3. HEALTH EFFECTS

3.1 INTRODUCTION

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

A glossary and list of acronyms, abbreviations, and symbols can be found in Chapter 10 and Appendix C.

The profile also contains a health consultation on tremolite asbestos, a name that has been used in the popular press to refer to fibrous amphibole that occurs in vermiculite ore from Libby Montana (Appendix F).

It is important to recognize that asbestos is not a single substance, but is the generic name for a family of six related polysilicate fibrous minerals of which one (chrysotile) belongs to the serpentine family and five (actinolite, amosite, anthophyllite, crocidolite, and tremolite) belong to the amphibole family. These minerals differ from each other in physical and chemical properties, and each mineral can exist in a wide range of fiber sizes. These differences between fiber type and, more importantly, fiber size (length and diameter) are believed to be important determinants of the health risks posed by asbestos.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those

that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of asbestos are indicated in Tables 3-1, 3-2, and 3-3 and Figures 3-1, 3-2 and 3-3. Because cancer effects could occur at lower exposure levels, Figures 3-1 and 3-4 show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

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

3.2.1 Inhalation Exposure

Units of Exposure. Consideration and comparison of quantitative data on asbestos inhalation studies are complicated by the fact that a number of different methods have been used to measure asbestos levels in air. Currently, the standard method for measuring asbestos concentrations in workplace air employs

phase contrast microscopy (PCM). A particle visible under PCM is counted as a fiber if it is $5 micrometers (µm) long and has a length/thickness ratio of $3:1. However, the method cannot detect fibers thinner than about 0.3 µm and cannot distinguish between asbestos fibers and other fibers (NIOSH 1987). Nevertheless, because currently available risk factors for asbestos are expressed in terms of PCM fibers, all air concentration data in this section are expressed in terms of PCM fibers/milliliter (f/mL) unless otherwise noted. It should be noted, however, that PCM analytical methods have improved substantially since early asbestos studies were performed, with an increase in numbers of fibers detected (Rickards 1994).

When data on airborne levels are available only in terms of mass/volume (e.g., mg/m^3), it is not possible to accurately convert these to units of PCM fibers/mL, because the ratio between mass and fiber number depends on fiber type and size distribution and because of the measuring technique employed. For the purposes of making rough calculations when a more accurate conversion factor is not available, it has been assumed that a concentration of 1 mg/m^3 in air is equal to 33 PCM f/mL (EPA 1986a).

Older occupational studies measured dust exposure in units of million particles per cubic foot (mppcf). This method did not distinguish fibrous from nonfibrous particles and used relatively low magnification, so only the largest particles and fibers were detectable. When a more accurate value is not available, it has been assumed that a concentration of 1 mppcf is equal to 3 PCM f/mL (BOHS 1968).

Overview of Health Effects. Studies in humans and animals indicate that inhalation of asbestos fibers may lead to fibrotic lung disease (asbestosis), pleural plaques and thickening, and cancer of the lung, the pleura, and the peritoneum. It may also increase the risk of cancer at other sites, but the evidence is not strong. Significant effects on other tissues have not been detected. A number of researchers have found that the occurrence of asbestosis and lung cancer correlates with cumulative exposure (that is, the product of concentration [PCM fibers/mL] multiplied by years of exposure). Therefore, human exposures are expressed below as PCM f-yr/mL. Animal data are provided in terms of exposure level (PCM f/mL) and duration, and the cumulative exposure can be found simply by calculating the product. However, due to differences in clearance rates and lifespan as well as other differences, cumulative doses in animals are not expected to be directly comparable to cumulative doses in humans. Studies that provide reliable dose-response information on the inhalation effects of asbestos in humans are summarized in Table 3-1 and Figure 3-1, and data in animals are summarized in Table 3-2 and Figure 3-2. The findings are discussed below.

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
INTERMEDIATE EXPOSURE							
Systemic							
1	Human	6 mo aver. (occup)	Resp		25.1 M (increased incidence of parenchymal & pleural radiographic abnormalities, > 20 yr after first exposure)		Ehrlich et al. 1992 AM
2	Human	12.7 mo, mean (1 d to 17.3 yr, range) (occup)	Resp			54 M (increased risk for fatal nonmalignant respiratory disease)	Levin et al. 1998 AM
3	Human	8 mo (SD= 14.9) (occup)	Resp		53.2 M (minor parenchymal & pleural radiographic changes in about 10% & 30% of subjects, 20 years after exposure)		Shepherd et al. 1997 AM
Cancer							
4	Human	12.7 mo, mean (1 d to 17.3 yr, range) (occup)				54 M (CEL: increased SMRs for lung cancer & pleural mesothelioma)	Levin et al. 1998 AM

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
CHRONIC EXPOSURE							
Systemic							
5	Human	7.9 yrs, median (occup)	Resp			32 M (slightly increased incidence of fatal nonmalignant or malignant respiratory disease with 20-40 year latency)	Albin et al. 1996 CH AM CR
6	Human	10+ yr (occup)	Resp	25 M	38 M (increased percentage (7%) of workers with early signs of respiratory impairment)		BOHS 1983 CH
7	Human	>20 yr, most cases	Resp			1271 M (autopsied cases of asbestosis with median lung fiber concentration, 41 f/ug tissue)	Case and Dufresne 1997 CH
8	Human	<10, 11-20, >20 yr (occup)	Resp	20 M	62 M (increased incidence of subjects with parenchymal & pleural abnormalities in chest x-ray)		Dave et al. 1997 NS
9	Human	1.1-2.7 yr (occup)	Resp	23 M		71 M (increased risk for fatal asbestosis)	de Klerk et al. 1991 CR
10	Human	10-30 yr (occup)	Resp	17		68 (increased SMRs for fatal pneumoconiosis)	Dement et al. 1994; Brown et al. 1994 CH
11	Human	>15 yr (occup)	Resp	2.6 M			Demers et al. 1998 NS

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
12	Human	6-14 yr (occup)	Resp		30 M (increased prevalence of breathlessness)	616 M (increased prevalence of breathlessness and low FVC)	Enarson et al. 1988 CH
13	Human	>9 yr (occup)	Resp			100 M (increased prevalence of fatal asbestosis & non-malignant respiratory disease)	Finkelstein 1983 CH CR
14	Human	9.9 & 7.5 yr, M&F (occup)	Resp	4	22 M (increased score for pulmonary fibrosis in autopsy cases; 3.3 on a scale of 12)	73 M (increased score for pulmonary fibrosis autopsy cases; 7.9 on a scale of 12)	Green et al. 1997 CH
15	Human	3-51 yr (occup)	Resp			300 M (increased prevalence of fatal asbestosis)	Henderson and Enterline 1979 CH CR AM
16	Human	3.8 yr aver. (occup)	Resp			99 M (fatal asbestosis with latency of +20 yr)	Hughes et al. 1987 CH CR AM
17	Human	1->20yr (occup)	Resp		70 M (5% excess of subjects with lung parenchymal abnormalities)		Irwig et al. 1979 CR AM
18	Human	19.7-21.1 yr (2.3-51 yr)	Resp	5 M	20 M (increased risk for profusion of opacities & wall thickening in chest x-rays)		Jakobsson et al. 1995b CH CR AM
19	Human	5-31 yr (occup)	Resp	18	207 (significantly increased incidence of chronic laryngitis)		Kambic et al. 1989 AM CH CR
20	Human	(occup)	Resp	45		195 M (increased rate of fatal pneumoconiosis)	Liddell et al. 1997 CH

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
21	Human	1-20 yr (occup)	Resp	15 M		45 M (increased rate of fatal nonmalignant respiratory disease)	McDonald et al. 1982 CH AM CR
22	Human	1-20 yr (occup)	Resp	90 M		180 M (increased rate of fatal nonmalignant respiratory disease)	McDonald et al. 1983 CH
23	Human	20+ yr (occup)	Resp			450 M (increased rate of fatal asbestosis)	Nicholson et al. 1979 CH
24	Human	>5 yr (occup)	Resp			170 M (increased rate of fatal nonmalignant respiratory disease)	Peto et al. 1985 CH CR
25	Human	NS (occup)	Resp	3.5		15 M (increased incidence of autopsy cases with slight to severe asbestosis, 16-30 yr after first exposure)	Sluis-Cremer 1991 CR AM
26	Human	15 yr aver. (occup)	Resp			20 M (cases of pulmonary fibrosis with functional impairment)	Wollmer et al. 1987 CH
	Cancer						
27	Human	> 3 mo (occup; full range not reported				26 M (CEL: mesothelioma)	Albin et al. 1990a CH CR AM
28	Human	7.9 yrs, median (occup)				32 M (CEL: mesothelioma)	Albin et al. 1996 CH AM CR

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL		Reference/ chemical form[b]
					Less serious (f-yr/mL)	Serious (f-yr/mL)	
29	Human	1-20 yr (occup)				400 M (CEL: lung cancer, mesothelioma)	Amandus and Wheeler 1987 TR AC
30	Human	40 yr residential (20-70 yr, range)				27 M (CEL: 4 M & 2F cases of mesothelioma in a 10-yr period among <200 villagers)	Coplu et al. 1996 TR
31	Human	1.0, 1.6 yr (occup)				55 M (CEL: lung cancer)	de Klerk et al. 1991; 1996 CR
32	Human	10-30 yr				5 M (CEL: increased SMRs for lung cancer)	Dement et al. 1994; Dement and Brown 1994; Brown et al. 1994 CH
33	Human	(occup)				180 M (CEL: lung cancer, gastrointestinal cancer, mesothelioma)	Enterline et al. 1987 CH CR AM
34	Human	>9 yr (occup)				44 M (CEL: lung cancer, mesothelioma)	Finkelstein 1983 CH CR
35	Human	1- >60 mo				14 M (CEL: mesothelioma)	Hansen et al. 1998 CR
36	Human	3-51 yr (occup)				180 M (CEL: lung cancer, mesothelioma)	Henderson and Enterline 1979 CH CR AM
37	Human	3.8 yr aver. (occup)				50 M (CEL: lung cancer, mesothelioma)	Hughes et al. 1987 CH CR AM

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
38	Human	NS (occup)				0.7 B (CEL: significant association between pleural malignant mesothelioma & asbestos occupational exposure; case/control study)	Iwatsubo et al. 1998 NS
39	Human	1->20 yr (occup)				1050 M (CEL: lung cancer)	Liddell et al. 1997 CH
40	Human	1-20 yr (occup)				90 M (CEL: lung cancer)	McDonald et al. 1982 CH AM CR
41	Human	1-20 yr (occup)				90 M (CEL: lung cancer)	McDonald et al. 1983 CH
42	Human	>2 yr (occup)				10 (CEL: lung cancer, gastrointestinal cancer and mesothelioma)	Newhouse and Berry 1979 CR CH AM
43	Human	20+ yr (occup)				450 M (CEL: lung cancer, mesothelioma)	Nicholson et al. 1979 CH
44	Human	>5 yr (occup)				72 M (CEL: lung cancer, mesothelioma)	Peto et al. 1985 CH CR

TABLE 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human Studies (continued)

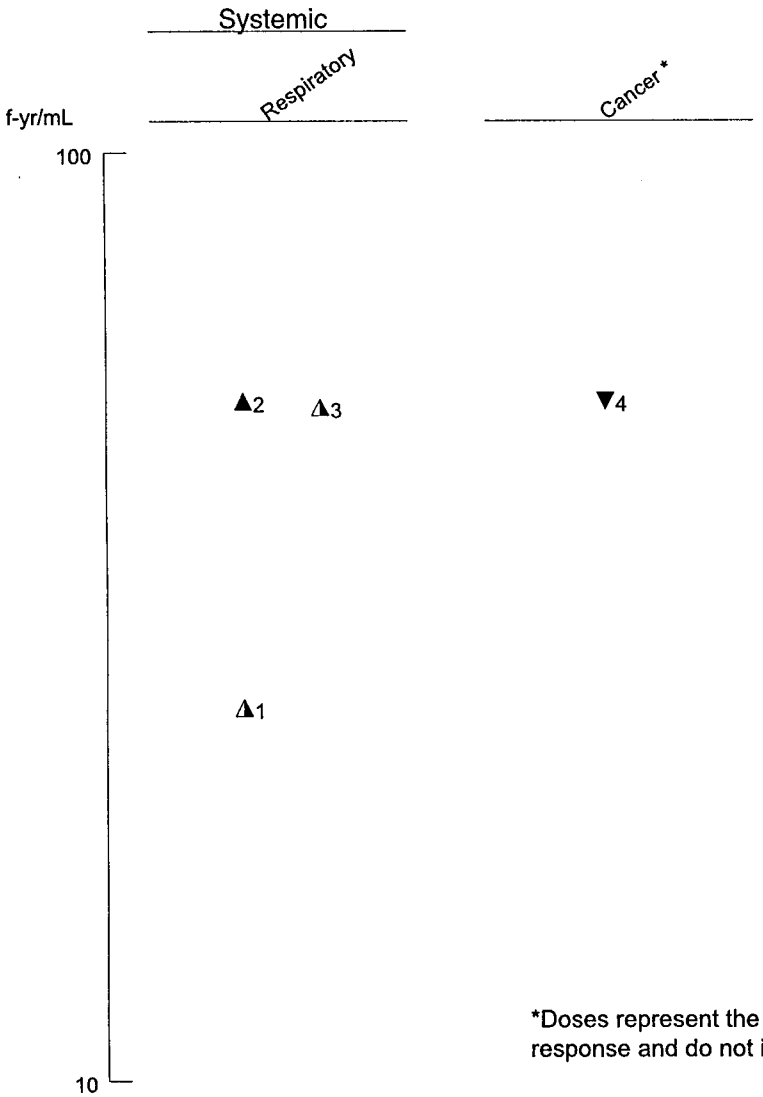
Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (f-yr/mL)	LOAEL Less serious (f-yr/mL)	LOAEL Serious (f-yr/mL)	Reference/ chemical form[b]
45	Human	<2 - >10 yr (occup)				450 M (CEL: lung cancer, mesothelioma)	Weill et al. 1979 CH CR AM

[a]The number corresponds to entries in Figure 3-1.
[b]The first type of asbestos listed below represents that which predominated in the workplace air; other secondary types that may have been present follow.

AC = actinolite; AM = amosite; aver. = average; B = both (male/female); CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); F = female; f/ug = fibers per microgram; FVC = forced vital capacity; f-yr/mL = fiber-years per milliliter; LOAEL = lowest-observed-adverse-effect-level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect-level; NS = not specified; (occup) = occupational; Resp = respiratory; SD = standard deviation; SMR = standard mortality ratio; TR = tremolite; yr = year(s)

Figure 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human studies

Intermediate (15-364 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	Δ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

Figure 3-1. Levels of Significant Exposure to Asbestos - Inhalation - Human studies (*continued*)

Chronic (≥365 days)

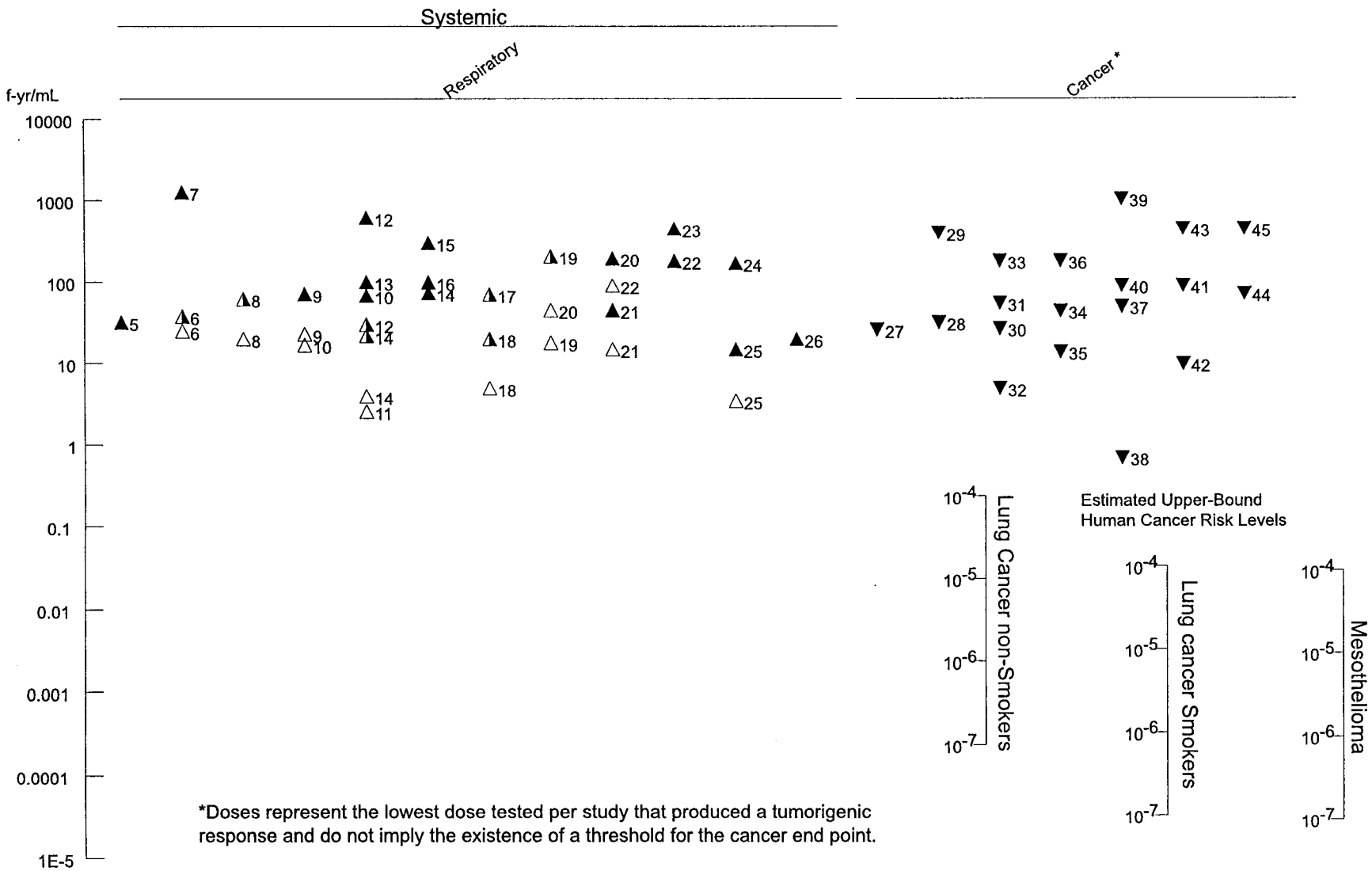


TABLE 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
ACUTE EXPOSURE							
Systemic							
1	Mouse B10.D2/nSn	5 hr	Resp			132 M (fibrosis)	McGavran et al. 1989 CH
INTERMEDIATE EXPOSURE							
Systemic							
2	Rat PVG	15 wk 5 d/wk 7 hr/d	Resp			330 M (diffuse fibrosis)	Donaldson et al. 1988a CH
CHRONIC EXPOSURE							
Systemic							
3	Rat Wistar	1 yr 1-5 d/wk 7 hr/d	Resp			70 M (fibrosis)	Davis et al. 1980a CH
4	Rat Wistar	1 yr 1-5 d/wk 7 hr/d	Resp			330 M (fibrosis)	Davis et al. 1980a AM
5	Rat NS	12 mo	Resp			330 (fibrosis)	Davis et al. 1980b AM CH
6	Rat Wistar	12 mo 5 d/wk 7 hr/d	Resp			1600 M (fibrosis)	Davis et al. 1985 TR
7	Rat Wistar	12 mo 5 d/wk 7 hr/d	Resp			2060 M (fibrosis)	Davis et al. 1986a AM-L

TABLE 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)		Reference/ chemical form
8	Rat CD	2 yr 4 d/wk 4 hr/d	Resp			54	(fibrosis)	Reeves et al. 1974 CH
9	Rat CD	2 yr 4 d/wk 4 hr/d	Resp			1105	(fibrosis)	Reeves et al. 1974 CR
10	Rat NS	2 yr 4 d/wk 4 hr/d	Resp			860	(fibrosis)	Reeves et al. 1974 AM
11	Rat Wistar	24 mo 5 d/wk 7 hr/d	Resp			350	(fibrosis)	Wagner et al. 1974 AM AN CR CH
12	Rat Wistar	12 mo 5 d/wk 7.5 hr/d	Resp			430	(fibrosis)	Wagner et al. 1980a CH
	Cancer							
13	Monkey Baboon	4 yr 5 d/wk 6 hr/d				1110 M	(CEL: mesothelioma)	Goldstein and Coetzee 1990 AM
14	Monkey Baboon	4 yr 5 d/wk 6 hr/d				1130	(CEL: mesothelioma)	Goldstein and Coetzee 1990 CH CR
15	Monkey Baboon	6 hr/d 5 d/wk up to 898 d				1100 M	(CEL: pleural and peritoneal mesothelioma)	Webster et al. 1993 AM
16	Rat Wistar	1 yr 5 d/wk 7 hr/d				1170	(CEL: lung adenoma, adenocarcinoma, and mesothelioma)	Davis and Jones 1988 CH-S

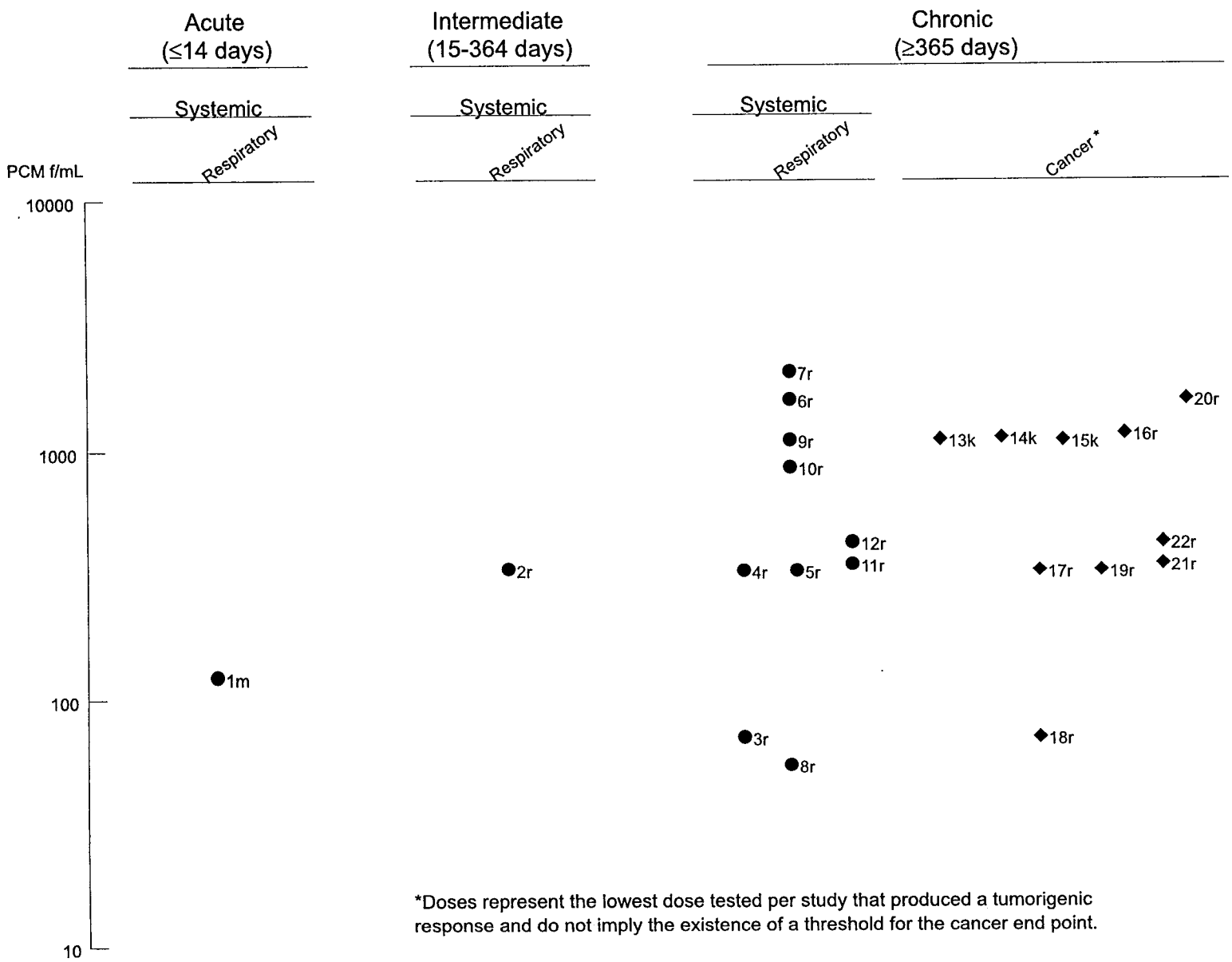
TABLE 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal Studies (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (PCM f/mL)	LOAEL Less serious (PCM f/mL)	LOAEL Serious (PCM f/mL)	Reference/ chemical form
17	Rat Wistar	1 yr 1-5 d/wk 7 hr/d				330 M (CEL: lung carcinomas, adenocarcinomas)	Davis et al. 1980a AM
18	Rat Wistar	1 yr 1-5 d/wk 7 hr/d				70 M (CEL: lung adenomas, adenocarcinomas, and squamous carcinomas)	Davis et al. 1980a CH
19	Rat NS	12 mo				330 (CEL: lung adenomas and carcinomas)	Davis et al. 1980b AM CH
20	Rat Wistar	12 mo 5 d/wk 7 hr/d				1600 M (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Davis et al. 1985 TR
21	Rat Wistar	24 mo 5 d/wk 7 hr/d				350 (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Wagner et al. 1974 AM AN CR CH
22	Rat Wistar	12 mo 5 d/wk 7.5 hr/d				430 (CEL: lung adenoma, adenocarcinoma, squamous carcinoma, and mesothelioma)	Wagner et al. 1980a CH

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

AM = amosite; AN = anthophyllite; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); PCM f/mL = phase contrast microscopy fibers per milliliter; hr = hour(s); L = long; LOAEL = lowest-observed-adverse-effect-level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect-level; Resp = respiratory; S = short; TR = tremolite; wk = weeks(s); yr = year(s)

Figure 3-2. Levels of Significant Exposure to Asbestos - Inhalation - Animal studies



3.2.1.1 Death

No studies were located in which acute- or intermediate-duration inhalation exposure to asbestos led to lethality in humans or animals. Inhalation exposure to asbestos can lead to death or a shortened lifespan from asbestosis or cancer, as discussed in Sections 3.2.1.2 and 3.2.1.8, respectively.

3.2.1.2 Systemic Effects

No studies were located regarding significant hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, or metabolic effects in humans or animals after inhalation exposure to asbestos. Systemic effects observed after inhalation exposure and discussed below include respiratory, cardiovascular, and gastrointestinal effects. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects are summarized in Tables 3-1 and 3-2, and plotted in Figures 3-1 and 3-2.

Respiratory Effects. Numerous studies in humans have established that inhalation exposure to asbestos fibers can lead to a characteristic pneumoconiosis termed asbestosis. Published definitions of asbestosis generally concur that it is a diffuse interstitial fibrosis of the lungs caused by the inhalation of asbestos fibers (American Thoracic Society 1986; International Expert Meeting on Asbestos 1997; Mossman and Churg 1998). Persons with fully developed asbestosis have shortness of breath (dyspnea), often accompanied by rales or cough (Churg 1986a; Enarson et al. 1988; Finkelstein 1986), and display deficits in pulmonary function variables such as forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (Glencross et al. 1997; Kilburn and Warshaw 1994; Miller et al. 1994; Rom 1992; Schwartz et al. 1994; Shepherd et al. 1997). In severe cases, impairment of respiratory function may ultimately result in death, and asbestosis has been associated with excess mortality in a number of groups of asbestos workers (Armstrong et al. 1988; de Klerk et al. 1991; McDonald et al. 1983; Peto et al. 1985; Selikoff et al. 1979).

Available evidence indicates that all asbestos fiber types are fibrogenic, although there may be some differences in potency among fiber types (Bignon and Jaurand 1983; Churg 1993; Davis 1972; EPA 1986a; Kamp and Weitzman 1997; McDonald et al. 1999). Most studies in humans have involved exposure to predominantly chrysotile, the most widely used type of asbestos (Albin et al. 1996; Berry et al. 1979; BOHS 1983; Case and Dufresne 1997; Cullen and Baloyi 1991; Dement et al. 1983; McDonald et al. 1983, 1984, 1999; Nicholson et al. 1979), but asbestosis has also been noted in populations exposed

mainly to amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; de Klerk et al. 1991, 1996; Luo et al. 1992; Sluis-Cremer 1991; Wignall and Fox 1982), tremolite (McDonald et al. 1986a), and anthophyllite (Meurman et al. 1974; Sluis-Cremer 1991). A number of animal studies have indicated that long fibers (e.g., 5 μm or more) have a higher fibrogenic activity, while short fibers have a lower fibrogenic activity (Adamson and Bowden 1987a, 1987b; Davis and Jones 1988; Davis et al. 1986a; Platek et al. 1985). This relationship may be associated with the inability of macrophages to engulf and remove fibers that are significantly larger than themselves (Bignon and Jaurand 1983).

