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 acrolein. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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.

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

3.2.1.1 Death

The only available information regarding lethal effects in humans after inhalation exposure to acrolein was provided by Gosselin et al. (1979), who described the cases of 2- and 4-year-old boys exposed for 2 hours to acrolein-containing smoke from an overheated fryer. The 2-year-old boy died 24 hours later of asphyxia. The data from this case report must be considered qualitative only, since smoke components other than acrolein may have contributed to the injury.

The data in experimental animals clearly indicate that respiratory toxicity is a primary cause of acrolein lethality following inhalation and show an inverse relationship between the exposure concentration and the time it takes for death to occur after acute-duration exposures. Exposure of rats to airborne concentrations of acrolein of 100–40,000 ppm for short periods of time (<l hour) caused death ranging from minutes to 11 days (Catilina et al. 1966; Crane et al. 1986; Skog 1950). Death was attributed to obstruction of trachea and bronchi, pulmonary edema, or hemorrhage. Single and repeated exposures to 3–4 ppm acrolein caused death in rats and monkeys before the 10^{th} day of exposure (Carpenter et al. 1949; Kutzman 1981; Kutzman et al. 1984, 1985; Lyon et al. 1970). Respiratory congestion was observed in the monkeys. Animal data regarding cause of death are in good agreement with observations made in humans after accidental exposure (Gosselin et al. 1979). Reliable LOAELs for lethality in experimental animals following inhalation exposure to acrolein are presented in Table 3-1 and Figure 3-1.

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Monkey	6 wk 5 d/wk 8 hr/d				3.7 (1/9 died)	Lyon et al. 1970	Death occurred 9 days into exposure.
2	Rat (Wistar)	1 d 10 min/d				327 (LC50) 327 M (LC50)	Catilina et al. 1966	Group size and incidence rates not reported.
3	Rat (NS)	1 d 30 min/d				130 (28/48 died)	Skog 1950	
Systemic								
4	Human	1 d 1 hr/d	Resp		0.3[b] (decreased respiratory rate, nose and throat irritation)		Weber-Tschopp et al. 1977	

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
5	Rat (Wistar)	1 x 4 hr	Resp		1 M (lipid peroxidation of respiratory tissues as indicated by reduced levels of ascorbic acid, alpha-tocopherol, reduced glutathione, thiols, angiotensin -converting enzyme, lactase, lactase dehydrogenase, catalase and glutathione peroxidase activities. Increased levels of TBARS, conjugated dienes, superoxide dismutase activity)	2 M (desquamized and mononuclear cells, hyperemia, and emphysema)	Arumugam et al. 1999	
6	Rat (Wistar)	6 hr/d 3 d	Resp		0.67 F (nasal epithelial dysplasia, moderate necrosis, desquamation, basal cell hyperplasia)		Cassee et al. 1996	
					1.4 F (nasal epithelial cell proliferation, reduced glutathione activity)			
					0.25 F (nasal epithelial dysplasia, slight necrosis, desquamation, basal cell hyperplasia)			

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
7	Rat (Wistar)	1 d 10 min/d	Resp			327 (epithelial desctruction) 283 M (mucosal secretions, ciliary destruction, moderate laryngeal edema, scattered punctuate hemorrhaging)	Catilina et al. 1966	Group size and incidence rates not reported.
8	Rat (Fischer- 344)	1 x/d 40 min	Resp		9.1 M (increased albumin in nasal lavage fluid)		Morris 1996	
9	Rat (Fischer- 344)	1 x/d 50 min	Resp		2 M (vasodilation of upper respiratory tract)		Morris et al. 1999	
10	Rat	5 d 4 hr/d	Hepatic		4 (decrease in relative liver weight)		Murphy et al. 1964	
			Bd Wt		4 (decreased body weight)			
11	Rat	20-81 hr	Hepatic	1	2.1 (increase in liver weight)		Murphy et al. 1964	
12	Rat	9 d 4 hr/d	Hepatic		3.9 (decrease in relative liver weight)		Murphy et al. 1964	

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
13	Rat	1 d 4 hr/d	Resp		12	(severe respiratory tract irritation)			Murphy et al. 1964	
14	Rat	1 d 30 min/d	Resp				130	(lung hemorrhage)	Skog 1950	
15	Mouse	5 d 6 hr/d	Resp		1.7	(RD50, olfactory exfoliation erosion, ulceration, necrosis and squamous metaplasia)			Buckley et al. 1984	
16	Mouse	4 d 3 hr/d	Resp		1.7	(RD50)			Kane and Alarie 1977	
17	Mouse (C57BL/6N)	1 x/d 50 min	Resp		1.1	(increased airflow resistance)			Morris et al. 2003	
18	Mouse (C57BL/6N)	1 x/d 10 min	Resp		1.3	(decreased breathing rate and airway resistance; increased respiratory pause)			Morris et al. 2003	
19	Mouse (C57BL/6N)	1 x/d 10 min	Resp		0.3	(decreased breathing rate relative to non-diseased animals)			Morris et al. 2003	Compared effects in allergic airway-diseased and non-diseased animals.

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
20	Mouse	1 d 30 min/d	Resp		2.9 (RD50)		Nielsen et al. 1984	
21	Mouse (Swiss-Webster)	1 d 10 min/d	Resp		1.03 (RD50)		Steinhagen and Barrow 1984	
22	Mouse (B6C3F1)	1 d 10 min/d	Resp		1.41 (RD50)		Steinhagen and Barrow 1984	
23	Gn Pig	1 d 60 min/d	Resp		17 (decreased respiratory rate)		Davis et al. 1967	
24	Gn Pig	1 d 2 hr/d	Resp	0.6			Murphy et al. 1963	
Immuno/ Lymphoret								
25	Mouse	5 d 3 hr/d			0.1 (decreased resistance to respiratory tract infection)		Aranyi et al. 1986	
26	Mouse	1 d 8 hr/d			3 (decreased resistance to respiratory tract infection)		Astry and Jakab 1983	
INTERMEDIATE EXPOSURE								
Death								
27	Rat (Fischer- 344)	6 hr/d 5 d/wk 62 d				4 M (32/57 died)	Kutzman 1981	

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Systemic								
28	Rat	>60<180 d 7 d/wk 24 hr/d	Resp		0.55 M (increased relative lung weight)		Bouley et al. 1975	
			Hepatic		0.55 M (increased relative liver weight)			
			Bd Wt		0.55 M (decreased body weight gain)			
29	Rat (Wistar)	8 wk 10 min/d	Resp			262 M (peribronchiolar hemorrhage; bronchial lumen obstruction)	Catilina et al. 1966	Group size and incidence rates not reported.
30	Rat (Fischer- 344)	62 d 5 d/wk 6 hr/d	Resp		1.4 (lung hyperplasia)	4 (lung edema and decreased function)	Costa et al. 1986	
			Bd Wt		4 (decreased body weight gain)			

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
31	Rat	13 wk 5 d/wk 6 hr/d	Resp		0.4[c]	(nasal squamous epithelial metaplasia)	4.9	(lung hemorrhage, necrotizing rhinitis)	Feron et al. 1978	
			Cardio	1.4	4.9	(increase in heart weight)				
			Hemato	4.9						
			Hepatic	4.9						
			Renal	1.4	4.9	(increase in kidney weight)				
32	Rat (Fischer- 344)	6 hr/d 5 d/wk 62 d	Resp		1.4	(bronchiolar epithelial hyperplasia, necrosis)			Kutzman 1981	
			Bd Wt		4 M	(decreased body weight gains)				

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
33	Rat	62 d 5 d/wk 6 hr/d	Resp		1.4	(bronchiolar inflammation)	4	(bronchiolar necrosis)	Kutzman et al. 1985	
			Cardio		1.4					
					4	(increase in heart weight)				
			Hepatic		1.4					
			Renal		4	(increase in kidney weight)				
			Bd Wt		4	(decrease in body weight gain)				
34	Rat	3 wk 5 d/wk 6 hr/d	Resp		3	(epithelial dysplasia)			Leach et al. 1987	
			Bd Wt		3	(decreased body weight gain)				
35	Rat	6 wk 5 d/wk 8 hr/d	Resp		0.7	(peribronchial inflammation)			Lyon et al. 1970	
			Renal	3.7						
			Dermal	3.7						
			Bd Wt		3.7	(decreased body weight gain)				

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
36	Rat	90 d 7 d/wk 24 hr/d	Resp	1.8			Lyon et al. 1970	
			Cardio	1.8				
			Hemato	1.8				
			Hepatic	0.22	1	(focal necrosis)		
			Renal	1.8				
			Dermal	1.8				
			Bd Wt		1	(decreased body weight gain)		
37	Rat	61 d 24 hr/d	Hemato	0.32			Sinkuvene 1970	
			Bd Wt	0.06	0.32	(decreased body weight gain)		
38	Gn Pig (Hartley)	90 d 7 d/wk 24 hr/d	Resp	0.22	1	(pulmonary inflammation)	Lyon et al. 1970	
			Hemato	1.8				
			Hepatic	0.22	1	(liver inflammation)		

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form	Comments
39	Gn Pig (Hartley)	6 wk 5 d/wk 8 hr/d	Resp		0.7	(peribronchial inflammation)			Lyon et al. 1970	
			Hemato	3.7						
			Renal	3.7						
			Dermal	3.7						
			Bd Wt	3.7						
40	Hamster	13 wk 5 d/wk 6 hr/d	Resp	0.4	1.4	(nasal epithelial inflammation)	4.9	(tracheal metaplasia, necrotizing rhinitis)	Feron et al. 1978	
			Cardio	1.4	4.9	(increased heart weight)				
			Hemato		4.9	(increases in PCV)				
			Hepatic	4.9						
			Renal	1.4	4.9	(increase in kidney weight)				
			Bd Wt	1.4	4.9	(decreased body weight gain)				
Immuno/ Lymphoret										
41	Rat	3 wk 5 d/wk 6 hr/d		3					Leach et al. 1987	
42	Rat	3 wk 5 d/wk 6 hr/d		3					Sherwood et al. 1986	

