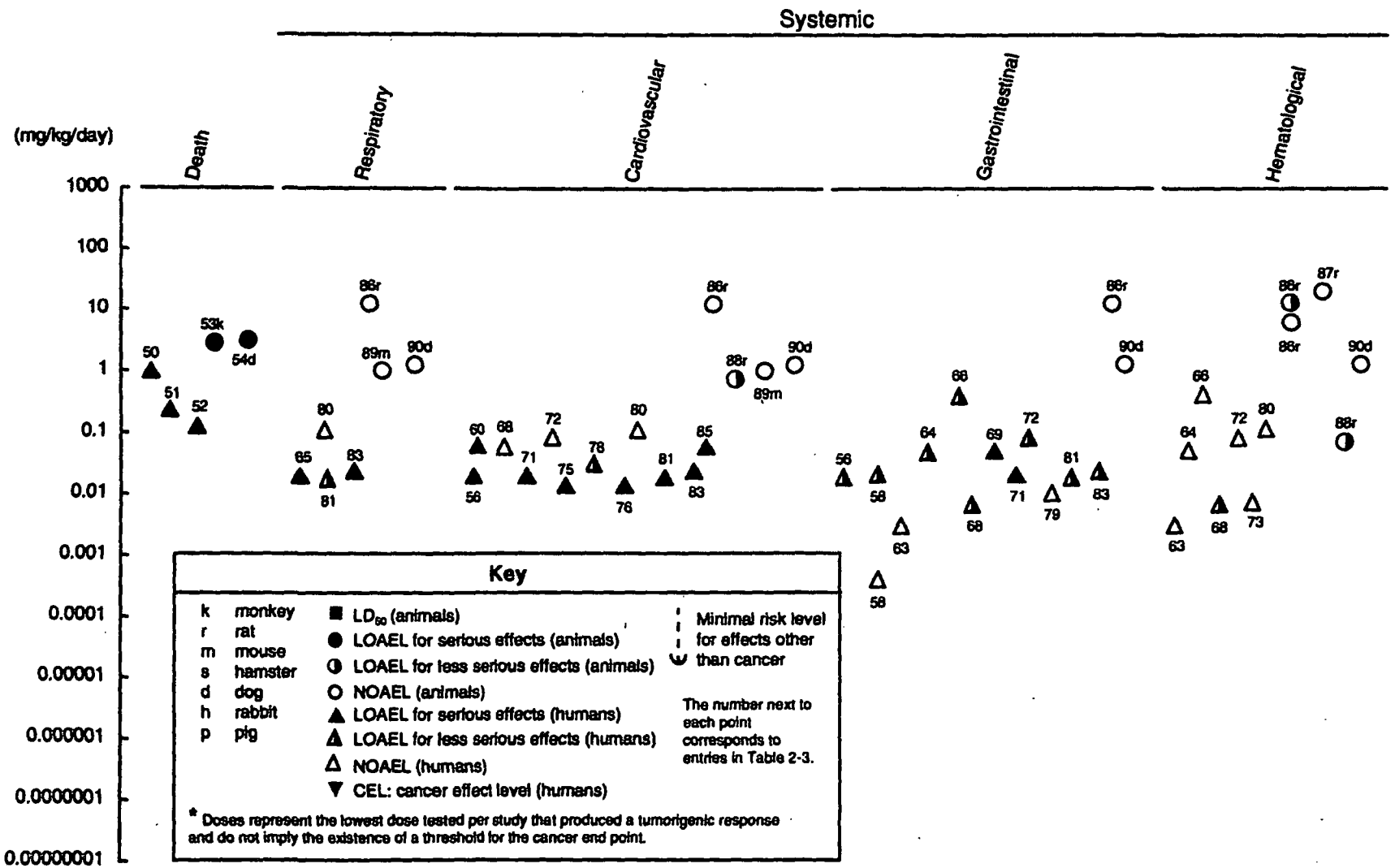

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Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (cont.)

Chronic (≥365 days)

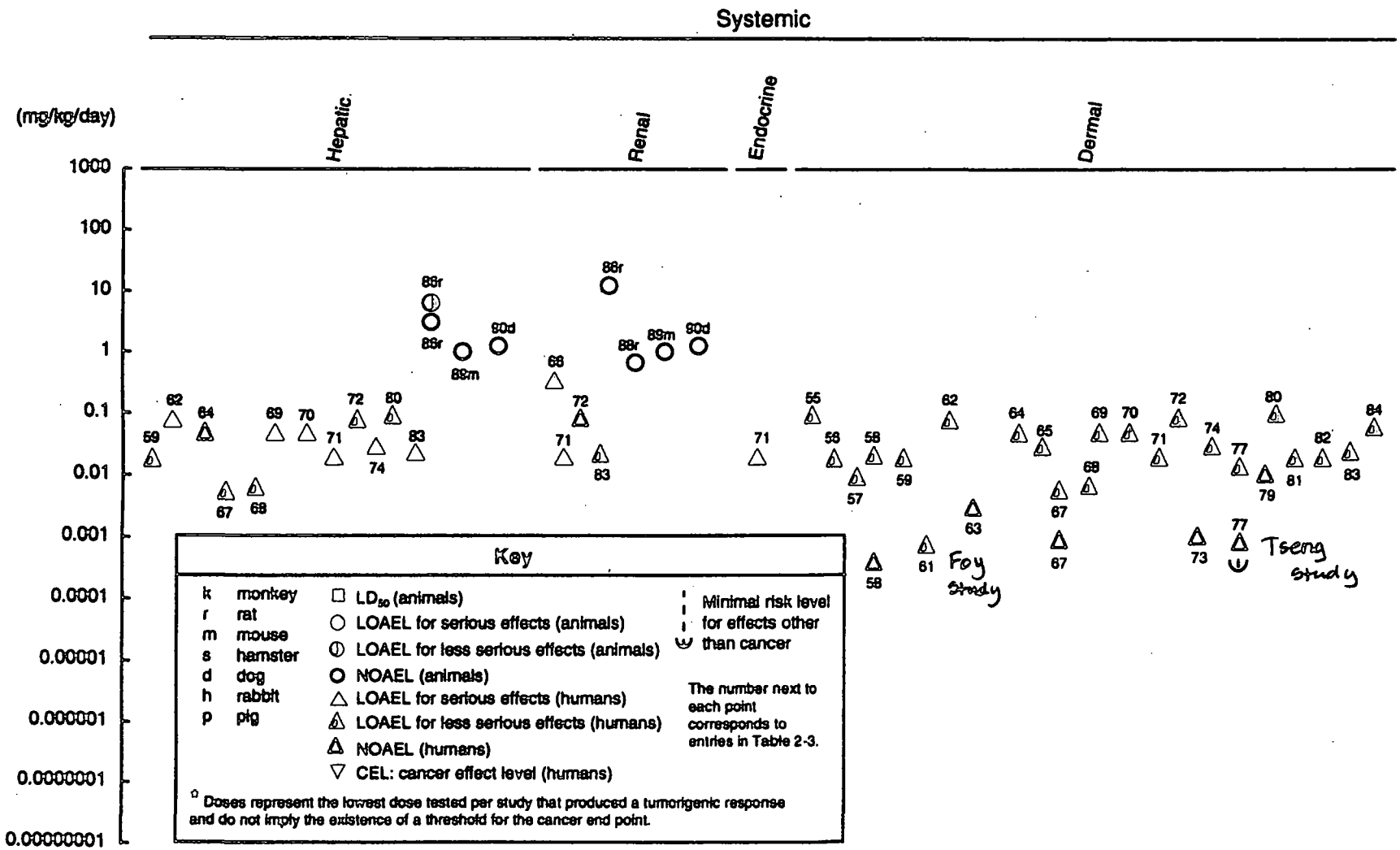

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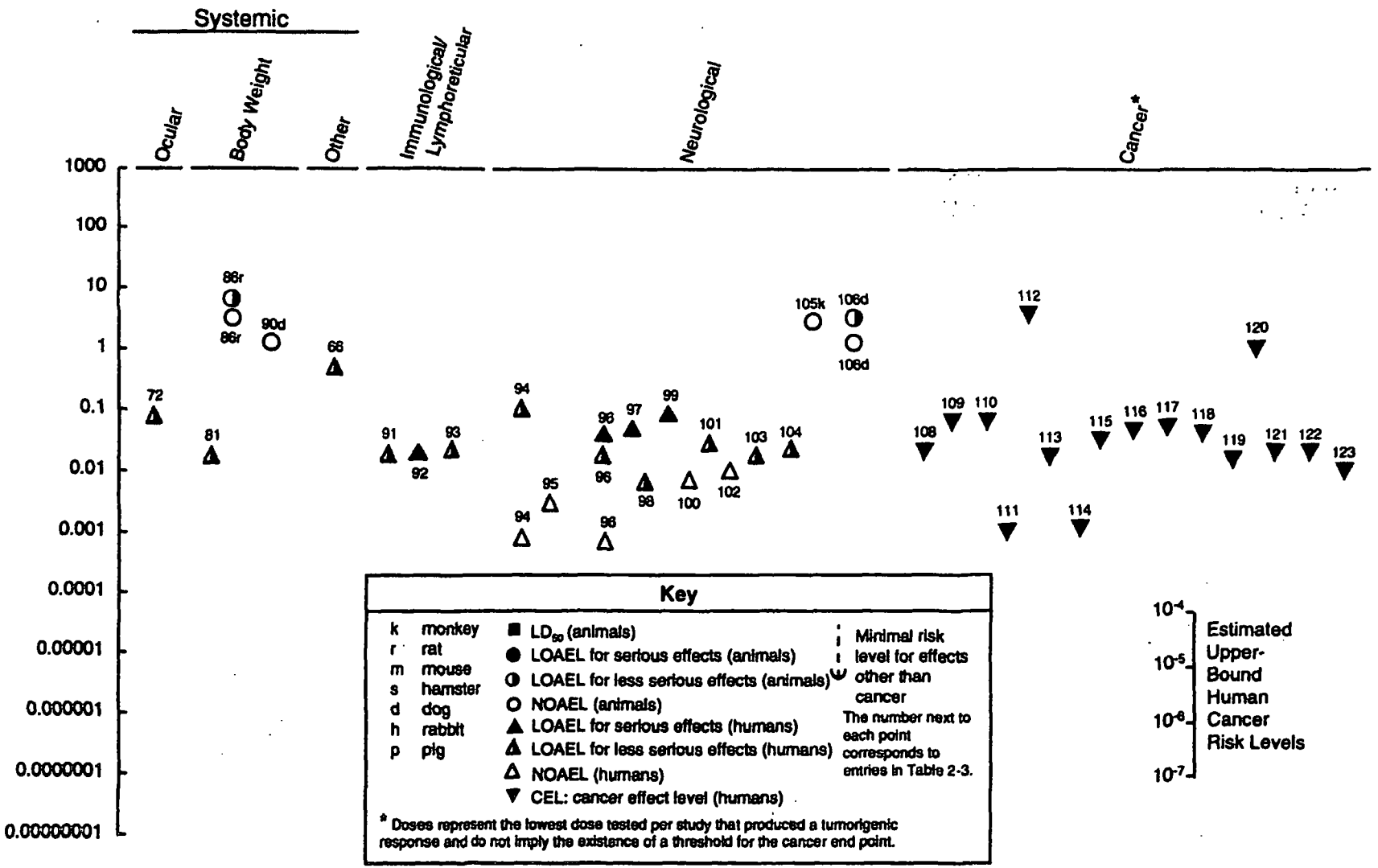
Figure 2-3. Levels of Significant Exposure to Inorganic Arsenic - Oral (cont.)