Results from human studies, however, suggest that short asbestos fibers may also play a role in pulmonary fibrosis. In autopsy studies of groups of chrysotile miners and millers (Churg et al. 1989a) and amosite-exposed shipyard and insulation workers (Churg et al. 1990) with asbestosis, histologically-graded fibrosis was positively correlated with mean amphibole fiber concentration in lung tissue, but was negatively correlated with mean amphibole fiber length. Churg et al. (1989a, 1990) noted that the inverse relationship between degree of fibrosis and amphibole fiber length was suggestive that short fibers may be more important in the genesis of pulmonary fibrosis than was commonly believed based on the findings from animal studies showing a positive relationship between fiber length and fibrogenic activity. Case (1994) noted, however, that men with asbestosis in the group of autopsied chrysotile miners and millers showed lung concentrations of tremolite fibers longer than 8 μm that were higher than concentrations in men without asbestosis, and that six of seven miners/millers having any chrysotile or tremolite fibers longer than 20 μm had asbestosis. The latter observations suggest the importance of longer fibers. Case (1994) hypothesized that the greater concentrations of long tremolite fibers in these cases of asbestosis might also produce increased levels of shorter fibres (at autopsy) due to fiber breakage with time of retention in the lung. Case (1994) suggested that the counting method employed by Churg et al. (1989a, 1990) (that included short fibers down to the limits of detection) may more accurately quantify short fiber fragments, and that the fiber size class that is most responsible for fibrosis is unclear. Case (1994) further hypothesized that long fibers may initiate events, and that shorter fiber fragments, once they are present, may have increased effects on macrophage activity and subsequent fibrosis. Surface area has been proposed to play a role in amphibole fiber toxicity (Lippmann 1988), and, since shorter, thinner fibers have proportionally greater surface areas than longer, thicker fibers, may be involved in the inverse relationship observed by Churg et al. (1989a, 1990).

As shown in Table 3-1 and Figure 3-1, cumulative exposure levels that have been associated with radiographic, histologic, spirometric, or clinical signs of lung fibrosis in groups of chronically exposed workers include 38 f-yr/mL in British asbestos textile factory workers (BOHS 1983), 62 f-yr/mL in

Indian asbestos cement workers (Dave et al. 1997), 30 f-yr/mL in British Columbian chrysotile miners and millers (Enarson et al. 1988), 22 f-yr/mL in autopsied cases of deceased South Carolina chrysotile textile factory workers (Green et al. 1997), 10–30 f-yr/mL (midpoint=20 f-yr/mL) in Swedish asbestos cement workers (Jakobsson et al. 1995b; Wollmer et al. 1987), 70 f-yr/mL in South African crocidolite and amosite miners (Irwig et al. 1979), and 15 f-yr/mL in autopsied cases of deceased crocidolite and amosite miners and millers (Sluis-Cremer 1991).

Table 3-1 and Figure 3-1 also show that significantly increased mortality rates associated with asbestosis or other nonmalignant respiratory disease have been reported in groups of exposed workers with cumulative exposure estimates ranging from 32 to 1,271 f-yr/mL (Albin et al. 1996; Brown et al. 1994; Case and Dufresne 1997; de Klerk et al. 1991; Dement et al. 1994; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; Liddell et al. 1997; Nicholson et al. 1979; Peto et al. 1985; Sluis-Cremer 1991).

Whereas these studies involved chronic exposure to asbestos, increased incidences of radiographic abnormalities indicative of pulmonary fibrosis have been found in studies of New Jersey and Texas workers involved in the manufacture of amosite-insulated materials who were predominantly exposed for intermediate durations (medians of 6–12 months) at fiber concentrations that were as high as 5–100 f/mL, many fold higher than the current U.S. permissible exposure limit for workplace air, 0.1 f/mL (Ehrlich et al. 1992; Levin et al. 1998; Shepherd et al. 1997). These studies add to the evidence that asbestos-induced respiratory disease can take a long time (10–20 years) to develop and, in some individuals, continues to progress long after exposure has ceased (Finkelstein 1986; Mossman and Churg 1998; Wagner et al. 1974). Churg (1993) noted that early cases of asbestosis, when workplace air fiber concentrations were very high, had shorter latent development periods (5–6 years), compared with estimates of 10–20 years latency from studies of workers more recently exposed to lower fiber concentrations. This comparison suggests that there is an inverse relationship between intensity of exposure and time of disease development.

Several of the studies of occupationally exposed workers in Table 3-1 and Figure 3-1 provide general descriptions of exposure-response relationships for asbestos-induced nonmalignant respiratory effects, showing increasing severity or incidence of disease with increasing cumulative exposure and providing some indications of no-effect levels ranging from 2.6 to 90 f-yr/mL for signs of asbestosis or increased mortality associated with asbestosis (BOHS 1983; Dave et al. 1997; de Klerk et al. 1991; Dement et al. 1994; Demers et al. 1998; Green et al. 1997; Jakobsson et al. 1995b; Liddell et al. 1997; McDonald et al.

1983; Sluis-Cremer 1991; Wollmer et al. 1987). There are several complexities, however, in defining exposure-response relationships for asbestos-induced pulmonary fibrosis that make it difficult to derive reliable risk estimates for low-level exposure from the available studies. The complexities include uncertainties in exposure assessments for the studied workers, the variability among estimates of risk from various studies, inconsistent adjustment across studies for the possible confounding effect of tobacco smoking on development of pulmonary fibrosis, the possibility of differences in potency among different types of asbestos, the possibility of differential misdiagnosis and/or different end points in different studies, the likelihood of disease progression after exposure ceases, and the likelihood that mortality studies underestimate occurrence of asbestosis since asbestosis does not always cause death.

Another difficulty arises from the use of cumulative exposure (the product of exposure duration x intensity) as a surrogate exposure metric in the available studies. Finkelstein (1995) noted that the use of cumulative exposure requires the assumption that duration and intensity are equally important in determining the effective dose. Finkelstein further noted that if exposure estimates are inaccurate or inconsistently measured (which can be the case for many retrospective epidemiology studies), a finding of a statistically significant association between cumulative exposure and a health outcome can mislead one in having confidence in an apparent exposure-response relationship that is principally influenced by duration of exposure and not by exposure intensity.

In a recent review of the epidemiological evidence for asbestosis exposure-response relationships, the World Health Organization Task Group on Environmental Health Criteria for Chrysotile Asbestos (WHO 1998) concluded that “asbestotic changes are common following prolonged exposures of 5 to 20 f/mL” (these correspond to cumulative exposures of 50–200 f-yr/mL for a 10-year exposure) and that “the risk at lower exposure levels is not known.” This group further concluded that although there may be subclinical respiratory changes induced by chrysotile at current levels of occupational exposure, “they are unlikely to progress to the point of clinical manifestation.”

Presenting an alternative viewpoint, Stayner et al. (1997) statistically analyzed updated asbestosis-related mortality data for a cohort of South Carolina asbestos textile workers (the same data reported by Brown et al. 1994 and Dement et al. 1994) and predicted, by extrapolation, an excess lifetime risk of 2/1,000 for asbestosis mortality in white men exposed for 45 years at the Occupational Safety and Health Administration (OSHA) permissible exposure level for all forms of asbestos of 0.1 f/mL (4.5 f-yr/mL). Stayner et al. (1997) noted five major areas of uncertainty associated with this estimate including the extrapolation from relatively high exposure intensity to low intensity (average for the cohort was about

6 f/mL), the questionable accuracy of the exposure estimates for the cohort members, the absence of information on individual smoking habits in this cohort, the likelihood of disease misclassification, and the selection of an appropriate statistical model.

Several authors consider the mortality experience of the Carolina textile cohort to be atypical relative to other asbestos-exposed cohorts and, in the absence of a reliable explanation of this uniqueness, have cautioned against its use in quantitative health assessments for other exposure scenarios to asbestos fibers (Case et al. 2000; Hodgson and Darnton 2000). Estimates of lung cancer risk based on the South Carolina cohort are notably higher than estimates derived from other occupational cohorts exposed to predominately chrysotile asbestos (e.g., the Quebec chrysotile miner and miller cohort) or to mixed types of asbestos in other textile operations (Dement et al. 1994; Hodgson and Darnton 2000; Liddell et al. 1997, 1998; McDonald 1998b; Stayner et al. 1997). Stayner et al. (1997) acknowledged this difference, but concluded that "it would be prudent" to use estimates of risk from both cohorts to predict a range of potential risks for current occupational scenarios. The reasons for the difference are unknown, but may apply to both asbestosis and lung cancer. Proposed explanations include the possibility of uniform underestimation of exposure in the Carolina cohort, the possibility of exposure to longer and thinner fibers in the Carolina textile mill, and the possibility that mineral oil that was used to spray the raw fiber in Carolina (as a dust suppression measure) may have contributed to the increased incidence of lung cancer, but evidence for or against any of these possibilities is not strong (Case et al. 2000; Dement et al. 1994; McDonald 1998b; Stayner et al. 1997). For example, comparison of lung fiber concentrations in autopsied individuals from the Carolina and Quebec cohorts provide confirmatory information that the Quebec cohort was likely exposed to higher air concentrations of asbestos fibers of all length categories (including those >18 μm in length) than the Carolina cohort, although when all fibers were considered together, the mean fiber length of detected fibers in the Carolina group was greater than that of the Quebec cohort (Case et al. 2000; Sebastien et al. 1989). In an internal case-control analysis of the Carolina textile mortality experience, odds ratios for lung cancer were not significantly different among groups of subjects with different probable levels of oil exposure (Dement et al. 1994), but others have questioned the ability to correctly assign subjects in the cohort to oil exposure categories (Hodgson and Darnton 2000; McDonald 1998b).

A chronic inhalation MRL for asbestos-induced nonmalignant respiratory disease has not been derived (as reflected by a lack of MRL designation in Table 3-1 and Figure 3-1), because of the large degree of uncertainty in extrapolating to low levels of exposure from the available epidemiological data for workers with high levels of exposure (see also Chapter 2). The use of the data for the South Carolina textile

workers, the Quebec chrysotile miners and millers, or other occupational cohorts to estimate risk for development of fatal asbestosis with chronic exposure to asbestos at fiber concentration ranges likely to be encountered in ambient, nonoccupational outdoor or indoor air (about $3x10^{-6}$ to $6x10^{-3}$ PCM f/mL, see Chapter 6 for more information) would require additional extrapolation, and be even more uncertain, than the risk estimate for exposure to 0.1 f/mL from the Stayner et al. (1997) analysis.

Inhalation of asbestos fibers can lead not only to injury to the lung parenchyma, but also to a number of changes in the pleura (Boutin et al. 1989; Churg 1986a; Ehrlich et al. 1992; Jones et al. 1988b). The most common lesions are pleural plaques. These are generally oval areas of acellular collagen deposits, usually located on the inferior and posterior surfaces of the pleura. Diffuse thickening and fibrosis of the pleura may also occur, as may pleural effusions. The incidence of pleural abnormalities (usually detected by x-ray examination) is often quite high (10–60%) in people employed in asbestos-related occupations for subchronic (Ehrlich et al. 1992) and chronic durations (Amandus et al. 1987; Anton-Culver et al. 1989; Baker et al. 1985; Bresnitz et al. 1993; Gibbs 1979; Hsiao et al. 1993; Jarvholm et al. 1986; McDonald et al. 1986b; Ohlson et al. 1985; Ren et al. 1991; Viallat and Boutin 1980). Pleural abnormalities are also common in household contacts and family members of asbestos workers (where exposure is presumably due to asbestos carried home on the work clothes) (Anderson et al. 1976, 1979), in people living in areas where tremolite asbestos-containing whitewash materials have been used (Baris et al. 1988b; Constantopoulos et al. 1985, 1987b; Çöplü et al. 1996; Dumortier et al. 1998; Metintas et al. 1999; Sakellariou et al. 1996; Yazicioglu et al. 1980), and in people who live in regions with high asbestos levels in the soil (Boutin et al. 1989; Churg and DePaoli 1988; Jarvholm et al. 1986; Luo et al. 1992; Rey et al. 1993). An elevated incidence of pleural abnormalities (3.7%) was noted in long-time (70-year) residents of an area with elevated levels of asbestos in soil (Boutin et al. 1989). Cumulative exposure to asbestos in these residents was estimated to be 0.12 f-yr/mL. The incidence of pleural abnormalities (specifically, pleural thickening) in members of the general population of the United States was found to be 2.3% in males and 0.2% in females, most of which is probably due to occupational exposure to asbestos (Rogan et al. 1987). The health significance of asbestos-induced pleural abnormalities is not precisely defined; some researchers consider pleural plaques to be essentially benign (Jones et al. 1988b; Ohlson et al. 1984, 1985), whereas others have noted isolated pleural plaques to be associated with decreased ventilatory capacity (Bourbeau et al. 1990). In addition, some investigators (Edelman 1988c; Hillerdal 1994; Hillerdal and Henderson 1997; Nurminen and Tossavainen 1994) have suggested that pleural plaques are predictors of increased risk for lung cancer, whereas another analysis (Weiss 1993) have suggested that they are not. Diffuse pleural thickening can lead to decreased ventilatory capacity, probably because of the restrictive effect of pleural fibrosis (Baker et al. 1985; Britton 1982; Churg

1986a; Jarvholm and Larsson 1988; Jones et al. 1988b; McGavin and Sheers 1984; Miller et al. 1992; Rom and Travis 1992; Schwartz et al. 1990). In some cases, pulmonary impairment from pleural thickening can be very severe, even causing death (Miller et al. 1983).

Asbestos exposure may also produce adverse effects in the upper airways. A statistically significant higher incidence of laryngitis was noted in workers with chronic cumulative exposures >27 f-yr/mL compared with controls and exposed workers with cumulative exposures <18 f-yr/mL (Kambic et al. 1989; Parnes 1990). Although this effect has not been reported in a large number of studies, it is consistent with the idea of asbestos acting as an irritant on the laryngeal mucosa.

Fibrosis has been produced in animals by inhalation or by intratracheal exposure to chrysotile (Chang et al. 1988; Davis et al. 1980a, 1980b; Donaldson et al. 1988a; Green et al. 1986; Hesterberg et al. 1995, 1996, 1997; Mast et al. 1994, 1995; McGavran et al. 1989; Wagner et al. 1980a), amosite (Davis et al. 1986a; Reeves et al. 1971, 1974; Webster et al. 1993), anthophyllite (Wagner et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), and tremolite (Davis et al. 1985; Green et al. 1986; Sahu et al. 1975). There are some data from animal studies to suggest that crocidolite causes more severe inflammatory disease than chrysotile and is retained longer within the lungs (Berube et al. 1996; McConnell et al. 1994). As shown in Table 3-2 and Figure 3-2, fibrosis has been noted in rodents after exposure to 132 f/mL for 5 hours (McGavran et al. 1989), exposure to 330 f/mL for 7 hours/day, 5 days/week for 15 weeks (Donaldson et al. 1988a), and chronic exposure to 54–2,060 f/mL (Davis et al. 1980a, 1980b, 1985, 1986a; Reeves et al. 1974; Wagner et al. 1974, 1980a). In animals, histological signs of tissue injury can be detected at the site of deposited fibers within a few days, although in humans, measurable abnormalities of lung function do not usually appear for a number of years (Dement et al. 1983; Hughes et al. 1987; Kagan 1988; Schwartz et al. 1993).

Studies in animals indicate that asbestosis stems from the inflammatory response triggered in the lung by the deposition of asbestos fibers (Davis 1970; Quinlan et al. 1995), and that the inflammatory response to asbestos is enhanced by multiple exposures to asbestos fibers (Coin et al. 1996). Fibers deposited in the ciliated portion of the airway are removed by mucociliary transport (see Section 3.4.4) and do not appear to injure the lung. However, fibers deposited in the terminal bronchioles and alveoli are not cleared as rapidly, and these can stimulate an influx of macrophages (Chang et al. 1988), which then release a variety of inflammatory mediators (chemoattractants, lysosomal enzymes, activated oxygen species, growth factors, etc.) (Davis 1972; Hansen and Mossman 1987; Kagan 1988; Miller et al. 1978; Schwartz et al. 1993). This is thought to be responsible for the gradual loss of some epithelial cells and the

deposition of collagen by fibroblasts (Davis and Jones 1988; Davis et al. 1986c). With continued duration of exposure to asbestos fibers, increasing amounts of fibers are found in the lung interstitium and are associated with progressive interstitial fibrotic reactions (Pinkerton et al. 1984).

One of the many growth factors found in fibrotic lungs is tumor necrosis factor α (TNF-α). TNF-α is a powerful inducer of epithelial and mesenchymal cell proliferation which has been suggested as a central mediator of fibrotic lung disease. A recent study has demonstrated that genetically-altered mice without TNF-α receptor fail to develop fibro-proliferative lesions in response to asbestos exposure (Liu et al. 1998).

Cardiovascular Effects. No studies were located regarding a direct effect upon the cardiovascular system in humans after inhalation exposure to asbestos. However, increased ($p<0.01$) mortality from cardiovascular disease in workers exposed to asbestos has been reported (Doll 1955). Fibrosis of the lung can lead to increased resistance to blood flow through the pulmonary capillary bed, leading in turn to pulmonary hypertension and compensatory hypertrophy of the right heart (Selikoff and Lee 1978). This condition is known as cor pulmonale. Cor pulmonale may be detected by standard clinical and radiological tests of cardiac function and by changes in the electrocardiogram (Kokkola and Huuskonen 1979), although this is not a very sensitive test (Selikoff and Lee 1978). Cor pulmonale is usually associated with severe cases of asbestosis (Lemen et al. 1980), although pulmonary hypertension has been reported in some cases prior to measurable decreases in respiratory function (Tomasini and Chiappino 1981). Limited data from case reports suggest that constrictive pericarditis due to fibrous thickening may result from asbestos exposure (Davies et al. 1991).

No studies were located regarding cardiovascular effects in animals after inhalation exposure to asbestos.

Gastrointestinal Effects. The majority of asbestos fibers that are deposited in the respiratory tract during inhalation exposure are transported by mucociliary action to the pharynx, where they are swallowed (see Section 3.4). Consequently, the gastrointestinal epithelium is also directly exposed to fibers. While there is some evidence that inhalation exposure to asbestos may increase the risk of gastrointestinal cancer in humans (see Section 3.2.1.8), no information was located to indicate that any nonneoplastic effects occur in the gastrointestinal system after inhalation exposure.

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to asbestos.

3.2.1.3 Immunological and Lymphoreticular Effects

A number of studies have investigated the status of the immune system in humans who have been exposed to asbestos. Although there is some variability, most studies indicate that cell-mediated immunity (measured by tests of dermal sensitization *in vivo* and lymphocyte responsiveness and function *in vitro*) is depressed in workers who have radiological evidence of asbestosis (deShazo et al. 1988; Gaumer et al. 1981; Kagan et al. 1977; Lange et al. 1986). For example, natural killer (NK) cells (unique lymphocytes thought to be a first line of defense against cancer cells) isolated from peripheral blood of patients with asbestosis had impaired cytotoxic potency (Kubota et al. 1985; Tsang et al. 1988). Additionally, decreased NK cell activity and increased NK cell number were noted in the peripheral blood of retired asbestos cement workers (Froom et al. 2000). Alterations in lymphocyte (Sprince et al. 1991, 1992) and leukocyte (Hurbankova and Kaiglova 1993) distribution have been noted in asbestos-exposed workers. Increased numbers of lymphocytes and $CD4^+$ cells were reported in men with occupational exposure to asbestos (Rom and Travis 1992), although numbers of total circulating lymphocytes were similar in asbestos workers compared to controls in another study (Al Jarad et al. 1992). Mediastinal lymph node enlargement has been reported in asbestosis patients (Sampson and Hansell 1992). Increased levels of IgA and IgG have been reported in asbestos-exposed individuals (Hurbankova and Kaiglova 1993; Nigam et al. 1993), and concentrations of autoantibodies (rheumatoid factor, antinuclear antibodies) tend to be abnormally high in asbestos-exposed workers (Anton-Culver et al. 1988; Pernis et al. 1965; Warwick et al. 1973; Zerva et al. 1989). In some cases, increased autoantibodies can lead to rheumatoid arthritis (Caplan's Syndrome), although this is more common in coal miners and workers with other pneumoconioses than in workers with asbestosis (Constantinidis 1977; Greaves 1979). Immunological abnormalities are usually mild or absent in asbestos-exposed workers who have not developed clinical signs of asbestosis (deShazo et al. 1988; Kagan 1988; Selikoff and Lee 1978; Warwick et al. 1973). Although the biological significance of these immunological changes is difficult to judge, they are of special concern because depressed immune function might be a factor in the etiology of asbestos-induced cancer (Lew et al. 1986). Exposures to asbestos associated with immunological effects generally have not been quantified.

Results from animal studies provide supporting evidence of direct and indirect effects of asbestos on the immune system, although the specific roles of these effects in the etiology of asbestos-induced pulmonary diseases are not well understood and are under current investigation. In support of observations of suppressed activity of peripheral natural killer cells in patients with asbestosis, the number and cytotoxic activity of interstitial pulmonary natural killer cells were found to be decreased in mice exposed to

inhaled chrysotile fibers (13.3 mg/m^3) 3 hours/day for 3 days compared with nonexposed controls (Rosenthal et al. 1998). In support of asbestos-induced hyperactivity of humoral immunity, humans occupationally exposed to crystalline asbestos display elevated serum γ-globulins (Lange et al. 1974). Results from experiments with genetically immunodeficient mice support the hypotheses that T lymphocytes may play a protective role against asbestos-induced lung inflammation and subsequent fibrotic responses, and that impaired cell-mediated immunity may be a predisposing factor in asbestos fibrosis. In these experiments, immunodeficient mice showed a larger increase in cell numbers in pulmonary lavage fluid (predominantly due to increase in neutrophils) and increased severity of pulmonary lesions in response to inhaled asbestos compared with immunologically normal mice of the same background or immunologically deficient mice that were "reconstituted" with lymphocytes (Corsini et al. 1994).

No studies were located regarding the following effects in humans or animals after inhalation exposure to asbestos:

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

A voluminous body of evidence establishes that inhalation exposure to asbestos increases the risk of lung cancer and mesothelioma in humans and animals. Some evidence suggests that inhalation exposure to asbestos increases the risk of cancer at other sites as well (especially the gastrointestinal tract). Each of these carcinogenic effects are discussed separately below.

Lung Cancer. Evidence for the role of asbestos in human lung cancer is derived primarily from studies of the cause of death of occupationally-exposed workers. For example, the causes of death in a very large cohort of insulation workers (17,800 men) in the United States and Canada have been studied (Selikoff et al. 1979). Between 1967 and 1976, there were 2,271 deaths in this group, of which 486 were attributable to lung cancer. This is 4.6 times the number of lung cancer deaths that would have been expected in this group based on the lung cancer rates in the average male population of the United States. Similar findings have been reported in a very large number of analogous studies under a wide variety of occupational circumstances. In a review, a statistically significant ($p<0.05$) increase in lung cancer death rates had been reported in 32 of 41 recent studies (EPA 1986a). In a recent meta-analysis of 69 asbestos-

exposed occupational cohorts reporting on cancer morbidity and mortality, Goodman et al. (1999) calculated a lung cancer meta-standard mortality ratio (SMR) of 1.63 (95% confidence interval [CI]=1.58–1.69); the highest meta-SMR (1.92, CI=95%=1.76–2.09) was among asbestos products manufacturing workers. Lung cancer has also been reported in household contacts and family members of asbestos workers, where exposure is presumably due to asbestos carried home on the work clothes (Magnani et al. 1993).

There is little doubt that all types of asbestos can cause lung cancer. For example, statistically significant increases in lung cancer mortality have been reported in workers exposed primarily to chrysotile (Case and Dufresne 1997; Dement et al. 1983, 1994; Huilan and Zhiming 1993; Liddell et al. 1997, 1998; McDonald et al. 1980, 1983, 1984, 1993, 1997; Nicholson et al. 1979), amosite (Seidman et al. 1979), crocidolite (Armstrong et al. 1988; de Klerk et al. 1989, 1991, 1996; Sluis-Cremer 1991; Wignall and Fox 1982), anthophyllite (Meurman et al. 1974, 1994), and tremolite (Amandus and Wheeler 1987; Kleinfeld et al. 1974; McDonald et al. 1986a), or to multiple fiber types (Albin et al. 1996; Enterline et al. 1987; Henderson and Enterline 1979; Hughes et al. 1987; Magnani and Leporati 1998; McDonald et al. 1982; Newhouse and Berry 1979; Peto et al. 1985; Weill et al. 1979).

As with most carcinogenic agents, there is a substantial latency period (10–40 years in humans) between the onset of exposure to asbestos and the occurrence of lung cancer (Dement et al. 1983; Huilan and Zhiming 1993; McDonald et al. 1983; Nicholson et al. 1979; Selikoff et al. 1979; Sluis-Cremer 1991). After sufficient time (e.g., 20 years), the risk of lung cancer in exposed workers is generally observed to increase in proportion to the cumulative exposure (f-yr/mL). Most researchers have found that the chances that asbestos exposure will lead to lung cancer depends not only on the cumulative dose of asbestos, but also on the underlying risk of lung cancer due to other factors (Enterline et al. 1987; EPA 1986a; McDonald et al. 1982, 1983; Peto et al. 1985). For example, asbestos exposure results in a greater increase in lung cancer risk in smokers than nonsmokers, possibly because smokers have a higher underlying risk of lung cancer than nonsmokers. Alternatively, the greater increase in lung cancer risk in smokers may be due to a synergism between tobacco smoke and asbestos fibers. (see Section 3.9 for additional discussion of the interaction between smoking and asbestos).

Using a predictive model based on an analysis of 11 sets of lung cancer mortality data for groups of textile production workers (Dement et al. 1983; McDonald et al. 1982, 1983; Peto 1980), friction products workers (Berry and Newhouse 1983; McDonald et al. 1984), insulation products workers (Seidman 1984; Selikoff et al. 1979), and cement products workers (Finkelstein 1983; Henderson and

Enterline 1979; Weill et al. 1979), EPA (1986a) estimated that continuous lifetime exposure to air containing 0.0001 f/mL of asbestos would result in about two cases of lung cancer per 100,000 smokers, a factor of 10 higher than that estimated for nonsmokers (0.2 per 100,000). EPA (1986a) excluded available data for asbestos miners and millers (McDonald et al. 1980; Nicholson et al. 1979; Rubino et al. 1979) from the analysis, based on the judgement that fiber characteristics of "preprocessed" asbestos in these environments would be different from those of "processed" asbestos fibers in the general environment. The corresponding cumulative lifetime exposures associated with excess risks of 10^{-7}–10^{-4} are shown in Figure 3-1. For smokers, cumulative exposures of 0.000035, 0.00035, 0.0035, and 0.035 f-yr/mL represent excess lung cancer risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} respectively. For nonsmokers, cumulative exposures of 0.00035, 0.0035, 0.035, and 0.35 f-yr/mL represent excess lung cancer risks of , 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} respectively. Appendix D provides further details on the derivation of these risk estimates. While these values have been considered to be the best available for assessing risk from environmental exposures to airborne asbestos, the range of uncertainty is probably a factor of 2.5–10 (EPA 1986a). Currently (in 2001), EPA is in the process of reviewing their cancer risk estimates for asbestos fibers.

Several authors have suggested that the EPA model may overestimate the lung cancer risk from exposure to asbestos (Camus et al. 1998; Hughes 1994; Lash et al. 1997). An alternative statistical analysis of studies relating occupational cumulative exposure to asbestos and lung cancer mortality arrived at lung cancer potency estimates that were 4- to 24-fold lower than the EPA model potency estimate (Lash et al. 1997). Hughes (1994) noted that exclusion of the chrysotile asbestos miner and miller data in the EPA analysis led to a higher estimate of potency (i.e., slope of the exposure-response relationship) than would have been obtained if the data were included, and suggested that a lower potency estimate would be more appropriate for populations exposed to nontextile chrysotile such as that used in buildings. Camus et al. (1998) reported that the EPA model predicted a relative risk for death from lung cancer in a group of nonoccupationally exposed women who lived in two regions of Quebec with chrysotile mines that was at least 10-fold higher than the observed upper range for excess lung cancer deaths for this group. No statistically significant lung cancer excess was observed in this group of women. The SMR was 0.99 (95% CI 0.78–1.25), based on 71 observed lung cancer cases among 2,242 deaths from all causes (Camus et al. 1998). In defense of the EPA model predictions, Landrigan (1998) noted that "the strong possibility exists that the Camus calculations underestimate the risk of asbestos exposure", due to "1) the average fiber diameter in the Quebec mining townships is probably larger than average diameter encountered in industrial operations in the United States, because asbestos in the Quebec townships had not been subjected to the extensive machining that asbestos found in U.S. textile factories typically

undergoes; and 2) prevalence of cigarette smoking is much lower among women in rural Quebec than among blue-collar workers in the American south."

Although a number of studies seem to suggest that not all asbestos fibers types are equally likely to lead to lung cancer, the human evidence is disputed (see Hodgson and Darnton 2000, McDonald and McDonald 1997, and Stayner et al. 1996 for differing views on the evidence for differing lung cancer potency among asbestos fiber types). Some of this variation in potency between fibers may be due to differences between mineral types with respect to surface properties such as surface charge density (Bonneau et al. 1986; Davis et al. 1988), iron content (Lund and Aust 1992), and durability (Lippmann 1990), but the bulk of the available data indicate that fiber size (fiber thinness and length) may be the most important determinant of carcinogenic potential (see Section 3.5).

Some epidemiological studies have detected little or no increase in lung cancer risk until the cumulative dose of asbestos exceeds 25–100 f-yr/mL (Berry and Newhouse 1983; Hughes and Weill 1980; McDonald et al. 1980; Weill et al. 1979), and this has led to the proposal that there may be a dose threshold for asbestos-induced lung cancer (Browne 1986a, 1986b; Hodgson and Darnton 2000). However, a number of other studies indicate that lung cancer risk is linearly related to cumulative dose without any obvious threshold (Dement et al. 1983; Finkelstein 1983; Henderson and Enterline 1979; Hughes et al. 1987; McDonald et al. 1983; Seidman et al. 1979). In general, dose-response data from epidemiological studies lack the statistical power to detect small effects at low doses, so it is not possible to conclude from such data that a hazardous chemical does (or does not) have a threshold dose.