Table 3-1 Levels of Significant Exposure to Acrolein - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Neurological								
43	Monkey	90 d 7 d/wk 24 hr/d		1.8			Lyon et al. 1970	
44	Rat	62 d 5 d/wk 6 hr/d			4 (increase in brain weight)		Kutzman et al. 1984	
45	Hamster	13 wk 5 d/wk 6 hr/d		4.9			Feron et al. 1978	
Reproductive								
46	Rat (Fischer- 344)	6 hr/d 5 d/wk 62 d		4			Kutzman 1981	

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

b Used to derive an acute inhalation MRL of 0.003 ppm; dose divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL).

c Used to derive an intermediate inhalation MRL of 0.00004 ppm; dose adjusted for duration and inter-species dosimetry of a category 1 gas, and divided by an uncertainty factor of 300 (3 for interspecies dosimetry, 10 for human variability and 10 for use of a LOAEL).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50%; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; PCV = packed cell volume; ppm = parts per million; RD50 = 50% decrease in respiratory rate; Resp = respiratory; TBARS = thiobarbituric acid reactive substances; wk = week(s); x = time(s)

Figure 3-1 Levels of Significant Exposure to Acrolein - Inhalation

Acute (≤14 days)

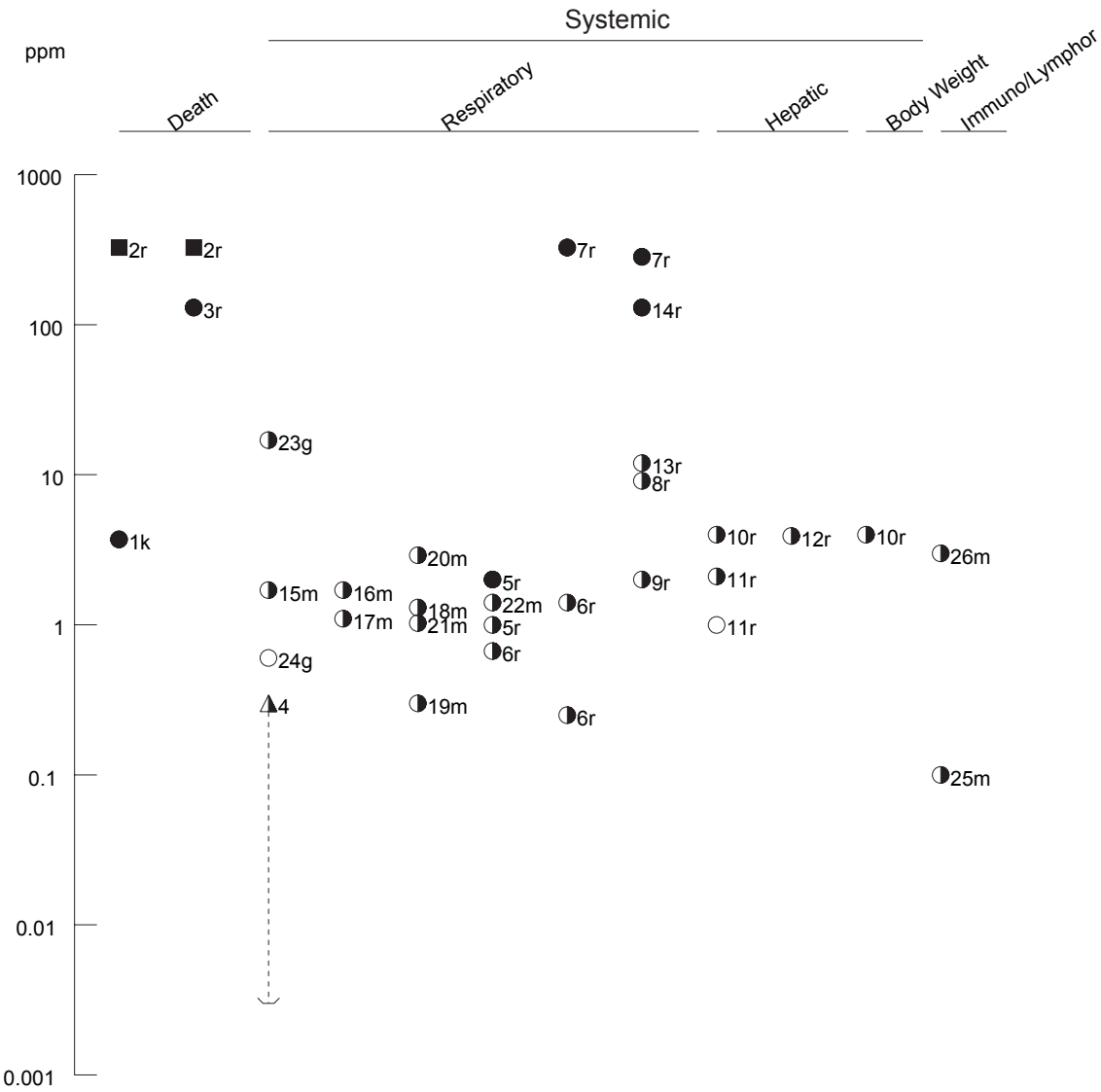


Figure 3-1 Levels of Significant Exposure to Acrolein - Inhalation *(Continued)*

Intermediate (15-364 days)

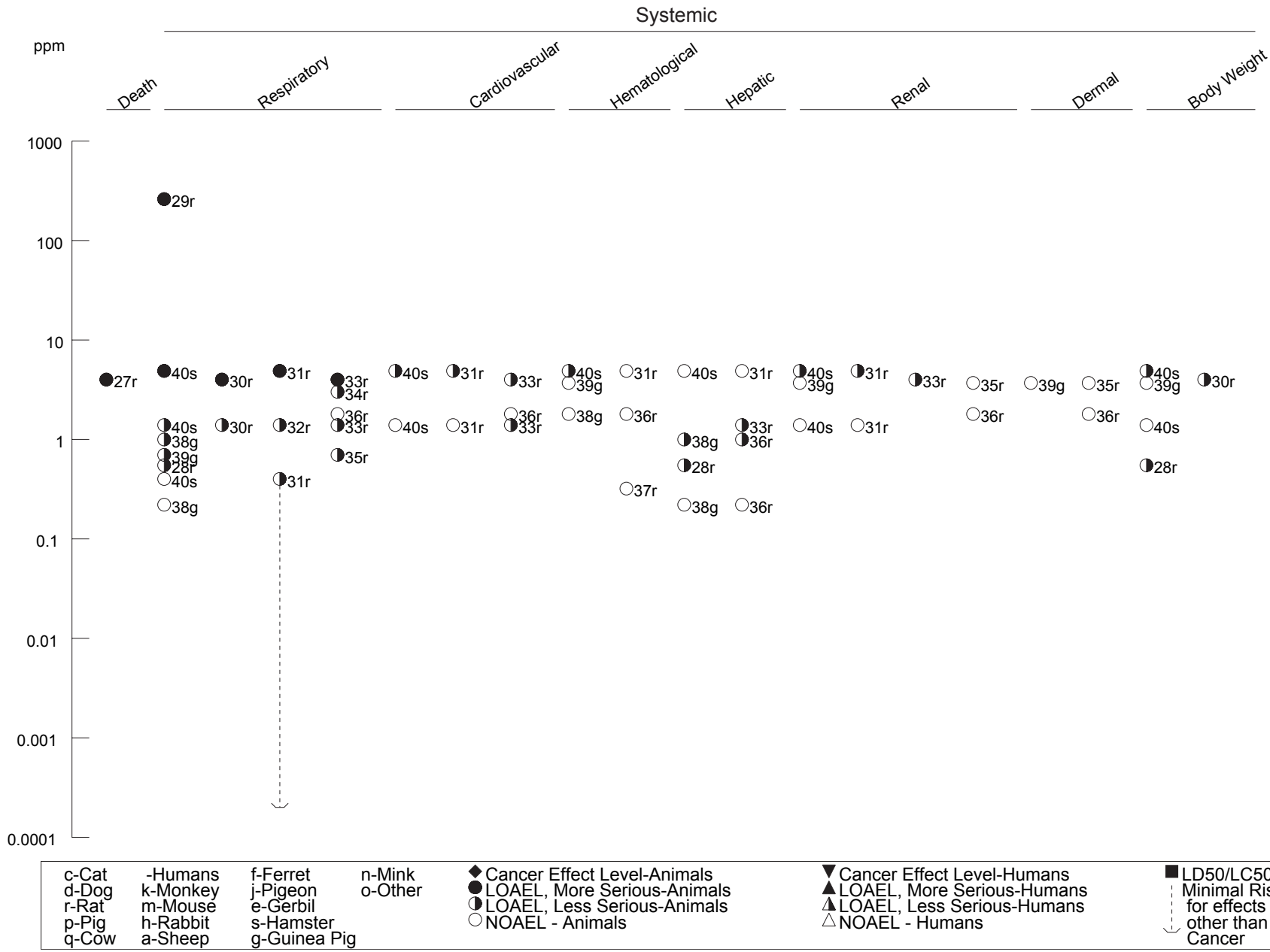
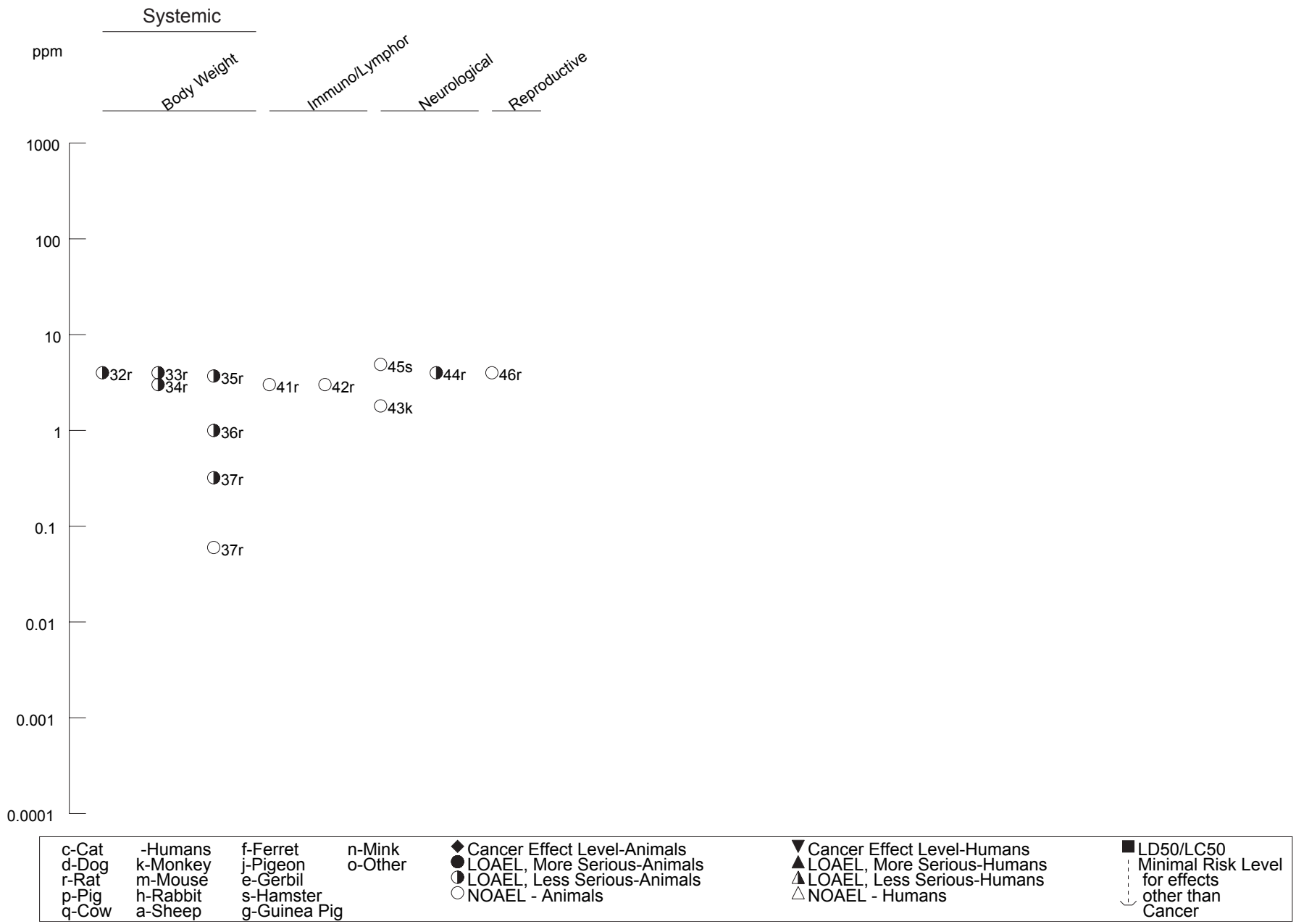