Chronic (≥365 days)



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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 contain both gastrointestinal effects soon after ingestion, with 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. Two people in a family of 8 died from ingestion of water containing about 110 ppm of arsenic (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). Chronic ingestion of drinking water at doses of 0.13–1 mg As/kg/day for up to 39 years has been associated with increased mortality (Tsuda et al. 1995; Zaldivar 1974; Zaldivar and Guillier 1977).

Lethal doses in animals are somewhat higher than the estimated lethal dose in humans. For example, acute LD_{50} values for arsenate and arsenite in rats and mice range from 15 to 112 mg As/kg (Dieke and Richter 1946; Gaines 1960; Harrisson et al. 1958; Kaise et al. 1985). Most deaths occurred within 1 day of exposure, but no details on the cause of death were reported. Data on lethality from repeated exposures are sparse, but average chronic exposures of about 3 mg As/kg/day as arsenate or arsenite have been noted to cause death in dogs (Byron et al. 1967) and monkeys (Heywood and Sortwell 1979).

Reliable LOAEL and LD_{50} 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 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 NOAEL 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

Ingestion of arsenic by humans is usually not associated with serious injury to the respiratory system, although pulmonary edema and hemorrhagic bronchitis may occur in moderate to severe cases (e.g., Campbell and Alvarez 1989; Fincher and Koerker 1987; Quatrehomme et al. 1992). It is possible that this is primarily a secondary effect due to injury to the pulmonary vasculature (see Cardiovascular Effects, below), although there are no studies specifically on this point. Acute accidental ingestion of 43.3 mg/kg arsenic (as arsenic trioxide) was associated with shortness of breath and decreased oxygen saturation (Moore et al. 1994). Intermediate exposure of 2–3 weeks to 0.05 mg As/kg/day in soy sauce caused sore throat and upper respiratory tract symptoms (Mizuta et al. 1956). Chronic exposure to 0.02 mg As/kg/day in drinking water for up to 12 years has been associated with arterial thickening, interstitial fibrosis, bronchitis, bronchiectasis and pneumonia, and inflammation of the bronchi and larynx (Rosenberg 1974; Zaldivar 1974).

No respiratory effects have been reported in animals after acute oral exposure to inorganic arsenic. However, rhesus monkeys exhibited bronchopneumonia with hemorrhagic edema and necrosis after ingesting 2.8 mg As/kg/day for 28 days (Heywood and Sortwell 1979). Mice given 0.75 mg As/kg/day in drinking water for 32 days exhibited an 11% increase in lung weight, suggesting edema, although no histopathology was performed (Healy et al. 1998). No respiratory effects were noted in dogs or rats or mice after chronic oral exposure to arsenate or arsenite (Byron et al. 1967; Schroeder et al. 1968).

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). 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). Several researchers have presented evidence that other factors besides arsenic (e.g., other water contaminants, dietary deficits) may play a role in the etiology of

this disease (Ko 1986; Lu et al. 1990; Yu et al. 1984). While this may be true, the clear association between the occurrence of Blackfoot disease and the intake of elevated arsenic levels indicates that arsenic is at least a contributing factor. Moreover, effects of arsenic on the vascular system have also been reported in a number of other populations. For example, 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). 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 (Mazumder et al. 1988; Silver and Wainman 1952). 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, mice or dogs exposed to up to 20 mg/kg/day As arsenate or arsenite for 2 years (Byron et al. 1967; Schroeder and Balassa 1967; Schroeder et al. 1968).

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 arsenic (e.g., Armstrong et al.

1984; Campbell and Alvarez 1989; Cullen et al. 1995; Fincher and Koerker 1987; Franzblau and Lilis 1989; 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; Haupert et al. 1996; Holland 1904; Huang et al. 1985; Mazumder et al. 1988; Mizuta et al. 1956; Nagai et al. 1956; Silver and Wainman 1952; Wagner et al. 1979; Zaldivar 1974), but effects are usually not detectable at exposure levels below about 0.01 mg As/kg/day (Harrington et al. 1978; Valentine et al. 1985). These symptoms generally decline within a short time after exposure ceases. More severe symptoms (hematemesis, hemoperitoneum, gastrointestinal hemorrhage and necrosis) have been associated with extremely high acute ingestion (93 mg As/kg) or with chronic ingestion of 0.03–0.05 mg As/kg as a medicinal preparation (Lander et al. 1975; Morris et al. 1974; Quatrehomme et al. 1992). Similar signs of gastrointestinal irritation have been observed in studies in monkeys given a complex arsenate salt for 2 weeks, and inflammation of the small intestine was observed after treatment for 4 weeks (Heywood and Sortwell 1979), although no histological evidence of gastrointestinal injury was detected in rats or dogs exposed to arsenate or arsenite for 2 years at doses up to 20 or 3 mg As/kg/day, respectively (Byron et al. 1967).

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). 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), intermediate (Franzblau and Lilis 1989; Goldsmith and From 1986; Heyman et al. 1956; Mizuta et al. 1956; Westhoff et al. 1975), and chronic oral exposures (Glazener et al. 1968; Kyle and Pease 1965; Nagai et al. 1956; Tay and Seah 1975) at 1, 0.05, or 0.03 mg/kg/day As, respectively. 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). Hematological effects are usually not observed in humans exposed to levels of 0.07 mg As/kg/day or less (Cullen et al. 1995; Harrington et al. 1978; Huang et al. 1985; Silver and Wainman 1952; Southwick et al. 1981), although intermediate-duration exposure to 0.045–0.05 mg/kg/day resulted in mild anemia in one study (Mizuta et al. 1956) and evidence of enhanced erythropoiesis (presumably in response to anemia) in another study (Wagner et al. 1979). Chronic exposure to 0.007 mg/kg/day in drinking water also resulted in anemia (Mazumder et al. 1988). Hematological effects have also been absent in cases of acute exposure to doses as high as 43 mg/kg when treatment has been administered (Lugo et al. 1969; Moore et al. 1994).

Hematological effects of ingested arsenic have not been thoroughly studied in laboratory animals, but no significant hematological effects have been detected in monkeys exposed to 5.7 mg/kg/day As in arsenate for 2 weeks (Heywood and Sortwell 1979), or in rats or dogs exposed to up to 20 mg/kg/day As as arsenate or arsenite for 1–2 years (Byron et al. 1967; Kroes et al. 1974; Schroeder et al. 1968). Rats exposed to arsenate for 6 weeks or more 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).

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; 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). These effects are most often observed after chronic exposure to doses of 0.02–0.1 mg As/kg/day (Chakraborty and Saha 1987; Franklin et al. 1950; Mazumder et al. 1988; Silver and Wainman 1952; Wade and Frazer 1953) but may also occur after acute exposures to higher doses (Armstrong et al. 1984; Quatrehomme et al. 1992) and after chronic exposure to lower doses (Haupert et al. 1996; Mazumder et al. 1988). However, acute exposure to doses of 0.02 mg/kg does not cause hepatic effects, even in infants (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 (Mazumder et al. 1988; Morris et al. 1974; Piontek et al. 1989; Szuler et al. 1979), leading in some cases to portal hypertension and bleeding from esophageal varices (Szuler et al. 1979). 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/kg/day As 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; Neiger and Osweiler 1989; Schroeder and Balassa 1967), although enlargement of the common bile duct was noted in rats given either arsenate or arsenite for 2 years (Byron et al. 1967).

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). 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; 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). In rare cases, renal failure may occur (e.g., Fincher and Koerker 1987; Lugo et al. 1969), probably as a result of fluid imbalances or vascular injury (Rosenberg 1974; Zaldivar 1974). Glomerular congestion has been observed after a acute exposure to high doses (Quatrehomme et al. 1992). Studies in animals also indicate that the kidney is not a major target organ (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). 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). 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 intermediate- or chronic-duration oral exposure (e.g., 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; Huang et al. 1985; Haupert et al. 1996; Lander et al. 1975; Luchtrath 1983; Mazumder et al. 1988; Mizuta et al. 1956; Morris et al. 1974; Nagai et al. 1956; Piontek et al. 1989; Rosenberg 1974; Saha and Poddar 1986; Silver and Wainman 1952; Szuler et al. 1979; Tay and Seah 1975; Tseng et al. 1968; Wade and Frazer 1953; Wagner et al. 1979; 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. However, 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; Franklin et al. 1950; Huang et al. 1985; Luchtrath 1983; Mazumder et al. 1988; 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; Harrington et al. 1978; Mazumder et al. 1988; 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 (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 b in Table 2-3. However, a recently published study indicates that children in Thailand exposed to arsenic, tin, and tungsten may exhibit this effect of arsenic exposure at an average level of 0.0008 mg As/kg/day (Foy et al. 1992).