Studies in animals have reported increased incidence of lung cancer following chronic inhalation exposure to chrysotile (Davis and Jones 1988; Gross et al. 1967; Reeves et al. 1974; Wagner et al. 1974, 1980a), amosite (Davis et al. 1980a, 1980b, 1986a; Reeves et al. 1974), crocidolite (Reeves et al. 1971, 1974; Wagner et al. 1974), anthophyllite (Wagner et al. 1974), and tremolite (Davis et al. 1985). Exposure levels that have resulted in increased lung tumor frequency in animals range from 70 to 1,600 PCM f/mL. In general, tumors were characterized as adenomas, adenocarcinomas, and squamous cell carcinomas. There is some evidence from animal studies that mineral-fiber lung tumors arise from fibrotic areas of the lung (Davis and Cowie 1990).

Mesothelioma. Mesotheliomas are tumors arising from the thin membranes that line the chest (thoracic) and abdominal cavities and surround internal organs. Mesotheliomas are relatively rare in the general population, but are often observed in populations of asbestos workers. For example, in the mortality

study of insulation workers (in which 2,227 total deaths were analyzed), there were 175 deaths attributable to mesotheliomas, 63 arising from the pleural membrane, and 112 arising in the peritoneum (Selikoff et al. 1979). In contrast, published estimates of annual general population incidences of mesothelioma deaths include 2.8 and 0.7 per million for North American males and females, respectively, in 1972 (McDonald and McDonald 1980), an average of 1.75 per million in the U.S. for the period 1987–1996 (NIOSH 1999), and, for United States white males (the U.S. group with the highest mortality rate), 3.61 per million in 1987 and 2.87 per million in 1996 (NIOSH 1999). Mesotheliomas are often difficult to diagnose, so use of death certificate information may lead to an underestimate (Selikoff et al. 1979) or an overestimate (Bignon et al. 1979) of the true incidence of this disease.

Case-control studies have observed strong associations between the development of mesothelioma and occupational exposure to asbestos fibers (McDonald and McDonald 1980; McDonald et al. 1997; Spirtas et al. 1988, 1994; Teschke et al. 1997; Teta et al. 1983). For example, in a case-control study of 208 cases of malignant mesothelioma and 533 controls (who died of other noncancer causes) registered by the Los Angeles County Cancer Surveillance Program, the New York State Cancer Registry, and 39 large Veteran's Administration Hospitals, an elevated odds ratio of 9.8 (95% CI 4.7–21.1) was found for mesothelioma in men who reported ever having been occupationally exposed to asbestos (Spirtas et al. 1994). In a study of 344 North American malignant mesothelioma cases and 344 matched controls, employment for 10 or more years in the following trades was associated with increased relative risks of 46.0 (confidence intervals were not reported) for insulation work, 6.1 for asbestos production and manufacture, 4.4 for heating trades, 2.8 for shipyard work, and 2.6 for construction work (McDonald and McDonald 1980). In a study of 51 mesothelioma cases and 154 population-based controls from British Columbia, elevated odds ratios were found for several occupations likely to have involved asbestos exposure including sheet metal workers (OR=9.6, 95% CI 1.5–106), plumbers and pipe fitters (OR=8.3, 95% CI 1.5–86), and shipbuilding workers (OR=5.0, 95% CI 1.2–23) (Teschke et al. 1997).

Analyses of trends in mesothelioma mortality in Britain and Western Europe (Peto et al. 1995, 1999) indicate that the worst-affected birth cohort is men born around 1945–1950 (1/150 were projected to die of mesothelioma), whereas similar analyses of trends in the United States (Price 1997) indicate that the worst affected cohort is the 1925–1929 male birth cohort (with an estimated lifetime risk of 2/1,000). These trends mirror trends in raw asbestos consumption and a reduction in workplace airborne asbestos levels, with maximum exposure in the United States from the 1930s to the 1960s and in Britain and Western Europe in the 1970s (Peto et al. 1995, 1999; Price 1997). NIOSH (1999) has reported that age-

adjusted mortality rates for malignant neoplasm of the pleura in U.S. males showed a decline during the 1987–1996 period from 3.61 per million in 1987 to 2.87 per million in 1996.

Cases of mesothelioma have been reported in adults who had no occupational exposure to asbestos, but who lived with a parent, spouse, or sibling who was an asbestos worker and presumably carried asbestos home on the work clothes (Anderson et al. 1976; Inase et al. 1991; Magee et al. 1986; Magnani et al. 1993; McDonald and McDonald 1980; Voisin et al. 1994). As with other asbestos-related respiratory health effects, asbestos-induced mesothelioma appears to have a long latent period of development. For example, Anderson et al. (1976) described two cases of women who presumably experienced household contact with asbestos as children, when their fathers worked with asbestos, and developed clinically detected pleural mesothelioma more than 30 years later. In a review of 1,105 cases of malignant mesotheliomas associated with occupational exposure to asbestos, Lanphear and Buncher (1992) reported that 99% had a latent period >15 years, and calculated a median latent period of 32 years.

Cases of death from mesothelioma have been reported in studies of workers or in persons exposed environmentally to each of the main types of asbestos, including predominantly chrysotile (Albin et al. 1990a, 1990b; Berry 1997; McDonald et al. 1993; Selcuk et al. 1992; Tulchinsky et al. 1992), amosite (Levin et al. 1998; Seidman et al. 1979), crocidolite (Armstrong et al. 1988; de Klerk et al. 1989; Edward et al. 1996; Hansen et al. 1998; Jones et al. 1980a), tremolite (Amandus and Wheeler 1987; Baris et al. 1988a, 1988b; Constantopoulos et al. 1987a; Erzen et al. 1991; Kleinfeld et al. 1974; Langer et al. 1987; Luce et al. 2000; Magee et al. 1986; McConnochie et al. 1987; Metintas et al. 1999; Sahin et al. 1993; Sakellariou et al. 1996; Schneider et al. 1998; Selcuk et al. 1992; Yazicioglu et al. 1980), and a nonspecified asbestos type (Iwatsubo et al. 1998).

Although these findings suggest that all asbestos types can cause mesothelioma, there are several studies that suggest that amphibole asbestos (asbestiform tremolite, amosite, and crocidolite) may be more potent than chrysotile (Berry and Newhouse 1983; Churg 1986b; Churg and Wright 1989; Henderson and Enterline 1979; Hodgson and Darnton 2000; Hughes et al. 1987; Jones et al. 1980a; McDonald et al. 1989, 1997; Newhouse and Sullivan 1989; Rödelsperger et al. 1999; Rogers et al. 1991; Sluis-Cremer et al. 1992; Weill et al. 1979). For example, a group of workers in a friction materials plant that used mainly chrysotile, but also used crocidolite on two occasions, has been studied (Berry and Newhouse 1983). In a case-control analysis, it was found that the workers dying from mesothelioma (11 cases) were 8 times more likely to have been exposed to crocidolite than workers dying from other causes (Berry and Newhouse 1983). In case-control analyses of fiber concentrations in autopsied lungs of mesothelioma

subjects and subjects who died of other causes, relative risk for mesothelioma was significantly related to increasing concentrations of amphibole fibers longer than 5 µm (Rödelsperger et al. 1999), 8 µm (McDonald et al. 1989), or 10 µm (Rogers et al. 1991); significant relationships with increasing concentrations of chrysotile fibers were less apparent in these studies. In another approach, the chrysotile and amphibole content of lungs from persons dying from mesothelioma was examined, and it was found that mesotheliomas occurred in amphibole workers with much lower fiber burdens than those observed for chrysotile workers. The authors concluded that amphiboles were two orders of magnitude more potent for inducing mesothelioma than chrysotile (Churg and Wright 1989). This has led to the hypothesis that many cases of mesothelioma in chrysotile-exposed workers are actually due to the presence of amphibole contamination (Churg 1988; McDonald et al. 1989). However, it is difficult to draw strong inferences regarding the relative potency of different mineral types from lung burden data, because amphiboles are more stable in lung tissue than chrysotile (see Section 3.4.3.1). Based on an analysis of the ratio of excess deaths from mesothelioma to excess deaths from lung cancer in a number of studies, EPA concluded that crocidolite could be 2–4 times more potent for mesothelioma than chrysotile, but that this difference was generally overshadowed by differences in fiber size distribution and differences between cohorts (EPA 1986a). In a more recent analysis of exposure-response relationships for mesothelioma mortality in studies of 17 asbestos-exposed occupational cohorts, Hodgson and Darnton (2000) concluded that relative potencies ("exposure specific risk of mesothelioma") are in a ratio of 1:100:500 for chrysotile, amosite, and crocidolite, respectively.

Several studies (Newhouse and Berry 1976, 1979; Nicholson et al. 1982; Peto et al. 1982) have indicated that the risk of mesothelioma from a given level of exposure to asbestos depends primarily upon the time elapsed since exposure (latency), with risk increasing exponentially with time after a lag period of about 10 years. Whereas early studies indicated that diagnosis with mesothelioma was fatal within a short period of time, other studies indicate that survival time after diagnosis may be influenced by exposure intensity. In contrast to the situation for lung cancer, the effect of asbestos on mesothelioma risk does not appear to be increased by smoking (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980).

Using a predictive model developed from mesothelioma data from studies of asbestos insulation workers (Peto et al. 1982), asbestos textile workers (Peto 1980), amosite factory workers (Seidman 1984), and asbestos-cement workers (Finkelstein 1983), EPA (1986a) estimated that continuous lifetime exposure to air containing 0.0001 f/mL of asbestos would result in about 2–3 cases of mesothelioma per 100,000 persons. The corresponding cumulative lifetime exposures associated with excess risks of 10^{-4}–10^{-7} are shown in Figure 3-1. Cumulative exposure levels of 0.031, 0.0031, 0.00031, and

0.000031 f-yr/mL represent excess mesothelioma risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4}, respectively. Appendix D provides further details on the derivation of these risk estimates. Currently (in 2001), EPA is in the process of reviewing their cancer risk estimates for asbestos fibers.

In a recent analysis of the mesothelioma mortality data among 17 asbestos-exposed cohorts, Hodgson and Darnton (2000) estimated that cumulative exposures of 0.005, 0.01, or 0.1 f-yr/mL to crocidolite would produce about 10, 20, or 100 mesothelioma deaths per 100,000, respectively; for amosite, the respective mesothelioma risk estimates were 2, 3, or 15 deaths per 100,000. For chrysotile, Hodgson and Darnton (2000) concluded that mesothelioma risks were "probably insignificant", but noted that "highest arguable estimates" were insignificant, 1, and 4 deaths per 100,000 for cumulative exposure levels of 0.005, 0.01, and 0.1 f-yr/mL.

Animal studies also indicate that inhalation exposure to asbestos produces mesotheliomas. Mesotheliomas have been observed in rats exposed to chrysotile, amosite, anthophyllite, crocidolite, or tremolite at concentrations ranging from 350 to 1,600 f/mL for 1–2 years (Davis and Jones 1988; Davis et al. 1985; Wagner et al. 1974, 1980a) and in baboons exposed to either 1,110–1,220 f/mL for 4 years (Goldstein and Coetzee 1990) or 1,100–1,200 f/mL for up to 898 days (Webster et al. 1993). Incidences of mesothelioma ranged from 0.7 % to 42% in these studies.

Cancer at Other Sites. Mortality studies of asbestos workers have revealed small increases in the incidence of death from cancer at one or more sites other than the lung, the pleura, or the peritoneum, mostly in tissues of the gastrointestinal system. For example, a total of 99 deaths from cancers of the esophagus, stomach, colon, or rectum were observed in a cohort of 17,800 insulation workers, while only 59.4 deaths of this sort were expected (Selikoff et al. 1979). Similarly, 26 deaths from gastrointestinal cancer were observed in a group of 2,500 asbestos textile workers, where only 17.1 were expected (McDonald et al. 1983). In this study, there was an approximately linear increase in gastrointestinal cancer death rate with cumulative exposure to asbestos. Similar increases in gastrointestinal cancer rates in asbestos workers have been reported in other studies (Armstrong et al. 1988; Enterline et al. 1987; Gerhardsson de Verdier et al. 1992; Jakobsson et al. 1994; Kang et al. 1997; Neugut et al. 1991; Newhouse and Berry 1979; Pang et al. 1997; Raffn et al. 1989, 1996b; Seidman et al. 1979, 1986). Other mortality studies (e.g., Albin et al. 1990a; Hughes et al. 1987; McDonald et al. 1993; Peto et al. 1985) of asbestos workers, however, found no significantly increased risk for gastrointestinal or colorectal cancer. In a meta-analysis of available cohort studies, Frumkin and Berlin (1988) calculated, for cohorts having latent periods of 10–20 years and displaying SMRs for lung cancer greater than 2, pooled SMRs of

1.46 (95% CI, 1.00–2.13) for gastric cancer, 1.68 (1.34–2.09) for colorectal cancer, and 1.66 (1.32–2.08) for all gastrointestinal cancers. Homa et al. (1994) found similar results in another meta-analysis of the data. Homa et al. (1994) concluded that the results "suggested that exposure to amphibole asbestos maybe associated with colorectal cancer, but these findings may reflect an artifact of uncertification of cause of death". Homa et al. (1994) also concluded that "the results also suggest that serpentine asbestos is not associated with colorectal cancer." Other reviewers have concluded that the available data do not establish a causal relationship between occupational exposure to asbestos and the development of gastrointestinal cancers (Doll and Peto 1985, 1987; Edelman 1988a, 1989; Goodman et al. 1999; Weiss 1995).

Some studies have also noted excess deaths from, or reported cases of, cancers at other sites, such as the kidney (Enterline et al. 1987; Selikoff et al. 1979), brain (Kishimoto et al. 1992), and bladder (Bravo et al. 1988). Several cases of malignant mesothelioma of the tunica vaginalis testis have been reported in patients with histories of occupational exposure to asbestos (Fligiel and Kaneko 1976; Huncharek et al. 1995; Serio et al. 1992). Several epidemiological studies have also reported an increased risk of laryngeal cancer in workers exposed to asbestos (Muscat and Wynder 1991; Parnes 1990; Raffn et al. 1989; Smith et al. 1990). In contrast, a number of other epidemiological studies have not detected statistically significant associations between increased risk of cancers at sites other than the lung, pleura, or peritoneum and asbestos exposure (Acheson et al. 1982; de Klerk et al. 1989; Hughes et al. 1987; McDonald et al. 1984; Meurman et al. 1974; Molinini et al. 1992; Nicholson et al. 1979; Wignall and Fox 1982; Wortley et al. 1992).

Reviewers of the available evidence for asbestos-related cancer at sites other than the lung, pleura, and peritoneum appear to concur that the evidence is not strong. For example, Doll and Peto (1985, 1987) concluded from their review of the available epidemiological data and biological evidence that misdiagnosis or chance may be the simplest and most plausible explanation of asbestos-related cancer at any other site than the lung, pleura, or peritoneum. Kraus et al. (1995) concluded from a meta-analysis of 31 cohort studies and 24 case-control studies that most studies did not find a statistically significant association between occupational exposure to asbestos and laryngeal cancer and that the evidence of a causal relationship was weak. A separate meta-analysis (Goodman et al. 1999) of asbestos-exposed occupational cohorts resulted in a meta-SMR for laryngeal cancer of 1.57 (95% CI 0.95–2.45), suggestive of a possible association between asbestos and laryngeal carcinoma. In this meta-analysis, there was no clear association with urinary, reproductive, lymphatic, or hematopoietic cancers. Browne and Gee (2000) reviewed all identified studies of asbestos workers providing data on laryngeal disease and

concluded that the evidence did not indicate a positive association between asbestos exposure and laryngeal cancer.

All Cancer Effect Level (CEL) values from each reliable study for cancer are summarized in Tables 3-1 and 3-2, and plotted in Figures 3-1 and 3-2.

3.2.2 Oral Exposure

Units of Exposure. The principal way that humans are exposed to asbestos by the oral route is through ingestion of asbestos-contaminated drinking water (see Chapter 6). As discussed in Section 6.4.2, most asbestos fibers in water are chrysotile and are <5 μm in length. The concentration of asbestos in water is generally determined by transmission electron microscopy (TEM), and the results are expressed as millions of TEM fibers per liter (MFL). Although most laboratories currently count fibers as those particles with lengths >5 μm and aspect ratios >3:1 (in concordance with most regulatory definitions of an asbestos fiber), some studies have reported fiber concentrations using a lower length criterion. Since it is very difficult to convert from MFL to other units of dose, human exposure to asbestos via drinking water is reported below simply in terms of exposure level (MFL). In contrast, animal studies usually describe oral exposure in terms of mass (mg/day), and it is not often possible to accurately convert from this dose to units of exposure equivalent to those used for humans. Consequently, animal doses are reported below in units of mg/kg/day, and information on fiber dimensions is included when available.

Overview of Oral Health Effects. Studies in humans and animals indicate that ingestion of asbestos causes little or no risk of noncarcinogenic injury. However, there is some evidence that acute oral exposure may induce precursor lesions of colon cancer, and that chronic oral exposure may lead to an increased incidence risk of gastrointestinal tumors. Studies that provide quantitative data on the effects of ingested asbestos are summarized in Table 3-3 and Figure 3-3, and the data are discussed below.

3.2.2.1 Death

No studies were located regarding death in humans or animals after acute or intermediate oral exposure to asbestos. Feeding studies in rats and hamsters indicate that ingestion of high amounts (1% in the diet, equivalent to doses of 500–800 mg/kg/day) of chrysotile, amosite, crocidolite, or tremolite does not cause premature lethality, even when exposure occurs for a lifetime (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c).

TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
INTERMEDIATE EXPOSURE							
Reproductive							
1	Rat F344/N	2-12 wk		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
2	Hamster Syrian	3-6 wk		830			NTP 1983, 1990a CH AM
Developmental							
3	Rat F344/N	2-12 wk		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
4	Mouse CD-1	15 d Gd1-15		33 F			Schneider and Maurer 1977 CH
5	Hamster Syrian	3-6 wk		830			NTP 1983, 1990a CH AM
CHRONIC EXPOSURE							
Systemic							
6	Rat Wistar	25 mo	Gastro	100 M			Bolton et al. 1982a AM CR CH
7	Rat Sprague-Dawley	1.5 yr	Gastro			20 M (altered permeability of the intestines)	Delahunty and Hollander 1987 CH

TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
8	Rat NS	21 mo	Resp	2500 M			Gross et al. 1974 CH
			Cardio	2500 M			
			Gastro	2500 M			
			Hemato	2500 M			
			Musc/skel	2500 M			
			Hepatic	2500 M			
			Renal	2500 M			
			Dermal	2500 M			
9	Rat MRC Hooded	15 mo	Gastro		140 M (increased DNA synthesis)		Jacobs et al. 1978b CH
10	Rat F344/N	lifetime	Resp	500			NTP 1985, 1988, 1990c CH CR TR
			Cardio	500			
			Gastro	500			
			Hemato	500			
			Musc/skel	500			
			Hepatic	500			
			Renal	500			
			Endocr	500			
			Dermal	500			
			Bd Wt	500			

TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
11	Rat F344/N	lifetime	Resp	500			NTP 1990b AM
			Gastro	500			
			Hepatic	500			
			Renal	500			
			Bd Wt		500 M (15 (at weaning) to 37% (at 8 weeks) decreased mean body weight gain)		
			Bd Wt		500 F (15 (at weaning) to 25% (at 8 weeks) decreased mean body weight gain)		
12	Hamster Syrian	lifetime	Resp	830			NTP 1983, 1990a CH AM
			Cardio	830			
			Gastro	830			
			Hemato	830			
			Musc/skel	830			
			Hepatic	830			
			Renal	830			
			Endocr	830			
			Dermal	830			
			Bd Wt	830			
	Neurological						
13	Rat F344/N	lifetime		500			NTP 1985, 1988, 1990b, 1990c CH CR TR AM
14	Hamster Syrian	lifetime		830			NTP 1983, 1990a CH AM

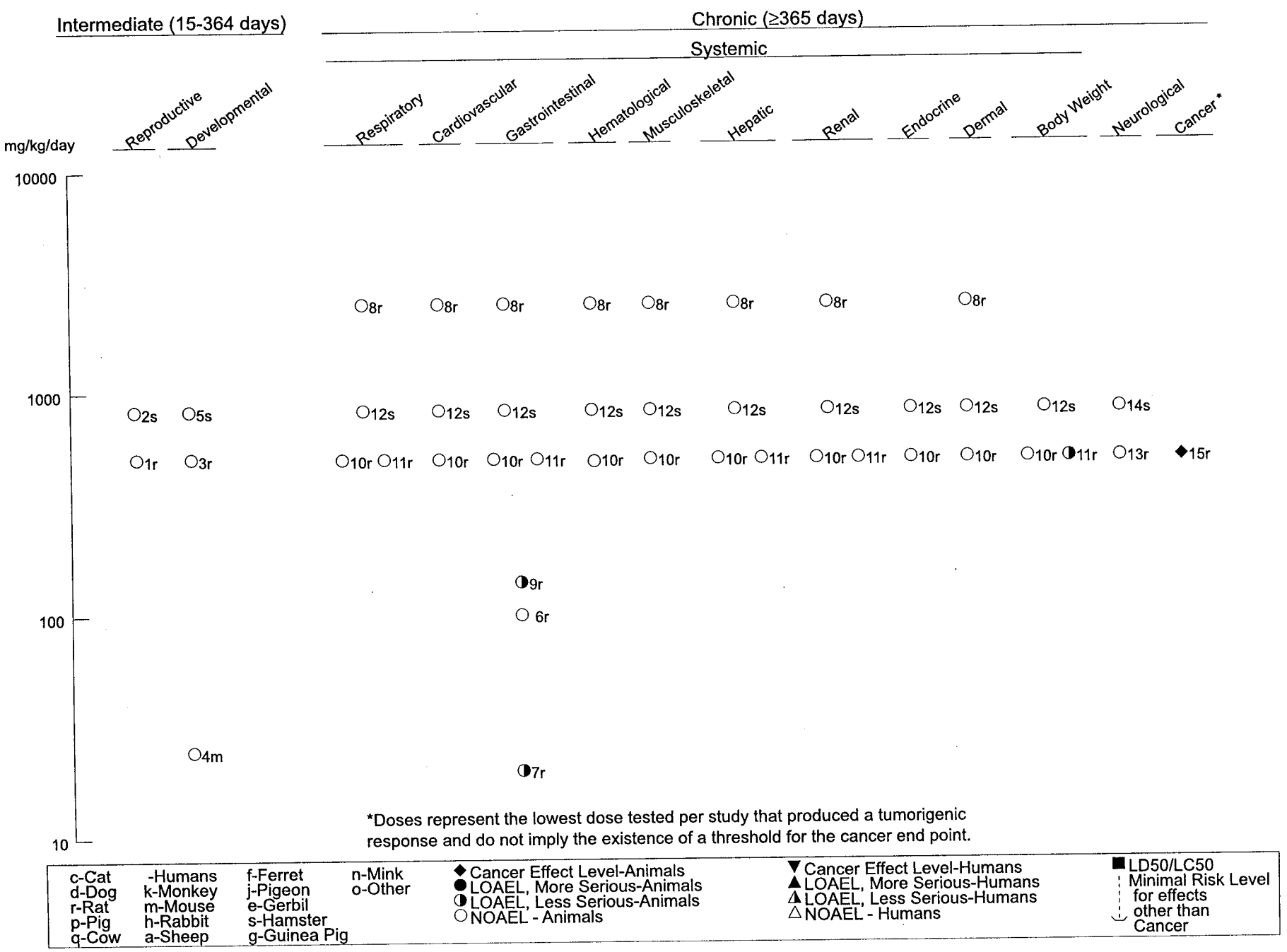
TABLE 3-3. Levels of Significant Exposure to Asbestos - Oral (continued)

Key to[a] figure	Species/ strain	Exposure/ duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference/ chemical form[b]
	Cancer						
15	Rat F344/N	lifetime				500 M (CEL: intestinal polyps)	NTP 1985 CH-I

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

AM = amosite; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; CH = chrysotile; CR = crocidolite; d = day(s); DNA = deoxyribonecleic acid; Endocr = endocrine; (F) = feed; F = female; Gastro = gastrointestinal; Gd = gestation day; Hemato = hematological; I = intermediate; LOAEL = lowest-observed-adverse-effect-level; M = male; mg/kg/day = milligrams per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect-level; NS = not specified; Resp = respiratory; TR = tremolite; (W) = water; wk = week(s); yr = year(s)

Figure 3-3. Levels of Significant Exposure to Asbestos - Oral



3.2.2.2 Systemic Effects

No studies were located regarding the respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or metabolic effects in humans after oral exposure to asbestos. Studies in rats and hamsters exposed to high doses (1% in the diet) of chrysotile, amosite, crocidolite, or tremolite have not detected histological or clinical evidence of injury to any systemic tissues (Gross et al. 1974; NTP 1983, 1985, 1988, 1990a, 1990b, 1990c), with the possible exception of mild effects on the gastrointestinal tract (see below). These findings are consistent with the concept that very few asbestos fibers cross from the gastrointestinal lumen into the blood (see Section 3.4.1), and that the risk of noncarcinogenic injury to tissues such as lung, heart, muscle, liver, kidney, skin, or eyes is negligible. The highest NOAEL values and all LOAEL values from reliable studies for systemic effects are summarized in Table 3-3 and plotted in Figure 3-3.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to asbestos. Because most ingested asbestos fibers are not absorbed into the body following oral exposure (see Section 3.4.1), the tissue most directly exposed to ingested asbestos is the gastrointestinal epithelium. A few studies in rats have described some histological or biochemical alterations in cells of the gastrointestinal tract after chronic exposure to oral doses of 20–140 mg/kg/day of chrysotile (Delahunty and Hollander 1987; Jacobs et al. 1978a, 1978b). Increased numbers of aberrant crypt foci, putative precursors of colon cancer, were induced in rats that were administered by gavage either a single dose (70 mg/kg/day) of chrysotile, a single dose (40 mg/kg/day) of crocidolite, or 3 doses (33 mg/kg/day) of crocidolite, although no dose-response was noted in the single dose of crocidolite regimen (Corpet et al. 1993). Mice that were administered either a single dose (100 mg/kg) of chrysotile or three doses (50 mg/kg/day) of crocidolite did not show increases in aberrant crypt foci (Corpet et al. 1993). However, no excess nonneoplastic lesions of the gastrointestinal epithelium have been detected in a number of other animal feeding studies (Bolton et al. 1982a; Donham et al. 1980; Gross et al. 1974), including an extensive series of lifetime studies in rats and Syrian hamsters in which such effects were carefully investigated (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). Thus, the weight of evidence indicates that asbestos ingestion does not cause any significant noncarcinogenic effects in the gastrointestinal system.

Body Weight Effects. A single study reported a 15–37% decrease in body weight gain in rats exposed to 500 mg/kg/day amosite (NTP 1990b). Changes in food consumption do not explain the decreased body weight gain since treated rats had slightly higher food intakes than controls. Effects on body weight gain have generally not been observed in other studies (Gross et al. 1974; NTP 1983, 1985, 1988, 1990a, 1990c). The significance of this finding, therefore, is uncertain.

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals after oral exposure to asbestos.

3.2.2.4 Neurological Effects

No studies were located to indicate that ingestion of asbestos leads to neurological effects in humans. No histological or clinical evidence of neurological injury was detected in rats or hamsters chronically exposed to high doses (500 and 830 mg/kg/day, respectively) of chrysotile, amosite, crocidolite, or tremolite in the diet (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). No clinical signs of neurological damage were noted after acute exposure of rats and mice to crocidolite (160 and 50 mg/kg/day, respectively) or to chrysotile (70 and 100 mg/kg/day, respectively) (Corpet et al. 1993).

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to asbestos. In animals, no histopathological changes in reproductive organs or effects on fertility were observed in rats or Syrian hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg/day, respectively) in the diet during gestation and lactation (through parental exposure) and throughout life until spontaneous death (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). The highest NOAEL values from reliable studies for reproductive effects are summarized in Table 3-3 and plotted in Figure 3-3.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to asbestos. No teratogenic effects were noted in rats or hamsters exposed to chrysotile, amosite, crocidolite, or tremolite (500 and 830 mg/kg/day, respectively) during gestation, lactation (though parental exposure), and throughout their lives until spontaneous death (NTP 1983, 1985, 1988, 1990b, 1990c), although standard developmental toxicity examinations of intrauterine contents at the end of gestation were not conducted in these bioassays. A slight reduction in pup birth weight was noted in some cases (NTP 1985, 1990a), but it seems unlikely that this was the result of any direct effect on the fetus. In the only available standard developmental toxicity study, no exposure-related effects on pregnancy outcome, percentages of resorptions, fetal weight, or number of malformed fetuses were found in mice exposed from gestation days 1 through 15 to drinking water containing 0, 1.43, 14.3, or 143 µg chrysotile asbestos/mL in drinking water (approximate doses of 0, 0.3, 3.3, and 33 mg/kg/day, respectively) (Schneider and Maurer 1977). The highest NOAEL values from reliable studies for developmental effects are summarized in Table 3-3 and plotted in Figure 3-3.

3.2.2.7 Cancer

As discussed in Section 3.2.1.8, a number of epidemiological studies of workers exposed to asbestos fibers in workplace air suggest that workers may have an increased risk of gastrointestinal cancers. It is usually assumed that any effect of asbestos on the gastrointestinal tract after inhalation exposure is most likely the result of mucociliary transport of fibers from the respiratory tract to the gastrointestinal tract (see Section 3.4.4). Because of these findings, a number of researchers have investigated the carcinogenic risk (especially the risk of gastrointestinal cancer) in humans and animals when exposure to asbestos occurs by the oral route.