Figure 3-1 Levels of Significant Exposure to Acrolein - Inhalation *(Continued)*

Intermediate (15-364 days)



3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, renal, or dermal effects in humans or animals after inhalation exposure to acrolein. NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. Champeix et al. (1966) reported a case of a 36-year-old male who was accidentally exposed to unknown concentrations of acrolein vapors in the workplace for <1 day (duration assumed). Observed symptoms included high fever, dyspnea, coughing, foamy expectoration, and cyanosis. Eighteen months after the exposure, the chronic pneumopathy and dyspnea persisted, although no information was reported regarding any pre-existing pulmonary conditions or possible lifestyle factors (i.e., smoking) that may have impacted the diagnosis.

Volunteers exposed to increasing levels of acrolein vapors for 35 minutes reported statistically significant nose irritation at 0.26 ppm, throat irritation at 0.43 ppm, and a decrease in respiratory rate at 0.60 ppm (Weber-Tschopp et al. 1977). No statistically significant difference was observed between controls and subjects exposed to 0.17 ppm. In the same study, constant exposure to 0.3 ppm acrolein for 40 minutes resulted in reports of mild nose irritation shortly after onset of exposure, while throat irritation was reported after 10 minutes. Severity of irritation was subjectively scored as “not at all’ to “a little”. A 20% decrease in respiratory rate was also observed. The significance of the decrease in respiratory rate is not clear, but in animals, particularly rodents, it is considered to represent a reflex response to protect the respiratory tract from toxicants (Alarie 1973). Based on the nose and throat irritation and a decrease in respiratory rate in humans exposed to acrolein, an acute-duration MRL of 0.003 ppm has been calculated from the LOAEL of 0.3 ppm (Weber-Tschopp et al. 1977).

Acute exposure of mice, rats, and guinea pigs to concentrations of 0.3–17 ppm acrolein for several minutes induced vasodilation (Morris et al. 1999), as well as an increase in airflow resistance and a reflex decrease in respiratory rate by activation of the sensory nerve endings in the nasal mucosa (Alarie 1973; Buckley et al. 1984; Davis et al. 1967; Kane and Alarie 1977; Leikauf et al. 1989a; Morris et al. 1999, 2003; Murphy et al. 1963; Nielsen et al. 1984; Steinhagen and Barrow 1984). Significantly decreased respiratory rates were observed in allergic airway-diseased mice compared to nondiseased mice exposed to 0.3 ppm acrolein for 10 minutes (Morris et al. 2003). Increased albumin levels were observed in nasal lavage fluid of rats exposed to 9.1 ppm for 40 minutes (Morris 1996). Olfactory exfoliation, erosion,

ulceration, necrosis, and squamous metaplasia were observed in mice exposed to 1.7 ppm for 5 days (Buckley et al. 1984). Several indicators of oxidative stress were reported in rats exposed to 1 ppm for 4 hours (Arumugan et al. 1999), including reduced lung levels of ascorbic acid, alpha-tocopherol, reduced glutathione, thiols, angiotensin-converting enzyme, lactase, lactase dehydrogenase, catalase and glutathione peroxidase activities and increased levels of TBARS, conjugated dienes, and superoxide dismutase activity. In the same study, desquamized and mononuclear cells, hyperemia, and emphysema were observed in lung tissues following a 2-ppm exposure for 4 hours. Emphysema was not reported in any other acute-duration study. Rats exposed to 0.25–0.67 ppm for 6 hours on 3 consecutive days exhibited focal basal cell metaplasia, reduced epithelial glutathione reductase activity, slight to moderate epithelial necrosis, and disarrangement and cell proliferation of the nasal respiratory epithelium in a dose-dependent manner (Cassee et al. 1996). Biochemical alterations in the nasal mucosa were observed in rats exposed to 0.1–2.5 ppm, but the toxicological significance of this finding is unclear (Lam et al. 1985). Rat lungs exhibited significantly reduced glutathione, ascorbic acid, and α-tocopherol levels as well as glutathione peroxidase, catalase, and superoxide dismutase activity levels following 4-hour exposures to 1 or 2 ppm acrolein (Arumugam et al. 1999). Exposure to concentrations of 1.7–6 ppm induced epithelial hyperplasia, inflammation, and moderate to severe histological alterations of the nasal, tracheal, and bronchial epithelium of mice, rats, guinea pigs, hamsters, and dogs (Buckley et al. 1984; Feron et al. 1978; Kilburn and Mackenzie 1978; Murphy et al. 1964). Severe respiratory tract irritation was observed in rats exposed to 12 ppm for 4 hours (Murphy et al. 1964). Exposures as short as 5 minutes to >100 ppm acrolein resulted in bronchial epithelial destruction, pulmonary edema, and lung hemorrhage in rats, guinea pigs, and dogs (Catilina et al. 1966; Dahlgren et al. 1972; Hales et al. 1988; Skog 1950).

Intermediate-duration exposures to acrolein concentrations between 0.4 and 5.0 ppm for up to 180 days caused increased relative lung weights, as well as histological alterations, inflammation across the entire respiratory tract, and edema of rats (Bouley et al. 1975; Costa et al. 1986; Feron et al. 1978; Kutzman 1981; Kutzman et al. 1984, 1985; Leach et al. 1987; Lyon et al. 1970), monkeys, guinea pigs, and dogs (Lyon et al. 1970), and rabbits and hamsters (Feron et al. 1978). Decreased pulmonary function was observed in rats exposed to 4 ppm for up to 62 days (Kutzman 1981). Daily 10-minute exposures of 262 ppm for 8 weeks resulted in peribronchial hemorrhage and bronchial lumen obstruction in rats (Catilina et al. 1966). Based on the nasal epithelial metaplasia in rats exposed to acrolein, an intermediate-duration MRL of 0.00004 ppm has been calculated from the LOAEL of 0.4 ppm (Feron et al. 1978).

In the chronic exposure study in rats (Le Bouffant et al. 1980), occasional emphysematous areas were reported in the alveoli after 18 months of exposure to 8 ppm acrolein for 1 hour daily, though the study is unclear as to whether this effect was attributable to the animal's exposure to acrolein, cigarette smoke, or a combination of the two.

The overall evidence from acute, intermediate, and chronic duration studies in experimental animals indicates that the respiratory system is a target for acrolein. While the entire respiratory tract may be affected by acrolein inhalation, the nasal epithelium appears to be more sensitive at lower exposures (<1 ppm), which is consistent with human perception of nasal irritation. The deeper respiratory regions (bronchiolar and alveolar regions) appear to be sensitive to higher exposure levels, with severe effects being observed from exposures of 100 ppm or higher. The available data do not suggest species differences in the respiratory toxicity of acrolein. Humans and animals appear to show similar low concentration effects (i.e., mild irritation). It should be noted, however, that rodents are obligate nose-breathers, while humans are mouth-breathers. As a result, the lower respiratory tract of rodents may not present as likely a target organ as that of humans.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to acrolein.

Nonspecific inflammatory lesions in the heart were reported in rats, dogs, monkeys, and guinea pigs after a continuous 90-day exposure to 0.22 ppm acrolein (Lyon et al. 1970). Also, an increase in relative heart weight was observed in hamsters and rats exposed to 4–5 ppm of acrolein (Feron et al. 1978; Kutzman et al. 1985). In both of these studies, dose-dependent changes in histology and gross pathology were only seen in the respiratory tract. Thus, the nonspecific cardiovascular effects may be secondary effects of acrolein on respiratory tissues.

Hematological Effects. No studies were located regarding hematological effects in humans following inhalation exposure to acrolein.