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

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

Organic Arsenicals

No studies were located regarding ocular effects in humans or animals after oral exposure to organic arsenicals.

2.2.2.3 Immunological Effects

Inorganic Arsenicals

No studies were located regarding immunological 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) (Kerkvliet et al. 1980).

Organic Arsenicals

No studies were located regarding immunological 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 (1 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; Danan et al. 1984; Fincher and Koerker 1987). Reports of high-level acute exposure indicate an absence of neurological effects when treatment is administered (Moore et al. 1994). Intermediate- and chronic-duration exposures to lower levels (0.05–0.5 mg As/kg/day) are typically characterized by a symmetrical peripheral neuropathy (Franzblau and Lilis 1989; Huang et al. 1985; Mizuta et al. 1956; Silver and Wainman 1952; 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). 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). No neurological effects could be detected in populations chronically exposed to doses of 0.01 mg As/kg/day or less (Harrington et al. 1978; Hindmarsh et al. 1977; Southwick et al. 1981; Valentine et al. 1985). Neurological effects have not been reported in dogs or monkeys chronically exposed to arsenate or arsenite by the oral route (Byron et al. 1967; Heywood and Sortwell 1979).

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

No studies were located regarding neurological effects in humans after oral exposure to organic arsenicals. However, 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 suggestive 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 regarding reproductive effects in humans after oral exposure to inorganic arsenicals, and only one study of reproductive function has been performed in animals. Lugo et al. (1969) reported a case of a mother who ingested inorganic arsenic (Cowley's Rat and Mouse Poison). A 17-year-old female was admitted for treatment of acute renal failure 24 hours after she ingested approximately 30 mL of arsenic trioxide (0.39 mg As/kg). Pelvic examination was conducted confirming a 30-week uterine pregnancy. She went into labor and delivered a live female infant weighing 2 pounds, 7 ounces with a 1-minute Apgar score of 4. The infant's clinical condition deteriorated and she died at 11 hours of age.

In the animal study (a 3-generation study in mice given sodium arsenite in drinking water at an average dose of 1 mg As/kg/day), no significant effects were detected on a number of reproductive parameters, although a trend toward a decreased number of pups per litter and slightly altered male:female sex ratio were observed (Schroeder and Mitchner 1971). In the absence of any further data, it is difficult to judge whether these effects are either statistically or biologically significant. Healy et al. (1998) observed an 8% decrease in testis weight in mice exposed to 0.0085 mg As/kg/day in the drinking water for 32 days. However, no functional tests were conducted.

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 which 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. 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. Due to the small number of cases (665 controls and 270 cases), this association might 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). However, a similar association was noted for mercury, potassium, silica, and water hardness, and 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, do support the view that high doses of ingested arsenic may be fetotoxic and weakly teratogenic. A low incidence (0.5–5%) of fetal malformations (mostly skeletal defects) was noted in mice exposed during pregnancy to 23–68 mg As/kg/day of sodium arsenite (Baxley et al. 1981; Hood et al. 1978). No teratogenicity was observed in hamsters exposed to 14 mg As/kg/day of sodium arsenite (Hood and Harrison 1982), but there was an increased incidence of fetal mortality, perhaps as a consequence of severe maternal toxicity (12–36% of the dams died) (Baxley et al. 1981; Hood and Harrison 1982). 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 is 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. 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). 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 given oral doses of DMA (Yamanaka et al. 1989a), an effect that 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; Hsueh et al. 1995; Luchtrath 1983; Morris et al. 1974; Piontek et al. 1989; Sommers and McManus 1953; Tay and Seah 1975; 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 a 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 which identify CEL values 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 (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. 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 μg As/L) of 5×10^{-5} (IRIS 1998). The average daily doses (expressed as mg As/kg/day) that correspond to

excess cancer risks of $1x10^{-4}$ to $1x10^{-7}$ are shown in Figure 2-3. The study design limited it usefulness to derive precise risk estimates.

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. 1997); 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, which might increase cancer risk in Taiwan (Beck et al. 1995); the likely possibility that arsenic is an essential nutrient at lower doses (EPA 1988e); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997).

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 (Andelman and Barnett 1983).

More recently, Wong et al. (1992) 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 2 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 2 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 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 more recent large-scale epidemiological studies in Taiwan, where clear associations and/or dose response trends have been detected for tumors of bladder, kidney, liver, and lung (Chen and Wang 1990; Chen et al. 1985, 1986, 1988a, 1988b, 1988c, 1992; Chiang et al. 1988; Chiou et al. 1995; Wu et al. 1989). Other studies in the literature suggest the associations are not as clear-cut (Bates et al. 1995; Chow et al. 1997; Cuzick et al. 1992). The EPA has not yet calculated a unit risk value or slope factor for arsenic-induced internal tumors.

More recently, 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-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 μg/kg/day of arsenic was estimated as 4.3×10^{-3}, 1.2×10^{-2}, 1.2×10^{-2}, and 4.2×10^{-3}, respectively, for males; and 3.6×10^{-3}, 1.3×10^{-2}, 1.7×10^{-2}, and 4.8×10^{-3}, respectively, for females in the study area.

Chiou et al. (1995) conducted a 7-year prospective cohort study in 4 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 for age, sex, and cigarette smoking. Blackfoot patients had a significantly increased cancer incidence after adjustment for cumulative arsenic exposure.

Chow et al. (1997) evaluated the incidence of bladder cancer in an area of chronic arsenic (As) exposure and 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 μg/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 μg/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 μg/L arsenic, and more than 2.5 million people may be supplied with water with levels above 25 μg/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 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. (1997) 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 μg As/L, respectively). A fluorescent version of the exfoliated bladder cell micronucleus (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 μg/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 μg/L for arsenic.

Yu et al. (1992) report the endemic occurrence of chronic arsenicism in a limited area on the southwest coast of Taiwan. The effects of arsenic on the mitogenic responses of mononuclear cells (MNC) derived from patients with arsenical skin cancers in that area were evaluated. 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}H]thymidine incorporation in MNC in all groups except the arsenical skin cancer group. However, when a low concentration of As_2O_3 (2.5×10^{-7} M) was added to PHA-stimulated MNC, a tremendous amplification of the uptake of [^{3}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 its specific etiology (i.e., 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 under nourishment. This study supports concerns about the differences between the Taiwanese and U.S. populations.

In contrast, Hopenhayn-Rich et al. (1996) 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 1961–1990 in the municipality of Skelleftea, Sweden, where a smelter released pollutants including lead, arsenic, copper, cadmium, and sulfur dioxide. Childhood cancer incidence was compared. There was an increased risk of childhood cancer (all types combined, 13 compared with an expected number of 6.7), but the association with arsenic is confounded by the presence of other metals.

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 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.

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. 1987). However, these data do not suggest that arsenic should be viewed as having any net therapeutic "anti-cancer" effect.

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 this compound could act as a cancer promoter (Johansen et al. 1984).

Yamamoto et al. (1995) also evaluated the carcinogenic effects of dimethylarsinic acid (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-hyroxybutyl)nitrosamine (BBN) in drinking water in weeks 1 and 2 and N-bis(2-hyroxypropyl)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.

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

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form
ACUTE EXPOSURE							
Immunological/Lymphoreticular							
	Gn pig (Hartley)	once		580 mg/L			Wahlberg and Boman 1986 As(+3)
	Gn pig (Hartley)	once	Dermal	4000 mg/L			Wahlberg and Boman 1986 As(+5)
INTERMEDIATE EXPOSURE							
Systemic							
	Mouse	18 wk 11x/wk	Dermal		2.5 F mg/kg (local hyperplasia, irritation)		Boutwell 1963 As(+3)

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

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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.

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 regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after 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 2.5 mg As/kg as sodium arsenite (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.

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 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. Studies in guinea pigs did not yield evidence of a sensitization reaction (Wahlberg

Organic Arsenicals

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

No studies were located regarding the following effects in humans or animals after 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

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 described cancer in humans after dermal exposure to inorganic 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:

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:

- Both arsenate and arsenite are well absorbed by both the oral and inhalation routes. Absorption by the dermal route has not been well characterized, but is low compared to the other routes. Inorganic arsenic in soil is absorbed to a lesser extent than solutions of arsenic salts.

- The rate of absorption of arsenic in highly insoluble forms (e.g., arsenic sulfide, lead arsenate) is much lower than that of more soluble forms via both oral and inhalation routes.

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

- The As(+3) form undergoes enzymic methylation primarily in the liver to form MMA and DMA. This reaction is believed to detoxify arsenic. The rate and relative proportion of methylation production varies among species. The rate of methylation may also vary among tissues.

- 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), indicating that the rate of absorption may be lower if the inhaled arsenic is in a highly insoluble form.

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=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 (As_2Se_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.

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}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. Hamsters appear to absorb somewhat less, 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 to 30% (Marafante and Vahter 1987).

Comparative oral absorption of arsenic as a soluble salt, in soil, and in household dust was studied in a group of three female cynomolgus monkeys (Wester et al. 1995). Bioavailability was assessed in comparison to an intravenous dose of sodium arsenate. Mean absolute percentage bioavailability based on urine arsenic excretion were reported at 67.6±2.6% (gavage), 19.2±1.5% (oral dust), and 13.8±3.3% (oral soil). Mean absolute percentage bioavailability based on blood arsenic levels were reported at 91.3±12.4% (gavage), 9.8±4.3% (oral dust), and 10.9±5.2% (oral soil). The arsenic in the dust and soil was approximately 3.5- to 5-fold (based on urine) and 8- to 9-fold (based on blood) less bioavailable than arsenic in solution.