Human Studies. A number of epidemiological studies have been conducted to determine if human cancer incidence is higher than expected in geographical areas where asbestos levels in drinking water are elevated (usually in the range of 1–300 MFL) (Andersen et al. 1993; Conforti et al. 1981; Howe et al. 1989; Kanarek et al. 1980; Levy et al. 1976; Polissar et al. 1982, 1984; Sadler et al. 1984; Sigurdson et al. 1981; Toft et al. 1981; Wigle 1977). Most of these studies have detected increases, some of which were statistically significant, in cancer death or incidence rates at one or more tissue sites (mostly gastrointestinal) in populations exposed to elevated levels of asbestos in their drinking water. However, the magnitudes of the increases in cancer incidence are usually rather small, may be related to other risk

factors such as smoking, and there is relatively little consistency in the observed increases, either within studies (i.e., between sexes) or between studies.

The basis of these inconsistent findings is not certain. On one hand, it seems likely that at least some of the apparent associations are random or are due to occupational exposures (Polissar et al. 1982, 1984; Toft et al. 1981; Wigle 1977). On the other hand, failure of some studies to detect effects may be due to lack of statistical power, stemming from limitations regarding study design, exposure level and duration, latency since exposure, population size and mobility, population density, exposure to other risk factors, differences in sensitivity between sexes and groups, differences in asbestos fiber types and size, and numerous other possible confounding factors. In a review of data from eight independent epidemiological studies, it was concluded that the number of positive findings for neoplasms of the esophagus, stomach, pancreas, and prostate were unlikely to have been caused by chance alone (Marsh 1983). In another review, Kanarek (1989) noted that there were relatively consistent findings for increased stomach and pancreatic cancer among the studies. However, none of the studies provided a basis for identification of an oral exposure level that may be definitely stated as having caused increased death from cancer. Part of the uncertainty may be attributable to differences in analytical methods used in the different studies to measure fiber concentrations in drinking water (e.g., differences in selection of dimensional criteria for definition of a fiber, in sampling techniques, and in processing techniques). In a more recent review, Cantor (1997) concluded that results from epidemiologic studies of populations exposed to high concentrations of asbestos in drinking water are inconsistent and are not adequate to evaluate cancer risk from asbestos in drinking water, but noted that some of the results are suggestive of elevated risks for gastric, kidney, and pancreatic cancer. Cantor (1997) further noted that the issue of asbestos in drinking water causing these types of cancer warrants further investigation.

Animal Data. Early animal studies on gastrointestinal cancer from ingested asbestos were mostly negative (Cunningham et al. 1977; Gross et al. 1974), although some studies yielded increases in tumor frequency that were not statistically significant (Bolton et al. 1982a; Donham et al. 1980; Ward et al. 1980). More recently, a series of large scale, lifetime feeding studies have been performed by the National Toxicology Program (NTP). In this series of studies, animals were exposed during gestation and lactation (through parental diets) and throughout their lives until spontaneous death occurred. These studies have also yielded mostly negative results, although some suggestive increases in tumor frequencies did occur (see Table 3-4). An increased incidence of benign adenomatous polyps of the large intestine was observed in male rats exposed to 500 mg/kg/day intermediate range chrysotile (65% of all fibers over 10 μm) in the diet (NTP 1985). These tumors were not observed either in female rats or in

Table 3-4. Summary of NTP Lifetime Asbestos Feeding Studies

Asbestos type	Species	Median length (μm)	Size distribution	Carcinogenic effects	Comments	Conclusion	Reference
Amosite	Rat	4.37	74% >6 μm	Increased C-cell carcinoma (males)	Not considered treatment related	Not carcinogenic	NTP 1990b
				Increased leukemia (males)	Questionable biological and statistical significance		
	Syrian hamster	4.37	74% >6 μm	None		Did not cause a carcinogenic response	NTP 1983
Crocidolite	Rat	10	73% >8 μm	None		Did not cause a carcinogenic response	NTP 1988
Tremolite	Rat	No data	22% >5 μm	None		Did not cause a carcinogenic response	NTP 1990c
Chrysotile (short range)	Rat	0.66	30% >4.5 μm	None		No evidence of carcinogenicity	NTP 1985
Chrysotile (intermediate range)	Rat	0.82	60% >5.4 μm	Benign intestinal polyps (males)	Not significant based on concurrent controls; highly significant based on historical controls	Some evidence of carcinogenicity	NTP 1985
				Clitoral gland neoplasm (females)	Not significant compared to historical controls	No evidence of carcinogenicity	

Table 3-4. Summary of NTP Lifetime Asbestos Feeding Studies *(continued)*

Asbestos type	Species	Median length (μm)	Size distribution	Carcinogenic effects	Comments	Conclusion	Reference
Chrysotile (short range)	Syrian hamster	0.66	30% >4.5 μm	Adrenal cortical adenomas (males)	Not significant compared to historical controls	Not carcinogenic	NTP 1990a
Chrysotile (intermediate range)	Syrian hamster	0.82	60% >5.4 μm	Adrenal cortical adenomas (males and females)		Not carcinogenic	NTP 1990a

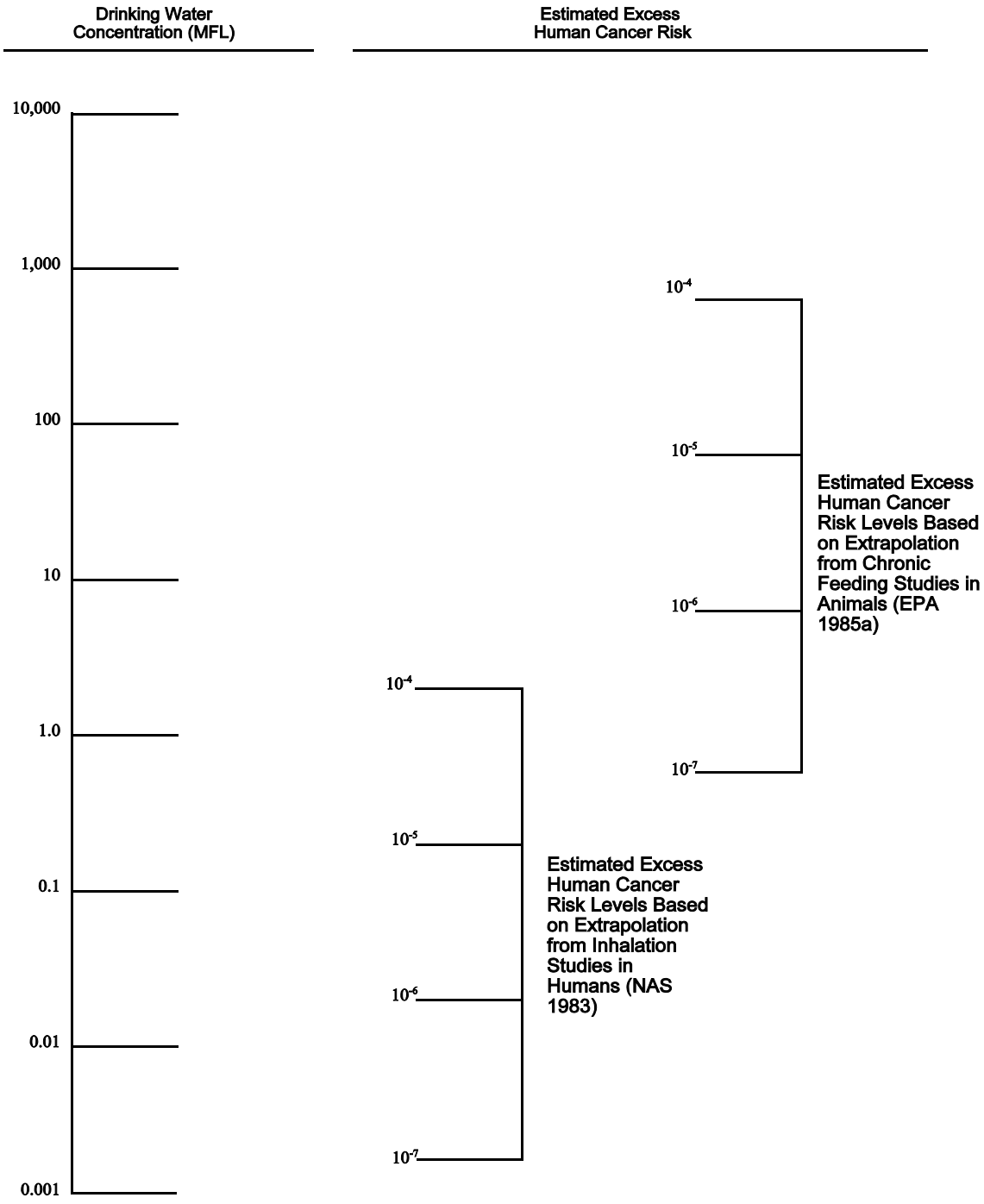
Syrian hamsters exposed to the same diet. Aberrant crypt foci, putative precursors of colon cancer, were induced in rats given acute doses of chrysotile (70 mg/kg/day) or crocidolite (33 mg/kg/day) by gavage (Corpet et al. 1993). Overall, however, the data were interpreted as providing "some evidence" of carcinogenicity for intermediate range chrysotile fibers. No tumorigenicity was noted for short-range chrysotile (NTP 1985).

Quantitative Risk Estimate. None of the available epidemiological studies of cancer risk in humans exposed to asbestos in drinking water are suitable for estimating quantitative dose-response relationships. However, both EPA and the National Academy of Sciences (NAS) have sought to estimate the risk of gastrointestinal cancer after oral exposure by extrapolating dose-response data from occupational studies (EPA 1980a; NAS 1983). As noted before, this approach rests on the assumption that the observed excess gastrointestinal cancer risk in the occupational studies is due to the swallowing of fibers that have been deposited in the respiratory tract. These calculations indicate that lifetime ingestion of water containing 1.0 MFL would produce an excess gastrointestinal cancer risk of about $3x10^{-5}$–$1x10^{-4}$ (EPA 1980a; NAS 1983). It should be noted that this approach requires a number of assumptions, and that the risk estimates should be considered to be only approximate. It is also important to note that if these risk estimates are correct, then the expected relative risk of gastrointestinal cancer in populations consuming drinking water at concentrations of 1–200 MFL would be quite low, and would likely not be consistently detectable in epidemiological studies (NAS 1983).

Another quantitative estimate of gastrointestinal cancer risk has been calculated based on the incidence of benign intestinal polyps in male rats exposed to 500 mg/kg/day of chrysotile (65% >10 μm long) in the diet (EPA 1985a). This calculation indicates that the lifetime excess risk from ingesting water containing 1.0 MFL would be about $1.4x10^{-7}$.

Figure 3-4 summarizes the risk estimates of NAS (1983) and EPA (1985a). It should be noted that these estimates differ by several orders of magnitude. Based on extrapolation from human inhalation studies, exposure levels of 0.0011, 0.011, 0.11, and 1.1 MFL in drinking water represent excess gastrointestinal cancer risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4}, respectively. Based on animal data, exposure levels of 0.71, 7.1, 71, and 710 MFL in drinking water represent excess gastrointestinal cancer risks of 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4}, respectively. There are many possible reasons for this substantial difference, including uncertainty in each model's assumptions or conversion factors, differences in fiber potency (due to differences in type and/or length), and inherent differences between humans and rats. Appendix D provides further details

Figure 3-4. Summary of Calculated Gastrointestinal Cancer Risks from Ingestion of Asbestos



on the derivation of these risk estimates. Currently (2001), EPA is in the process of reviewing their cancer risk estimates for exposure to asbestos fibers.

3.2.3 Dermal Exposure

The only adverse health effect that has been reported after dermal contact with asbestos is the formation of small "warts" or corns. No quantitative dose-response data are available, but in a group of workers installing amosite insulation in ships, nearly 60% of the people had one or more of these lesions, mostly on the hands (Alden and Howell 1944). All of the workers with lesions reported an original pricking sensation and the feeling of a small splinter-like foreign body. This strongly indicates that the lesions are associated with penetration of the skin by a macroscopic spicule, although histological examination of the corns did not reveal the presence of a fiber. The corns develop within about 10 days and are painful at first. They later become highly cornified and do not appear to be of pathological concern (Alden and Howell 1944; Dupre et al. 1984; Selikoff and Lee 1978).

No studies were located regarding the following health effects in humans or animals after dermal exposure to asbestos:

3.2.3.1 Death
3.2.3.2 Systemic Effects
3.2.3.3 Immunological and Lymphoreticular Effects
3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.3 GENOTOXICITY

The genotoxicity of asbestos has been investigated *in vivo*, as summarized in Table 3-5, and *in vitro*, as summarized in Table 3-6.

Studies of exposed asbestos workers, residentially exposed Turkish villagers, mesothelioma patients, and lung cancer patients suggest that asbestos is genotoxic. The number of chromosomal aberrations and the rate of sister chromatid exchange were significantly elevated in the peripheral blood lymphocytes of

Table 3-5. Genotoxicity of Asbestos *In Vivo*

Species (test system)	End point	Results	Reference	Form
Mammalian cells:				
Human blood leukocytes	DNA strand breakage	+	Marczynski et al. 1994a	NS
Human blood leukocytes	DNA damage	+	Marczynski et al. 2000a	NS
Human blood leukocytes	DNA damage	+	Marczynski et al. 2000b	NS
Human blood lymphocytes	Chromosomal aberration	+	Fatma et al. 1991	NS
Human blood lymphocytes	Sister chromatid exchange	+	Donmez et al. 1996	AC
Human blood lymphocytes	Sister chromatid exchange	(+)	Rom et al. 1983	NS
Human blood lymphocytes	Sister chromatid exchange	(+)	Lee et al. 1999	CH
Human mesothelioma cells	Chromosomal aberration	+	Hansteen et al. 1993	CR, AM, AN
Human mesothelioma cells	Chromosomal aberration	+	Tiainen et al. 1989	CR, AM, AN
Human mesothelioma cells	Chromosomal aberration	+	Tammilehto et al. 1992	NS
Human mesothelioma cells	Chromosomal aberration	+	Pelin-Enlund et al. 1990	NS
Human mesothelioma cells	Chromosomal aberration	–	Segers et al. 1995	CR, CH
Human mesothelioma cells	Gene mutation (p53)	–	Kitamura et al. 1998	NS
Human mesothelioma cells	Gene mutation (p53)	–	Ni et al. 2000	NS
Human lung carcinoma cells	Gene mutation (FHIT)	+	Nelson et al. 1998	NS
Human lung carcinoma cells	Gene mutation (p53)	+	Guinee et al. 1995	NS
Human lung carcinoma cells	Gene mutation (p53)	+	Nuorva et al. 1994	NS
Human lung carcinoma cells	Gene mutation (p53)	+	Wang et al. 1995b	NS
Rat leukocytes	DNA strand breakage	–	Marczynski et al. 1994b	CR
Rat lung and liver cells	DNA strand breakage	+	Marczynski et al. 1994b	CR
Rat lung and liver cells	DNA strand breakage	+	Marczynski et al. 1994c	CR
Rat bone marrow cells	Chromosomal aberration	+	Fatma et al. 1992	CH
Rat mesothelioma cells	Chromosomal aberration	+	EPA 1988j	CH
Rat mesothelioma cells	Gene mutation (p53)	–	Ni et al. 2000	CR
Rat bone marrow cells	Sister chromatid exchange	–	Varga et al. 1996a	AN
Rat bone marrow cells	Sister chromatid exchange	–	Varga et al. 1996b	CR
Mouse lung cells	Gene mutation (*lacI*)	(+)	Rihn et al. 2000	CR

Table 3-5. Genotoxicity of Asbestos *In Vivo (continued)*

Species (test system)	End point	Results	Reference	Form
Nonmammalian cells:				
Drosophila	Chromosomal aberration	+	Osgood and Sterling 1991	AM, CH
Drosophila	Chromosomal aberration	–	Osgood and Sterling 1991	CR, TR

– = negative result; + = positive result; (+) = weakly positive; AC = actinolite; AM = amosite; AN = anthophyllite; CH = chrysotile; CR = crocidolite; FHIT = a tumor suppressor gene; NS = not specified; p53 = a tumor suppressor gene; TR = tremolite

Table 3-6. Genotoxicity of Asbestos *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	No data	–	Chamberlain and Tarmy 1977	CR, CH, AM,
S. typhimurium TA102	Gene mutation	No data	+	Faux et al. 1994	AN
Escherichia coli CP2	Gene mutation	No data	–	Chamberlain and Tarmy 1977	CR, AN
Mammalian cells:					
Human mesothelial cells	Chromosomal aberrations	No data	+	Olofsson and Mark 1989	CR, CH, AM
Human mesothelial cells	Chromosomal aberrations	No data	+	Dopp et al. 1997	AM, CR, CH
Human mesothelial cells	Chromosomal aberrations	No data	(+)	Pelin et al. 1995a	AM
Human mesothelial cells	Chromosomal aberrations	No data	+	Takeuchi et al. 1999	CR
Human lymphocytes	Chromosomal aberrations	No data	+	Valerio et al. 1980	CH
Human fibroblasts	Chromosomal aberrations	No data	–	Sincock et al. 1982	CH
Human lymphoblastoid cells	Chromosomal aberrations	No data	+	Sincock et al. 1982	CH
Human blood lymphocytes	Chromosomal aberrations	No data	+	Korkina et al. 1992	CH
Human lymphocytes	Chromosomal aberrations	No data	+	Emerit et al. 1991	CH
Human amniotic fluid cells	Chromosomal aberrations	No data	+	Dopp and Schiffman 1998	AM, CR, CH
Human promyelotic leukemia cells	Chromosomal aberrations	No data	–	Takeuchi et al. 1999	CR
Human fibroblasts	Sister chromatid exchange	No data	–	Casey 1983	NS
Human lymphoblastoid cells	Sister chromatid exchange	No data	–	Casey 1983	NS
Human peripheral lymphocyte	Gene mutation (HLA-A)		–	Both et al. 1994	CH
Human peripheral lymphocyte	Gene mutation (HLA-A)	No data	+	Both et al. 1994	CR
Human TK6 cells	Gene mutation (HGPRT; T)	No data	–	Kelsey et al. 1986	CR

Table 3-6. Genotoxicity of Asbestos *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Human-hamster hybrid cells	Gene mutation (HGPRT)	No data	+	Hei et al. 1992	CH
Human mesothelioma cells	Gene mutation (HLA-A)	No data	+	Both et al. 1995	CR
Human bronchial cells	DNA strand breakage	No data	–	Lechner et al. 1983	CR, CH, AM
Human mesothelial cells	DNA strand breakage	No data	+	Ollikainen et al. 1999	CR
Rat pleural mesothelial cells	Chromosomal aberrations	No data	+	Kravchenko et al. 1998	CH
Rat pleural mesothelial cells	Chromosomal aberrations	No data	+	Yegles et al. 1995	CH, CR, AM
Rat liver epithelial cells	Gene mutation (HGPRT)	No data	–	Reiss et al. 1982	CR, CH, AM
Rat fibroblast cells	Gene mutation (*lacI*)	No data	+	Lezon-Geyda et al. 1996	CH
Rat mesothelial cells	Sister chromatid exchange	No data	–	Kaplan et al. 1980	NS
Rat embryo cells	DNA strand breakage	No data	+	Libbus et al. 1989	CR
Rat mesothelial cells	Unscheduled DNA synthesis	No data	+	Dong et al. 1994	CH,CR
Rat mesothelial cells	Aneuploidy	No data		Yegles et al. 1993	CR
Mouse fibroblasts	Cell transformation	No data	–	Brown et al. 1983	CR,AM
Hamster tracheal epithelial	DNA strand breakage	No data	–	Mossman et al. 1983a	CR, CH
Chinese hamster CHO xrs-5	DNA strand breakage	No data	+	Okayasu et al. 1999a	CH
Chinese hamster CHO–K1 cells	Chromosomal aberrations	No data	+	Sincock 1977	CR, CH,
Chinese hamster CHO–K1 cells	Chromosomal aberrations	No data	+	Sincock and Seabright 1975	AM, AN
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Kenne et al. 1986	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Kelsey et al. 1986	CR
Chinese hamster CHO cells	Chromosomal aberrations	No data		Sincock et al. 1982	CH
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	EPA 1988j; Palekar et al. 1987	CR, CH
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Trosic et al. 1997	CH

Table 3-6. Genotoxicity of Asbestos *In Vitro (continued)*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Chinese hamster CHO cells	Chromosomal aberrations	No data	+	Donaldson and Golyasnya 1995	AM
Chinese hamster CHO cells	Gene mutation (HGPRT)	No data	–	Kenne et al. 1986	CR, CH, AM
Chinese hamster CCL 39 cells	Gene mutation (HPRT)	No data	(+)	Huang 1979	CR, CH, AM
Chinese hamster CHO cells	Sister chromatid exchange	No data	–	Kelsey et al. 1986	CR
Chinese hamster CHO cells	Sister chromatid exchange	No data	–	Casey 1983	NS
Chinese hamster CHO cells	Sister chromatid exchange	No data	+	Livingston et al. 1980	CR, CH, AM
Chinese hamster CHO cells	Sister chromatid exchange	No data	+	Babu et al. 1980	CH
Chinese hamster V79–4 cells	Sister chromatid exchange	No data	+	Price-Jones et al. 1980	CR
Chinese hamster V79 cells	Sister chromatid exchange	No data	–	Lu et al. 1994a	CH
Chinese hamster V79 cells	Sister chromatid exchange	No data	+	Trosic et al. 1997	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Lu et al. 1994a	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Lu et al. 1994b	CH
Chinese hamster V79 cells	Micronucleus assay	No data	+	Keane et al. 1999	CH
Syrian hamster cells	Chromosomal aberrations	No data	+	Lavappa et al. 1975	CH
Syrian hamster cells	Chromosomal aberrations	No data	+	Oshimura et al. 1986	CH
Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Dopp et al. 1995a, 1995b	AM, CR, CH
Syrian hamster embryo cells	Chromosomal aberrations	No data	+	Dopp and Schiffman 1998	AM, CR, CH
Syrian hamster embryo cells	Cell transformation	No data	+	Hesterberg and Barrett 1984	CH, CR
Syrian hamster embryo cells	Cell transformation	No data	–	DiPaolo et al. 1983	AM, AN, CH, CR
Calf thymus DNA	DNA damage	No data	+	Adachi et al. 1992a	CR, CH, AM

– = negative result; + = positive result; (+) = weakly positive result; AM = amosite; AN = anthophyllite; CH = chrysotile; CHO = Chinese hamster ovary; CR = crocidolite; DNA = deoxyribonucleic acid; HGPRT and HPRT = hypoxanthine-guanine phosphribosyl transferase genetic locus; HLA-A = human lymphocyte antigen A genetic locus; NS = not specified; T = thymidine kinase genetic locus

asbestos workers compared to a control population (Fatma et al. 1991). The mean sister chromatid exchange rate was significantly increased (p=0.002) in nonsmoking asbestos insulators compared to a control population (Rom et al. 1983). The increase in sister chromatid exchange rate was not statistically significant in smoking asbestos insulators, and for the whole group (smokers and nonsmokers), the increase approached statistical significance (p=0.056). A marginally significant difference (p=0.069) in mean sister chromatid exchange rate between chrysotile-exposed workers and controls became significant (p=0.0473) after controlling for the effects of age and smoking (Lee et al. 1999). A group of residents from a Turkish village in which actinolite asbestos was used to paint walls and floors of homes had an elevated mean sister chromatid exchange rate in lymphocyte cells compared with a nonexposed control population (Donmez et al. 1996). An increased incidence of DNA double-strand breaks was noted in the leukocytes of asbestos workers compared to controls (Marczynski et al. 1994a). Increased incidences of DNA double strand breaks in lung and liver tissue (Marczynski et al. 1994b, 1994c) and chromosomal gaps and breaks in bone marrow cells (Fatma et al. 1992) were observed in rats exposed via intratracheal instillation of crocidolite instilled intratracheally with suspensions of crocidolite and chrysotile asbestos, respectively. In other studies, no increased frequency of sister chromatid exchange was found in bone marrow cells from rats orally exposed to anthophyllite or crocidolite (Varga et al. 1996a, 1996b). Asbestos induced aneuploidy in *Drosophila* (Osgood and Sterling 1991). In this assay system, chrysotile was more effective than amosite, whereas crocidolite and tremolite were relatively ineffective. Several studies have reported either chromosomal aberrations in the pleural effusion of mesothelioma patients (Hansteen et al. 1993) or significant correlations between specific chromosomal abnormalities and lung burden of asbestos in mesothelioma patients (Pelin-Enlund et al. 1990; Tammilehto et al. 1992; Tiainen et al. 1989). However, it is uncertain as to whether these chromosomal abnormalities were responsible for the development of mesothelioma, or whether the abnormalities were a result of the disease. Chromosomal aberrations in mesothelioma cells were not found in one study of human patients (Segers et al. 1995). Significant increases in the excretion of the DNA adduct 8-hydroxydeoxyguanosine, a marker of DNA damage, have been observed in the white blood cells and urine of asbestos workers (Marczynski et al. 2000a, 2000b; Tagesson et al. 1993). Abnormal p53 protein accumulation (suggestive of mutation in the p53 tumor suppressor gene) was detected significantly more often (p=0.027) in primary tumor tissue from lung cancer patients exposed to asbestos than in lung cancer patients without exposure (Nuorva et al. 1994). Mutations in the p53 gene occurred more frequently in two studies of primary tumor tissue from lung cancer patients with asbestos exposure compared with lung cancer patients without asbestos exposure (Guinee et al. 1995; Wang et al. 1995b). In another study of tumor tissue from lung cancer patients, asbestos exposure and smoking duration were each significantly associated ($p<0.01$) with deletions in the protein coding regions of another candidate tumor suppressor gene, FHIT (Nelson et

al. 1998). In contrast, mutations in the p53 gene were not found in tumor tissue samples from small numbers of mesothelioma patients (Kitamura et al. 1998; Ni et al. 2000) with definite histories of asbestos exposure or in rats with crocidolite-induced mesotheliomas (Ni et al. 2000).

Tests for gene mutations have been mixed, both *in vivo* and *in vitro*. Asbestos fibers were not mutagenic in initial tests of standard strains of *Salmonella typhimurium* and *Escherichia coli* (Chamberlin and Tarmy 1977), but mutagenic responses were found in a *S. typhimurium* strain, TA102, that is especially sensitive to oxidative mutagens (Faux et al. 1994).

In vitro tests on human peripheral lymphocytes and mesothelioma cells have been mixed with both positive and negative results for tests with crocidolite and chrysotile (Both et al. 1994, 1995; Hei et al. 1992; Kelsey et al. 1986). Studies by Both and coworkers (Both et al. 1994, 1995) suggest that crocidolite is a more potent mutagen than chrysotile, and that asbestos susceptibility is cell line specific. Cell line specificity may be due to differential phagocytic activity, with those cells exhibiting high levels of phagocytosis (e.g., mesothelioma cells) being more susceptible to asbestos (Takeuchi et al. 1999) than cells without such activity (e.g., lymphocytes). Studies in animal systems present a similar picture. Hei and coworkers reported an increased frequency of mutations in human-hamster hybrid cells exposed to chrysotile (Hei et al. 1992). These mutations consisted primarily of large deletions, which may not be detected as easily in other assay systems. Marginal evidence for weak mutagenicity of chrysotile, crocidolite, and amosite in Chinese hamster ovary (CHO) cells was reported by Huang (1979).

A large number of studies indicate that asbestos fibers can cause chromosomal aberrations in Chinese hamster ovary (CHO) and Syrian hamster embryo (SHE) cells. The aberrations include aneuploidy (usually polyploidy), fragmentation, breaks, rearrangements, gaps, dicentrics, inversions, and rings (Donaldson and Golyasnya 1995; Kelsey et al. 1986; Kenne et al. 1986; Lavappa et al. 1975; Oshimura et al. 1986; Palekar et al. 1987, 1988; Sincock 1977; Sincock and Seabright 1975; Sincock et al. 1982; Trosic et al. 1997). Aneuploidy was also induced in rat mesothelial cells *in vitro* using crocidolite (Yegles et al. 1993). Chromosomal aberrations have been produced by chrysotile in eight studies using human mesothelial, lymphocyte, and amniotic fluid cells (Dopp and Schiffmann 1998; Dopp et al. 1997; Emerit et al. 1991; Korkina et al. 1992; Olofsson and Mark 1989; Pelin et al. 1995b; Takeuchi et al. 1999; Valerio et al. 1980), but not in two others that used fibroblast and promyelocytic leukemia cells (Sincock et al. 1982; Takeuchi et al. 1999). The mechanism by which these clastogenic effects occur may be related to physical interference with chromosome segregation by the asbestos fiber during the mitotic process (Barrett et al. 1989; Malorni et al. 1990; Palekar et al. 1987).

Results of tests for other genotoxic effects (increased sister chromatid exchange, DNA strand breaks, DNA hydrolysis, cell transformations) have been mixed, with both negative (Brown et al. 1983; Casey 1983; DiPaolo et al. 1983; Kaplan et al. 1980; Kelsey et al. 1986; Lechner et al. 1983; Lu et al. 1994a; Mossman et al. 1983a; Price-Jones et al. 1980) and positive (Adachi et al. 1992a; Babu et al. 1980; Dong et al. 1994; Hesterberg and Barrett 1984; Libbus et al. 1989; Livingston et al. 1980; Okayasu et al. 1999a; Ollikainen et al. 1999; Trosic et al. 1997) results being noted. Adachi et al. (1992a) reported DNA damage as indicated by the formation of 8-hydroxy-2'-deoxyguanosine when fibers were incubated with calf thymus DNA and hydrogen peroxide. DNA strand breaks were noted in rat embryo cells exposed to crocidolite and CHO exposed to chrysotile (Okayasu et al. 1999a; Osgood and Sterling 1991). Emerit et al. (1991) reported that chrysotile induces the formation of a clastogenic factor when cultured rat pleural mesothelioma cells are exposed to the fibers *in vitro*, as ultrafiltrates of culture media from these cells induced chromosome damage in cultures of human lymphocytes used as a test system. These effects are equivocal, however, as there was no dose-response. Chrysotile induced increased numbers of cells with micronuclei (Keane et al. 1999; Lu et al. 1994b) and with two or more nuclei (Lu et al. 1994a) in Chinese hamster lung (V79) cells. Increases in unscheduled DNA synthesis have been reported using rat pleural mesothelial cells after exposure to crocidolite and chrysotile (Dong et al. 1994). Of special interest, the cell transformation reported by Hesterberg and Barrett (1984) was abolished when the fibers were milled to a short length.