No adverse hematological effects were observed in rats, guinea pigs, dogs, male hamsters, and monkeys exposed to 0.2–4.9 ppm of acrolein for an intermediate duration (Feron et al. 1978; Lyon et al. 1970). However, statistically significant increased numbers of erythrocytes, hemoglobin, and lymphocytes were observed in female hamsters exposed at 4.9 ppm (Feron et al. 1978). The study authors did not discuss the implications of these changes. The toxicological significance of these changes, if any, is unknown.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to acrolein.

Effects reported in rats after a 4-hour exposure to 8 ppm of acrolein included increases in alkaline phosphatase and tyrosine transaminase activities; however, these changes could represent adaptive responses (Murphy 1965; Murphy et al. 1964). Liver necrosis (minute foci without a specific pattern) was reported in rats and guinea pigs after intermediate-duration exposure to 1 ppm acrolein, but this effect was not found at a higher concentration (Lyon et al. 1970). Relative liver weight increases were observed in rats exposed to 0.55 ppm for 60–180 days (Bouley et al. 1975) and 4 ppm for 62 days (Kutzman et al. 1984). An increase in relative liver weight was observed in rats exposed to 2.1 ppm for up to 81 hours (Murphy et al. 1964), while a decrease in relative liver weight resulted from exposure to 3.9 ppm for 5 or 9 days. No adverse liver effects were seen in hamsters, rabbits, monkeys, dogs, or guinea pigs exposed to ≤4.9 ppm acrolein (Feron et al. 1978).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to acrolein.

Renal effects in guinea pigs, dogs, and monkeys were described as nonspecific (Lyon et al. 1970). An increase in amorphous material in the urinary sediment was observed in rats, hamsters, and rabbits after intermediate-duration exposure to 4.9 ppm acrolein (Feron et al. 1978). However, without further characterization of the sediment, the significance of this finding is unclear. Increases in kidney weights were seen in rats and hamsters exposed to 4–5 ppm for 9–13 weeks (Feron et al. 1978; Kutzman et al. 1985).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to acrolein.

Increased adrenal weights (up to 20% relative to controls 100 hours after exposure) were reported in rats after acute exposures to 6.4 ppm for 4 hours (Murphy et al. 1964). However, the toxicological significance of this difference cannot be ascertained since variation or statistical significance between groups was not reported.

Ocular Effects. Eye irritation appears to be the most sensitive effect of airborne acrolein. This effect, however, is point-of-contact limited and is independent of acrolein inhalation. Therefore, ocular effects are discussed in detail in Section 3.2.3, Dermal Exposure.

Body Weight Effects. In intermediate-duration studies, depressed body weight gains were reported in rats, hamsters, monkeys, and rabbits exposed to 0.32–4.9 ppm acrolein (Bouley et al. 1975; Feron et al. 1978; Kutzman 1981; Kutzman et al. 1984, 1985; Leach et al. 1987; Lyon et al. 1970; Sinkuvene 1970). Significant differences in food consumption of rats were measured during exposure. However, food consumption increased significantly following cessation of exposure (Bouley et al. 1975). Anorexia was observed in rats exposed to 12 ppm for 4 hours (Murphy et al. 1964). It is not known why food consumption rates decreased during exposure. It is possible that animals minimized their activity levels in order to minimize respiration rates and, thus, relieve the discomfort of inhaling acrolein.

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to acrolein.

Short-term exposures to acrolein reduced bactericidal activity of the respiratory tract in experimental animals. Aranyi et al. (1986) observed a significantly lower removal by alveolar macrophages of *Klebsiella pneumoniae* bacteria from a 3-hour aerosol infection following a 5-day exposure to 0.1 ppm acrolein in mice. No difference was observed in rats for this same exposure/infection protocol (Sherwood et al. 1986). Similarly, 8-hour exposures to 3 and 6 ppm acrolein in mice showed a concentration-related reduction in clearance of *Staphylococcus aureus* from an 8-hour pulmonary infection; however, exposures to 8–10 ppm did not significantly add to the impairment of bactericidal activity (Astry and Jakab 1983). Rats exposed to 0.55 ppm for 10–26 days had significantly lower numbers of alveolar macrophages, but rats exposed for 60–180 days showed no significant difference in macrophage levels (Bouley et al. 1975). No statistically significant differences in mortality were observed in rats intravenously exposed to *Listeria monocytogenes* following a 3-week exposure to up to 3 ppm acrolein (Leach et al. 1987). These studies do not suggest that inhaled acrolein causes an immune system effect, but the reduction in removal of bacteria from the alveolar spaces may result from the destruction of functionality of alveolar macrophages present in the respiratory epithelium. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to acrolein.

Springall et al. (1990) indicate that acrolein may induce release of peptides that could play a role in the physiological response to irritants. Concentrations of acrolein between 22 and 249 ppm for 10 minutes induced a dose-related decrease in substance P (a short-chain polypeptide that functions as a neurotransmitter or neuromodulator) and calcitonin gene-related peptide in nerve terminals innervating the trachea of rats (Springall et al. 1990). No change was seen in total nerve distribution and number or in vasoactive intestinal peptide. Likewise, substance P-mediated vasodilation of the rat upper respiratory tract was observed at 20 ppm, but not at 2–10 ppm, for 50 minutes (Morris et al. 1999).

In intermediate duration studies (Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970), the neurological effects identified consisted of increases in the brain/body weight ratio and nonspecific inflammatory responses in sections of the brain (it is not clear from the original papers whether sections refer to anatomical areas or to histological preparations). These effects were observed in rats, guinea pigs, dogs, and monkeys at comparable concentrations of acrolein. The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to acrolein.

Two studies were identified regarding the reproductive effects of inhaled acrolein. Bouley et al. (1975) exposed male and female rats to 0.55 ppm acrolein continuously for 26 days (3 days prior to mating and presumed gestational days 0 through 22) and reported that exposure did not affect the number of pregnancies or the number and weights of the fetuses. Although Bouley et al. (1975) examined the most relevant indices and an adequate number of animals were tested, the use of only one dose level limits the reproductive assessment derived from this study. Kutzman (1981) found no effect on the reproductive fitness of rats exposed to 0.4–4 ppm for 62 days. The NOAEL value for reproductive effects in rats after an intermediate-duration exposure is recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to acrolein.

3.2.1.7 Cancer

No studies were located regarding carcinogenic effects in humans after inhalation exposure to acrolein.

Only two studies in animals were located that examined the carcinogenic potential of acrolein after inhalation exposure. Feron and Kruysse (1977) exposed hamsters to a single acrolein concentration of 4.0 ppm for 7 hours/day, 5 days/week for 52 weeks and found no evidence of respiratory tract tumors or tumors in other tissues and organs. However, this study is considered to be of too short duration to determine carcinogenicity. The maximum tolerable dose (MTD) of acrolein appears to have been achieved in this study, as indicated by the significant decrease in body weights of treated animals. Le Bouffant et al. (1980) exposed rats to 8 ppm acrolein for 1 hour/day, 7 days/week for 18 months and reported no evidence of tumors in the respiratory tract or in other tissues and organs. An MTD does not appear to have been achieved in this study due to the short daily duration of exposure.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding lethality in humans after oral exposure to acrolein.

The oral LD_{50} for rats was reported as 46 mg/kg, with a range of 39–56 mg/kg (Smyth et al. 1951). However, a single oral dose of 10–25 mg/kg in rats was lethal to over 40% of the animals (Draminski et al. 1983; Sakata et al. 1989; Sprince et al. 1979). Loss of reflexes occurred after 3 hours, and increased lethargy gradually led to death. Most of the animals died 3–8 hours after dosing (Sprince et al. 1979). Furthermore, increased maternal mortality was observed in rats treated with 10 mg/kg/day and in rabbits treated with 2 mg/kg/day during gestational days 7–19 (King 1982; Parent et al. 1993), although the rabbit deaths appeared to be related to misdosing. No increase in deaths was observed in a two-generation reproductive study, in which rats were treated by gavage with 7.2 mg/kg/day (King 1984).

The overall survival rate was not affected in dogs exposed to 1.5 mg/kg/day by capsule dosing for the first 4 weeks and 2 mg/kg/day for the remainder of the 12-month study (Parent et al. 1992b). Decreased survival was, however, reported in male and female mice gavaged with 20 mg/kg/day for 14 weeks (NTP 2006), in male and female rats gavaged with 6 mg/kg/day for 93–149 days (Parent et al. 1992c), and in male mice gavaged with 4.5 mg/kg/day for 18 months (Parent et al. 1991a). Survival of male and female rats was significantly decreased following intermediate-duration gavage exposure of 10 mg/kg/day for 14 weeks (NTP 2006). Use of thickening agents in the dosing solutions of the NTP (2006) study may have increased the residence time of acrolein and contributed to the observed mortality. Chronically gavaged male mice and female rats receiving 4.5 and 0.5 mg/kg/day, respectively, experienced increased mortality, although the cause of mortality from the chronic exposure was not determined (Parent et al. 1991a, 1992a). Chronic exposure of rats to 36 mg/kg/day or less of acrolein via the drinking water did not affect mortality (Lijinsky and Reuber 1987). There is high uncertainty in the actual acrolein dosage received by the rats, as 36 mg/kg/day is higher than the range of lethal doses of 10–25 mg/kg reported above (Draminski et al. 1983; Sakata et al. 1989; Sprince et al. 1979). High instability of acrolein in water reported by the study authors (18% reduction after 6 days at 5 °C; 27% reduction after 3 days at 22 °C) likely resulted in unknown doses, making it difficult to compare the dose-response from Lijinsky and Reuber (1987) to other studies. Reliable LOAELs for death in each species and duration category are listed in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, or ocular effects in humans after oral exposure to acrolein. However, studies were located regarding these end points in several species of animals. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Abnormal breathing was observed in rats gavaged with 10 mg/kg/day for 14 weeks (NTP 2006) and 6 mg/kg/day for 93–149 days (Parent et al. 1992c). No histopathological changes were observed in the respiratory systems of rats after intermediate-duration exposure to 7.2 mg/kg/day (King 1984). Similarly, no changes were observed during histopathological examination of respiratory tract tissues from rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b) chronically exposed to 2.5, 4.5, or 2 mg/kg/day, respectively.