Oral absorption of arsenic from contaminated soil has also been measured in rabbits (Freeman et al. 1993). Approximately 80% of the arsenic in the soil was excreted in feces, compared to 50% of a gavage dose of sodium arsenate. Arsenic in the soil was primarily in the form of sulfides, which are less water soluble than sodium arsenate.

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 [^{73}As] as arsenic acid (H_3AsO_4) alone and mixed with soil has been

measured in skin from cadavers (Wester et al. 1993). Labeled arsenic was applied to skin in diffusion cells and transit through the skin into receptor fluid measured. After 24 hours, 0.93% of the dose passed through the skin and 0.98% remained in the skin after washing. Absorption was lower with [^{73}As] mixed with soil: 0.43% passed through the skin over 24 hours and 0.33% remained in the skin after washing.

Dermal absorption of arsenic has been measured in Rhesus monkeys (Wester et al. 1993). After 24 hours, 6.4% of [^{73}As] as arsenic acid was absorbed systemically, as was 4.5% of [^{73}As] mixed with soil. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solutions of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver, and spleen over the next 5 days (Dutkiewicz 1977). The rate of uptake was estimated to be 1–33 $\mu g/cm^2/hr$. 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.

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 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. 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. Similar results have been obtained in mice and hamsters given oral doses of arsenate or arsenite, where elevated levels of arsenic were found 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). In mice, radiolabel from orally administered 74-As was widely distributed to all tissues, with the highest levels in kidney and liver. No obvious differences between As(+3) and As(+5) were found, although residual levels after 24 hours tended to be higher for As(+3) than As(+5) (Vahter and Norin 1980). In hamsters, increases in tissue levels were noted after oral treatment with As^{+3} for most tissues (hair, kidney, liver, lung, skin, muscle), with the largest increases in liver and lung (Yamauchi and Yamamura 1985).

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.

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. In the rat, a large majority of the arsenic becomes bound to hemoglobin in red blood cells, and very little reaches other tissues (Lanz et al. 1950). For this reason, the rat is probably not an appropriate toxicokinetic model for distribution, metabolism, or excretion of arsenic by humans.

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 detoxify arsenic by changing 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.

The basic type of evidence which 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 As(+3), inorganic As(+5), MMA, and DMA in urine (Buchet et al. 1981a, 1981b; Crecelius 1977; 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, the time after exposure, the route of exposure, the dose level, and the 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). The rabbit has a similar ratio of metabolites (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.

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 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 μm, for MMA methyltransferase it is 1,000 μm. The purified activity is specific for arsenite and MMA; selenite, selenate, selenide, and catechols do not serve as substrates.

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 or so of the total daily methyl intake (Mushate 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, $(CH_3)_3AsO$) (Yamauchi and Yamamura 1984; Yamauchi et al. 1988). However, the methylarsenates are not demethylated to inorganic arsenic either in humans (Buchet et al. 1981a; Marafante et al. 1987b) or in animals (rats and hamsters) (Stevens et al. 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). A similar pattern 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). Clearance is even more rapid in mice and hamsters, with 90% removed in two 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 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

Species extrapolation. Species extrapolation was not attempted in this model.

Interroute extrapolation. Interroute extrapolation was not attempted in 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. 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 animal experiments. 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 do not appear to be stored or sequestered in the body.

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 can't 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 2–10 mg/kg have caused death in humans. Lower doses (0.05–0.5 mg/kg/day) over longer periods (weeks to months) cause gastrointestinal, dermal and neurological effects. These effects appear to be a result of direct cytotoxicity. Long-term exposure (years) to drinking water at levels of approximately 0.02 mg/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 of 0.05–0.07 mg/m^3. 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.

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+/K+ balance, protein synthesis, etc.).

Carcinogenesis. The EPA and the 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).

Several cellular model systems are in use to elucidate the molecular mechanisms of arsenic carcinogenicity, that is, how arsenic can induce a permanent change in the genome resulting in transformation.

Effects of arsenic on DNA methylation are the focus of two models. 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). 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 (Zhao et al. 1997). These cells exhibited aberrant gene expression and had undergone malignant transformation as demonstrated by the induction of tumors when injected into Nude mice. Changes in methylation of DNA can affect its structural stability and result in chromosomal damage leading directly to transformation.

The tissue-specificity of arsenic carcinogenicity in humans is being studied in primary human epidermal keratinocytes (Germolec et al. 1997). 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-α), and the cytokine tumor necrosis factor alpha (TNF-α). Arsenic in drinking water also increased the number of skin papillomas in transgenic mice in which dermal application of phorbol esters induce 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 exposure, carcinogenicity in skin and other organs after oral exposure. Second, the pattern of metabolism in humans (significant excretion of the monomethylated form of inorganic arsenic) is unlike other mammalian species. 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 (above), 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^3.

The oral route of exposure can be the predominant exposure pathway 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 (above), 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 exposures, most reported LOAEL values are about 1 mg As/kg/day (see Figure 2-3). However, these data are mainly from case reports of fatal or near-fatal exposures, so it is likely that lower acute doses could also produce the characteristic signs of acute arsenic toxicity. For intermediate-duration exposure, most oral LOAELs range from about 0.05 to 0.5 mg As/kg/day, while chronic LOAELs range from about 0.01 to 0.1 mg As/kg/day, while chronic oral NOAEL values range from 0.0004 to 0.0009 mg As/kg/day (see Figure 2-3). Based on these data, the chronic oral MRL is estimated to be 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 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Minimal Risk Levels for Arsenic.

Inhalation MRLs.

No inhalation MRLs were derived for arsenic.

Oral MRLs.

- 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 not 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 NOAEL (0.0008 mg/kg/day) was limited by the fact that the majority of the control population was less than 20 years of age, and the incidence of skin lesions increased as a function of age (see Appendix A for MRL worksheets).

No acute- or intermediate-duration oral MRLs were 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. Lethal oral doses are usually higher in animals (15–110 mg As/kg) (Gaines 1960; Harrisson et al. 1958), consistent with the general trend that animals are less sensitive to arsenic than humans. 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^3) (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 hoarseness, bronchitis, and rhinitis (Dunlap 1921; Morton and Caron 1989). However, chronic functional 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; Fincher and Koerker 1987). 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. Respiratory effects are usually not listed among the symptoms in humans exposed to moderate or low oral doses of inorganic arsenic (e.g., Borgono and Greiber 1972; Chakraborty and Saha 1987; Mizuta et al. 1958), although specific functional or histological studies have not been performed in these groups.

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). If so, Blackfoot disease *per se* may not be likely to occur in other areas, but less severe signs of vascular injury (Raynaud's disease, cyanosis of fingers and toes) have been noted in several other populations exposed to inorganic arsenic, both by inhalation (Lagerkvist et al. 1986, 1988) and by the oral route (Borgono and Greiber 1972; Roth 1957; Zaldivar 1977). The mechanism of this effect is not clear, but histological examination of blood vessels from exposed persons reveals an intimal thickening that may lead to vessel occlusion (Rosenberg 1974).

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., Armstrong et al. 1984; Levin-Scherz et al. 1987; Lugo et al. 1969) and after repeated exposure to lower doses (e.g., Borgono and Greiber 1972; 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 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 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; Mazumder et al. 1988; Mizuta et al. 1956; Silver and Wainman 1952; Wade and Frazer 1953). However, there is usually only marginal evidence of hepatic cell injury (e.g., elevated serum enzyme levels) (Armstrong et al. 1984; Franzblau and Lilis 1989), and histological examination suggests that the principal lesion is a portal tract fibrosis and cirrhosis that results in portal hypertension (Franklin et al. 1950; 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 (Armstrong et al. 1984; Jenkins 1966; Mizuta et al. 1956) or by the inhalation route (Bolla-Wilson and Bleecker 1987; Ide and Bullough 1988). 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; Mazumder et al. 1988; Nagai et al. 1956; 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). These effects appear to be of relatively little health significance in their own right, although 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 3. Chronic inhalation data suggest that exposure of workers to about 0.1–1.0 mg As/m^3 may lead to hyperkeratinization and hyperpigmentation (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. Little information was located on ocular effects of organic arsenicals.

Immunological Effects. No studies were located on immune 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), 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). 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 system is probably not a major target of arsenic, but the data are too sparse to draw firm conclusions.

No studies were located regarding immunological 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).

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. Only 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, only one study (Schroeder and Mitchner 1971), a 3-generation oral exposure study in mice, has been performed in animals. This study revealed no significant effects on reproductive success at 1.2 mg/kg/day, although a slight trend toward decreased pups per litter and a slightly altered male:female ratio were noted. In the absence of additional data, no firm conclusions can be drawn, but this study does not indicate that inorganic arsenic is a potent reproductive toxicant.

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. A study by Lugo et al. (1969) reported that an infant born at 30 weeks gestation after maternal ingestion of 0.39 mg/kg As exhibited multiple developmental effects, and died at 11 days of age. Studies in animals, however, do 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 (Nagymajtenyi et al. 1985), oral exposure of mice and hamsters (Baxley et al. 1981; Hood and Harrison 1982; Hood et al. 1978), 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 and Bishop 1972; Mason et al. 1989; Willhite 1981). However, in all cases the doses required to cause these effects were high (2–20 mg As/kg/day by injection, 20–70 mg As/kg/day by the oral route, 20 mg As/m^3 by inhalation), and often resulted in significant maternal toxicity or even lethality (Baxley et al. 1981; Hood and Bishop 1972; Hood and Harrison 1982). 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 1.5 μm, and decreased final cell number in preimplantation embryos in culture at 0.1 μm (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 (Wlodarczyk 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.

Genotoxic Effects. There have been a large number of studies of the genotoxic effects of arsenic. Tables 2-12 and 2-13 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 2-13).

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 mutations and DNA strand breaks (see Table 2-14).