These observations, especially the findings of cytogenotoxicity, are consistent with the greater observed carcinogenic potential of long asbestos fibers, and support possible mechanisms by which asbestos might be acting.

3.4 TOXICOKINETICS

Asbestos fibers may enter the body after inhalation or oral exposures. It is unlikely that any appreciable uptake of asbestos will occur after dermal exposure. The deposition and fate of the fiber in the lungs is largely dependent on its size and shape. Fibers that are deposited in the respiratory tract may be removed by mucociliary clearance or by macrophages, or they may be retained in the lung. Very few of the long fibers are likely to move through the lungs and be distributed to tissues other than the mesothelium. Longer fibers that are retained in the lung may undergo a number of processes including translocation, dissolution, fragmentation, splitting, or protein encapsulation. Long fibers that reside in the lung can become encapsulated in protein, forming what is often referred to as an "asbestos body" (the term "ferruginous body" is used when the nature of the core fiber is not known). These bodies are golden

brown in appearance, owing to the presence of iron. The protein coat is rich in ferritin (an iron storage protein) possibly arising from macrophages and giant cells. The formation of asbestos bodies may represent an attempt of macrophages to digest long fibers extracellularly (Koerten et al. 1990a, 1990b). Fibers that are retained in the lung or mesothelium for long periods of time are capable of producing chronic inflammation and fibrotic and tumorigenic effects. These effects may be mediated by direct interactions between the fiber and key cellular macromolecules, or they may be mediated by the production of reactive oxygen species and other cellular factors originating from alveolar macrophages. Fibers that enter the gastrointestinal tract, either by ingestion or mucociliary transport from the lungs, are mostly excreted in the feces, although a small fraction of the fibers may become lodged in cells or penetrate the gastrointestinal lining and enter other tissues.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

When asbestos fibers are inhaled, many are deposited on the epithelial surface of the respiratory tree. The number of fibers that are deposited, and the location within the airway where deposition occurs, is a function of the aerodynamic properties of the fibers. In humans, the fibers depositing in the upper airway consist mainly of relatively thick fibers (greater than about 3 μm), with thinner fibers being carried deeper into the distal airways and alveolar regions (Timbrell 1982). In rats, about 30–40% of typical fibers of chrysotile, amosite, and crocidolite, are retained, with most of these (about 60%) being deposited in the upper airways (nose, throat, and trachea) (Evans et al. 1973; Morgan et al. 1975). The median length for these fibers was 1–2 μm, while the median diameter was 0.2–0.4 μm. After intratracheal administration of chrysotile and amosite asbestos fibers in hamsters, chrysotile fibers were found to be primarily located near air duct bifurcations, while amosite fibers tended to be more distributed over the bronchial surface (Kimizuka et al. 1992). Many of these smaller fibers deposit preferentially at bifurcations in the terminal bronchioles and alveolar ducts (Brody 1986; Evans et al. 1973), with the number of fibers deposited at each location decreasing in proportion to the preceding airway path length and the number of preceding branch points (Pinkerton et al. 1986).

3.4.1.2 Oral Exposure

Animal studies indicate that most asbestos fibers that are ingested are not absorbed across the walls of the gastrointestinal tract (Gross et al. 1974). However, electron micrographic studies indicate that some fibers penetrate into the gastrointestinal epithelium (Storeygard and Brown 1977; Westlake et al. 1965). In addition, some fibers pass through the gastrointestinal wall and reach blood, lymph, urine, and other tissues (Carter and Taylor 1980; Cunningham and Pontefract 1973; Cunningham et al. 1977; Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983; Sebastien et al. 1980b; Weinzweig and Richards 1983). The mechanism by which asbestos fibers pass through the gastrointestinal wall is not known with certainty, but it has been noted that a wide variety of very small particles (i.e., 1 μm or less; e.g., starch granules, cellulose particles, pollen) can cross the gut by passing between (not through) the cells of the epithelial layer in a process termed persorption, and it seems likely that this may account for uptake of asbestos fibers as well (Volkheimer 1974). Available data are not sufficient to make a precise estimate of the fraction of ingested fibers that pass through the gastrointestinal wall, but there is agreement that it is a very small amount (Sebastien et al. 1980b; Weinzweig and Richards 1983). Several researchers have found that the average length of fibers in extra-gastrointestinal tissues or fluids is shorter than the average length of the fibers ingested (Cunningham et al. 1977; Patel-Mandlik and Millette 1983; Weinzweig and Richards 1983), suggesting that short fibers pass through the gastrointestinal epithelium more easily than long fibers.

3.4.1.3 Dermal Exposure

As discussed above (see Section 3.2.3), asbestos fibers can penetrate into the skin, producing asbestos warts. No studies were located that indicate that asbestos fibers can pass through the skin into the blood.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

As noted above, only a tiny fraction of inhaled fibers penetrate through the epithelial layer of the lungs. No quantitative studies were located regarding the distribution of these fibers in the rest of the body after inhalation exposure, but some appear to be retained in the pleura, with others passing into the lymphatics (Brody 1993; Hillerdal 1980; Holt 1983; Rudd 1989). Those fibers that enter the lymphatics are presumably able to reach other tissues of the body. Dogs exposed by nose-only inhalation to neutron-

activated crocidolite were found to have small amounts of radioactivity in the blood, liver, head, and gastrointestinal tract (Griffis et al. 1983). However, it is also possible that some small proportion of fibers originally deposited in the respiratory tract may reach other tissues following mucociliary transport of fibers to the gastrointestinal tract and uptake from that tissue (see Section 3.4.1.2).

Distribution of asbestos fibers within the lung has been investigated in a number of studies. Most fibers deposited in the airways are removed from the lung by mucociliary transport or by macrophages (see Section 3.4.4), but a small fraction remain in the lung for long periods (Jones et al. 1988a). In addition, some fibers appear to pass from the lung to the pleura (Boutin et al. 1996; Hillerdal 1980; Rudd 1989; Viallat et al. 1986). In humans, the presence of asbestos fibers in the pleura after inhalation exposure has been demonstrated by a number of researchers (Boutin et al. 1996; Jones et al. 1980b; Roggli and Longo 1991; Sebastien et al. 1980a; Stephens et al. 1987), but some concerns have been discussed of the possibility of contamination of tissues during pathological processing and fiber analysis (Case 1994). Available data are not sufficient to estimate the fraction of deposited asbestos fibers that penetrate the lung in this way, but it is probably quite small.

Intracellularly, asbestos fibers tend to be located near the nucleus. *In vitro* studies have indicated that during endocytosis, asbestos fibers were observed to be transported along the microtubule network to the perinuclear region (Cole et al. 1991; Malorni et al. 1990). The proximity of asbestos fibers to the nucleus may be an important factor regarding their genotoxicity and carcinogenicity.

Providing limited evidence that some transplacental transfer of asbestos fibers may occur, one group of investigators has reported that asbestos fibers were detected more frequently and at higher mean concentrations in human fetal and placental tissues associated with stillborn infants compared with placental tissue associated with liveborn infants from the same hospital (Haque et al. 1991, 1992, 1996, 1998). In the latest study from this group, asbestos fibers were found in 50% of fetal digests and 23% of placental digests from stillborn infants compared with 15% of liveborn placentas. Mean fiber concentrations in stillborn tissues and placenta tissues were comparable to one another (30,000–60,000 f/g), but were much greater than mean fiber concentration in liveborn placentas (19 f/g) (Haque et al. 1998). The source of maternal exposure in these studies was unknown, but was presumed by Haque et al. (1998) to be a mix of oral and inhalation environmental (not occupational) exposure. It is unknown if the increased number of fibers in the stillborn fetuses is attributable to increased maternal exposure to asbestos or to changes in fetal or placental factors, unrelated to asbestos exposure, influencing fiber tissue accumulation.

3.4.2.2 Oral Exposure

Asbestos fibers have been detected in blood (Weinzweig and Richards 1983) and lymph (Sebastien et al. 1980b) of rats exposed to oral doses of asbestos, suggesting that fibers penetrating the gut might be carried to tissues throughout the body. In support of this, asbestos fibers have been detected in the lung, kidney, liver, brain, heart, and spleen of rats that had been exposed to asbestos in the diet (Cunningham et al. 1977; Pontefract and Cunningham 1973). Highest levels of fibers were found in the omentum (a fold of the peritoneum connecting abdominal viscera to the stomach), supporting the idea that the fibers were emanating from the gastrointestinal tract. Although the diet fed to the animals was prepared using corn oil to minimize asbestos fiber inhalation, the possibility that some fiber inhalation took place cannot be eliminated (Cunningham et al. 1977).

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of asbestos fibers after dermal exposure. It is generally considered that dermal uptake of asbestos is not significant.

3.4.2.4 Other Routes of Exposure

The distribution of asbestos fibers has been investigated in a number of studies after exposure via intratracheal or intravenous injection. The translocation of chrysotile fibers from the lung to the pleura and mesothelium has been observed in rats exposed by intratracheal injection (Fasske 1988; Viallat et al. 1986). Following intravenous injection of chrysotile fibers into pregnant rats, fibers were detected by electron microscopy at higher levels in liver and lung tissue in fetuses of exposed dams compared with levels in fetuses from nonexposed dams (Cunningham and Pontefract 1974). Asbestos fibers also were detected in digests of fetal and placental tissue following intravenous injection of pregnant mice with single doses of crocidolite suspensions (Haque and Vrazel 1998). These findings support those of Haque et al. (1991, 1992, 1996, 1998), suggesting that some transplacental transfer of asbestos fibers may occur.

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

Asbestos fibers are not metabolized in the normal sense of the word, and amphibole fibers that are retained in the lung do not appear to undergo any major changes (Bellmann et al. 1987; Carter and Taylor 1980; Roggli et al. 1987a). However, chrysotile fibers appear to undergo some type of breakdown or alteration in the lung. This conclusion is based primarily on measurements of asbestos levels in the lung as a function of exposure duration. With continuing exposure of animals, amphibole levels tend to rise linearly, whereas chrysotile levels reach a steady-state concentration within several months (Wagner et al. 1974) (see also Section 3.5.1). These data from animal studies are supported by a number of human studies in which the ratio of amphibole to chrysotile concentration in lung tissue was much higher than expected based on the composition of the inhaled fibers (Jones et al. 1980a, 1980b; Pooley 1976; Stephens et al. 1987; Wagner et al. 1982a, 1982b, 1986). Long chrysotile fibers (>10 or 18 μm) are expected to accumulate in humans with continued exposure, based on observations of an association between duration of exposure of chrysotile miners and millers and lung chrysotile fiber concentrations >18 μm in length (Case et al. 2000) and estimations of long clearance half times (>8 years) for lung-sequestered fibers in chrystotile miners and millers (Finkelstein and Dufresne 1999). Finkelstein and Dufresne (1999) discerned patterns in their data suggestive that lung concentrations of chrysotile fibers would reach plateaus in humans after decades of exposure under occupational conditions.

The basis of this apparent loss of chrysotile fibers is not clear, but it may be related to a slow dissolution of the fibers in tissue fluids or in macrophages (Fasske 1988; Jaurand et al. 1984), or to a separation of the fibers into much finer component fibrils (Bellmann et al. 1987; Coin et al. 1992, 1994; Cook et al. 1982; Roggli et al. 1987a). In the latter case, the apparent loss of fibers could be an artifact due to the inability of normal methods for fiber isolation and quantification in tissues to detect very fine fibrils. Loss of chrysotile has been reported to be related to the fragmentation of long fibers, resulting in the formation of smaller fibers (Churg et al. 1989a, 1989b). There appears to be preferential clearance of short asbestos fibers compared to long ones (Coin et al. 1992; Finkelstein and Dufresne 1999). For example, based on an analysis of lung fiber concentrations in 72 chrysotile miners and millers, years of exposure, and time since last exposure, long-term clearance half-times were estimated to be about 4 and 8 years for chrysotile fibers <5 μm and >10 μm in length, respectively (Finkelstein and Dufresne 1999). In contrast, clearance half-times were about 8 and 16 years for tremolite fibers <5 μm and >10 μm in length, respectively. (Short-term clearance times could not be measured in this analysis of lung fiber concentrations in

chronically exposed miners and millers.) Long fibers that reside in the lung can form asbestos bodies. The formation of asbestos bodies might represent an attempt by macrophages to digest these fibers extracellularly (Koerten et al. 1990a, 1990b).

3.4.3.2 Oral Exposure

No studies were located regarding any changes in asbestos fibers in the gastrointestinal tract *per se*. However, chrysotile fibers incubated in simulated gastric juice underwent leaching of magnesium ion from the silica framework, with a resultant change in net fiber charge from positive to negative (Seshan 1983), and chrysotile fibers with altered appearance and x-ray diffraction patterns were detected in the urine of animals (Hallenbeck and Patel-Mandlik 1979; Patel-Mandlik and Millette 1983). These observations, although limited, suggest that chrysotile fibers undergo some metal ion exchange and alterations in gross structure in biological fluids after oral exposure. Asbestos bodies have been detected is tissues such as the colon (Ehrlich et al. 1992), suggesting that this process may occur in extrapulmonary tissues as well.

3.4.3.3 Dermal Exposure

No studies were located regarding any changes in asbestos fiber composition or structure after dermal exposure.

3.4.3.4 Other Routes of Exposure

As stated above, asbestos fibers are not metabolized in the true sense of the word; however, a number of animal studies indicate that chrysotile fibers are physically altered in the lung after intratracheal injection. Following phagocytosis, chrysotile fibers were observed to decrease in size, become transparent, and, in some cases, break into fragments (Fasske 1988). Longitudinal splitting, resulting in a greater number of thinner fibers was noted for actinolite and amosite (Cook et al. 1982), and fragmentation, resulting in shorter fibers, was observed for chrysotile (Churg et al. 1989a, 1989b). These changes in fiber shape and size may directly impact fiber clearance and toxicity in the lung.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The principal pathway by which fibers are removed from the respiratory tract is mucociliary transport. This is mediated by ciliated epithelial cells that produce and move the layer of mucus coating the epithelial tissue upwards toward the throat, where it is swallowed. Fibers deposited in this mucus layer are swallowed into the alimentary canal and most are ultimately excreted in the feces (Cunningham et al. 1976; Evans et al. 1973; Griffis et al. 1983; Morgan et al. 1978). However, a small number of fibers may penetrate through the epithelial layers of the lung and/or the gastrointestinal tract and are transferred to the blood and eventually to the kidney, where some of them may be excreted in the urine (Finn and Hallenbeck 1984). In addition, some fibers are not cleared from the lung, leading to a gradual accumulation with time (Case et al. 2000; Finkelstein and Dufresne 1999; Jones et al. 1988a; Wagner et al. 1974).

Animal studies indicate that clearance of fibers from the upper airways generally occurs within a few hours (Bolton et al. 1983; Evans et al. 1973). However, clearance from the lower airways is slower, with half-times ranging up to 160 days (Bellmann et al. 1987; Coin et al. 1992; Evans et al. 1973; Morgan et al. 1978). This slow clearance is mediated largely by macrophages, which engulf fibers in the bronchioles and alveoli (which are not ciliated), and carry them to the ciliated portion of the airway for transport upward (Holt 1974). Macrophages may also translocate some fibers from the lung to the pleura (Holt 1983). The clearance of chrysotile fibers from the lungs is dependent on fiber length. Animal and human data indicate that long fibers (in excess of 5 or 10 μm) are cleared from the lower airways more slowly than short fibers (Bellmann et al. 1987, 1994; Davis et al. 1986a, 1988; Finkelstein and Dufresne 1999; Morgan et al. 1978; Roggli et al. 1987a; Searl 1997; Warheit et al. 1997), probably because long fibers cannot be easily engulfed and moved by a single macrophage (Morgan et al. 1978). Fibers less than 1 μm in length were cleared from the rat lung with a half-life of less than 10 days, whereas fibers longer than 16 μm were cleared with a half-life of greater than 100 days (Coin et al. 1992; Searl 1997). Pulmonary clearance half-times for asbestos fibers must be viewed with caution, however, as a first-order kinetic model is generally not an adequate fit for the data (Hesterberg et al. 1996; Searl 1997). The preferential clearance of chrysotile over amphiboles (Finkelstein and Dufresne 1999; Jones et al. 1994) may be attributed to fragmentation of long fibers, resulting in the formation of shorter fibers which are more readily engulfed and moved by a single macrophage (Jones et al. 1994).

3.4.4.2 Oral Exposure

Nearly all asbestos fibers that are ingested are excreted in the feces. This is essentially complete within 48 hours following a single oral dose (Gross et al. 1974). Small numbers of fibers may also be excreted in the urine (Boatman et al. 1983; Hallenbeck and Patel-Mandlik 1979), but this accounts for only a very small fraction of the ingested dose (Cook and Olson 1979).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of asbestos fibers after dermal exposure. It is generally considered that dermal exposure does not result in uptake of asbestos.

3.4.4.4 Other Routes of Exposure

Similar to observations made in inhalation studies, studies in which animals were exposed by intratracheal injection indicate that chrysotile fibers are preferentially cleared from the lung over amphiboles (Churg et al. 1989a, 1989b; Sebastien et al. 1990). The enhanced clearance was generally attributed to fragmentation of fibers, rather than dissolution. The resulting fibers are shorter and more readily engulfed and moved by alveolar macrophages.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al.

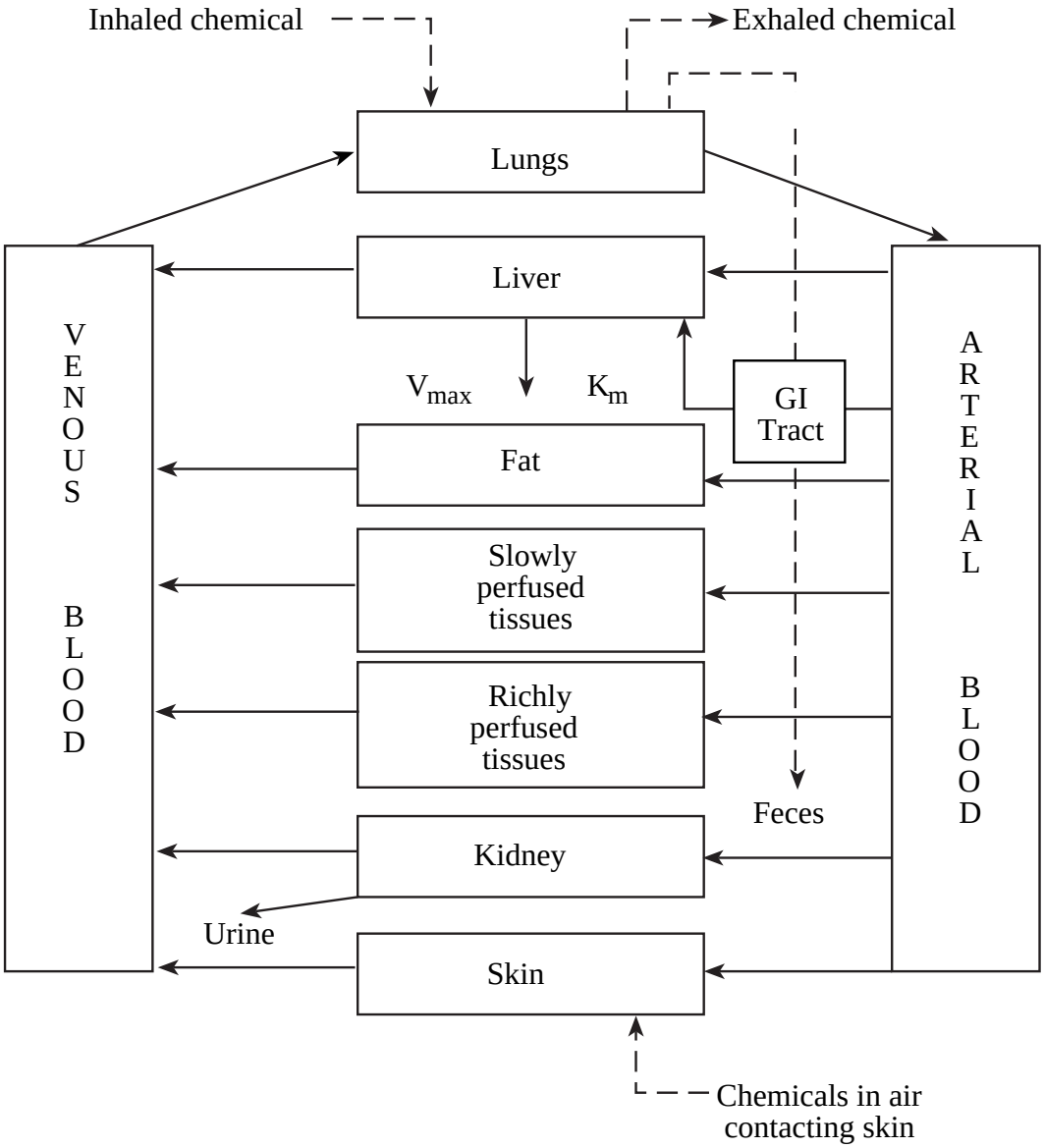
1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

3.4.5.1 Summary of PBPK Models

No PBPK models specific for asbestos were located. While a number of physiologically-based models for deposition and clearance of inhaled insoluble material have been developed (ICRP 1994; Phalen et al. 1991; Stober and McClellan 1997; Stober et al. 1994), a direct application of these models to the kinetics of asbestos fibers in humans has not been reported.

3.4.5.2 Asbestos PBPK Model Comparison

The available models for evaluating the dispositional kinetics of insoluble materials vary considerably in their level of complexity, but they are predominantly based on similar basic concepts (for recent review, see Stober and McClellan 1997). Recent models for fiber deposition in rats (Asgharian and Anjilvel 1998) have been reported, as have several models for clearance (for recent review, see Stober and McClellan 1997). Many models focus on either deposition or clearance processes, rather than combining the two, although recent efforts have developed lung retention models for fibers in humans and rats that include deposition and clearance processes (Yu et al. 1996, 1997).

The most successful models divide the respiratory system into a number of compartments, with each compartment having a distinct set of deposition or clearance parameters. Deposition models generally divide based on the bronchiolar branch pattern, whereas clearance models tend to divide based on anatomical clearance pathways. For example, material deposited in the tracheobronchial region clears predominantly through the larynx and eventually to the gastrointestinal tract, doing so at a faster overall rate than clearance from the pulmonary region. As additional knowledge of the physiology of the various compartments is discovered, subcompartments are added, each with an additional set of parameters. By combining the parameters from the various subcompartments and estimating the overall contribution of that subcompartment to the total, an estimation of the overall kinetics of exposure can be achieved. The most recent example of this approach is the POCK (physiology-oriented compartmental kinetics) model (Stober et al. 1994), which has a large number of subcompartmental parameters, each with equations to model particle clearance. This would allow for the modeling of disease states wherein specific aspects of deposition and/or clearance are altered without significantly affecting the others (i.e., particle overload of alveolar macrophages). However, to date, the majority of models have focused primarily on particles rather than fibers (see Section 3.4.5.3 for further explanation).

3.4.5.3 Discussion of Model

Because the biopersistence of fibers, including asbestos, is a key determinant of their toxicity, the most appropriate models for the estimation of toxic responses are likely to be those that model the deposition and clearance of the inhaled fibers. Existing models lack a number of features that have prevented them from being adequately utilized to model the kinetics of asbestos exposures in humans. Perhaps the greatest hindrance to the development of PBPK models for asbestos (i.e., their parameterization, simulation, and validation) has been the lack of accurate exposure data to link with lung fiber burden data in humans. Exposure assessments in human studies have been primarily based on estimates made from descriptions of environmental conditions in the workplace, rather than direct measurements of airborne asbestos concentration. Additionally, measurements of pulmonary fiber content in humans are generally performed after the subject has died, often a number of years following the cessation of exposure. These two factors combine to make accurate modeling of asbestos deposition and clearance from the existing human data more difficult.

The majority of the existing kinetic models for describing the fate of fibers and particles within the respiratory system were developed based on inhalation studies in rats. While this has undoubtedly led to more accurate modeling, as the rat database is considerably more extensive than the human one, several aspects of rodent anatomy and physiology differ significantly from the corresponding human system. In particular, the respiratory system in rats is structured differently than humans. The rat lung possesses a different branching pattern, which is likely to affect the deposition of the asbestos fibers. The bronchial tree of the rat is also physically smaller than that of man. When combined with the fact that rats are obligate nose-breathers, which is not the case for humans, this results in fibers that are respirable by humans being not respirable by most rodents (Hofmann et al. 1989). These factors decrease the utility of the rodent models in predicting human disposition under similar exposure conditions.

An additional difficulty with many models lies in the fact that they were developed for modeling particles, not fibers. Differences in physical properties in these insoluble materials can influence deposition and clearance processes in the respiratory tract. For example, particles that are too large to be phagocytized by alveolar macrophages generally do not reach the deep lung, but instead deposit by impaction in the nasal passages or airways. In contrast, long, thin fibers (>15 μm in length, but <3 μm in diameter) are respirable and can reach the deep lung where they are unable to be phagocytized by macrophages, and thus, are unable to be effectively cleared. The decreased clearance rate of fibers with increasing fiber length is also not considered in the majority of the particle-based clearance models. Fiber

breakdown, lengthwise or transverse, is also not factored into particle-based models. These deficiencies make utilization of particle-based models of deposition and clearance for the prediction of the behavior of fibers, including asbestos, problematic.

Recently, mathematical models have been developed for the deposition and retention of refractory ceramic fibers in the alveolar region of lungs of rats (Yu et al. 1994, 1995, 1996) and humans (Yu et al. 1994, 1995, 1997). The development of the rat model was based on exposure and lung burden data (including information on distribution of fiber sizes) from studies of rats exposed chronically to airborne refractory ceramic fibers. The models include descriptions of deposition rates with tidal volume, breathing frequency, air concentration of fibers of specific diameters and lengths, and alveolar deposition fraction (a function of airway structure, lung morphometry, and ventilation parameters for fibers of specific diameters and lengths) as explanatory variables and description of rates of three simultaneous clearance processes (alveolar macrophage-mediated clearance, dissolution of fibers in the lung fluid, and breakage of long fibers into shorter fibers). Rates for the removal processes in humans were extrapolated from the rat data. The developed human model predicted lung burdens that were in general agreement with lung fiber counts for three workers exposed to refractory ceramic fibers (Yu et al. 1997). The development of similar rat and human models for asbestos fiber lung deposition and clearance may be useful to more accurately predict human health risks from available data from rat inhalation bioassays. The most useful models for deposition and clearance of asbestos fibers are likely to be complex and should account for differences associated with different types of asbestos fibers and different size distributions of fibers.

3.5 MECHANISMS OF ACTION

Fibers that persist within the lung or the mesothelium are capable of producing fibrogenic and tumorigenic effects in these tissues. Although the precise mechanisms by which asbestos fibers cause toxic injury have not been determined, data are available that indicate that both direct interaction between fibers and cellular components and cell-mediated pathways may be involved. In addition, the physical-chemical nature of the fiber appears to be an important determinant of toxicity. Though the various mechanisms are likely to interact extensively, they will be discussed individually below.

3.5.1 Pharmacokinetic Mechanisms

A number of physical and chemical properties such as fiber size, durability, and iron content are important determinants of asbestos toxicity. The dependence of toxicity on these fiber properties is discussed below.

Fiber Size. The size (length and diameter) of an asbestos fiber appears to be one of the most important determinants of its toxicity. Fiber size dictates respirability, deposition, and clearance from the lung. In general, only fibers <3 μm thick are capable of reaching lower airways (Timbrell 1982). Fibers longer than approximately 5–10 μm are generally cleared more slowly than fibers shorter than 5 μm (Bellmann et al. 1987; Finkelstein and Dufresne 1999; Hesterberg et al. 1996; Morgan et al. 1978; Roggli et al. 1987a; Searl 1997; Warheit et al. 1997). The maximum fiber length that can be engulfed by a single macrophage is approximately 16–17 μm (Coin et al. 1992; Lippmann 1990). Asbestos-associated diseases are attributable to fibers of different sizes. The strongest evidence for this conclusion comes from studies in animals, where chronic inhalation exposure to dust clouds rich in long fibers (those in excess of 5 μm) produces higher incidence of lung cancer than exposure to dust clouds rich in short fibers (mostly <5 μm) (Davis and Jones 1988; Davis et al. 1986a). Asbestosis has been associated with fibers longer than 2 μm, mesothelioma with fibers longer than 5 μm, and lung cancer with fibers longer than 10 μm (Lippmann 1988, 1990). The dose-response relationships for the production of mesothelioma in rats intraperitoneally injected with amosite, chrysotile, and crocidolite were similar when doses were expressed in terms of the number of long (>4–8 μm), thin (<0.25 μm) fibers (Davis et al. 1991a; Stanton et al. 1981). Lippman (1988, 1990) noted that, in general, fiber widths <0.1 μm have been associated with mesothelioma, but can be larger for asbestosis and lung cancer. It should be noted, however, that rats exposed to populations of relatively shorter and broader tremolite fibers (lengths greater than 4 μm and width up to 1.5 μm) showed a high incidence of mesothelioma (American Thoracic Society 1990; Stanton et al. 1981). Ultimately, the size of the fiber determines its residence time in the lung. Longer fibers remain in the lung or mesothelium, whereas shorter fibers are cleared (Coin et al. 1992; Searl 1997). Fibers with lengths >15–20 μm are incompletely ingested and dissolved by pulmonary macrophages, which is thought to lead to chronic and persistent inflammation and tissue damage (Coin et al. 1992; Davis 1989; Davis et al. 1986a; Eastes and Hadley 1996; Lippmann 1994).