Table 3-2 Levels of Significant Exposure to Acrolein - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat	Gd 7-19 1 x/d (GW)				10 (14/40 died)	King 1982	
2	Rat (Fischer- 344)	1 x/d				25 M (5/12 died)	Sakata et al. 1989	No controls were used.
3	Rat	once (G)				11.2 (LD90)	Sprince et al. 1979	
Systemic								
4	Rat	Gd 7-19 1 x/d (GW)	Bd Wt	3.6	6 (decreased body weight gain)		King 1982	
5	Rat (Fischer- 344)	1 x/d	Gastro			25 M (severe erosive hemorrhagic gastritis, multi-focal ulceration of forestomach and glandular stomach)	Sakata et al. 1989	No controls were used.
6	Rabbit (New Zealand)	1 x/d Gd 7-19 (GW)	Bd Wt	0.75 F	2 F (transient depressed maternal body weight gain)		Parent et al. 1993	
Reproductive								
7	Rat	Gd 7-19 1 x/d (GW)		10			King 1982	

Table 3-2 Levels of Significant Exposure to Acrolein - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
Developmental									
8	Rat	Gd 7-19 1 x/d (GW)		6		10	(decreased litter weight, increased skeletal anomalies)	King 1984	
9	Rabbit (New Zealand)	1 x/d Gd 7-19 (GW)		2 F				Parent et al. 1993	
INTERMEDIATE EXPOSURE									
Death									
10	Rat (Fischer- 344)	1 x/d 13 wk (GW)				10	(17/20 died)	NTP 2006	
11	Rat (Sprague-Dawley)	1 x/d 93-149 d (GW)				6	(increased mortality)	Parent et al. 1992c	
12	Mouse (B6C3F1)	1 x/d 13 wk (GW)				20	(20/20 died)	NTP 2006	

Table 3-2 Levels of Significant Exposure to Acrolein - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
13	Rat	115 d 1 x/d (GW)	Resp	7.2			King 1984	
			Cardio	7.2				
			Gastro	4	5.4 (stomach ulcerations)			
			Hemato	7.2				
			Musc/skel	7.2				
			Hepatic	7.2				
			Renal	7.2				
			Dermal	7.2				
			Bd Wt	5.4	7.2 (decreased body weight in F0 generation)			
14	Rat (Fischer- 344)	1 x/d 13 wk (GW)	Resp			10 (abnormal breathing)	NTP 2006	
			Gastro	1.25 F	2.5 F (forestomach squamous epithelial hyperplasia)	10 (forestomach necrosis and hemorrhage in females; glandular stomach hemorrhage in both males and females)		
			Hepatic		5 F (increased relative liver weight)			

Table 3-2 Levels of Significant Exposure to Acrolein - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Rat (Sprague-Dawley)	1 x/d 93-149 d (GW)	Resp			6 (rales, labored/irregular breathing, gasping, hyperpnia in F0 and F1 generations)	Parent et al. 1992c	
			Gastro		3 (forestomach and glandular stomach hyperplasia, ulcers)	6 (glandular stomach hemorrhage)		
			Renal		6 M (reddish-brown urine)			
			Bd Wt		6 M (decreased body weight gains in F0 and F1 generations)			
16	Mouse (B6C3F1)	1 x/d 13 wk (GW)	Gastro	1.25[b]	2.5 (forestomach squamous epithelial hyperplasia)	10 M (stomach necrosis and hemorrhage)	NTP 2006	
			Hepatic		10 M (increased absolute and relative liver weight)			
Reproductive								
17	Rat	115 d 1 x/d (GW)		7.2			King 1984	
18	Rat (Sprague-Dawley)	1 x/d 93-149 d (GW)		6			Parent et al. 1992c	

Table 3-2 Levels of Significant Exposure to Acrolein - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Developmental								
19	Rat (Sprague-Dawley)	1 x/d 93-149 d (GW)			6 (decreased pup body weight)		Parent et al. 1992c	
CHRONIC EXPOSURE								
Death								
20	Rat (Sprague-Dawley)	1 x/d 102 wk (GW)				0.5 F (increased mortality)	Parent et al. 1992a	
21	Mouse (CD-1)	18 mo 7 d/wk 1 x/d (GW)				4.5 M (increased mortality)	Parent et al. 1991a	
Systemic								
22	Rat (Sprague-Dawley)	1 x/d 102 wk (GW)	Resp	2.5			Parent et al. 1992a	
			Gastro	2.5				
			Hemato	2.5				
			Musc/skel	2.5				
			Hepatic	2.5				
			Endocr	2.5				
			Ocular	2.5				
			Bd Wt	2.5				

Table 3-2 Levels of Significant Exposure to Acrolein - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Mouse	18 mo 7 d/wk 1 x/d (GW)	Resp	4.5			Parent et al. 1991a	
			Cardio	4.5				
			Gastro	4.5				
			Hemato	4.5				
			Musc/skel	4.5				
			Hepatic	4.5				
			Renal	4.5				
			Endocr	4.5				
			Dermal	4.5				
			Ocular	4.5				
			Bd Wt	0.5	4.5 M (decreased body weight gain)			

Table 3-2 Levels of Significant Exposure to Acrolein - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
24	Dog (Beagle)	365 d 1 x/d (C)	Resp	2			Parent et al. 1992b	
			Gastro	0.1	0.5 (vomiting after daily dosing, incidence decreased after week 4)			
			Musc/skel	2				
			Hepatic	2				
			Renal	2				
			Endocr	2				
			Dermal	2				
			Ocular	2				
			Bd Wt	2				
Cancer								
25	Rat (Sprague-Dawley)	1 x/d 102 wk (GW)		2.5			Parent et al. 1992a	
26	Mouse	18 mo 7 d/wk 1 x/d (GW)		4.5			Parent et al. 1991a	

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

b Used to derive an intermediate oral MRL of 0.004 mg/kg/day, based on a BMDL10 (benchmark dose lower confidence limit 10%) of 0.36 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for human variability and 10 for species extrapolation).

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; LD90 = lethal dose, 90% kill; LOAEL = lowest-observed-adverse-effect level; M = male; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Figure 3-2 Levels of Significant Exposure to Acrolein - Oral

Acute (≤14 days)

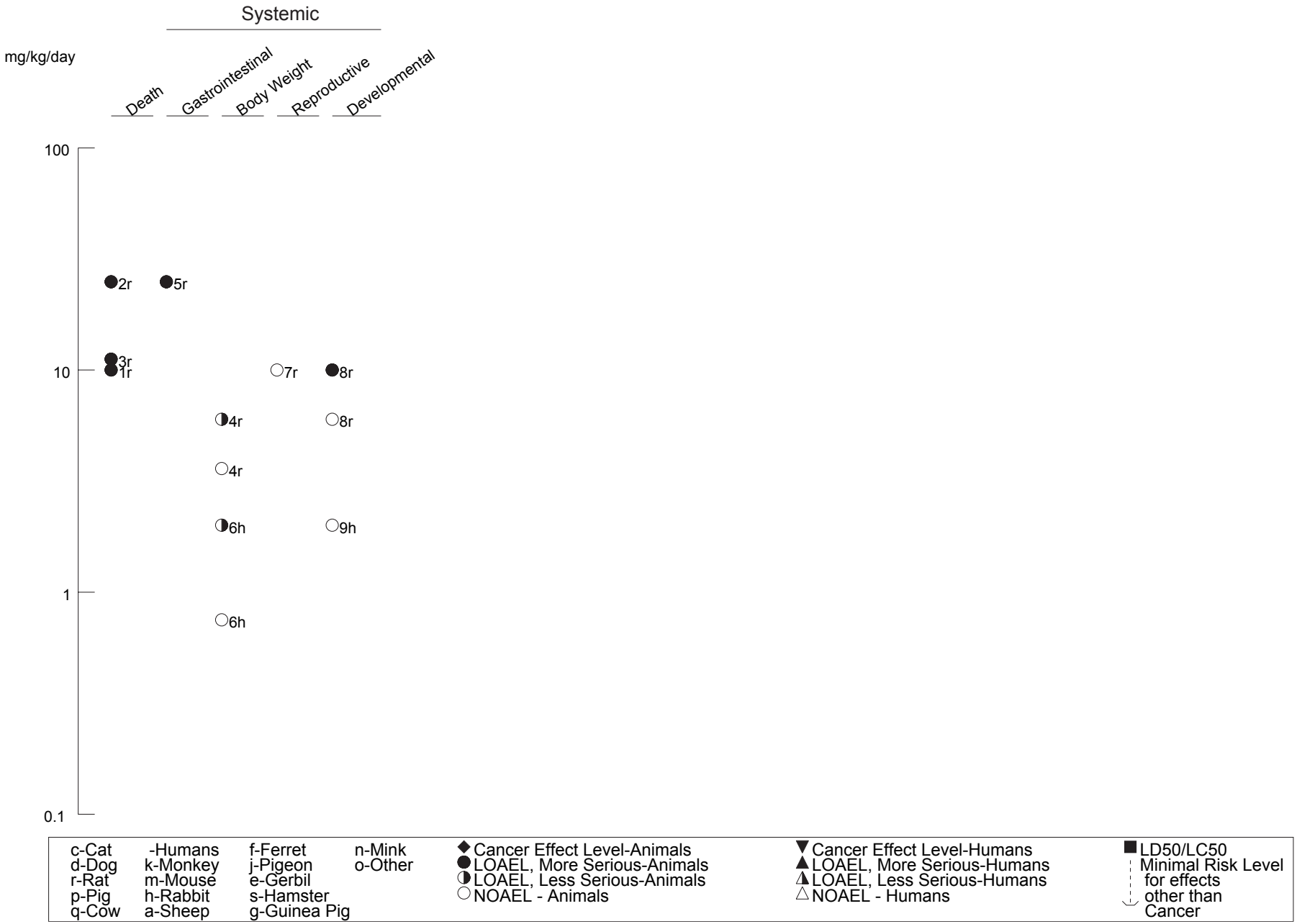


Figure 3-2 Levels of Significant Exposure to Acrolein - Oral *(Continued)*

Intermediate (15-364 days)