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., Axelson et al. 1978; Enterline and Marsh 1982; Lee-Feldstein 1986; Pinto et al. 1977; 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 1998). This is supported by the U.S. Public Health Service, which has also classified arsenic as a known human carcinogen (NTP 1994). 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; Mazumder 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 levels of arsenic in drinking water (e.g., Tseng et al. 1968; Wu et al. 1989; 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. 1985, 1986, 1988a, 1988b, 1988c; Chiang et al. 1988; Wu et al. 1989) 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 in Taiwan by Tseng et al. (1968). This slope factor was calculated using a model that assumes the dose-response curve is linear at low doses. Recently, it has been suggested that this slope factor may over-estimate cancer risks at low dose, since low doses may be largely "detoxified" by *in vivo* methylation, producing a nonlinear dose-response curve (Marcus and Rispin 1988). Additional considerations currently under intense debate include the adequacy of the model used by EPA and the accuracy and reliability of the Taiwan exposure data (Brown et al. 1997); a number of host and environmental factors among the Taiwanese that may not be applicable elsewhere (Carlson-Lynch et al. 199); a possible threshold for arsenic carcinogenicity and nonlinearities in the dose-response curve (Abernathy et al. 1996; Slayton et al. 1996); and the possibility of significant exposure to arsenic from sources other than the well water (Chappell et al. 1997).

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 (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 essentially, although not rigorously established, is plausible.

If arsenic is essential or beneficial to animals, then it could be important to humans as well. If so, the daily requirement for humans probably lies somewhere between 10 and 50 μg/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 μg/day; see Section 5.5), and no cases of arsenic deficiency in humans have ever been reported.

2.6 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 due to maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 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 pre-natal and post-natal 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 and 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 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 the newborn who has a low glomerular filtration rate and has 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 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, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for 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). In studies of chronic exposure, children appear to be more severely affected, probably due to a higher exposure per body weight (Foy et al. 1992).

Inorganic arsenic has been characterized as a reproductive and 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. Neural tube defects are the predominant and consistent malformation in most mammalian species tested (Chaineau et al. 1990; Mirkes and Cornel 1992; Morrissey and Mottet 1983; Mottet and Ferm 1983; Willite and Ferm 1984). In humans, prenatal exposure to acute high doses of inorganic arsenic results in miscarriage and early neonatal death (Bollinger et al. 1992; Lugo et al. 1969). Prolonged low-dose human arsenic exposure has been associated with multiple adverse reproductive outcomes including spontaneous abortion, stillbirth, developmental impairment, and congenital malformation (Aaschengrau et al. 1989; Borzsonyi et al. 1992; Beckman 1978; Zierler et al. 1988). The association between prenatal arsenic exposure and congenital malformations has not been fully established, but in light of arsenic's teratogenic potential in other mammalian species, humans are likely to be sensitive to these effects.

Children appear to be more sensitive to the effects of arsenic, presumably because of a higher body burden. However, there is no evidence that the pharmacokinetics of arsenic differ in children. Foy et al. (1992) describes systemic effects of chronic arsenic exposure in children living in tin and tungsten mining areas 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 As poisonings was conducted in the fall of 1987. The case reports of 4 children were presented. All of the children had hyperkeratosis and hyperpigmentation of the extremities, including

tibia, palms, and soles. The child who was exposed to 2.7 mg As/L also had generalized pigmentation of the feet (Blackfoot Disease). 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 As levels ranged from 0.087 to 4.60 μg/mL and the As level in hair ranged from 0.06 to 14.4 μg/g. The authors concluded that the finding of typical skin manifestations of chronic As poisoning suggests that it may take a considerably shorter period of time to develop these manifestations than previously thought. 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 (Somogyi and Beck 1994).

There is no information in the literature describing storage of arsenic in maternal tissues. Nor is there any information specifically describing metabolism of arsenic in children. No PBPK models specifically targeted at fetuses, infants or children, or pregnant women or lactating women were found in the literature.

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 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.

There are no biomarkers that have been specifically identified for children exposed to arsenic. In addition, no unique interactions of arsenic with other chemicals have been identified in children.

2.7 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 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 2.7.1.

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 2.7.2.

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

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). It is not known if chemicals likely to be encountered in the environment cause significant effects on the methylating capacity of humans.

2.9 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 may result in reduced detoxification or excretion of arsenic, or compromised function of target organs affected by arsenic. Populations who are at greater risk due to their unusually high exposure to arsenic are discussed in Section 5.6, Populations With Potentially High Exposure.

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).

2.10 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:

Tintinalli JE, Ruiz E, and Krone RL (eds.) 1996. Emergency medicine. A comprehensive study. American College of Emergency Physicians. 4th Edition. The McGraw-Hill Companies, Inc.

Goldfrank RL, et al. 1994. Goldfrank's toxicologic emergencies. Appleton and Lange 5th Edition.

Ellenhorn MJ and Barceloux DG 1988. Medical toxicology diagnosis and treatment of human poisoning. Elsevier Science Publishing Company, Inc.

2.10.1 Reducing Peak Absorption Following Exposure

No data were located regarding the reduction of absorption after inhalation exposure to arsenic.

There are a number of methods for reducing absorption of arsenic following oral exposure. In cases of acute high-dose exposure, the removal of arsenic from the gastrointestinal tract may be facilitated by gastric lavage, stomach intubation, induced emesis, or use of cathartics (saline, sorbitol) within a few hours after ingestion (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). 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 which 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

Table 3-1. Chemical Identity of Arsenic and Selected Inorganic Arsenic Compounds[a]

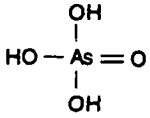
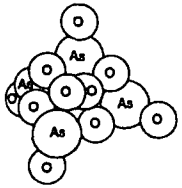
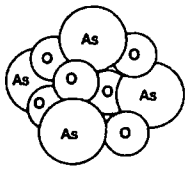
Characteristic	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Synonym(s)	Arsenic black; colloidal arsenic; gray arsenic	Orthoarsenic acid	Arsenic (V) oxide; arsenic acid anhydride; diarsenic pentoxide	Arsenic oxide; arsenious acid; arsenious oxide; white arsenic
Registered trade name(s)	No data	Dessican L-10[eb]; Scorch[eb]	No data	Arsenolite[ed];Claudelite[ed]
Chemical formula	As	H_3AsO_4	$As_2O_5(As_4O_{10})$	$As_2O_3(As_4O_8)$
Chemical structure	As			
Identification numbers:				
CAS registry	7440-38-2	7778-39-4	1303-28-2	1327-53-3
NIOSH RTECS	CG0525000	CG070000	CG2275000	CG3325000
EPA hazardous waste	D004	D004, P011	D004, P011	D004, P012
OHM/TADS	No data	No data	No data	No data
DOT/UN/NA/IMCO shipping	UN1558/ IMCO 6.1	UN1553 (liquid) UN1554 (solid) / IMCO 6.1	UN1559/ IMCO 6.1	UN1561/ IMCO 6.1
HSDB	509	431	429	419
NCI	No data	No data	No data	No data

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Table 3-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a]

Property	Arsenic	Arsenic acid	Arsenic pentoxide	Arsenic trioxide
Molecular weight	74.92	150.95[f]	229.84	187.84
Color	Gray	White	White	White[d]
Physical state	Solid	Solid	Solid	Solid[d]
Melting point	817 °C at 28 atm	35.5 °C	Decomposes at 315 °C	312.3 °C
Boiling point	613 °C sublimes	Loses H_2O at 160 °C	No data	465 °C[d]
Density at °C	5.727 g/cm^3	2.0–2.5 g/cm^3	4.32 g/cm^3	3.738 g/cm^3
Odor	Odorless[e]	No data	No data	Odorless[e]
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	Insoluble	3,020 g/L at 12.5 °C	1,500 g/L at 16 °C 767 g/L at 100 °C	37 g/L at 20 °C 115 g/L at 100 °C
Organic solvent(s)	No data	Soluble in alcohol	Soluble in alcohol	Slightly soluble in alcohol[e]
Acids	Soluble in nitric acid	No data	Soluble in acid[e]	Soluble in HCl[b]
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 373 °C[e] 40 mmHg at 483 °C[e] 100 mmHg at 518 °C[e]	No data	No data	66.1 mmHg at 312 °C[e]
Henry's law constant at 24.8 °C	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	Nonflammable[e]
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 °C mg/m^3 to ppm (v/v) in air at 25 °C	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data
Valence states	0[b]	+5[b]	+5[b]	+3[b]

Table 3-3. Physical and Chemical Properties of Arsenic and Selected Inorganic Arsenic Compounds[a] (continued)

Property	Calcium arsenate	Gallium arsenide	Sodium arsenate	Sodium arsenite
Molecular weight	398.08	144.64	185.91[e]	129.91
Color	Colorless[c]	Dark gray	No data	Gray-white
Physical state	Solid	Solid	Solid[d]	Solid
Melting point	1.455 °C	1238 °C	57 °C[d]	No data
Boiling point	No data	No data	No data	No data
Density at °C	3.62 g/cm^3	5.31[d] g/cm^3	1.87[d] g/cm^3	1.87 g/cm^3
Odor	Odorless[e]	No data	Odorless[e]	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	0.13 g/L at 25 °C	No data	Soluble in water, glycerol[d]	Very soluble
Organic solvents	Insoluble	No data	Slightly soluble in alcohol[d]	Slightly soluble in alcohol
Acids	Soluble in dilute acids[e]	No data	No data	No data
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure at 25 °C	No data	No data	No data	No data
Vapor pressure at 30 °C	No data	No data	No data	No data
Henry's law constant at 24.8 °C	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits in air	No data	No data	No data	No data
Conversion factors: ppm (v/v) to mg/m^3 in air at 25 °C; mg/m^3 to ppm (v/v) in air at 25 °C	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data
Valence states	+5[b]	-3	+5	+3

[a] All information obtained from Weast 1985, except where noted.
[b] EPA 1982D
[c] Sax and Lewis 1989
[d] Merck 1989
[e] HSDB 1990
[f] Value for H_3AsO_4 - ½ H_2O

5.4.3 Soil

Arsenic is found in the earth's crust at an average level of 2 ppm (NAS 1977b). Most natural soils contain low levels of arsenic, but industrial wastes and pesticide applications may increase concentrations. Background arsenic concentrations in soil range from about 1 to 40 ppm, with a mean value of about 5 ppm (Beyer and Cromartie 1987; Eckel and Langley 1988; EPA 1982a; NAS 1977a). The concentrations of arsenic in 40 Florida soil profiles (94 samples) have been measured. The geometric mean concentration of arsenic was 1.1 mg/kg, which is lower than the average of U.S. soils (Ma et al. 1997). Soils overlying arsenic-rich geologic deposits, such as sulfide ores, may have soil concentrations two orders of magnitude higher (NAS 1977a).