Interestingly, Churg et al. (1989a, 1990) reported that the severity of fibrosis in asbestos workers exposed primarily to tremolite and chrysotile, or amosite was positively correlated with lung fiber concentrations, but was negatively correlated with fiber length. The negative correlation (while not establishing

causation between short fibers or fiber fragments and fibrosis) suggests that short fibers may be more important to some aspects of asbestos-mediated toxicity than previously thought. As discussed by Case (1994) (see also Section 3.2.1.2), observation of the negative correlation of fibrosis score with fiber length may be dependent on the selection of fiber length counting criterion. Case (1994) has hypothesized that long fibers may initiate events and shorter fiber fragments, once formed in the lung, may increase effects on macrophage activity and subsequent fibrosis. Another possible explanation for this observation is that fiber size is also related to fiber surface area (Lippman 1988, 1990). As mentioned above, fiber surface properties are important to toxicity. Smaller thinner fibers have a greater surface area per unit mass than larger thicker fibers, thereby allowing for greater interaction with cell macromolecules. In addition, increased surface area may be important to providing more catalytically active iron sites (see below) for hydroxyl radical formation from reactive oxygen species.

Fiber Durability. Fiber biopersistance is believed to be a major mechanism of fiber-induced pathogenicity (Hesterberg et al. 1998a, 1998b). Numerous studies have indicated that some asbestos fibers, particularly chrysotile fibers, undergo fragmentation (latitudinal breakage) and/or splitting (longitudinal breakage) (Bellmann et al. 1987; Churg et al. 1989a, 1989b; Coin et al. 1992; Cook et al. 1982; Fasske 1988; Roggli et al. 1987a). The importance of fiber size and surface area with respect to toxicity is discussed above. Both fragmentation and splitting serve to increase the number of fibers and fiber surface area; therefore, toxicity of the resulting fibers is likely to increase as well. However, fiber fragmentation results in shorter fibers which are more readily cleared from the lungs by alveolar macrophages, whereas fiber splitting is likely to result in no change in fiber clearance. Differences in fiber durability may account for the differences observed in fiber potency between chrysotile and amphiboles.

Fiber Type. A diversity of opinion exists regarding relative potencies of various asbestos fiber types with respect to fibrogenicity and carcinogenicity. Some investigators have proposed that amphibole fibers, such as tremolite, are more potent than chrysotile fibers in inducing fibrotic lung disease and lung cancer (Hodgson and Darnton 2000; McDonald 1998a; McDonald and McDonald 1997; McDonald et al. 1999; Mossman et al. 1990a). Others have suggested that the differences in the potency of chrysotile and amphibole fibers in inducing lung cancer cannot be reliably discerned from available data (Stayner et al. 1996). It is generally agreed that exposure to amphibole fibers can produce mesothelioma, and that the potency of amphibole fibers to produce mesothelioma is greater than that of chrysotile. Some investigators have indicated that mesotheliomas among chrysotile-exposed workers are largely caused by small amounts of tremolite fibers found in mined and processed chrysotile (Churg 1988; Churg et al.

1993; Lippmann 1994; McDonald 1998a; McDonald et al. 1997). Others indicate that chrysotile fibers may also induce mesothelioma (Frank et al. 1998; Langer and Nolan 1998; Smith and Wright 1996). In a statistical analysis of mesothelioma and lung tumor data from a series of studies in which rats were exposed to airborne asbestos fibers of different types (chrysotile, amosite, crocidolite, and tremolite), Berman et al. (1995) concluded that amphibole fibers were more potent than chrysotile in inducing mesotheliomas, but no difference could be discerned in potencies of these fiber types to induce lung tumors. Apparent differences in potency among fiber types may be related to differences in lung retention. Amphibole fibers appear to be retained in the lung for longer periods than chrysotile fibers (Albin et al. 1994; Churg 1994; Churg et al. 1993; Davis 1989; Wagner et al. 1974). It has been suggested that such differences in retention may serve as a partial explanation of why amphibole fibers appear to be more potent in producing mesotheliomas than chrysotile fibers (Mossman et al. 1990a; American Thoracic Society 1990) (see also Section 3.4.3.1).

Iron Content. Iron is a redox-active metal and can catalyze the formation of hydroxyl radicals from superoxide and hydrogen peroxide via the Haber-Weiss reaction (the potential role of oxidant species in asbestos toxicity is discussed in Section 3.5.2). Evidence supporting the importance of iron in asbestos-induced toxicity include the success of iron chelators (desferrioxamine) in inhibiting the production of reactive oxygen species and subsequent toxicity (Goodglick et al. 1989; Kamp et al. 1992; Lund and Aust 1991b; Mahmood et al. 1993; Simeonova and Luster 1995). Desferrioxamine has also been shown to decrease the ability of asbestos fibers to induce DNA single-strand lesions (Chao and Aust 1994; Kienast et al. 2000). Silicate fibers capable of producing pneumoconiotic changes were also able to serve as Haber-Weiss catalysts, whereas silicate fibers that were nonpneumoconiotic lacked this activity (Kennedy et al. 1989).

There are several possible sources of iron in the lung that may contribute to asbestos toxicity. One source of iron is the fiber itself. Crocidolite and amosite asbestos may contain levels of 26–36% iron by weight (Lund and Aust 1991a). A second source of iron is as a contaminant of asbestos. Iron-containing minerals such as pyrite, magnetite, nemalite, and iron ore often occur as contaminants of asbestos and can be deposited in the lung along with asbestos fibers (Fontecave et al. 1990). A third possible source of iron is from within the exposed animal. Ferritin (an iron-containing protein) is present in macrophages and giant cells. Iron metabolism was found to be altered in these cells by the presence of poorly digestible fibers (Koerten et al. 1990a). Iron is also a component of the protein-coat covering asbestos bodies (Ghio et al. 1997; Koerten et al. 1990a, 1990b). The extent to which each of these sources of iron

contribute to the catalysis of hydroxyl radical formation *in vivo* is uncertain and warrants further investigation.

3.5.2 Mechanisms of Toxicity

This section provides an overview of several potential mechanisms involved in the development of asbestos-induced health effects (direct interaction with macromolecules, active oxygen mechanisms, and other cell-mediated mechanisms). An expert panel convened by IARC concluded in 1996, "Overall, the available evidence in favor or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (IARC Expert Panel 1996). Pulmonary inflammatory factors (a subset of other cell-mediated mechanisms) were considered by the IARC panel as having the most support among the potential mechanisms involved. For additional information on the molecular mechanisms of asbestos-induced pulmonary disease discussed below, including potential interactions between a number of the mechanisms, see recent reviews (Kamp and Weitzman 1999; Kinnula 1999; Lee and Testa 1999; Murthy and Testa 1999; Robledo and Mossman 1999).

Direct Interaction. Asbestos fibers can adsorb to a variety of cellular macromolecules (e.g., proteins, membrane lipids, RNA, DNA). In rat lung microsomes, chrysotile fibers were found to bind to cytochrome P-450, thereby decreasing mono-oxygenase activity (Khan et al. 1992; Rahman et al. 1990). Chrysotile and crocidolite fibers were found to bind to artificial lipid membranes *in vitro*, thereby increasing membrane rigidity (Gendek and Brody 1990). This effect was also noted in erythrocytes, and may be responsible in part for the *in vitro* hemolytic activity of asbestos fibers. The interaction between asbestos fibers and cell membranes was mediated in part by surface charge (positively charged chrysotile fibers can become associated with negatively charged membrane constituents), and also fiber binding to fibronectin, a glycoprotein found in abundance in the alveolar lining fluid (Brown et al. 1991). Dielectric changes in membrane properties and cell interiors have been observed in cultured human mesothelial cells exposed to crocidolite fibers (Dopp et al. 2000). Peterson et al. (1993) noted that the integrity of cultured human lung epithelial cells was compromised by chrysotile, resulting in increases in epithelial permeability that occurred in the absence of cell death and inflammatory cells. The coulombic forces between the asbestos fiber and macromolecules (DNA, RNA, and protein) may induce conformational changes (Brown et al. 1998; Chang et al. 1990), and these changes could affect protein function and chromosomal fidelity. Surface charge density may also be an important factor in fiber potency (Bonneau et al. 1986; Davis et al. 1988). In some studies, asbestos fibers were observed to interfere with

cytokinesis (Jensen and Watson 1999). Fibers found to be translocated near the nucleus can interact with the cytoskeleton and interfere with chromosome segregation (Ault et al. 1995; Malorni et al. 1990) or with micronucleus formation (Lu et al. 1994a). Deletions of chromosome segments (particularly the short arm of chromosome 3 and portions of chromosomes 1, 6, 9, 15, and 22) have been noted in human mesothelioma cells or cell lines (Balsara et al. 1999; Barrett et al. 1989; Bell et al. 1997; Cheng et al. 1993, 1994; Flejter et al. 1989; Lee et al. 1996; Lu et al. 1994b; Taguchi et al. 1993), and interference with chromosome segregation may at least partially account for this (Barrett et al. 1989). Recent work by J.R. Testa and coworkers (see Murthy and Testa 1999) indicates that certain tumor suppressor genes are frequently altered in the regions of asbestos-induced deletions, although underlying mechanisms have not been clearly elucidated.

Additional evidence supporting the importance of fiber surfaces comes from studies in which the fiber surfaces have been altered. Modification of asbestos fiber surfaces with certain dyes, alkyl groups, or phosphate was found to decrease their *in vitro* hemolytic and cytotoxic activity (Awadalla et al. 1990; Brown et al. 1990, 1991; Habashi et al. 1991). However, relative to untreated chrysotile fibers, alteration of the fiber surface chemistry (via HCl treatment) did not significantly alter the results of a genotoxicity test that assessed the induction of micronuclei in Chinese hamster lung fibroblasts treated *in vitro* (Keane et al. 1999). Cyclical stretching of cultured human alveolar cells during exposure to asbestos fibers (as might occur during normal breathing) resulted in increased production of the proinflammatory cytokine interleukin-8, presumably in response to a direct mechanical interaction between asbestos fibers and the alveolar cells. This response was enhanced when the fibers were coated with fibronectin (Tsuda et al. 1999). In general, these data suggest that direct interactions between asbestos fibers and key cellular molecules may be responsible, at least in part, for asbestos-related health effects.

Active Oxygen Mechanism. In response to asbestos fibers, alveolar macrophages produce reactive oxygen species in an attempt to digest the fiber. The reactive oxygen species include hydrogen peroxide and superoxide radical anion (O_2^-) (Cantin et al. 1988; Case et al. 1986; Hansen and Mossman 1987; Nyberg and Klockars 1991; Roney and Holian 1989). These reactive oxygen species are relatively mild oxidants. However, they can spontaneously react with each other, producing hydroxyl radicals that are much more potent oxidants. This reaction is often referred to as the Haber-Weiss or Fenton reaction (Garcia et al. 1988; Weitzman and Graceffa 1984; West 1985). The Haber-Weiss reaction is greatly enhanced in the presence of redox-active metals such as iron. Numerous *in vitro* studies have linked the production of reactive oxygen species to asbestos-induced lipid peroxidation (Fontecave et al. 1990; Goodglick et al. 1989; Yano 1988), cytotoxicity (Garcia et al. 1988; Goodglick and Kane 1990; Iguchi

and Kojo 1989; Kennedy et al. 1989; Shatos et al. 1987), cell proliferation (Marsh and Mossman 1991), genotoxicity (Chao et al. 1996; Fung et al. 1997a; Kienast et al. 2000; Korkina et al. 1992; Lund and Aust 1991a, 1992; Xu et al. 1999), and apoptosis (Broaddus et al. 1996, 1997). *In vitro* studies have also shown that the effects of asbestos are diminished by the addition of catalase and superoxide dismutase (enzymes that catalyze the decomposition of reactive oxygen species), free radical scavengers (ascorbic acid, bemitil, mannitol, salicylate, 5,5'-dimethyl-1-pyroline N-oxide, rutin, vitamin E) (Brown et al. 1998; Faux and Howden 1997; Garcia et al. 1988; Goodglick and Kane 1990; Goodglick et al. 1989; Iguchi and Kojo 1989; Kienast et al. 2000; Korkina et al. 1992; Lund and Aust 1992; Yano 1988), or calcium channel inhibitors (Ishizaki et al. 1997; Lim et al. 1997). Cell membrane lipids have been shown to undergo peroxidation, resulting in increased membrane permeability in rat lung fibroblasts cultured with asbestos (Iguchi et al. 1993). Additional evidence supporting the involvement of reactive oxygen species in asbestos toxicity comes from *in vivo* studies. Intratracheal instillation of chrysotile asbestos in rats has been shown to lead to hydroxyl radical formation (Schapira et al. 1994). Activities of superoxide dismutase, glutathione peroxidase, and catalase were significantly elevated in rats exposed to crocidolite by inhalation (Janssen et al. 1992). Decreases in a number of antioxidants known to protect against oxidative stress were observed in alveolar macrophages or the bronchoalveolar lavage of rats exposed to asbestos fibers via intratracheal instillation (Abidi et al. 1999; Kaiglová et al. 1999). Levels of superoxide dismutase and plasma malondialdehyde (an indicator of lipid peroxidation) were significantly elevated in asbestos workers compared to controls (Kamal et al. 1989, 1992). Lipid peroxidation was noted in cells and fluid from bronchoalveolar lavage of rats after exposure to crocidolite (Ghio et al. 1998; Petruska et al. 1991); endogenous peroxidase activity was noted in macrophages from pleural lavage of mice after intraperitoneal injection of crocidolite (Branchaud et al. 1993). Cytotoxic and oxidative responses indicative of oxidative stress were observed in alveolar macrophages and peripheral red blood cells (RBCs) of rats exposed to crocidolite or chrysotile fibers via intratracheal instillation (Afaq et al. 1998). Interestingly, uptake of asbestos fibers into epithelial cells is increased by reactive oxygen species (Hobson et al. 1990; Peterson and Kirschbaum 1998). Overall, the data collectively indicate that the production of reactive oxygen species is likely to be an important component of the mechanism of asbestos-induced toxicity.

Other Cell-Mediated Mechanisms. In addition to the release of active oxygen species, alveolar macrophages and other cells, including pleural mesothelial and lung cells, release a number of cellular factors in response to asbestos exposure. These factors are mediators of a number of cellular reactions including inflammation, macrophage recruitment and cell proliferation (for reviews, see Driscoll et al. 1997; Xing et al. 1999). Chronic stimulation of these pathways can result in a gradual loss of some

epithelial cells, proliferation and deposition of collagen by fibroblasts, or alterations of cellular phenotype (Davis and Jones 1988; Davis et al. 1986c; Holian et al. 1997; Lasky et al. 1996). These data suggest that the effects of asbestos exposure may be mediated by stimulation of the autocrine (same cell) and paracrine (different cell) systems.

Recent work has suggested potentially important mechanistic roles for a number of nuclear regulatory proteins, oncogenes, proto-oncogenes, and second messenger proteins. Among these are nuclear factor-κβ (NF-κβ) (Barchowsky et al. 1998; Cheng et al. 1999b; Driscoll et al. 1998; Faux and Howden 1997; Luster and Simeonova 1998; Mossman et al. 1997; Oettinger et al. 1999; Simeonova and Luster 1996), activator protein-1 (AP-1), including its subunits of c-fos, c-jun, and fra-1 (Faux and Howden 1997; Fung et al. 1997b; Heintz et al. 1993; Janssen et al. 1995; Mossman et al. 1997; Sandhu et al. 2000; Zanella et al. 1999), p53 (Hayashi et al. 1996; Johnson and Jaramillo 1997), *ras* (Hayashi et al. 1996; Nelson et al. 1999), tyrosine kinases (Peterson and Kirschbaum 1998), and protein kinase c (PKC) (Fung et al. 1997b; Lim et al. 1997; Simeonova and Luster 1996). Interestingly, a number of these factors have been shown to influence the production of other cellular factors (Barnes 1997; Blackwell and Christman 1997; Cheng et al. 1999b). Additionally, cellular oxidant status has been shown to influence the behavior of AP-1 and NF-κβ (Janssen and Sen 1999; Janssen et al. 1995; Simeonova et al. 1997). The latter two observations have served to further the view that NF-κβ and AP-1 play roles in asbestos-induced lung injury, as they would allow for the integration of several of the mechanisms proposed above (i.e., asbestos-associated iron could generate oxygen radicals, leading to the increased activity of nuclear factors, which induce cytokine genes, leading to cell infiltration and proliferation).

A number of the factors mentioned above also participate in the pathways regulating pulmonary inflammation. Although poorly understood, the inflammatory response is thought to play an important role in the development of asbestos-induced pulmonary disease and is the one mode of toxic action for which there are supporting human data from *in vitro* and *in vivo* studies (IARC Expert Panel 1996). Asbestos exposure has been shown to elicit a complement-dependant increase in the number of alveolar macrophages at sites of asbestos deposition (Warheit et al. 1984, 1985, 1986, 1988). Other chemotactic factors include leukotrienes (Dubois et al. 1989; Garcia et al. 1989; Hayes et al. 1990), prostaglandins (Bissonnette et al. 1989, 1990; Garcia et al. 1988), and interleukins (Boylan et al. 1992; Griffith et al. 1994; Luster and Simeonova 1998; Perkins et al. 1993). One factor that has been particularly well-studied with regards to its role in the asbestos-induced inflammatory response is TNF-α. A number of studies have demonstrated a role of TNF-α in the inflammatory response following asbestos exposure in animals (Dubois et al. 1989; Liu et al. 1998; Simeonova and Luster 1995) and humans (Zhang et al.

1993). Asbestos-associated TNF-α has been shown both to induce and to be induced by oxidant species (Pietarinen-Runtti et al. 1996; Simeonova and Luster 1995). Reduction of TNF-α *in vivo* results in a protection from asbestos-induced fibrotic changes (Brass et al. 1999; Liu et al. 1998). Some of the asbestos-induced inflammatory reactions may be related to fiber type. For example, crocidolite, but not chrysotile, induced increased production of TNF-α and interleukin 1β in cultured rat alveolar macrophages exposed for up to 14 days, whereas chrysotile, but not crocidolite, increased production of superoxide anion and nitric oxide radicals (Mongan et al. 2000).

3.5.3 Animal-to-Human Extrapolations

The vast majority of experimental studies of asbestos have been performed in rodent model systems. Results from inhalation studies indicate that rats are suitable qualitative models for asbestos-induced pulmonary diseases, demonstrating chronic inflammation, pulmonary fibrosis (see Section 3.2.1.2), lung cancer (see Section 3.2.1.8), and mesothelioma (see Section 3.2.1.8) following chronic asbestos exposure. Hamsters seem to be more sensitive than rats to mesothelioma development, but less sensitive to the development of pulmonary tumors (Warheit and Hartsky 1994).

Some investigators have suggested that rats may be less sensitive to the development of asbestos-related mesotheliomas than humans. Rödelsperger and Woitowitz (1995) reported, based on the studies of McDonald et al. (1989, 1993) and Doll and Peto (1985), an increased risk in humans for mesothelioma at pulmonary fiber burdens as low as 0.2 f/µg dry weight, whereas a 44-week rodent exposure yielded a 6,000-fold higher lung fiber burden (1,250 f/µg), but less than a 1% incidence of mesothelioma. One possible explanation for this putative difference in sensitivity is that the shorter lifespan of rodents compared to humans, combined with the long latency period for asbestos-related diseases (generally $10 years), does not allow for late-developing respiratory effects to develop in rodents. Alternately, it may relate to differences in deposition and clearance patterns between rats and humans (Asgharian et al. 1995; Hofmann et al. 1989). However, this alternative explanation is difficult to verify because the deposition and clearance patterns for asbestos in humans are poorly described. Additional research on deposition and clearance of asbestos fibers in humans may help to properly address this issue.

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans or animals after exposure to asbestos. No *in vitro* studies were located regarding endocrine disruption by asbestos.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

As discussed in Section 3.2 and Chapter 2, numerous studies of occupationally-exposed adult workers identify respiratory effects including interstitial fibrosis, lung cancer, and pleural and/or peritoneal mesotheliomas, as critical health effects, of concern from exposure to airborne asbestos. Typically, these health effects follow chronic exposures and exhibit latencies of 10–40 years, although some cases of asbestosis and pleural plaques have been reported following subchronic exposure.

Some investigators have associated childhood exposures (e.g., from asbestos-laden clothing of occupationally-exposed family members or close childhood proximity to asbestos mining operations) with development of asbestos-related respiratory diseases in adulthood (Anderson et al. 1976; Inase et al. 1991; Magee et al. 1986; McDonald and McDonald 1980; Voisin et al. 1994; Wagner et al. 1960). Malignant mesothelioma is a rare childhood neoplasm that does not appear to be associated with asbestos exposure, in contrast to mesothelioma in adults. Only 80 suspected cases were identified in the literature as of 1988 (Fraire et al. 1988); of these, only 2 girls (3 and 17 years of age) had a history of possible exposure to asbestos. In a more recent published case report, mesothelioma was diagnosed in a 17-year-old boy who lived in a rural setting, had no familial relations with an asbestos worker, and had been exposed daily to asbestos fibers in a cosmetic talc from about 9–12 years of age (Andrion et al. 1994). There was no information regarding the asbestos level in the talc, but the boy exhibited a lung tissue asbestos concentration of 0.51×10^6 f/g dry tissue (62% chrysotile and 38% tremolite). It is not recommended that this value be compared to the mean lung asbestos fiber concentration of 0.11×10^6 f/g , reported by Case et al. (1994) for 60 U.S. children, because there are appreciable variations in lung burden methods and results between laboratories. Andrion et al. (1994) noted, however, that based on lung fiber concentrations determined by their referring laboratory for 85 general autopsy cases of adult subjects living in a polluted urban setting, the boy's asbestos fiber burden was unusually high for a rural dweller and was within the range for the highest 16^{th} percentile of this sample of urban dwellers (range from 0.2 to 3.0×10^6 f/g). The estimated latency period of 8 years is short relative to a latency period of greater than 15 years in 99% of 1,105 adult cases of asbestos-induced mesotheliomas in occupationally-exposed workers reviewed by Lanphear and Buncher (1992). It is uncertain if the relatively short latency period in this case was related to an increased age-related susceptibility, a relatively high exposure level, or an individual susceptibility unrelated to age.

A cohort of 4,659 former residents of Wittenoom, Western Australia, who had lived there between 1943 and 1993 for at least 1 month, and were environmentally, but not occupationally, exposed to asbestos (crocidolite), was studied by Hansen et al. (1998). The rate of mesothelioma in the cohort increased significantly with time from first environmental exposure, duration of exposure, and cumulative exposure.

However, incidence of mesothelioma was not significantly related to age of first exposure (treated as a continuous variable and adjusting for all other variables). Those first exposed as children under 10 years of age exhibited a lower incidence of mesothelioma than those first exposed at an older age.

The lack of reports of asbestos-related respiratory diseases in children suggest that children may not develop respiratory diseases during childhood in response to environmental or "paraoccupational" exposure to asbestos. The long-term retention of asbestos fibers in the lung and the long latency period for onset of asbestos-related respiratory diseases suggest that individuals exposed earlier in life may be at greater risk to the eventual development of respiratory problems than those exposed later in life, but direct evidence for this hypothesis is not available. In contrast, incidence of mesothelioma was not significantly related to age of first exposure in the study by Hansen et al. (1998).

Studies examining age-related susceptibility to airborne asbestos in animals were not located. There was no indication from the available literature that specialized respiratory defense mechanisms might be less active or underdeveloped in children relative to adults. An association has been noted between the slow N-acetyltransferase 2 (NAT2) genotype and the increased risk for developing mesothelioma or nonmalignant respiratory disease in adults exposed to high levels of asbestos (Hirvonen et al. 1995, 1996; see Section 3.10 for more details). To date, it is uncertain if that reported early developmental differences in the expression of NAT2 (Leeder and Kearns 1997) may lead to developmental differences in susceptibility to asbestos toxicity.

No information was located specifically concerning health effects in children exposed to asbestos by the oral or dermal routes. Childhood exposures are likely to result in responses similar to those reported in adults (see Sections 3.2.2 and 3.2.3).

No human studies were located regarding asbestos-related developmental toxicity by any exposure route, but one group of investigators has reported that asbestos fibers were detected more frequently and at higher mean concentrations in tissues from stillborn infants than in placental tissues from live births (Haque et al. 1991, 1992, 1996, 1998). It is unclear if the differences in asbestos tissue counts between these stillborn and liveborn groups are related to either differences in maternal environmental exposure leading to transplacental transfer of fibers, nonexposure-related differences in fetal or placental factors leading to a breach of the normal fetal/placental barrier and an accumulation of fibers in fetal and placental tissue, or sample contamination. Transplacental transfer of asbestos fibers has been demonstrated in pregnant rats and mice given single bolus intravenous injections of asbestos suspensions

(Cunningham and Pontefract 1974; Haque and Vrazel 1998), but the tissue counts in both of these experiments were highly variable. For example, the range of concentrations in 36 digests of fetal tissues sacrificed 1 hour after injection in the mouse experiment ranged from 116 to 30,342 f/g (Haque and Vrazel 1998). This variability may due to an inconsistent mass breakthrough of fibers associated with the bolus intravenous administration (Cunningham and Pontefract 1974). It is expected that the extent of transplacental transfer of fibers would be much less with inhalation, oral, or dermal exposures.

No animal developmental toxicity studies were located for inhalation or dermal routes of exposure. Results from chronic oral studies in rats and hamsters provided no indication of potential for developmental toxicity (exposure was through gestation, weaning, and adulthood), except for some slight reductions in pup birth weight (which might possibly be secondary to asbestos exposure) (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). Likewise, no exposure-related developmentally toxic effects were found in pregnant mice exposed during gestation to asbestos in drinking water at concentrations as high as 143 µg/mL (Schneider and Maurer 1977).

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic 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 asbestos are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by asbestos are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Asbestos

Principal biomarkers of exposure to asbestos fibers include the detection and counting of fibers or asbestos bodies in bronchoalveolar lavage fluid samples (De Vuyst et al. 1982, 1988, 1997; Dumortier et al. 1990, 1998; Roggli et al. 1994a; Sebastien et al. 1988a; Teschler et al. 1994; Tuomi et al. 1991b), sputum samples (McDonald et al. 1988, 1992; Sebastien et al. 1988b), or in autopsied or surgically resected lung tissue samples (Case 1994; Churg 1982; Churg and Warnock 1981; Churg and Wright 1994; Churg et al. 1993; de Klerk et al. 1996; Dodson et al. 1999; Dufresne et al. 1995, 1996a, 1996b; Sebastien et al. 1989). Asbestos bodies are collections of fibers (usually of length >8 μm) with a protein-iron coating (also known as ferruginous bodies) that, when observed in lung tissue sections in conjunction with fibrosis, have been proposed to be used in the diagnosis of asbestosis (Churg 1989; Craighead et al. 1982). Whereas light microscopy can be used to detect and count asbestos bodies, most uncoated fibers in tissue or fluid samples are too small to be visible (Dodson et al. 1999). Transmission or scanning electron microscopy is used to detect and count uncoated asbestos fibers in lung tissue or fluid samples, and electron diffraction or energy-dispersive x-ray analysis is used to determine asbestos type (e.g.,

chrysotile, anthophyllite, tremolite) (NIOSH 1994b). These biomarkers provide indicators of retained internal dose, the cumulative net result of deposition and clearance of inhaled asbestos fibers.

Analyses of bronchoalveolar lavage fluid samples or sputum samples can directly reflect alveolar concentrations of retained fibers and, although they do not reflect the proportion of deposited fibers that may move to the interstitium (Case 1994; Pinkerton et al. 1984), can provide information regarding past exposure to asbestos, especially to amphibole fibers. Obtaining sputum samples is much less invasive than obtaining bronchoalveolar lavage samples. In Libby, Montana vermiculite miners and millers exposed to fibrous tremolite, counts of asbestos bodies in sputum samples closely reflected intensity and duration of past exposure (Sebastien et al. 1988b), but asbestos body counts in sputum samples from volunteers from other cohorts of workers exposed to asbestos (predominately chrysotile or lower levels of amphibole fibers than in Libby) did not reliably reflect past levels of exposure (McDonald et al. 1988, 1992). Concentrations of asbestos bodies in bronchoalveolar lavage fluid samples have been reported to reflect past exposure to asbestos fibers in a number of studies (De Vuyst et al. 1988, 1997; Dumortier et al. 1990, 1998; Roggli et al. 1994a; Teschler et al. 1994; Tuomi et al. 1991b) and to correlate with lung tissue concentrations of asbestos bodies (De Vuyst et al. 1988; Sebastien et al. 1988a; Teschler et al. 1994), but exposure to amphibole fibers may be better reflected than exposure to chrysotile fibers. For example, Sebastien et al. (1988a) reported a statistically significant correlation ($r=0.74$, $p<0.0001$) between concentrations of asbestos bodies in bronchoalveolar fluid samples (which ranged from 0.05 to 10^4 asbestos bodies/mL) and concentrations in lung parenchyma tissue samples (which ranged from 40 to 8.9×10^6 asbestos bodies/g dried lung parenchyma) in 69 patients who had either an open lung biopsy or an autopsy. Sebastien et al. (1988a) concluded that bronchoalveolar concentrations exceeding 1 asbestos body /mL predict that the parenchymal concentration will be in excess of 1,000 asbestos bodies/g dry tissue and that the patient will have experienced "a nontrivial asbestos exposure." Dumortier et al. (1990) reported that, in brake lining and asbestos cement workers, the core fiber of the asbestos bodies was usually amphibole fibers, but chrysotile cores were found in most recently exposed brake lining workers examined. A statistically significant correlation between asbestos body concentrations in bronchoalveolar fluid samples and lung parenchyma samples was also found in 20 patients with histories of occupational exposure to mixed (chrysotile and amphibole) asbestos fibers (Teschler et al. 1994). Concentrations of uncoated amphibole fibers (fibers were counted as particles with nearly parallel long edges, lengths >1 µm, and aspect ratios >3:1) in bronchoalveolar fluid samples were correlated with concentrations of uncoated amphibole fibers in lung parenchyma, but concentrations of uncoated chrysotile fibers in fluid samples were not correlated with concentrations in lung parenchyma samples (Teschler et al. 1994). Teschler et al. (1994) concluded that concentrations of asbestos bodies and amphibole fibers in

bronchoalveolar fluid samples reliably predict lung concentrations of retained amphibole fibers, but not retained chrysotile fibers, and that negative findings for asbestos bodies in bronchoalveolar fluid samples do not necessarily rule out significant exposure to asbestos fibers.