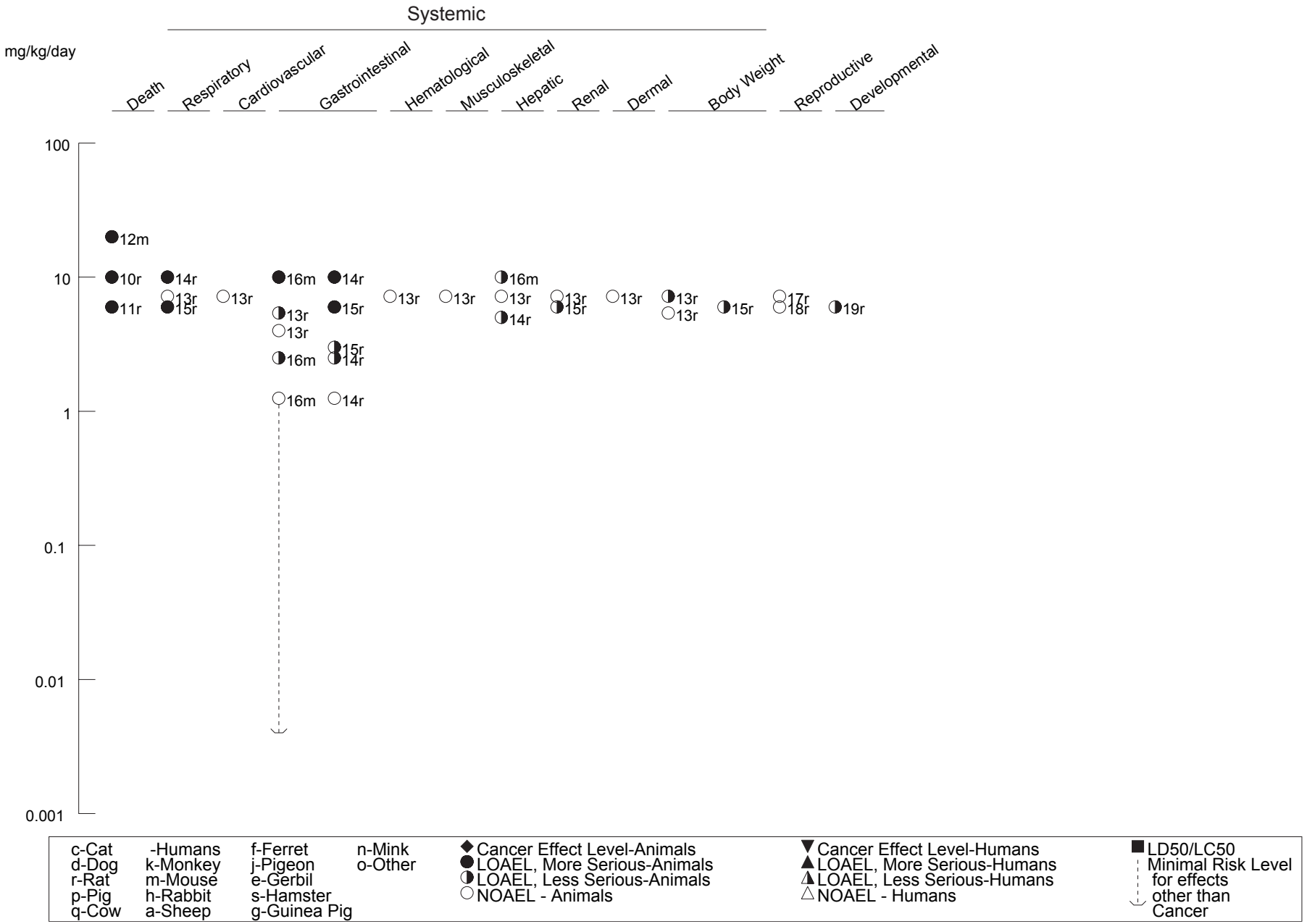
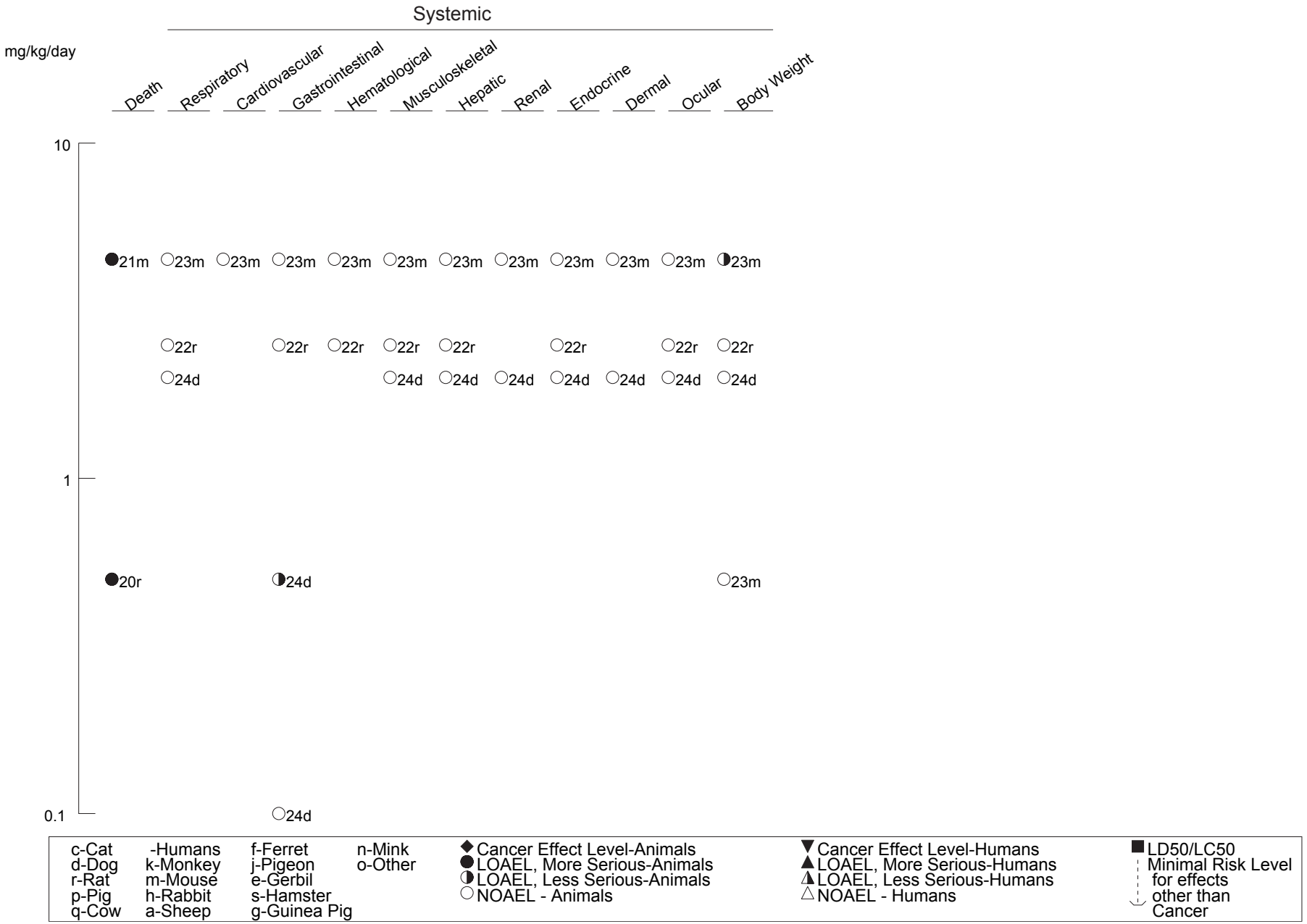


Figure 3-2 Levels of Significant Exposure to Acrolein - Oral *(Continued)*

Chronic (≥365 days)



Cardiovascular Effects. Histopathological examination of the cardiovascular system revealed no effects after intermediate-duration exposure to acrolein in rats (King 1984) or after chronic exposure in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b).

Gastrointestinal Effects. Gastrointestinal irritation is the primary effect of oral exposure to acrolein. Though the clinical signs are consistent and dose-related across acute and intermediate exposures, possible adaptation to irritating effects may have important implications for chronic exposures. Rats administered a single gavage dose of 25 mg/kg of acrolein in saline showed severe multifocal ulceration of the forestomach and glandular stomach 48 hours after dosing, though no controls were used for comparison. The areas of ulceration showed severe inflammation, focal hemorrhage, and edema (Sakata et al. 1989). Gastric mucosa ulcerations were also observed in rabbits given gavage doses of 4 mg/kg/day during gestational days 7–19 (Parent et al. 1993, dose range-finding study) and in rats given gavage doses of 5.4 mg/kg/day for 115 days (King 1984). Stomach hemorrhage was observed in male and female rats gavaged with 10 mg/kg/day and male and female mice gavaged with 20 mg/kg/day, while stomach necrosis was observed in female mice gavaged with 20 mg/kg/day for 14 weeks (NTP 2006). Forestomach squamous epithelial hyperplasia was observed in male and female rats gavaged with 5 and 2.5 mg/kg/day, respectively, for 14 weeks (NTP 2006), while glandular stomach squamous epithelial hyperplasia was seen in male and female mice gavaged with 2.5 mg/kg/day for the same time period. The addition of a thickening agent in the dosing solution may have served to extend the residence time of acrolein in the stomach, resulting in the observed effects at these doses. Glandular stomach hyperplasia, ulcers, and hemorrhage were found in rats gavaged with 3 mg/kg/day for 93–149 days (Parent et al. 1992c). No significant gastrointestinal effects of acrolein exposure, however, were reported in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b) after chronic gavage dosing with up to 2.5, 4.5, or 2 mg/kg/day, respectively. While no unusual gross pathological lesions in the gastrointestinal tract were observed in dogs given up to 2 mg/kg/day for 12 months (Parent et al. 1992b), increased incidences of vomiting were observed shortly after dosing, suggesting gastrointestinal irritation. However, adaptation seemed to occur in the 2 mg/kg/day group as late as 51 weeks into the study, as vomiting frequency was sharply reduced compared to the first 4 weeks of the study. Based on the occurrence of forestomach squamous epithelial hyperplasia in rats given gavage doses of acrolein, an intermediate-duration MRL of 0.004 mg/kg/day has been calculated from the 95% lower confidence limit on the benchmark dose for 10% extra risk ($BMDL_{10}$) of 0.36 mg/kg/day (NTP 2006). Although humans do not have a forestomach, this study provides an example of gastrointestinal mucus membrane irritation. Similar irritative effects are expected in humans.