Arsenic concentrations up to 27,000 ppm were reported in soils contaminated with mine or smelter wastes (EPA 1982a). Arsenic in soil in communities surrounding former smelters is a public health concern, especially for infants and children who may consume significant quantities of soil. The average arsenic levels in the top 2 cm of different soil types in the vicinity of a former copper smelter in Anaconda, Montana, ranged from 121 to 236 μg/g, and levels were significantly related to proximity and wind direction to the smelter site (Hwang et al. 1997).

Soil on agricultural lands treated with arsenical pesticides may retain substantial amounts of arsenic. One study reported an arsenic concentration of 22 ppm in treated soil compared to 2 ppm for nearby untreated soil (EPA 1982a). Arsenic was measured in soil samples taken from 10 potato fields in Suffolk County on Long Island, New York, where sodium arsenite had been used for vine control and fall weed control for many years. Lead arsenate also may have been used as an insecticide in certain areas. The mean arsenic levels taken at a depth of 0-18 cm from each of the 10 fields ranged from 27.8±5.44 mg/kg dry weight (n=10) to 51.0±7.40 mg/kg dry weight (n=10). These levels were markedly higher than the level of 2.26±0.33 mg/kg (n=10) for untreated control soils (Sanok et al. 1995). An analytical survey was conducted in 1993 to determine the concentrations of arsenic and lead in soil samples from 13 old orchards in New York State. Lead arsenate was used for pest control in fruit orchards for many years, and residues remain in the soil. Concentrations of arsenic ranged from 1.60 to 141 ppm (mg/kg) dry weight (Merwin et al. 1994).

The possible presence of toxic compounds in waste materials has raised concerns about the fate of these compounds either during the composting process or when the composted product is applied to soils. Three

waste compost products generated at the Connecticut Agricultural Experiment Station had arsenic levels of 12.8, 9.8, and 13 mg/kg dry weight, respectively (Eitzer et al. 1997). These are lower than the EPA 503 regulatory limit for arsenic of 41 mg/kg for agricultural use of sewage sludge (EPA 1993b).

There has been concern regarding the cross-border contamination between the United States and Mexico. An example is the contamination of the Mexican community of Anapra in Ciudad Juarez, Chihuahua, from a lead smelter in El Paso, Texas, that ceased operation in 1985. Three geographical locations varying in distance from the smelter source were evaluated for arsenic levels in the soil. Mean arsenic levels of the 3 sectors at increasing distance from the source were 25.2 mg/kg (n=8), 21.4 mg/kg (n=7), and 19.5 mg/kg (n=4). Soil from a control area located 25 km away from the smelter had a mean concentration of 8.6 mg/kg (n=3) (Diaz-Barriga et al. 1997).

Contamination by heavy metals is a serious problem in some developing countries. Arsenic levels ranging from 0.1 to 80 g/kg (100 to 80,000 mg/g) have been measured in sediments in the highly contaminated Sepetiba Bay in Brazil. A zinc factory near the bay uses ~1,500 tons of arsenic per year to purify the electrolytic solution used to produce zinc and cadmium (Moreira 1996). In Zimbabwe, surface soil (~10 cm depth) at abandoned mine dumps contained arsenic at an average concentration of 9.53±0.25 mg/g (9,530±250 mg/kg). Soil near a river stream about 400 meters from the mine dumps contained 0.55±0.04 mg/g (550±40 mg/kg) of arsenic (Jonnalagadda and Nenzou 1996).

Sediments in aquatic systems often have higher arsenic concentrations than those of the water (Welch et al. 1988). Most sediment arsenic concentrations reported for U.S. rivers, lakes, and streams range from 0.1 to 4,000 ppm, but much higher levels may occur in areas of contamination (Heit et al. 1984; NAS 1977a; Welch et al. 1988).

During August through November 1992 and August 1993, bed sediment in the South Platte River Basin (Colorado, Nebraska, Wyoming) was sampled and analyzed for 45 elements, including arsenic. The range of arsenic found was 2.8–31 μg/g (mg/kg) dry weight, and the geometric mean (n=23) was 5.7 μg/g (Heiny and Tate 1997). Measured concentrations of total arsenic in sediments from Clark Fork River in western Montana decreased from 404 μg/g dry weight at the farthest upstream sampling station to 11 μg/g at the most downstream station. Sediment samples from the Milltown Reservoir had arsenic concentrations ranging from 6 to 56 μg/g dry weight (Brumbaugh et al. 1994).

Surficial sediments collected from 18 locations in 3 major tributaries to Newark Bay, New Jersey, were analyzed for 7 toxic metals, including arsenic (Bonnevie et al. 1994). The highest concentrations of arsenic (dry weight) were found in the Rahway River adjacent to a chemical plant (58 mg/kg) and in the Hackensack River adjacent to a coal-fired power plant (49 mg/kg). The average arsenic concentration for all sediments was 17±16 mg/kg. Sediments collected from 7 sites in Baltimore Harbor, Maryland, at 5 seasonal periods between June 1987 and June 1988 had a geometric mean maximum of 7.29 μg/g (mg/kg) dry weight and a geometric mean minimum of 1.25 μg/g (mg/kg) (Miles and Tome 1997). This harbor is one of two sub-tributaries of the Chesapeake Bay where contaminants have been discharged on a large scale. Metal concentrations have been measured in sediments from the Times Beach Confined Disposal Facility, an area of documented chemical contamination in Buffalo, New York (Roper et al. 1996); arsenic concentrations ranged from 27.5 to 54.0 mg/kg dry weight.

In the past few years, it has been suggested that the wood preservative most commonly used in dock pilings and bulkheads (chromated copper arsenate) can be toxic to estuarine organisms. Wendt et al. (1996) measured arsenic in surficial sediments and oysters from creeks with high densities of docks and from nearby reference creeks with no docks. The average concentrations in the sediments ranged from 14 to 17 μg/g throughout the study area, which is within the range of natural background levels.

Typically, it has been assumed that 100% of arsenic that is ingested is bioavailable (EPA 1984), based on toxicological studies using pure salts. However, this approach is flawed for evaluating the bioavailability of metals from soils, because solid phases in soil are typically much less soluble than metal salts. Oxidation reactions on mineral surfaces result in armoring of the primary mineral grain by a secondary reaction product. Also, the arsenic-bearing phase is often encapsulated in an insoluble matrix such as silica, further diminishing arsenic availability. In contrast to soluble arsenic salts, the dissolution of arsenic-bearing solids is limited by the refractory nature of arsenic sulfides (Davis et al. 1992).

In a study of the bioavailability of arsenic in soils from the Butte, Montana, mining district, Davis et al. (1992) prepared a soil that was representative of a mine waste site minimally impacted by smelting activity by blending 5 separate Butte soils to achieve an arsenic concentration of 1,380 mg/kg (μg/g). Based on *in vitro* results, the arsenic in the soil was demonstrated to be 5 times less bioavailable than arsenic from Na_2HAsO_4. The low bioavailability factors observed for arsenic-bearing soils from a former smelting site in Anaconda, Montana, were explained by the sparingly soluble nature of the arsenic-bearing phases, the

presence of authigenic carbonate and silicate rinds, the kinetic hindrance to dissolution, and the inaccessibility of encapsulated arsenic (Davis et al. 1996)

Data from another study of arsenic in soils and sediments at the Milltown Reservoir Sediments Superfund site in Montana indicated that the bioavailabilities of arsenic, cadmium, copper, lead, and zinc were equal to or less than 0.2% for internal organs and 0.1% for carcasses on a μg/g tissue wet weight basis. These results suggest that the bioavailable fraction of mining waste metals in riparian wetland soils may be quite small (Pascoe et al. 1994).

Hamel et al. (1998) used synthetic gastric juice to estimate the bioaccessible fraction of metals in the stomach with varying liquid to solid ratios. They found that the bioaccessibility was not the same for each metal within a soil, nor between the soils. Bioaccessibility was defined for their study as the maximal amount of metal that is soluble in a synthetic gastric juice and is, therefore, potentially available for uptake across the intestinal lumen, while bioavailability was defined as the amount that was actually taken across the cell membranes. Arsenic bioaccessibility for National Institute of Standards and Technology (NIST) Montana Soil SRM 2710, with a certified arsenic concentration of 626 μg/g, was fairly consistent across the liquid-to-solid ratios and ranged from 41.8±18% to 56±21%. The extractability of a hazardous waste contaminated soil from Jersey City, New Jersey, was different than that observed for the Montana NIST soil. For the Jersey City soil, which had as arsenic concentration of 1,120 μg/g, there was an increase in the bioaccessible arsenic as the liquid-to-solid ratio increased. Bioaccessible arsenic ranged from 4.5±0.8% (at a liquid-to-solid ratio of 100:1) to 25±9% (at a ratio of 5,000:1).

5.4.4 Other Environmental Media

Arsenic is found in many types of food. The highest levels are detected in seafood, meats, and grains. Typical U.S. dietary levels of arsenic in these foods range from 0.02 ppm in grains and cereals to 0.14 ppm in meat, fish, and poultry (Gartrell et al. 1986), but there is a wide range of values. Shellfish and other marine foods contain the highest arsenic concentrations (Jelinek and Corneliussen 1977). Mean levels in fish and seafood are usually about 4–5 ppm (Bennett 1986; Schroeder and Balassa 1966) but may be as high as 170 ppm (NAS 1977b). Some arsenic concentrations found in fish and shellfish are summarized in Table 5-2.