Analysis of concentrations of asbestos bodies (by light microscopy) or asbestos fibers (by electron microscopy) in lung tissue samples may represent more accurate reflections of past asbestos exposure than analysis of bronchoalveolar fluid or sputum samples, but these approaches are not without difficulties, especially for assaying exposure to chrysotile fibers, which are more rapidly cleared than amphibole fibers (Case 1994; Churg and Wright 1994). Although asbestos bodies can form on lung retained chrysotile, amphibole cores appear to be more prevalent in general populations and asbestos-exposed occupational groups, even though exposure may have primarily involved chrysotile (Case 1994; Dumortier et al. 1990). Correlations between lung concentrations of asbestos bodies and concentrations of retained uncoated asbestos fibers in numerous studies have been observed most consistently for amphibole fibers and generally not for chrysotile fibers (Albin et al. 1990b; Case et al. 1994; Karjalainen et al. 1996a, 1996b).

Comparison of lung fiber concentrations across studies and laboratories and establishment of benchmark lung fiber concentrations to indicate occupational exposure are difficult due to differences in preparative and sampling methods, types of electron microscope and magnification, and criteria for defining and counting fibers (Gylseth et al. 1985). In addition, numerous studies of measured indices of occupational asbestos exposure, such as years of exposure or cumulative exposure, and lung retained fiber concentrations generally have shown significant correlations between exposure and concentrations of retained amphibole fibers, but do not generally show a correlation between exposure and retained chrysotile fiber concentrations (see Churg and Wright 1994 for review of many of these studies). These findings are generally taken to reflect much faster clearance of the major proportion of deposited chrysotile fibers compared with amphibole fibers. However, studies (Case 1991; Case and Sebastien 1987, 1989) conducted by a single laboratory of Quebec chrysotile miners and millers, their families, residents without familial connections to the mines and mills, and referent residents who did not live close to the mines found that lung concentrations of chrysotile fibers, tremolite fibers, and asbestos bodies were related to increasing proximity of residence to the mines and increasing degree of domestic or occupational exposure. From the results of these studies, Case (1994) concluded that asbestos body concentrations over 250 asbestos bodies/g dry lung and chrysotile or tremolite fiber concentrations greater than $1x10^5$ fibers/g dry lung were “robust indicators of mining area residence”.

For the attribution of asbestos exposure in individual cases, recommendations have been made to combine all available exposure data, including work history, radiological and histological findings, and lung concentrations of asbestos bodies and fibers when appropriate (Case 1994; Karajalainen et al. 1996a, 1996b). Benchmark concentrations of $0.1–1x10^6$ fibers/g dry lung have sometimes been used as indicators of occupational asbestos exposure (Case 1994; International Expert Meeting on Asbestos 1997). Their application to ascertain or validate occupational exposure in individual cases, however, especially those involving chrysotile exposure, is expected to result in both false positives and false negatives, because of the variability in the association between exposure measures and retained fiber concentrations (Becklake and Case 1994; Case 1994; Karajalainen et al. 1994a; Takahashi et al. 1994; Williams et al. 1995). Some of this variability is likely attributable to analytical variability due to contamination or loss in processing, variability in retention of fibers in different regions of the lung and variability in sampling of different lung regions, variability in exposure parameters including fiber type, length, and width, and variability in individuals' physiological parameters influencing retention.

Concentrations of retained fibers in autopsied or resected lung tissue samples also have been used as exposure variables in several case-control studies designed to characterize potential dose-response relationships for asbestos-induced mesothelioma and attribute risk to specific fiber types and size classes (McDonald et al. 1989; Rödelsperger et al. 1999; Rogers et al. 1991). Results from these studies indicated that relative risk for mesothelioma was significantly related to increasing concentrations of amphibole fibers longer than 5 µm (Rödelsperger et al. 1999), 8 µm (McDonald et al. 1989), or 10 µm (Rogers et al. 1991). Significant relationships with increasing concentrations of retained chrysotile fibers were less apparent in these studies. Rödelsperger et al. (1999) and McDonald et al. (1989) did not find statistically significant trends for increasing relative risks (odds ratios) with increasing retained chrysotile fiber concentrations. Rogers et al. (1991) found a statistically significant trend for increasing relative risks with increasing chrysotile fiber concentration (all lengths included), but this was only found in a subgroup of cases and controls with only chrysotile fibers detected in their lungs.

Asbestos fibers have also been measured in urine (see Section 7.1), and limited data indicate that above average exposures in the workplace (Finn and Hallenbeck 1984) and through drinking water (Cook and Olson 1979) can be detected by this means. However, only a tiny fraction of inhaled or ingested fibers is excreted in the urine, and the quantitative relationship between exposure and urinary fiber concentration appears quite variable. Moreover, urinary levels presumably are mainly a reflection only of recent exposures. Thus, urinary analysis for fibers has not been established or validated as a reliable means of biomonitoring for chronic asbestos exposure.

3.8.2 Biomarkers Used to Characterize Effects Caused by Asbestos

The most common means of characterizing the effects of inhalation exposure to asbestos in living persons is the chest x-ray (e.g., Amandus et al. 1987; Anton-Culver et al. 1989; Jones et al. 1988b; McDonald et al. 1986b). The International Labour Office (ILO) established a classification system for profusion of opacities in chest radiographs that includes four categories of increasing severity, each with three subcategories: 0 (0/-, 0/0, 0/1); 1 (1/0, 1/1, 1/2); 2 (2/1, 2/2, 2/3), and 3 (3/2, 3/3, 3/4) (ILO 1989). Chest radiographs are capable of detecting both pleural and parenchymal abnormalities, but sensitivity and specificity are limited (Gefter and Conant 1988). In particular, x-ray changes are rarely detectable until after some degree of physiological impairment has occurred (Aberle et al. 1988a). A more sensitive method is gallium-67 lung scanning, which often can detect asbestos-induced inflammation and other lung abnormalities prior to their detection by x-ray (Bisson et al. 1987; Hayes et al. 1989; Klaas 1993). Computerized tomography (CT) and high-resolution computed tomography (HRCT) may also be superior to conventional radiological examination in some cases (Aberle et al. 1988a, 1988b; Akira et al. 1991; Al Jarad et al. 1993; Friedman et al. 1988; Gamsu et al. 1989; Klaas 1993; Murray et al. 1995; Neri et al. 1994, 1996; Oksa et al. 1994; Sluis-Cremer et al. 1984). Magnetic resonance imaging may also be used to identify asbestos-induced lung abnormalities (Bianchi et al. 1997; Boraschi et al. 1999).

Quantitative analysis of lung function is also used for evaluating the effects of asbestos inhalation (e.g., Ernst et al. 1989; Finkelstein 1986; Kilburn et al. 1995). The specific end points of greatest value are FEV_1 and FVC, since these are most affected by fibrotic changes in the lung. Changes in biphasic lung carbon monoxide diffusing capacity may be better suited for detecting early decreases in lung function due to asbestos exposure (Dujic et al. 1992; Wang et al. 1998). Most studies find that respiratory changes parallel radiological changes (e.g., Britton 1982; Cordier et al. 1987; Di Lorenzo et al. 1996; Dujic et al. 1992; Markowitz et al. 1997; Miller et al. 1996), although several studies report measurable respiratory decrements in the absence of radiological changes (Ohlson et al. 1984; Wang et al. 1997; Weill et al. 1975).

The American Thoracic Society (1986) adopted a set of criteria for the diagnosis of asbestosis that includes a reliable history of asbestos exposure, an appropriate time interval between exposure and detection, and the following clinical criteria: (a) chest radiographic evidence of small irregular opacifications of a profusion of 1/1 or greater using the ILO classification; (b) a restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal; (c) a diffusing capacity below the lower limit of normal; and (d) bilateral late or pan inspiratory crackles at the posterior lung bases not

cleared by cough. The International Expert Meeting on Asbestos (1997) similarly specified that the confident diagnosis of interstitial fibrosis of the lung as a consequence of exposure to asbestos dust (i.e., asbestosis) requires, in addition to clinical features and architectural tissue abnormalities typical of interstitial fibrosis, a history of significant exposure to asbestos dust, or the detection of asbestos fibers or bodies in lung tissue greatly in excess of that seen in the general population. This group further specified that a histological diagnosis of asbestosis requires identification of diffuse interstitial fibrosis in lung tissue remote from tumors, in addition to the presence of 2 or more asbestos bodies in 1-cm^2 areas of sectioned lung tissue or uncoated lung-retained fiber counts outside of the range for general-population counts from the same laboratory.

Examination of cells and cellular factors present in lung lavage fluid and blood serum may be used to indicate early changes associated with asbestos-induced fibrosis. A number of human studies have shown that the differential cell count (Hayes et al. 1989; Rom 1991) and levels of fibronectin (Begin et al. 1986; Rom 1991), procollagen III (Begin et al. 1986), and hyaluronic acid (Cantin et al. 1992) are elevated in the lung lavage fluid of asbestos workers as compared to nonexposed controls. A significant elevation of the amino-terminal peptide of procollagen III (PIIINP) was found in the serum of asbestos workers when compared to controls (Cavalleri et al. 1991). Also, excretion of the oxidative DNA adduct, 8-hydroxy-deoxyguanosine, has been shown to be increased in the urine of asbestos workers and therefore, might be used to indicate DNA damage (Tagesson et al. 1993).

It is important to stress that radiological, lung lavage, and respiratory tests must be evaluated in conjunction with thorough occupational and environmental history and physical examination. Other causes of lung injury (e.g., smoking, occupational exposures to other chemicals, lung infections) also must be considered when evaluating exposure to asbestos.

3.9 INTERACTIONS WITH OTHER CHEMICALS

In epidemiological studies, an interaction between two risk factors is generally defined as a departure from an additive or multiplicative model of relative risks when both risk factors are present (Steenland and Thun 1986). With respect to lung cancer, some studies indicate that the interaction between asbestos and smoking is greater than additive (DHHS 1985; Selikoff et al. 1968). The most dramatic data include an age-standardized mortality ratio of 5.17 for nonsmoking asbestos workers, 10.85 for smokers not exposed to asbestos, and 53.20 for asbestos-exposed smokers (Hammond et al. 1979). The risk from combined exposure clearly exceeds the predicted risk based on additivity (15.0), and the data suggest a

multiplicative interaction. Other studies have found that smoking increases the risk of lung cancer from asbestos exposure more than predicted by additivity, but often less than predicted by a multiplicative model (Liddell et al. 1997, 1998; McDonald et al. 1980; Saracci 1987; Selikoff et al. 1980; Thomas and Whittemore 1988).

The mechanism by which smoking and asbestos interact to increase risk of lung cancer is not known, but several hypotheses (which are not mutually exclusive) have been suggested. One possible mechanism is a smoking-induced decrease in clearance of fibers from the lung, perhaps by interference with ciliary action or macrophage activity (Plowman 1982), leading in turn to increased penetration of the respiratory epithelium by fibers (Hobson et al. 1988; McFadden et al. 1986). For example, significantly higher concentrations of chrysotile and amosite fibers were found in airway mucosa of lungs from smokers, compared with nonsmokers, who had heavy occupational exposure to asbestos (Churg and Stevens 1995). In guinea pigs, clearance of short chrysotile fibers was decreased by 30% after 1 month in those coexposed to cigarette smoke compared to animals exposed to chrysotile alone (Churg et al. 1992). Exposure of explanted rat tracheobronchial epithelial cells to ozone or cigarette smoke resulted in increased retention of asbestos fibers, suggesting that a direct enhancement of fiber uptake may also be involved (Churg et al. 1996, 1998). Increased asbestos fiber retention was also noted in rats exposed to ozone *in vivo* (Pinkerton et al. 1989). Another proposal is that asbestos fibers (either in air or in the lung) may adsorb carcinogenic substances present in smoke, thereby increasing levels of these substances in the lung (Menard et al. 1986; Mossman et al. 1983b). Asbestos fibers may also catalyze the transformation of other compounds to reactive intermediates (Graceffa and Weitzman 1987). Kamp et al. (1998) speculated that iron-induced reactive oxygen species, produced following exposure to both cigarette smoke and asbestos fibers, might cause damage to DNA in pulmonary epithelium. Finally, on the assumption that cancer is a multistep process, asbestos and smoking could interact by affecting different steps in the process. An interaction of this sort between dimethylbenzanthracene and asbestos has been demonstrated in a two-stage carcinogenicity assay *in vitro* (Topping and Nettesheim 1980), with asbestos displaying effects characteristic of a promoter. Asbestos and chemical carcinogens may act synergistically to cause cell proliferation (Mossman et al. 1984; Sekhon et al. 1995) and metaplasia in cells of the lung, events proposed to be involved in tumor development (Mossman et al. 1984).

There is also good evidence that smoking increases the risk of asbestosis. For example, the death rate from asbestosis was found to be 2.8 times higher in asbestos-exposed smokers than in asbestos-exposed nonsmokers (Hammond et al. 1979; Selikoff et al. 1980). Evidence of increased frequency of clinical signs of asbestosis (rales, dyspnea, crepitations) in smoking versus nonsmoking workers has been

observed (Berry et al. 1979; Lerman et al. 1986), as has a synergistic effect of smoking on the occurrence of parenchymal opacities in the lungs of asbestos workers (Blanc et al. 1988). On the other hand, several researchers have reported that the effects of asbestos and smoking on these signs are additive rather than synergistic (Begin et al. 1987a; Hnizdo and Sluis-Cremer 1988; Weiss 1984).

In contrast to the interactive effect of smoking on lung cancer and fibrosis, smoking does not appear to increase the risk of mesothelioma (Berry et al. 1985; Hammond et al. 1979; Selikoff et al. 1980).

Data are not available on interactive effects between asbestos and other substances after oral exposure of humans. In animals, chronic oral exposure to asbestos caused no convincing increase in tumors in animals that had been treated with a known intestinal carcinogen (dimethylhydrazine) compared to the incidence in animals treated with dimethylhydrazine alone (NTP 1983, 1985, 1990b). However, these studies were judged to be inconclusive, since the doses of dimethylhydrazine employed gave either too few or too many gastrointestinal tumors to allow easy detection of an effect by asbestos (NTP 1983, 1990b). Gamma radiation, in combination with asbestos fibers, has been shown to synergistically enhance the oncogenic transformation of mouse embryo fibroblasts (Hei et al. 1984).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to asbestos than will most persons exposed to the same level of asbestos in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of asbestos, or compromised function of organs affected by asbestos. Populations who are at greater risk due to their unusually high exposure to asbestos are discussed in Section 6.7, Populations With Potentially High Exposures.

Studies of workers who are exposed to asbestos in workplace air indicate that not all people who are exposed to equal doses of asbestos are equally affected. As discussed in Section 3.9, it is likely that one main source of this variability in susceptibility between people is smoking history or the degree of exposure to other risk factors with which asbestos interacts. As discussed in Section 3.7, another potential factor may be age at first exposure. The long-term retention of asbestos fibers in the lung and the long latency period for the onset of asbestos-related respiratory diseases suggest that individuals exposed earlier in life may be at greater risk to the eventual development of respiratory problems than those exposed later in life. A recent study of nonoccupationally exposed residents of an Australian

asbestos-mining region, however, found no significant association between age of first exposure and incidence of mesothelioma (Hansen et al. 1998).

Variability in susceptibility to asbestos-induced respiratory tissue damage may be related to individual genetic differences in ability to detoxify reactive electrophilic molecules (e.g., reactive oxygen radicals and nitrogen oxide) produced during pulmonary disposition of fibers. Glutathione S-transferases have been proposed to be important Phase II enzymes that protect against electrophile-induced tissue damage by catalyzing conjugation with reduced glutathione. One class of glutathione S-transferases, GSTμ, has been hypothesized to be particularly important, as deletion of the GSTM1 gene that encodes this enzyme has been associated with increased risk for mesothelioma (Hirvonen et al. 1995), other cancers (Hirvonen 1997), and nonmalignant pulmonary disorders (Hirvonen et al. 1996; Kelsey et al. 1997) in case-control studies of asbestos-exposed people. In contrast, no significant association has been found for deficiency of the θ class of glutathione S-transferases (encoded by the GSTT1 gene) and increased risk for asbestos-related nonmalignant lung disorders (Hirvonen et al. 1996; Jakobsson et al. 1995a; Kelsey et al. 1997). The null GSTM1 and GSTT1 genotypes occur in about 50 and 15–25% of Caucasians, respectively (Hirvonen 1997).

NAT2 is another Phase II enzyme that displays genetic polymorphisms (one associated with slow acetylation and another with fast acetylation) that also may be associated with susceptibility to asbestos toxicity. Among a group of subjects exposed to high levels of asbestos, individuals who lacked the GSTM1 gene and had the slow NAT2 genotype showed a 4-fold increased risk for developing nonmalignant respiratory disorders and an 8-fold increased risk for developing mesothelioma compared with individuals with the GSTM1 gene and the fast NAT2 genotype (Hirvonen et al. 1996). In another study, no significant association was found between the NAT2 and GSTM1 genotypes and lung cancer; however, subjects in this study were exposed to relatively low levels of asbestos (Saarikoski et al. 2000). Although the mechanism of how slow acetylation may increase susceptibility to asbestos is uncertain, Hirvonen et al. (1995, 1996) have hypothesized that, compared with fast acetylators, slow NAT2 acetylators may accumulate greater amounts of polyamines (which stimulate cell proliferation) due to a slower acetylation rate in their catabolism. Related to this hypothesis is the observation that asbestos fibers induce ornithine decarboxylase in hamster cells, resulting in stimulation of polyamine synthesis and resultant cell proliferation (Marsh and Mossman 1991). Other less specific lines of evidence provide support for the hypothesis that genotype may be important in determining susceptibility to asbestos-related disease. For example, Huncharek et al. (1996) found increased incidence of cancer among parents of mesothelioma cases compared with parents of controls without mesothelioma.

As discussed in Section 3.2.1.3, results from experiments showing a larger increase in cell numbers in pulmonary lavage fluid and increased severity of pulmonary lesions in response to inhaled asbestos in immunologically deficient mice compared with immunologically normal mice of the same genetic background (Corsini et al. 1994) suggest that genetic differences in cell-mediated immunological capabilities may be another predisposing factor in the etiology of asbestos-induced lung diseases.

Recent studies have shown that a high percentage of human mesotheliomas also test positive for the presence of Simian Virus 40 (SV40). Based on this finding, it has been suggested that SV40-infected individuals who are exposed to asbestos might be at increased risk for developing mesothelioma (see summaries of Carbone 1999 and Carbone et al. 2000).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to asbestos. 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 asbestos. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Standard texts of medical toxicology (e.g., Ellenhorn et al. 1997; Goldfrank et al. 1998) do not provide specific information about treatment immediately following exposure to asbestos since the major health hazards of asbestos are associated with chronic rather than acute exposure.

3.11.1 Reducing Peak Absorption Following Exposure

The most important route of asbestos exposure is inhalation, but acute effects are not of primary concern as the major health hazards that are associated with chronic exposure, and can have latencies of more than 30 years. Public health initiatives have therefore focused on reducing initial exposure rather than reducing postexposure absorption.

3.11.2 Reducing Body Burden

As discussed in Section 3.4.4 inhaled asbestos fibers that are deposited in the lung are principally removed by mucociliary transport into the alimentary canal and eventually are excreted in the feces.

Chrysotile fibers appear to be cleared more readily than amphibole fibers, and long fibers are cleared more slowly than short fibers (Coin et al. 1992; Morgan 1991).

One study suggests that subjects who stop smoking after already having been exposed to asbestos see some improvement in lung health (Waage et al. 1996), but long term data for the efficacy of cessation of smoking in large cohorts of individuals previously exposed to asbestos are not available.

To date, there is no method to remove asbestos from lungs. As discussed in Section 3.9, smoking and exposure to asbestos appear to interact synergistically to produce pulmonary fibrosis and lung cancer. This interaction may be explained, at least in part, by demonstrations that smoking impairs the ability of the lungs to remove inhaled fibers (Churg and Stevens 1995; Churg et al. 1992). These findings suggest that cessation of smoking may lead to enhanced fiber clearance in asbestos-exposed workers who are also smokers. Workers likely to be exposed to asbestos through maintenance work in buildings (e.g., carpenters, plumbers, electricians, and custodial workers) should receive education about this possible synergism and be encouraged not to smoke.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanisms by which asbestos causes toxic effects have not yet been clearly determined, and there are no proven methods of interfering with them. Methods of interference can be suggested based on the current understanding of the mechanisms of action derived from animal and human studies, but these methods will require additional research before they can be put to use.

Current research on the toxic effects of asbestos suggests that both direct binding and cell-mediated pathways may be involved (see Section 3.5). Asbestos fibers can bind to various cell macromolecules (proteins, membranes, DNA, and RNA) leading to a variety of direct cellular effects such as increases in cell permeability, conformational changes affecting protein function, and physical interference with chromosome segregation leading to chromosome deletion (Barrett et al. 1989; Chang et al. 1990; Malorni et al. 1990). Modification of the surface of asbestos fibers can decrease their *in vitro* toxic effects (Awadalla et al. 1990; Brown et al. 1990, 1991; Habashi et al. 1991), and these data suggest that direct interactions between asbestos fibers and cell molecules are partly responsible for asbestos-related toxicity.

A second proposed mechanism in asbestos toxicity involves active oxygen species. When exposed to asbestos, alveolar macrophages attempt to phagocytize the fiber and then digest it by producing reactive

oxygen species. These include hydrogen peroxide and superoxide radical anion (O_2^-), which are relatively mild oxidants (Cantin et al. 1988; Case et al. 1986; Hansen and Mossman 1987). However, hydrogen peroxide and superoxide can spontaneously react with one another to produce hydroxyl radicals, which are much more potent oxidants. This reaction is enhanced by the presence of iron which can come from the fiber itself, as a contaminant associated with the asbestos, or from the exposed animal's tissues (Fontecave et al. 1990; Koerten et al. 1990a; Lund and Aust 1991a).

Both *in vivo* and *in vitro* studies have linked production of reactive oxygen species to asbestos-induced cellular effects including lipid peroxidation, cytotoxicity, cell proliferation, genotoxicity, and apoptosis (see Section 3.5). The uptake of asbestos fibers into epithelial cells is also increased by reactive oxygen species (Hobson et al. 1990; Peterson and Kirschbaum 1998).

Free radical scavengers may prove to be successful in interfering with the mechanism of action for asbestos. *In vitro* studies have shown that the effects of asbestos can be diminished by compounds that reduce the levels of reactive oxygen species, such as free radical scavengers (ascorbic acid, bemitil, mannitol, salicylate, 5,5'-dimetyl-l-proline N-oxide, rutin, vitamin E, vitamin A) and enzymes that catalyze the decomposition of reactive oxygen species (catalase, superoxide dismutase). An *in vitro* study assessing the antioxidant efficiency of the flavonoids, quercitin and rutin, and their ability to protect against asbestos-induced cell injury found that both compounds reduced both the production of oxygen radicals and the cell injury resulting from asbestos exposure (Kostyuk et al. 1996). One *in vivo* study reported a dose-dependent inhibition of lung injury, inflammation, and asbestosis in rats treated with polyethylene glycol-conjugated catalase (Mossman et al. 1990b).

Vitamin A has been widely studied in the field of cancer prevention, and studies have shown that smokers who consume more dietary vitamin A from foods have a lower risk for lung cancer (Mayne et al. 1998). Vitamin A is generally given as a dietary supplement in one of two forms, either as retinol (vitamin A) or as β-carotene, a precursor which is converted by the body to vitamin A. An investigation focusing on dietary intake of vitamin A in asbestos workers (40 subjects) reported that subjects who had developed bronchial metaplasia reported a lower intake of dietary vitamin A than those without the condition (Mayne et al. 1998).

Supplementing the diet with vitamin A (retinol or β-carotene) has been shown to increase ventilatory function (Chuwers et al. 1997). However, intervention trials with supplements of vitamin A have shown an increased risk of lung cancer, with the carotene and retinol efficiency trial, CARET, being terminated

early because interim results showed that the intervention group (treated simultaneously with both retinol and β-carotene) was developing more cancer than the controls (Omenn et al. 1996a, 1996b). A study carried out on a large cohort (1,024 individuals) of occupationally exposed asbestos workers in Australia (de Klerk et al. 1998) studied the relative efficacy of the two most common forms of vitamin A, β-carotene and retinol. The authors concluded that there was no benefit from the administration of β-carotene, but that there were significantly lower rates of mesothelioma among the subjects taking retinol. Another study by the same authors (Musk et al. 1998) found that subjects (1,203 exposed asbestos workers) supplied with vitamin A (retinol) had lower rates of malignant mesothelioma and lung cancer than subjects who chose not to participate. However, the reduction was not statistically significant, although it did increase with time and may therefore reflect a long-term protective effect. In general, results from the various clinical trials of vitamin A carried out to date do not look very promising. Supplements of β-carotene had detrimental effects, while the results with retinol are borderline.

Another possible method of reducing the production of hydroxy radicals is by the chelation of iron. Iron chelators such as deferoxamine have been successful at inhibiting the *in vitro* production of hydroxyl radicals (Goodglick et al. 1989; Lund and Aust 1991b; Weitzman and Graceffa 1984). By binding to asbestos fibers, deferoxamine blocks their ability to participate in redox reactions that produce hydroxyl radicals. A study in mice demonstrated the binding of desferroxamine to crocidolite fibers *in vivo* (Weitzman et al. 1988). It should be noted that other iron chelators such as citrate, EDTA, or nitriloacetate actually lead to an increased production of hydroxyl radicals (Lund and Aust 1991b, 1992). Although these chelators are successful in binding iron, they do not prevent iron from participating in the Fenton reaction, and it is possible that by mobilizing iron from the fiber, these chelators may actually make the iron more redox-active.

Adenosine 3',5'-cyclic monophosphate (cAMP) has been shown to reduce pulmonary edema and lung toxicity caused by factors other than asbestos. An *in vitro* study by Vatche and coworkers (Israbian et al. 1994) found that cAMP diminished asbestos-induced cytotoxicity by maintaining intracellular ATP levels and inhibiting cellular replication rather than by affecting asbestos-induced oxygen radical production. This may represent another alternative strategy to free-oxygen radical scavengers for limiting asbestos-induced lung damage.

In addition to the effects described above, cells exposed to asbestos respond by the production of a large number of different factors including, leukotrines, interleukins, growth factors, chemoattractants, and

nitric oxide (see Section 3.5). These factors mediate a wide range of cell responses including inflammation, macrophage recruitment, and cell proliferation. Recent research has also suggested that nuclear regulatory proteins, oncogenes, proto-oncogenes and secondary messenger proteins may play an important mechanistic role. Additional research to better understand the interaction of these responses may provide clues for the development of new therapeutic approaches.