Hematological Effects. No significant hematological effects were observed in rats given gavage doses of up to 7.2 mg/kg/day acrolein for 115 days (King 1984), in mice given gavage doses of up to 4.5 mg/kg/day acrolein for 18 months (Parent et al. 1991a), or in rats given gavage doses of up to 2.5 mg/kg/day for 2 years (Parent et al. 1992a). In dogs, decreased prothrombin times were seen in females while decreased serum protein, albumin, and calcium levels were observed in both sexes given 2 mg/kg/day for 12 months (Parent et al. 1992b). In the same study, mean corpuscular hemoglobin concentration (MCH) and mean corpuscular volume (MCV) were significantly increased in male dogs, but were depressed in females given gavage doses of 0.5 or 2 mg/kg/day. The authors could not provide an explanation for these hematological changes, but state that the changes were not thought to be toxicologically meaningful.

Metabolic Effects. Statistically significant decreases in serum calcium were observed in dogs given 2 mg/kg/day acrolein for 12 months (Parent et al. 1992b). Serum creatinine phosphokinase levels were depressed in rats given 0.05–2.5 mg/kg/day for 24 months (Parent et al. 1992a). However, the toxicological significance of these findings is not clear, since no treatment-related effects were observed in any organs or tissues upon gross pathological or histological examination.

Musculoskeletal Effects. No histopathological changes were observed in musculoskeletal tissues of rats after intermediate-duration exposure (King 1984). Similarly negative results were obtained in rats (Parent et al. 1992a), mice (Parent et al. 1991a), and dogs (Parent et al. 1992b) chronically exposed to acrolein, although the specific muscular tissues observed were not reported.

Hepatic Effects. Altered liver or kidney weights were reported in rats administered 1.5 mg/kg/day acrolein in drinking water for 30 days (Smyth et al. 1951), although no liver or kidney weight changes occurred following administration of 0.17 mg/kg/day. It is unclear if the altered organ weight occurred in the liver and/or kidneys, or if the organ weights increased or decreased. Increased relative liver weights occurred in female rats and male mice gavaged with 5 or 10 mg/kg/day, respectively, for 14 weeks (NTP 2006). No liver effects were observed upon gross pathological or histological examinations in rats after intermediate-duration exposure to 7.2 mg/kg/day acrolein (King 1984). Similarly, no significant hepatic changes were found in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b) after chronic exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively. Reduced serum protein and albumin levels were observed in dogs chronically given 2 mg/kg/day (Parent et al. 1992b). It is uncertain as to whether these effects are indicative of hepatic changes, as the authors of this study reported that there were no dose-related differences in liver pathology.

Renal Effects. As mentioned previously, altered kidney or liver weights were reported by Smyth et al. (1951) in rats given 1.5 mg/kg/day acrolein in drinking water for 30 days, with no effect on liver or kidney weights resulting from administration of 0.17 mg/kg/day. It is unclear from the report whether there was an alteration in kidney weight or liver weight or both, or if the organ weights increased or decreased. Reddish-brown urine was observed in rats during intermediate-duration exposure to 6 mg/kg/day (Parent et al. 1992c). No histopathological changes were reported in kidneys of rats after intermediate-duration exposure to 7.2 mg/kg/day (King 1984) or in rats (Parent et al. 1992a), mice (Parent et al. 1991a), and dogs (Parent et al. 1992b) after chronic exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively. Negative results were also obtained from the urinalysis of dogs exposed to 0.05–2 mg/kg/day for 12 months (Parent et al. 1992b). Reduced serum protein and albumin levels were observed in dogs chronically given 2 mg/kg/day (Parent et al. 1992b). It is uncertain as to whether these effects are indicative of renal changes, as the authors of this study reported that there were no dose-related differences in liver pathology.

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to acrolein.

No dermal effects were observed in rats receiving an intermediate-duration exposure of 7.2 mg/kg/day (King 1984).

Ocular Effects. No treatment-related ocular effects were reported in rats (Parent et al. 1992a), mice (Parent et al. 1991a), or dogs (Parent et al. 1992b) chronically exposed to acrolein.

Body Weight Effects. Rats treated with 2 mg/kg/day (King 1984) and rabbits treated with 6 mg/kg/day (Parent et al. 1993) during gestation days 7–10 exhibited reduced body weight gains, but the rabbits resumed body weights comparable to controls thereafter. Decreased body weight gains were reported in rats given intermediate-duration exposures of 6 and 7.2 mg/kg/day (King 1984; Parent et al. 1992c) and in mice given 4.5 mg/kg/day for 18 months (Parent et al. 1991a). No significant body weight changes were observed in dogs given 2 mg/kg/day for 12 months (Parent et al. 1992b) or in rats given 2.5 mg/kg/day for 2 years (Parent et al. 1992a).

3.2.2.3 Immunological and Lymphoreticular Effects

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

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to acrolein.

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects after oral exposure to acrolein.

Exposure of rats to 10 mg/kg/day acrolein during pregnancy had no effect on the number of implantations or resorptions or on the ratio of live/dead fetuses per litter (King 1982). No evidence of acrolein reproductive toxicity was found in a two-generation study in which rats of each generation were exposed to 7.2 mg/kg/day for 100–120 days prior to mating and then for 15 days during mating (King 1984). Reproductive performance was not affected in two generations of male and female rats given 1, 3, or 6 mg/kg/day acrolein for 96–149 days (Parent et al. 1992c). Offspring of rabbits given 0.1–2 mg/kg/day on gestation days 7–19 were not observed to have premature deliveries, spontaneous abortions, or statistically significant gross or soft tissue malformations or variations (Parent et al. 1993). However, in the preliminary dose-range study reported by Parent et al. (1993), a dose-related, but statistically untested, increase in embryonic resorptions was observed after exposure of dams to 1 mg/kg/day or more. No explanation for this discrepancy was given in the study, although the treatment groups in the range-finding study had only 3–4 animals, while the groups in the full study had 20 animals. No fetuses were alive in the litters of dams that were administered 4 mg/kg/day acrolein. The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to acrolein.

Developmental effects have been observed in animals after oral exposure. In a preliminary dose-range finding study, exposure of rabbits to ≥1 mg/kg/day resulted in dose-related increased incidences of fetal

resorption (Parent et al. 1993); however, fetal mortality was not affected in the primary study, in which rabbits were exposed to ≤2 mg/kg/day during gestation. No explanation for the discrepancy was provided, though maternal body weight loss in the range-finding study may have confounded fetal effects. It should be noted that the range-finding study utilized only 3–4 animals/dose group, while the definitive study used 20 animals/group, suggesting that greater weight should be given to the data from the full study. Body weights of pups from rats given 6 mg/kg/day through gestation and lactation were significantly reduced during gestation. Otherwise, litter viability and size, gestation duration, and pup growth and morphology were unaffected by acrolein exposure of the dams (Parent et al. 1992c). Increased incidences of skeletal anomalies and delayed ossification and decreased mean fetal weight and total litter weights were observed in the offspring of rats exposed to 10 mg/kg/day (King 1982). This dosage, however, was toxic to the dams, resulting in maternal deaths. The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to acrolein.

Questionable evidence of the carcinogenicity of acrolein in animals is provided by a few long-term studies. Lijinsky and Reuber (1987) reported a cancer bioassay in which groups of male rats were given acrolein in the drinking water at concentrations that provided doses of 0, 6, 14, or 36 mg/kg/day, 5 days/week for 104–124 weeks. One group of females was also given the highest dose on the same schedule as the males. The only indication of a carcinogenic effect of acrolein was the incidence of neoplasms of the adrenal cortex in high-dose female rats. The increased incidence of hyperplastic nodules of the adrenal cortex in 2 of 20 female rats was significant with respect to controls. Other studies failed to detect significant cancer incidence in animals. Gavage treatment of rats with 0.05–2 mg/kg/day failed to produce tumor incidences, including adrenal tumors, which were significantly different from controls (Parent et al. 1992a). Extensive histopathological examination did not reveal any carcinogenic effects in mice (Parent et al. 1991a), or dogs (Parent et al. 1992b) after oral exposure to 2.5, 4.5, or 2 mg/kg/day acrolein, respectively, for 12–24 months. Because of the disparate results of the Lijinsky and Reuber (1987) and Parent et al. (1991a and 1992a) studies, an independent pathology working group (PWG) re-evaluated the Lijinsky and Reuber tumor data (cited in Parent et al. 1992a). The PWG concluded that the incidence of cortical tumors in treated females was within the limits of historical controls and were of no biological significance for adrenal cancer from acrolein exposure.

The DHHS has not classified acrolein as to its carcinogenicity (NTP 2005). IARC has determined that acrolein is not classifiable as to carcinogenicity in humans (IARC 2004). The EPA has stated that the potential carcinogenicity of acrolein cannot be determined based on an inadequate database (IRIS 2007).

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding lethality in humans after dermal exposure to acrolein.

In rabbits administered several dilutions of acrolein percutaneously, the LD_{50} values ranged from 160 to 1,000 mg/kg body weight, depending on the vehicle and concentration (Albin 1962). It is uncertain whether the observed mortality was due to dermal absorption of acrolein or inhalation of off-gassing vapors from the skin applications. Salaman and Roe (1956) painted the backs of mice with 5 ppm acrolein (in sesame oil) for 10 weeks for a total dose of 12.6 mg and reported that acrolein did not cause mortality.

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals after dermal exposure to acrolein. Reliable LOAELs for systemic effects in humans are presented in Table 3-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to acrolein. When applied topically to the eyes of rabbits, acrolein (dose not reported) increased the heart rate (Basu et al. 1971). However, this effect is most likely due to the painful stimulation of the eye.