1.4 μg/cigarette for mainstream cigarette smoke (Smith et al. 1997). The wide range of arsenic yields for flue-cured cigarettes suggests that the field history, soil, and fertilizer conditions under which the tobacco is grown will affect the arsenic concentration (Smith et al. 1997). Arsenic emission factors of 0.015 to 0.023 μg/cigarette (mean 0.018±0.003 μg/cigarette) have been measured for sidestream smoke from a burning cigarette (Landsberger and Wu 1995). Arsenic has also been detected in several homeopathic medicines at concentrations up to 650 ppm (Kerr and Saryan 1986). Some Chinese proprietary medicines that are manufactured in China, Hong Kong, and other Asian countries have been reported to contain levels of inorganic arsenic ranging from 25 to 107,000 ppm (μg/g) (Chan 1994). Fifty medicinally important leafy samples that were analyzed for elemental concentrations contained arsenic at levels ranging from 0.12 to 7.36 mg/kg (μg/g), with a mean of 2.38±1.2 mg/kg (μg/g) (Reddy and Reddy 1997).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

For the general population, food is generally the greatest source of arsenic exposure. In the United States, food intake of arsenic has been estimated to be about 46 μg/day, with the largest contribution from meat, fish, poultry, grain, and cereal products (Gartrell et al. 1986). Some of this is probably in the form of organic arsenicals (see Section 5.4.4). Drinking water may also be a significant source of arsenic exposure. Estimates of arsenic intake for adults drinking 2 liters of water per day average about 5 μg/d (EPA 1982c), but could be higher (10–100 μg/d) where levels in water are above average. It is assumed that nearly all arsenic in drinking water is inorganic (EPA 1984a).

The U.S. Food and Drug Administration (FDA) conducts the Total Diet Study (TDS) to determine dietary intakes of pesticides, selected elements, and other chemicals. For the sampling period June 1984 to April 1986, the total daily intake of arsenic from foods was 58.1 μg for a 25–30-year-old male. Seafood contributed 50.8 μg (87% of the total) (Gunderson 1995a). For the sampling period July 1986 to April 1991, the total daily intake of arsenic from foods was lower, 38.6 μg for a 25–30-year-old male. Seafood again was the major contributor at 34.1 μg (88% of the total) (Gunderson 1995b). The latest TDS, for the sampling period September 1991 to December 1996, shows that arsenic, at ≥0.03 ppm (μg/g), was found in 55 (21%) of the 261–264 foods/mixed dishes analyzed. The highest concentrations again were found in seafood, followed by rice/rice cereal, mushrooms, and poultry. The estimated total daily intake of arsenic from foods was 56.6 μg for a 25- to 30-year-old male. Seafood was the major contributor, accounting for 88% to 96% of the estimated total arsenic intake of adults. For infants, 41% and 34% of the estimated

total arsenic intakes are from seafood and rice/rice cereals, respectively (Tao et al. 1998). The mean daily intakes (μg/kg body weight) for selected age groups for the two sampling periods are given in Table 5-3.

Average daily dietary exposures to arsenic were estimated for approximately 120,000 U.S. adults by combining data on annual diet, as measured by a food frequency questionnaire, with residue data for table-ready foods that were collected for the annual FDA Total Diet Study. Dietary exposures to arsenic were highly variable, with a mean of 50.6 μg/day (range, 1.01–1,081 μg/day) for a female and 58.5 μg/day (range, 0.21–1,276 μg/day) for a male (MacIntosh et al. 1996). Inorganic arsenic intake in 969 men and women was assessed by a semi-quantitative food frequency questionnaire in combination with a database for arsenic content in foods and by toenail concentrations of arsenic. The mean estimated average daily consumption of inorganic arsenic was 10.22 μg/day, with a standard deviation of 6.26 μg/day and a range of 0.93–104.89 μg/day (MacIntosh et al. 1997).

During a comprehensive total diet study extending from 1985 to 1988, the estimated daily dietary ingestion of total arsenic by the average Canadian was 38.1 μg and varied from 14.9 μg for the 1–4-year-old age group and 59.2 μg for 20–39-year-old males (Dabeka et al. 1993). Daily intakes of arsenic from food by women in the Shiga Prefecture, Japan, were investigated by the duplicate portion method and by the market basket method. In 1991 and 1992, the daily intakes determined by the duplicate portion method were 206 and 210 μg, respectively. Those determined by the market basket method were 160 and 280 μg, respectively (Tsuda et al. 1995).

Inhalation of arsenic from ambient air is usually a minor exposure route for the general population. For example, the dose to a person who breathes 20 m^3/day of air containing 20–30 ng/m^3 (see Section 5.4.1) would be about 0.4–0.6 μg/d. However, smokers may be exposed to arsenic by inhalation of mainstream smoke. Assuming that 20% of the arsenic in cigarettes is present in smoke, an individual smoking two packs of cigarettes per day would inhale about 12 μg of arsenic (EPA 1984a).

Occupational exposure to arsenic may be significant in several industries, mainly nonferrous smelting, arsenic production, wood preservation, glass manufacturing, and arsenical pesticide production and application. The electronics industry is expanding the use of gallium arsenide in the production of optoelectronic devices and integrated circuits, and workers in the industry where gallium arsenide is used can be exposed to hazardous substances such as arsenic, arsine, and various acids (Sheehy and Jones 1993).

Table 5-3. Mean Daily Intakes of Arsenic for Selected Population Groups

		Mean daily intake, μg As per kg body weight							
Dates of study	PTDI	6-11 mo	2 yr	14-16 yr female	14-16 yr male	25-30 yr female	25-30 yr male	60-65 yr female	60-65 yr male
6/84-4/86[a]	2.1[c]	0.82	1.22	0.54	0.6	0.66	0.76	0.71	0.74
7/86-4/91[b]	2.1[c]	0.5	0.81	0.36	0.39	0.44	0.51	0.46	0.48

[a] Gunderson 1995a
[b] Gunderson 1995b
[c] No agreement has been reached on a maximum acceptable intake for total arsenic; the FAO/WHO has assigned a Provisional Tolerable Daily Intake (PTDI) for inorganic arsenic of 2.1 μg/kg body weight for adults.

The current Occupational Safety and Health Administration (OSHA) PEL for arsenic in inorganic compounds is 10 μg/m^3, the OSHA action level is 5 μg/m^3 (OSHA 1989), and the National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) is 2 μg/m^3 for a 15-minute ceiling (NIOSH 1990). The OSHA PEL for arsine is 200 μg/m^3, but the NIOSH REL for arsine is the same as for arsenic, 2 μg/m^3 for a 15-minute ceiling. The American Conference of Governmental Industrial Hygienists (ACGIH) biological exposure index (BEI) for arsenic in urine is 50 μg arsenic per g of creatinine (ACGIH 1998).

NIOSH researchers conducted a study of arsenic exposures and control systems for gallium arsenide operations at 3 microelectronics facilities during 1986–1987 (Sheehy and Jones 1993). Results at one plant showed that in all processes evaluated but one, the average arsenic exposures were at or above the OSHA action level of 5 μg/m^3, with a maximum exposure of 8.2 μg/m^3. While cleaning the LEC pullers, the average potential arsenic exposure of the cleaning operators was 100 times the OSHA PEL. Area arsenic samples collected at the plant in breakrooms and offices, 20 to 60 feet from the process rooms, had average arsenic concentrations of 1.4 μg/m^3. At the other two plants, personal exposures to arsenic were well controlled for all processes evaluated.

A study has been conducted to examine the relationship between total arsenic levels in hair of employees in a semiconductor fabrication facility and job responsibility, a surrogate variable for arsenic exposure (de Peyster and Silvers 1995). Airborne arsenic was found in areas where equipment was being cleaned but was not found in administrative areas. The highest airborne arsenic level found in the study, 15 μg/m^3, was collected from the breathing zone of a maintenance employee who was cleaning a source housing over a period of 2 hours in an area with local exhaust ventilation. A concentration of 2 μg/m^3 was found during the remainder of the cleaning period (~53 min). Workers in maintenance who were regularly assigned to cleaning equipment, and therefore presumed to have the highest exposure potential, had a mean hair arsenic level of 42 ppb (0.042 μg/g). This was higher than the mean of 33 ppb (0.033 μg/g) observed in administrative controls, but the difference was not significant. Maintenance workers who only occasionally cleaned and maintained arsenic-contaminated equipment had a mean hair arsenic level of 34 ppb (0.034 μg/g), which was comparable to the controls. The highest group mean hair arsenic level of 44 ppb (0.044 μg/g), surprisingly, was found in supervisors and engineers who were presumed to have the lowest exposure potential of all workers in the process areas. However, the highest concentrations of hair arsenic in engineers, 76 and 106 ppb, were observed in 2 heavy smokers who smoked 1–2 packs of cigarettes per

day. A 2-way analysis of variance indicated that smoking appeared to be a significant contributing factor whereas occupational exposure was not.

Chromium, copper, and arsenic (CCA) preservatives are commonly used for treating timber used in constructions in marine and other humid environments or in contact with the ground. Exposure to CCA compounds may occur while working with the treated timber. Nygren et al. (1992) investigated the occupational exposure to airborne dust, chromium, copper, and arsenic in six joinery shops in Sweden where impregnated wood was used for most of their production. The mean airborne concentration of arsenic around various types of joinery machines ranged from 0.54 to 3.1 $\mu g/m^3$. No increased concentrations of arsenic were found in urine from the workers.

A study was carried out in Denmark to evaluate arsenic exposure in taxidermists, workers impregnating wood with CCA solutions, fence builders, construction workers, and workers impregnating electric pylons with arsenic solution (Jensen and Olsen 1995). Airborne arsenic exposure was documented in 19 of 27 individuals working with products containing arsenic. The maximum exposure concentration was 17.3 $\mu g/m^3$, found for a single worker who was filling an impregnation container with CCA paste. Median exposures for indoor workers producing garden fences and weekend cottages were 3.7 and 0.9 $\mu g/m^3$, respectively. The maximum urine concentration reported in the study was 294.5 nmol arsenic per mmol creatinine and was from the injector impregnating electric pylons. The median concentration in workers on electric pylons was 80 nmol arsenic per mmol creatinine, which was six times the concentration in reference individuals. Urine arsenic levels in workers producing garden fences and in taxidermists were 2.9 and 1.8 times the reference level, respectively.