3.12 ADEQUACY OF THE DATABASE

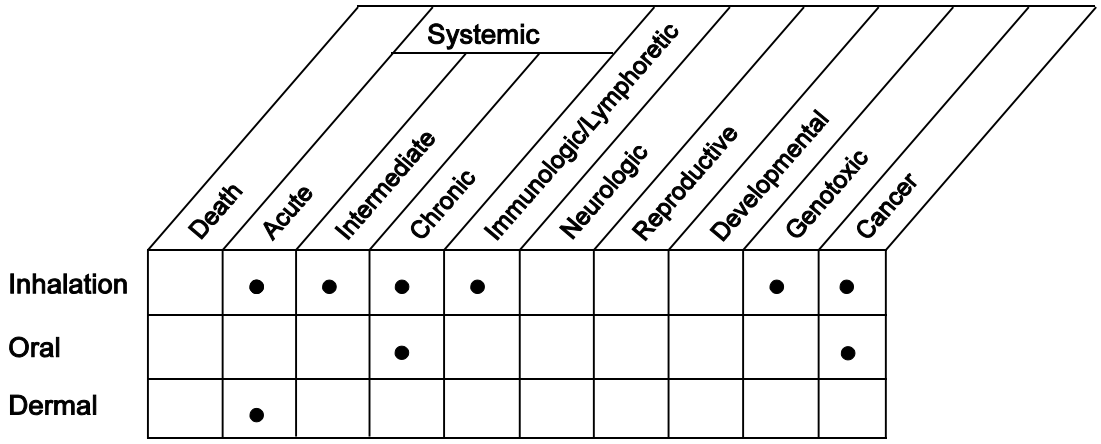
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of asbestos is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of asbestos.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

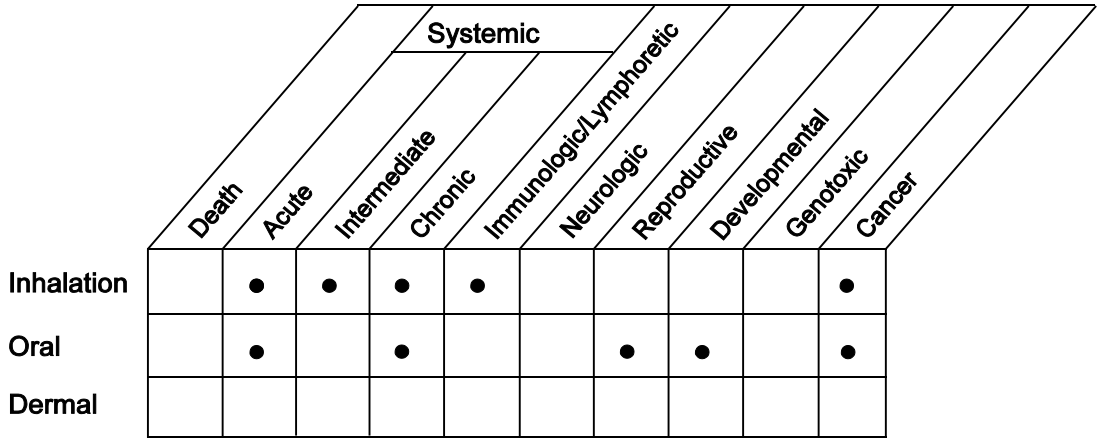
3.12.1 Existing Information on Health Effects of Asbestos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to asbestos are summarized in Figure 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of asbestos. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-6. Existing Information on Health Effects of Asbestos



Human



Animal

● Existing Studies

There have been a very large number of studies, both in humans and animals, focusing on the major health effects associated with inhalation (asbestosis, lung cancer, and mesothelioma) and oral exposure (gastrointestinal cancer). There have also been a number of studies on immune system changes in humans exposed by inhalation, but this has not been investigated in people exposed orally. There are few formal studies focusing on other possible effects of asbestos. However, because so few fibers are able to penetrate from the lungs or the gastrointestinal tract into the body, there is little reason to believe that other effects are of major concern.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Only a few inhalation or oral studies have sought to determine the effects of short-term exposures to asbestos. There are no human data on noncancer effects after acute exposures, and no acute-duration MRLs have been derived. However, there is one study in animals in which a single exposure produced fibrosis of the lung (McGavran et al. 1989), and one study that suggests that a single high inhalation exposure might cause cancer (Wagner et al. 1974). This is a potentially important point, since some people might have one or two significant exposures to asbestos during their life. With current regulations and state of knowledge regarding asbestos toxicity; however, the likelihood of acute high-level exposures for most people is small and studies of health effects in humans with such exposures are unlikely to be established. Additional studies on the long-term effects of acute inhalation exposure in animals may be useful to determine if this is of concern, and if it is, to define the dose-response relationship for cancer, fibrosis, and other biologic outcomes. Although oral exposure to high levels of asbestos is unlikely, acute oral exposure to asbestos in rats and mice have been shown to cause aberrant crypt foci, putative precursor lesions of colon cancer (Corpet et al. 1993). Further studies to investigate the development of these lesions, especially after the ingestion of asbestos in drinking water, may be useful.

Dermal exposure to amosite asbestos in shipbuilding workers resulted in the development of warts or corns, predominately on the hands (Alden and Howell 1944). The corns usually developed within 10 days of an original pricking sensation and the feeling of a small splinter-like foreign body. Histological examination of such corns did reveal the presence of asbestos fibers, and the corns were generally taken to be of no pathological concern (Alden and Howell 1944; Dupre et al. 1984; Selikoff and Lee 1978). There are no indications in available data that dermal absorption of asbestos fibers may occur to any significant extent.

Intermediate-Duration Exposure. Several studies (Ehrlich et al. 1992; Jones et al. 1980a; Seidman et al. 1979, 1986; Shepherd et al. 1997) in humans suggest that workers exposed to asbestos for periods of 1–12 months may subsequently develop asbestos-associated pleural changes or lung disease. However, these studies do not provide sufficient dose-response data to derive a reliable intermediate-duration inhalation MRL. A single study in animals reported fibrosis after intermediate exposure to asbestos (Donaldson et al. 1988a). Further inhalation studies in rats to investigate the fibrogenic and carcinogenic risks from intermediate-duration exposures may be helpful in assessing the risks in humans who may only be exposed for a limited period. It should be noted, however, that the parallel development of asbestos fiber lung retention models for rats and humans will likely increase the usefulness of the rat toxicity data. Such models may increase the accuracy of extrapolating from the rat data to predict human health risks (see Sections 3.4.5 and 3.5.3. for discussion of difficulties in developing these models). Several intermediate-duration oral studies in animals have been performed, and these have not revealed any evidence of noncancer effects (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c; Schneider and Maurer 1977). In the absence of data to suggest that a significant noncancer risk exists after oral exposure, it does not seem that additional studies of this sort are critical.

Chronic-Duration Exposure and Cancer. Epidemiological studies provide descriptions of exposure-response relationships for signs of lung fibrosis and for increased rates of mortality associated with nonmalignant respiratory disease in workers with estimated chronic cumulative exposures as low as about 15–70 and 30–1,200 f-yr/mL, respectively (see Section 3.2.1.2 for references). The studies, however, do not provide information for responses at lower cumulative exposure levels, at air levels experienced by more modern workers in regulated nations (from <0.1–0.2 to 2–5 f/mL), or at air levels that may be experienced by people in relatively polluted nonoccupational exposure scenarios (up to about 0.01 f/mL). No chronic inhalation MRL was derived due to the large degree of uncertainty in extrapolating from data for high-level exposures to low levels that might be experienced by populations surrounding hazardous waste sites with asbestos. Epidemiological research approaches that may decrease this uncertainty are described below in Section 3.12.2 Epidemiological and Human Dosimetry Studies.

Studies in animals provide supporting evidence for the fibrogenicity of airborne asbestos (see Section 3.2.1.2. for references). However, the extrapolation of exposure-response relationships for asbestos-induced lung fibrosis in laboratory animals to humans is not recommended due to the long persistence of fibers in humans, the relatively short life-span of laboratory animals, and the anatomical and physiological differences between laboratory animals and humans that influence rates of lung deposition and clearance of asbestos fibers. The development of physiologically-based mathematical

lung retention models for asbestos fibers in rats and humans and the application of the models to extrapolate from available rat chronic toxicity data may decrease uncertainty in predicting risks for pulmonary fibrosis (and respiratory tract cancers) in humans exposed to low levels of asbestos. This research approach is discussed further below in Section 3.12.2. More discussion of the difficulties in developing such models and extrapolating from animals to humans are discussed in Sections 3.4.5 and 3.5.3.

The carcinogenic effects of chronic inhalation exposure to asbestos (i.e., lung cancer and pleural mesothelioma) have been amply demonstrated, both in humans and animals (see Section 3.2.1.2 for references). However, a number of important issues remain to be resolved. In particular, it would be useful to know whether there are maximum and/or minimum lengths and diameters beyond which fibers lack carcinogenic effects, or whether there are continuous gradients of carcinogenicity as a function of fiber type, length, and diameter. In this regard, additional research on the mechanism of carcinogenicity may be more useful than additional epidemiological or chronic exposure animal studies. This would include studies on the molecular and cellular mechanisms by which asbestos fibers cause lung cancer and mesothelioma (and pulmonary fibrosis).

Along these same lines, further work would be helpful in defining other fiber characteristics that are important determinants of carcinogenicity. It is suspected, for example, that amphiboles, such as crocidolite and tremolite asbestos, are more likely to cause mesothelioma than chrysotile, but it is not certain if this is attributable to differences in fiber length alone or to differences in chemical properties (e.g., fiber morphometry, iron content, durability in biological fluids and tissues). Consequently, additional animal studies of the relative carcinogenic potency of airborne asbestos fibers of different types (e.g., chrysotile versus amphibole asbestos), carefully matched with regard to fiber size distribution, may be valuable.

Another area where further research may be useful is the synergistic interaction between asbestos and other risk factors for lung cancer, especially smoking. Particularly helpful may be further studies on the mechanism of such interactions, since this could help improve current means of predicting the consequences of exposures to substances such as cigarette smoke.

In view of the uncertainty regarding the risk of gastrointestinal cancer following direct or indirect ingestion of asbestos, further research in this area may be useful. Although an extensive series of lifetime feeding studies have already been performed by NTP, only two of these studies (NTP 1983, 1985)

focused on the issue of fiber length in oral carcinogenicity. Further studies to investigate the role of fiber length in gastrointestinal cancer may be useful, with special emphasis on whether there is a minimum length below which carcinogenic risk is minimal. This would have considerable practical consequence in evaluating the potential risk to human health associated with ingestion of asbestos in drinking water. Additional epidemiological studies that include exposure both after occupational inhalation and community drinking water ingestion could also be helpful, especially if they were carefully designed to address the uncertainties and limitations in the evidence currently available.

Genotoxicity. The genotoxic effects of asbestos have been studied *in vivo* to a limited extent in humans (Donmez et al. 1996; Fatma et al. 1991; Hansteen et al. 1993; Lee et al. 1999; Marczynski et al. 1994a, 2000a, 2000b; Pelin-Enlund et al. 1990; Rom et al. 1983; Tammilehto et al. 1992; Tiainen et al. 1989) and animals (EPA 1988j; Fatma et al. 1992; Marczynski et al. 1994b, 1994c). These studies generally reported chromosomal aberrations with asbestos exposure. Most *in vitro* studies in eukaryotic cells indicate that asbestos is clastogenic, causing a variety of chromosomal aberrations; some studies also suggest that asbestos may be mutagenic, although the results for tests of gene mutagenesis have been mixed, both *in vitro* and *in vivo* (see Section 3.3). Further studies to determine the mechanism of clastogenicity, the dependency of clastogenicity on fiber size and type, and the relative genotoxic sensitivity of different respiratory and gastrointestinal epithelial cells may lead to the identification of cellular, biochemical, or genetic responses to asbestos that may be amenable to therapeutic intervention.

Reproductive Toxicity. There are no studies in humans on the potential reproductive effects of asbestos exposure. There is limited evidence from studies in animals that chronic ingestion of asbestos does not injure reproductive tissues, and that exposure during gestation does not reduce fertility (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). This indicates that reproductive effects are probably not of concern, and indeed, there is little mechanistic basis for thinking that this could occur. For these reasons, further studies on this end point do not appear critical, but it should be noted that standard two-generation reproductive toxicity studies in animals exposed to ingested, inhaled, or dermally applied asbestos are not available.

Developmental Toxicity. Studies on potential developmental effects in humans exposed to asbestos are restricted to reports from one group of investigators reporting that asbestos fibers were detected in fetal and placental tissues from stillborn infants more frequently and at higher concentrations than in placental tissue from liveborn infants (Haque et al. 1991, 1992, 1996, 1998). Understanding of the toxicological significance of these observations awaits confirmation and explanation from further

research in other laboratories. It is presently unclear if the noted differences in fiber concentrations between stillborn and liveborn tissue are due to differences in maternal exposures, differences in fetal or placental factors unrelated to asbestos exposure, or specimen contamination.

Studies in animals have not detected any evidence of teratogenic effects in rats and hamsters exposed for life (including during gestation and lactation) to different types of asbestos by the oral route (NTP 1983, 1985, 1988, 1990a, 1990b, 1990c). However, decreased body weights at birth and later in life were noted in some cases (NTP 1985, 1990c). It seems likely that these effects either were random or were secondary to reduced food intake by the dams. No developmentally toxic effects were found following exposure of pregnant mice to asbestos in drinking water at concentrations as high as 143 µg/mL (Schneider and Maurer 1977). Asbestos fibers have been reported to cross the placenta following bolus intravenous injections of asbestos suspensions into rats and mice (Cunningham and Pontefract 1974; Haque and Vrazel 1998). These data were quite variable, and thus could be due, at least in part, to a mass breakthrough of fibers that might be associated with the bolus intravenous exposure protocol. It is expected that transplacental transfer of fibers following environmental exposures (inhalation, oral, or dermal) to asbestos may be of a much smaller magnitude.

The available data suggest that developmental toxic effects are not a critical public health concern from asbestos exposure. Additional animal studies on fetal and postnatal development as affected by inhalation exposure may be helpful to confirm or discard this suggestion.

Immunotoxicity. There are numerous studies of the immune system in workers (active or retired) exposed to asbestos in workplace air (deShazo et al. 1988; Froom et al. 2000; Kagan et al. 1977; Pernis et al. 1965; Sprince et al. 1991, 1992; Warwick et al. 1973). These studies indicate that the immune system may be depressed in individuals who have developed clinical signs of injury, such as asbestosis or cancer. However, the cause-effect relationship between the immunological changes and the asbestos-related diseases is not certain. Also, it is not known if similar effects occur after oral exposure, or if the effects are inhalation specific. Prospective studies on this subject may be useful, both in discerning the importance of immune system injury in the etiology of asbestos-induced disease, and determining whether impaired immune function can be used as a possible early test of individual sensitivity to asbestos.

Neurotoxicity. There are no reliable indications in studies of humans or animals that exposure to asbestos leads to neurotoxicity. Even though tests have not been performed to search for possible subtle effects, there is little reason to suspect that this is an effect of concern, and detailed studies on this effect do not appear to be essential.

Epidemiological and Human Dosimetry Studies. There have been a very large number of epidemiological studies performed on workers exposed in the past to relatively high concentrations of asbestos in air. Further epidemiological studies on populations with lower exposure levels may be useful to decrease the uncertainty that asbestos-induced respiratory diseases may develop with chronic exposure to current levels of asbestos inside buildings, in the ambient environment, and/or near waste sites. Prospective cohort mortality studies of workers involved in asbestos-related occupations under currently regulated conditions or retrospective studies of workers who entered asbestos-related occupations after 1970 or 1980 when respective occupational limits of 5 and 2 f/mL were recommended in the United States (ACGIH 1998) may be particularly useful. Other groups of people that may warrant study include family members of asbestos workers, maintenance workers (such as plumbers, electricians, carpenters, and custodial workers) in buildings with asbestos-containing materials, sailors exposed aboard ships, or nonoccupationally exposed residents of communities with current or past mining or manufacturing operations involving asbestos (e.g., Libby, Montana). End points of concern would include not only cancers, but also pulmonary fibrosis, pleural changes, and respiratory and immune function.

Of special value in any ongoing or future epidemiological study, either of health effects associated with the workplace or the ambient environment, are good exposure data, including quantitative data on the intensity and duration of exposure for each member of the study group, and the type and dimensions of the fibers involved. Accurate exposure data linked to lung fiber concentration data from resected or autopsied lung tissue (that describe distributions of fiber dimensions and mineralogical types) would be useful for the development of human lung retention models, similar to those being developed for refractory ceramic fibers (Yu et al. 1997) that incorporate current understanding of factors influencing the rates of deposition and clearance of asbestos fibers (e.g., breathing patterns, airway morphometry, fiber dimensions, and fiber mineralogy). Such models may decrease uncertainty in extrapolating from data for humans exposed to high exposure levels to predict risks for malignant or nonmalignant respiratory disease in humans exposed to low levels of asbestos. If rat lung retention models are also developed, then human lung retention models may be useful in extrapolating from available rat inhalation toxicity data to provide alternative estimates of human health risks associated with low-level exposure to asbestos.

Biomarkers of Exposure and Effect.

Exposure. The most relevant parameter for quantifying exposure to asbestos is the body burden of retained fibers (Case 1994; Churg 1982; Churg and Warnock 1981; Churg and Wright 1994; Dodson et al. 1999; Dufresne et al. 1995, 1996a, 1996b; Gylseth et al. 1985; Sebastien et al. 1989; Wagner et al. 1986). However, there are no methods currently available for measuring tissue levels of fibers in living persons other than by biopsy (see Section 3.8.1 for discussion of strengths and weaknesses of using retained fiber concentrations in lung tissue as indicators of past exposure). Uses of concentrations of asbestos bodies and uncoated fibers in bronchoalveolar lavage and sputum samples as biomarkers of exposure also have been examined in several studies, but these approaches have not been fully developed as quantitative indicators of exposure (see Section 3.8.1). Fibers can also be detected in urine and feces (Cook and Olson 1979; Finn and Hallenback 1984), but these methods would likely reflect only recent exposures (within the last several days) and not the cumulative tissue burden. Efforts to develop a noninvasive method for measuring fiber levels in tissues (especially in the lung) would be particularly valuable in assessing human exposures to asbestos.

Effect. No specific and sensitive biomarkers of asbestos-induced disease are known. Chest x-rays can detect both the noncarcinogenic and carcinogenic lesions produced by asbestos in the lung and pleura, but usually not until after significant injury or change has occurred (Anton-Culver et al. 1989; Jones et al. 1988b). Similarly, spirometric tests of lung function can detect early stages of asbestos-induced disease, but only after functional decrements (Ernst et al. 1989; Finkelstein 1986). Further studies would be valuable to determine if changes such as depressed immune system function or altered levels of other biochemical parameters can be used as an indicator of risk of asbestos-induced cancer or fibrosis. Also, further efforts would be valuable to improve diagnostic methods for detecting early asbestos-related effects, such as high-resolution computed tomography to detect pleural thickening or pleural plaques (Aberle et al. 1988a, 1988b) and lung carbon monoxide diffusing tests to detect early decreases in lung function (Dujic et al. 1992; Wang et al. 1998). In general, there is a need for the development of more noninvasive asbestos-specific biomarkers of effect. Additional research on potential associations between particular genetic polymorphisms and susceptibility to asbestos-induced lung disease may lead to new biomarkers of susceptibility.

Absorption, Distribution, Metabolism, and Excretion. Because asbestos consists of insoluble fibers, it does not undergo absorption, distribution, metabolism, or excretion in a fashion similar to most other chemicals. With respect to inhalation exposure, the toxicokinetic parameters of greatest relevance are the extent and location of fiber deposition in the respiratory tract, the rate of fiber removal by mucociliary transport, and translocation of fibers within and across the lung. A number of studies are available on lung deposition and clearance of asbestos fibers in animals (e.g., Bolton et al. 1983; Coin et al. 1992; Evans et al. 1973; Morgan et al. 1975; Timbrell 1982). Use of these data to develop predictive lung retention models for animals, parallel to the development of human lung retention models, may decrease the uncertainty in estimating human health risks associated with low-level exposure to asbestos fibers. In contrast to data for laboratory animals, human data poorly describe relationships between exposure levels and lung retention of asbestos fibers. Additional research linking accurate exposure data with lung fiber burden data in humans is likely to result in the development of human lung retention models and aid both in the description of patterns of deposition and clearance of asbestos fibers in humans. Additional studies on the dissolution and breakage of asbestos fibers of various dimensions and types in human and animal respiratory tract fluids and cells may also aid in the development of these models. Additional research clarifying the biological and mineralogical parameters that influence asbestos fiber migration and penetration through the lungs into the peripheral lung and pleural membrane, possibly determinants of mesothelioma risk, is also warranted.

Available data are not sufficient to make a precise estimate of the fraction of ingested fibers that pass through the gastrointentinal wall, but there is agreement that it is a very small amount and not of significant toxicological concern (Sebestien et al. 1980b; Weinzweig and Richards 1983).

Comparative Toxicokinetics. Available data from chronic rat inhalation bioassays show similar asbestos-induced respiratory effects to those in humans associated with occupational exposure to asbestos (pulmonary fibrosis, lung cancer, and pleural mesothelioma), but the use of the rat data to predict human health risks from exposure to airborne asbestos has a number of areas of uncertainty, including those associated with interspecies differences in lifespan, airway morphometry, and breathing patterns. The development of rat and human lung retention models that incorporate species differences in anatomical and physiological parameters influencing deposition and clearance of asbestos fibers may decrease the uncertainty in making human health risk predictions from the rat data and to allow comparisons with low-level risk estimates derived from the available epidemiological data. The previous section outlined several areas of comparative toxicokinetics research that are likely to aid in the development of these models.

Methods for Reducing Toxic Effects. The most important route of exposure to asbestos is by inhalation of asbestos fibers that are deposited in the lung. The acute effects of exposure have not been much studied, as the major health hazards are believed to be associated with chronic exposure. The mechanisms by which asbestos causes toxic effects have not yet been clearly determined (IARC Expert Panel 1996), and there are no proven methods of interfering with them, nor is it currently possible to reduce toxicity by reducing body burden after exposure. Further information as to the mechanisms of asbestos toxicity is a primary data need that may eventually lead to therapeutic approaches for reducing toxic effects from asbestos.

There is some evidence that smoking and asbestos inhalation interact synergistically to produce pulmonary fibrosis and lung cancer (see Section 3.9). One study suggests that subjects who stop smoking after having already been exposed to asbestos see some improvement in lung health (Waage et al. 1996), but long term data for the efficacy of cessation of smoking in large cohorts of asbestos-exposed individuals may help to confirm or reject this suggestion.

Current research on the mechanism of asbestos toxicity suggests that a combination of direct binding and cell mediated pathways are involved (see Section 3.5). *In vitro* studies indicate that involvement of iron-catalyzed production of reactive oxygen species in the mechanism of action for asbestos (Fontecave et al. 1990; Garcia et al. 1988; Korkina et al. 1992; Shatos et al. 1987; Weitzman and Graceffa 1984), and a large number of *in vitro* studies (see Sections 3.5 and 3.11) have shown that compounds that reduce the levels of reactive oxygen species, either by scavenging them, or by catalyzing their decomposition, can reduce the cell injury resulting from asbestos exposure. Inhibition of lung injury, inflammation, and asbestosis has been reported *in vivo* in an animal inhalation model of disease using polyethylene glycol-conjugated catalase (Mossman et al. 1990b).

A number of iron chelators have also been successful *in vitro* at limiting the production of hydroxyl radicals (Goodlick et al. 1989; Lund and Aust 1991b; Weitzman and Graceffa 1984). Some iron chelators, however, actually lead to increased production of hydroxyl radicals (Lund and Aust 1991b, 1992) and, although they chelate the iron, they do not prevent it taking part in the Fenton reaction. Their use as a treatment for asbestos exposure is therefore less likely than that of compounds that directly reduce the levels of reactive oxygen species. Additional *in vivo* studies that evaluate the efficacy of such compounds may lead to the development of a method for reducing the toxic effects of asbestos.

Adenosine 3',5'-cyclic monophosphate (cAMP) has been shown to reduce pulmonary edema and lung toxicity caused by factors other than asbestos. An *in vitro* study by Vatche and coworkers (Israbian et al. 1994) found that cAMP diminished asbestos-induced cytotoxicity by maintaining intracellular ATP levels and inhibiting cellular replication rather than by affecting asbestos-induced oxygen radical production. This may represent another worthwhile alternative strategy to free-oxygen radical scavengers for limiting asbestos-induced lung damage.

Children's Susceptibility. There is a lack of reports on asbestos-related respiratory diseases in children, but childhood exposure to asbestos has been associated with the development of respiratory diseases in adulthood (Anderson et al. 1976; Andrion et al. 1994; Fraire et al. 1988; Inase et al. 1991; Lanphear and Buncher 1992; Magee et al. 1986; Voison et al. 1994; Wagner et al. 1960). The long-term retention of asbestos fibers in the lung and the long latency period for the onset of asbestos-related respiratory diseases suggest that individuals exposed earlier in life may be at greater risk to the eventual development of respiratory problems than those exposed later in life. Direct evidence in support of this hypothesis, however, is not available. In contrast, no significant association was found between incidence of mesothelioma and age of first exposure in a study of residents of an Australian mining region who had no history of occupational exposure to asbestos (Hansen et al. 1998). To date, there is no persuasive evidence that children have a greater susceptibility to asbestos toxicity than adults.

If groups of children exposed to known levels of asbestos could be identified, the lifetime studies could be designed to assess long-term effects of childhood exposure to asbestos. Respiratory effect end points could be compared to those in occupationally-exposed adults in an effort to assess susceptibility in children relative to adults. However, due to changes in the use of asbestos during the past several decades, it may be difficult to identify such groups of children.

Animal experiments could be designed to determine whether there are age-related differences in pulmonary responses to inhaled asbestos fibers (e.g., fibrosis, cell proliferation, gene expression, macrophage production of reactive chemicals). For example, adult rats have been shown to display, within 20 days, a range of dose-related changes in pulmonary inflammation indices, increases in pulmonary cell proliferation, and increases in the severity of pulmonary fibrosis in response to short-term inhalation exposure to asbestos concentrations of approximately 60 and 2,800 f/mL (Quinlan et al. 1994, 1995). Comparing the results of these studies with results from replicate studies with juvenile rats may demonstrate age-related susceptibility to asbestos toxicity that is not directly related to latency of disease development in juveniles relative to adults. However, the relevance of such models for assessment of

age-related susceptibility of cancer effects in humans may be limited due to species differences in anatomy, physiology, and duration of lifetime.

Data needs related to developmental effects associated with prenatal and postnatal exposures to asbestos were discussed previously in Section 3.12.2.

Child health data needs relating to exposure are discussed in Section 5.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to Asbestos have been identified and are shown in Table 3-7.

Table 3-7. Ongoing Studies on the Health Effects of Asbestos[a]

Investigator	Affiliation	Research description	Sponsor
Aust, A E	Utah State University, Logan, UT	Role of O_2 radicals and iron in asbestos-induced cancer	NIEHS
Barrett, JC	NIEHS, NIH	Role of mutagenesis in carcinogenesis	NIEHS
Broaddus, VC	University of California San Francisco, San Francisco, CA	Protective role of apoptosis in asbestos pleural injury	NIEHS
Brody, AR	Tulane University of Louisiana, New Orleans, LA	Epithelial growth factors in environmental lung disease	NHLBI
Brody, AR	Tulane University of Louisiana, New Orleans, LA	Growth factors in asbestos-induced pulmonary fibrosis	NIEHS
Dinse, G	NIEHS, NIH	Statistical analysis of human cancer data	NIEHS, NIH
Garshick, E	Department of Veterans Affairs, Medical Center Brockton, MA	Screening for occupational and respiratory disorders	VA
Gerwin, BI	Division of Basic Sciences - NCI	In vitro studies of human mesothelial cells	NCI, NIH
Goodman, GE	Fred Hutchinson Cancer Research Center, Seattle, WA	Caret–coordinating center	NCI
Guthrie, GD	Mineralogical Society of America	Mineralogical Society of America Workshop on the health effects of mineral dusts	USDOE Energy Research
Hei, TK	Columbia University Health Sciences, New York, NY	Mechanisms of fiber carcinogenesis	NIEHS
Hei, TK	Columbia University Health Sciences, New York, NY	Mutagenicity of mineral fibers	NIEHS
Heintz, NH	University of Vermont & St Agric College, Burlington, VT	Asbestos and NO_2 in environmental lung disease	NIEHS
Ho, Y	Wayne State University, Detroit, MI	The nature of lung antioxidant defense mechanisms	NHLBI

Table 3-7. Ongoing Studies on the Health Effects of Asbestos *(continued)*

Investigator	Affiliation	Research description	Sponsor
Holian, A	University of Texas Health Science Center Houston, Houston, TX	Analysis of human macrophage function in response to fibrogenic particulates	NCRR
Hoyle, GW	Tulane University of Louisiana, New Orleans, LA	Pulmonary fibrosis in PDGF transgenic mice	NHLBI
Hunninghake, GW	University of Iowa, Iowa City, IA	Mechanisms of cytokine production in asbestosis	NCRR
Hunninghake, GW	Department of Veterans Affairs, Medical Center, Iowa City, IA	Regulation of alveolar macrophage function	VA
Kadiiska, M	NIEHS, NIH	Transition metal mediated free radical formation *in vitro* and *in vivo*	NIEHS
Kamp, DW	Department of Veterans Affairs, Medical Center, Chicago, Il	Mechanisms of asbestos-induced alveolar epithelial cell injury	VA
Kane, AB	Brown University, Providence, RI	Pathogenesis of mesenchymal tumors induced by asbestos	NIEHS
Kelsey, KT	Harvard University, Boston, MA	LOH at 3P and P53 and K-RAS mutation in lung cancer beta-carotene/retinol	NIEHS
Kriebel, D	University of Massachusetts Lowell, Lowell, MA	Lung cancer and exposure to chrysotile and amphiboles	NCI
Libbus, B	Integrated Laboratory S, Durham, NC	Fiber-induced DNA damage and carcinogenicity	HHS
Morris, GF	Tulane University of Louisiana, New Orleans, LA	P53 in asbestos induced lung disease	NIEHS
Mossman, BT	University of Vermont, Soule Medical Bldg, Alumni Building, Burlington, VT	EGFR signaling pathways by particulates in lung disease	NIEHS
Mossman, BT	University of Vermont, Soule Medical Bldg, Alumni Building, Burlington, VT	Molecular signaling by oxidant stress in lung epithelium	NHLBI

Table 3-7. Ongoing Studies on the Health Effects of Asbestos *(continued)*

Investigator	Affiliation	Research description	Sponsor
Oakes, D	University of Rochester, Rochester, NY	Statistical analysis of multiple event time data	NCI
Palmer, CJ	University of Vermont, Burlington, VT	Asbestos-induced cell proliferation via an ERK5 pathway	NIEHS
Rose, C	University of Colorado Health Sciences Center, Denver, CO	Sputum cytology and urinary bombesinlike peptide levels	NCRR
Schapira, RM	Department of Veterans Affairs, Medical Center, Milwaukee, WI	Lung arginine uptake and metabolism after particulate matter exposure	VA
Schenker, MB	University of California Davis, Davis, CA	Environmental asbestos and mesothelioma in California	NCI
Stewart, PA	NCI, NIH	Studies of occupational cancer—occupational exposure assessment	Division of Cancer Etiology
Takaro, T	University of Washington, Seattle, WA	Combined effect of radiation and asbestos in producing pulmonary fibrosis	NIOSH
Testa, JR[b]	Fox Chase Cancer Center, Philadelphia, PA	Molecular genetic alterations in malignant mesothelioma	NCI
Thorne, PS	University of Iowa, Iowa City, IA	Core–inhalation toxicology	NIEHS
Tolbert, PE	Emory University, Atlanta, GA	Environmental risk factors for lymphomas and sarcomas	NCI

[a]Information from FEDRIP (2000) unless otherwise indicated.
[b]Testa (1999)

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NHLBI = National Heart, Lung, and Blood Institute; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NIOSH = National Institute for Occupational Safety and Health; USDA = United States Department of Agriculture; USDOE = United States Department of Energy; VA = Veterans' Administration