NIOSH estimated that about 55,000 workers were occupationally exposed to arsenic in the early 1980s (NOES 1990). The principal exposure pathway is probably inhalation of arsenic adsorbed to particulates, but ingestion and possibly dermal exposure may also be common. Since arsenic is no longer produced in the United States (see Section 4.1) and many arsenical pesticide uses have recently been banned (see Chapter 7), it is likely that the number of workers occupationally exposed to arsenic has decreased in recent years.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgment of adults in avoiding hazards (NRC 1993).

Arsenic residues in communities near former smelters are a public health concern, especially for infants and children. Contaminated soils pose a particular hazard to children because of hand-to-mouth behavior and the subsequent ingestion of soil containing metals and other contaminants (Hamel et al. 1998). Absorption of arsenic occurs primarily from the fluid phase in the small intestine (Davis et al. 1992). Children have the ability to absorb higher percentages of metals through the digestive system into the bloodstream than do adults. The amount of metal absorbed is dependent on the individual, the form of the metal within the soil, and the soil's physical characteristics (Hamel et al. 1998). Hwang et al. (1997) conducted a study from the summer of 1992 through the summer of 1993 in Anaconda, MT, in the vicinity of a former copper smelter. Environmental samples and first morning voided urine samples from 414 children less than 72 months old were collected. Attention was focused on that fraction of the environmental source that was thought to be of the greatest risk to the child (i.e., arsenic in small particles [<250 μm]) that could most readily adhere to hands and toys and could be inadvertently ingested. Average arsenic levels in different types of soil ranged from 121 to 236 μg/g. Several studies have reported mean soil ingestion values for children ranging from 9 to 1,834 mg/day. Assuming that high arsenic exposure areas have average arsenic levels in soil from 60 to 150 μg/g, the resulting daily arsenic intake from soil could range from 1 to 275 μg per child. The geometric mean of speciated urinary arsenic (combined As^{3+}, As^{5+}, monomethylarsonic acid, and dimethylarsinic acid) was 8.6±1.7 μg/L (n=289) in the Hwang study. The mean total urinary arsenic level was 19.1 μg/L, which was 11–22 μg lower than those reported in

2 previous studies in Anaconda (Baker et al. 1977; Hartwell et al. 1983) and only slightly higher the value of 17.7 μg/L that was found in a survey conducted in Anaconda in 1985, when the smelter had already been shut down (Binder et al. 1987). A nationwide survey on arsenic exposure in the vicinity of smelter sites revealed that children without excess arsenic exposure had average total urinary arsenic levels ranging from 5 to 10 μg/L (Hwang et al. 1997). Compared to these values, the mean total urinary arsenic values found in the Hwang study were markedly higher, but they were still well below the WHO-recommended maximum excretion level for total arsenic of 100 μg/L as an action level for intervention. The investigators hypothesized that the relatively low urinary arsenic levels found in the study were probably a reflection of the low bioavailability of some forms of arsenic in contaminated soil. Hwang et al. (1997) stated that arsenic intake through skin contact is insignificant and may be neglected in the assessment of childhood arsenic exposure. They recommend that parents or guardians pay more attention to their children's activity, especially hand-to-mouth behavior, even though the environmental contaminants might be elevated only slightly.

Arsenic concentrations were very low in human milk sampled from 88 mothers in the Faroe Islands, where the seafood diet includes pilot whale meat and blubber. The total arsenic concentrations ranged from 0.1 to 4.4 μg/kg (0.0001–0.0044 μg/g), with a median of 1.6 μg/kg (0.0016 μg/g) (Grandjean et al. 1995). The available data do not suggest any major transfer of organoarsenic compounds from seafood to milk, and the concentrations of inorganic arsenic are low (Grandjean et al. 1995).

While the harmful effects of many components of tobacco smoke are well known, those due to heavy metals in the smoke have not been sufficiently emphasized. The adverse health effects of these toxic metals on the fetus through maternal smoking are of special concern (Chiba and Masironi 1992). The concentration of arsenic in tobacco is relatively low, usually below detectable limits (<1 μg/g). Although the concentrations of inorganic and organic arsenic in the urine of adults do not appear to be influenced by smoking, a positive association was found between urinary arsenic levels in children and parental smoking habits. The mean arsenic level in the urine of children of non-smoking parents was 4.2 μg/g creatinine, in children with 1 smoking parent it was 5.5 μg/g, and in children with both parents smoking it was 13 μg/g (Chiba and Maseroni 1992).

The use of Chinese herbal medicines (CHM) appears to be common among Chinese women. Both CHM and Chinese proprietary medicines (CPM) are used for treatment of minor ailments in babies and children. Herbal medicines are available in capsule or tablet form in drug stores, supermarkets, and by mail. The

CPM "Sin Lak Pill," "Lu Shen Wan," and other anti-asthma preparations have been found to contain inorganic arsenic levels ranging from 25 to 107,000 ppm (μg/g), and cases of acute arsenic poisoning have been found in children and adults using these CPM (Chan 1994). Babies and children are particularly at risk because they may be given higher doses of these preparation per kg of body weight than adults would normally consume. They may also lack the hepatic enzymes responsible for drug biotransformation and detoxification (Chan 1994).

Various metallic pigments and colors in the form of salts or lakes are used in toy production. Therefore, children may be exposed to toxic metals while playing with toys, especially when they lick, suck, or swallow a toy or a piece of a toy. Toys produced in European Union Markets must conform to restrictions concerning the bioavailability of toxic metals, including arsenic. The maximum limit for bioavailability of arsenic from the accessible parts of a toy is set to 0.1 μg/day. This corresponds to an arsenic migration limit of 25 mg/kg for all toy material, including modeling clay and paints (Rastogi and Pritzl 1996). A study was carried out to determine whether crayons, water colors, and water-based paints conform with the migration limits for toxic metals (Rastogi and Pritzl 1996). For the analysis, 94 samples representing 48 products were obtained from China, Taiwan, Japan, the United States. and European countries. Fifty-two samples showed migration of arsenic, ranging from 0.01 to 3.75 ppm (μg/g).

Parents can inadvertently carry hazardous materials home from work on their clothes, skin, hair, tools, and in their vehicles (DHHS 1995). Falk et al. (1981b) reported a case of hepatic angiosarcoma in a child that could be associated with arsenic contamination of a parent's clothing, the water supply, and the environment. The father worked in a copper mine and smelter area where his clothing was contaminated with dust containing arsenic. His daughter, who exhibited a high degree of pica, ate dirt from the yard and licked dirt off her father's shoes. In a study of arsenic levels in homes in Hawaii, Klemmer et al. (1975) found higher levels in homes of employees of firms that used arsenic for pesticides or wood preservation, compared to homes where the residents did work that did not involve arsenic. The concentration of arsenic in dust from the homes of workers exposed to arsenic ranged from 5.2 to 1080 ppm (μg/g), compared to concentrations of 1.1–31 ppm in dust from control homes.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to individuals who are occupationally exposed to arsenic (see Section 5.5), there are several groups within the general population that have potentially high exposures (higher than background levels)

to arsenic. These populations include individuals living in proximity to sites where arsenic was produced or disposed, and individuals living near one of the 916 NPL hazardous waste sites where arsenic has been detected in some environmental media (HazDat 1998). Other populations at risk of exposure include recreational and subsistence fishers who typically consume larger amounts of locally caught fish and shellfish than the general population, Native American populations who are subsistence hunters, nursing infants and young children, and subsistence farmers and their families who consume their own farm-raised meat and dairy products.

A study was conducted to determine if significant arsenic exposure was occurring at a Superfund site in Fort Valley, Georgia (Hewitt et al. 1995). Random urine, 24-hour urine, hair, and fingernail samples were collected at the end of the workweek from 40 employees at an active pesticide manufacturing facility where arsenical pesticides had been produced for over 50 years prior to the mid-1970s. Measurement of arsenic in the urine is considered to be the best method for monitoring recent exposure in industrial populations. Hair and fingernail analyses may provide an indication of exposures that occurred up to several month prior to testing, but both can adsorb and strongly retain arsenic from external sources. Since arsenic is rapidly cleared from the blood (half-life of 3–4 hours), blood arsenic levels are not considered suitable for monitoring populations for chronic low-level arsenic exposure. Results of the Hewitt study are summarized in Table 5-4. Urinary arsenic levels for all workers were well within the commonly accepted normal range of <100 μg/L.

As noted above, workers in a number of industries may have high exposures to arsenic, especially if proper safety procedures are not followed. For members of the general population, above-average exposure to arsenic from drinking water is possible in areas of high natural arsenic levels in groundwater or elevated arsenic levels in drinking water due to industrial discharges, pesticide applications, or leaching from hazardous waste facilities. Individuals living in the vicinity of large smelters and other industrial emitters of arsenic may be exposed to above-average arsenic levels both in the air and, as a result of atmospheric deposition, in water and soil.

Smokers and those regularly consuming large amounts of seafood may also be exposed to higher-than-average levels of arsenic.

Recreational and subsistence fishers that consume appreciably higher amounts of locally caught fish from contaminated waterbodies may be exposed to higher levels of arsenic associated with dietary intake.

Table 5-4. Arsenic Biomonitoring Results

Matrix	Number	Arsenic concentration		
		Arithmetic mean	Geometric mean	Range
Random urine, μg/L	39	11.6	9.5	ND-57
24-hr urine, μg/L	39	11.0	7.5	ND-54
Hair, μg/g	35	0.78	0.19	ND-6.3
Fingernails, μg/g	36	0.79	0.27	ND-6.1

ND = not detected (laboratory detection limits: urine = 1 μg/L; hair and nails = 0.01 μg/g)

Source: Hewitt et al. 1995