Dermal Effects. A 57-year-old man who accidentally spilled acrolein over his genital area experienced swelling of the penis and scrotum. After 15 days, the genital area was deeply ulcerated and gangrenous. No follow-up information was provided (Schöning 1966). Volunteers receiving topical applications of a 10% solution of acrolein in ethanol exhibited irritation, papillary edema, polymorphonuclear infiltrates, and epidermal necrosis 48 hours after exposure (Lacroix et al. 1976).

Table 3-3 Levels of Significant Exposure to Acrolein - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Systemic									
Human	1 d	Dermal				10 Percent (%)	(severe skin irritation)	Lacroix et al. 1976	
Human	1 d 5-10 min	Ocular		0.81 ppm	(eye irritation from vapor exposure)	1.22 ppm	(eye irritation from vapor exposure)	Sim and Pattle 1957	
Human	1 d 7.5 min/d	Ocular		0.3 B ppm	(eye irritation from vapor exposure)			Weber-Tschopp et al. 1977	

B = both males and females; d = day; LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; ppm = parts per million

Accidental exposure to vapors of acrolein produced burns of the cheeks and eyelids in a male subject (Champeix et al. 1966).

Ocular Effects. Volunteers reported statistically significant eye irritation in two of three different vapor-exposure scenarios (Weber-Tschopp et al. 1977). In 90-second fixed-concentration exposures, 0.6 ppm resulted in a significant increase in the number of positive reports scoring irritation as "a little." In an exposure to gradually increasing acrolein levels in which participants were queried every 5 minutes as to irritation, a significant number of positive reports of irritation, scored as "a little", were generated at the end of the first interval when the concentration was measured to be 0.09 ppm. Lastly, eye irritation from a 60-minute, 0.3-ppm exposure was scored by participants as "a little" at 10 minutes and "medium" at 40 minutes with no further increase in severity. In another human study, lacrimation occurred within 20 seconds in individuals exposed to 0.81 ppm, and within 5 seconds at 1.22 ppm (Sim and Pattle 1957). Human data summarized by Kane and Alarie (1977) show concentrations of acrolein between 0.5 and 5 ppm caused lacrimation and various degrees of eye irritation in exposure periods of 10 minutes or less.

The ocular effects observed in experimental animals are qualitatively similar to those described in humans. Vapor concentrations of acrolein higher than 1.0 ppm (1.8–3.7 ppm) caused eye irritation in dogs and monkeys as evidenced by lacrimation and closing of the eyes, but guinea pigs and rats appeared to be less sensitive, since 3.7 ppm had no noticeable effect (Lyon et al. 1970). No histological evaluation of the eye was conducted, but other reports indicate that ocular discharge was commonly seen (Murphy et al. 1964; Skog 1950).

3.2.3.3 Immunological and Lymphoreticular Effects

Rappaport and Hoffman (1941) reported the case of a male smoker who developed a severe skin reaction on the fingers of his right hand (which he used to hold the cigarette) and on his upper and lower lips. The patient was subjected to numerous allergy tests and found to be sensitive to acrolein, as well as other simple, short-chain aldehydes. It should be noted that this individual, a histology laboratory worker, was also likely to be exposed frequently to formaldehyde. It is difficult to determine whether the immunological response was a result of exposure to acrolein or other aldehydes.

No studies were located regarding immunological effects in animals after dermal exposure to acrolein.

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

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding carcinogenic effects in humans after dermal exposure to acrolein.

Salaman and Roe (1956) applied acrolein (in sesame oil) to the backs of mice once a day for 10 weeks. The total dose applied was 12.6 mg (5% solution). The authors reported no tumors at the site of application or at remote sites. These results should be interpreted with caution, since the duration of the study was too short to evaluate carcinogenic potential, and only 15 mice were used.

3.3 GENOTOXICITY

No studies were located regarding the genotoxic effects of acrolein in humans or animals by inhalation, oral, or dermal routes. Acrolein was not mutagenic *in vivo* as judged by the dominant lethal assay in the mouse (Epstein et al. 1972) or the sex-linked recessive lethal test in *Drosophila* (Zimmering et al. 1985).

The *in vitro* genotoxicity of acrolein has been investigated in prokaryotic and eukaryotic organisms and in mammalian cell systems. The overall evidence, presented in Table 3-4, indicates that acrolein is weakly mutagenic without activating systems and non-mutagenic in the presence of activating systems in *Salmonella typhimurium* (Andersen et al. 1972; Bartsch et al. 1980; Basu and Marnett 1984; Bignami et al. 1977; Eder et al. 1982; Florin et al. 1980; Foiles et al. 1989; Khudoley et al. 1987; Lijinsky and Andrews 1980; Loquet et al. 1981; Lutz et al. 1982; Marnett et al. 1985; Parent et al. 1996b; Waegemaekers and Bensink 1984) and *Escherichia coli* (Bilimoria 1975; Ellenberger and Mohn 1977; Hemminki et al. 1980; Parent et al. 1996b; VanderVeen et al. 2001; Von der Hude et al. 1988). In the yeast, *Saccharomyces cerevisiae*, acrolein was not mutagenic without activating systems (Izard 1973). In mammalian cells, acrolein gave positive results without activating systems (Au et al. 1980; Moule et al. 1971; Munsch et al. 1973, 1974). Acrolein inhibited the activity of DNA polymerase as well as DNA and RNA synthesis in rat liver cell nuclei (Crook et al. 1986a; Curren et al. 1988; Grafstrom et al. 1988; Krokan et al. 1985). The inconsistencies in the *in vitro* assay results may be due, in part, to the high cytotoxicity of acrolein to these systems.

Table 3-4. Genotoxicity of Acrolein *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Prokaryotic organisms:				
Gene mutation	*Salmonella typhimurium* plate incorporation	–	–	Andersen et al. 1972
		–	–	Florin et al. 1980
		–	–	Loquet et al. 1981
		–	–	Bignami et al. 1977
		–	(+)	Lijinsky and Andrews 1980
		–	+	Lutz et al. 1982
		–	+	Eder et al. 1982
		–	–	Basu and Marnett 1984
		No data		Bartsch et al. 1980
		No data	(+)	Khudoley et al. 1987
	Liquid preincubation test: TA1535, 1537, 1538	–	–	Parent et al. 1996b
	Liquid preincubation test: TA98	–	(+)	Parent et al. 1996b
	Liquid preincubation test: TA100	+	+	Parent et al. 1996b
	Liquid preincubation test	No data	+	Marnett et al. 1985
	Liquid preincubation method	No data	+	Foiles et al. 1989
		–	(+)	Waegemaekers and Bensink 1984
	E. coli PQ37 (SOS chromotest)	–	–	Von der Hude et al. 1988
	E. coli K-12/343/113 (plate incorporation)	–	No data	Ellenberger and Mohn 1977
	E. coli WP2uvrA (liquid preincubation)	–	(+)	Parent et al. 1996b
	E. coli WPuvrA (plate incorporation)	No data	(+)	Hemminki et al. 1980
	DNA polymerase deficiency (plate incorporation)	No data	+	Bilimoria 1975
	E. coli AB1157 derivatives	–	No data	VanderVeen et al. 2001
Eukaryotic organisms:				
Fungi:				
Gene mutation	*Saccharomyces cerevisiae* (plate incorporation)	No data	–	Izard 1973
Chromosomal aberrations	*S. cerevisiae* MB1072-2B (plate incorporation)	No data	–	Fleer and Brendel 1982

Table 3-4. Genotoxicity of Acrolein *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Mammalian cells:				
DNA, RNA synthesis	Rat liver cell nuclei	No data	+	Moule et al. 1971
DNA synthesis	Human fibroblasts (xeroderma pigmentusum and HeLa cells)	No data	–	Yang et al. 2002a
DNA polymerase activity	Rat liver	No data	+	Munsch et al. 1973, 1974
Chromosome breakage	Chinese hamster ovary cells	+	+	Au et al. 1980
Sister chromatid exchange	Chinese hamster ovary cells	+	+	Au et al. 1980
Gene mutation	Chinese hamster ovary cells	–	–	Parent et al. 1998a
DNA damage	Human myeloid cells K562	No data	+	Crook et al. 1986a
DNA damage	Human bronchial cells (culture)	No data	+	Grafstrom et al. 1988
DNA repair	Human bronchial cells (culture)	No data	+	Krokan et al. 1985
DNA repair	Human fibroblasts (culture)	No data	–	Curren et al. 1988
DNA repair	Human fibroblasts (xeroderma pigmentation)	No data	+	Curren et al. 1988
Gene mutation	Chinese hamster V79 cells	No data	+	Smith et al. 1990a
Gene mutation	Human fibroblasts (with *supF* plasmids)	No data	+	Kawanishi et al. 1998
Gene mutation	Human fibroblasts (xeroderma pigmentusum and HeLa cells)	No data	–	Yang et al. 2002a

+ = positive result; – = negative result; (+) = marginally positive result; DNA = deoxyribonucleic acid; RNA = ribonucleic acid

Acrolein also induced chromosome breakage and sister-chromatid exchange in Chinese hamster ovary cells. DNA damage was seen in human myeloid cells and bronchial cells in culture. Acrolein was not mutagenic to normal human fibroblasts in culture, but fibroblasts with a deficient DNA repair system showed a positive mutagenic response (Curren et al. 1988). Acrolein was also a potent inhibitor of the DNA repair enzyme 0_6-methylguanine-DNA methyl transferase. DNA base substitutions and intra-strand cross-links were observed in human fibroblasts containing shuttle vector plasmids bearing the *supF* marker gene (Kawanishi et al. 1998). The mechanism by which acrolein induces genotoxicity in mammalian cells is not known, but it has been shown that acrolein can form adducts with DNA, such as $1N_2$-propanodeoxyguanine (Chung et al. 1984; Foiles et al. 1989), $1N_6$-propanodeoxyadenine (Smith et al. 1990a), 3-[N_6-(2'-deoxyadenosinyl)]propanal and 9-(2'-reoxyribosyl-6-(3-formyl-1,2,5,6-tetrahydro-pyridyl)purine (Pawlowicz et al. 2006). Yang et al. (2002b) showed that acrolein adduction to DNA may be insignificant for the introduction of miscoding errors, as translesion DNA synthesis was high and miscoding incidence was <1% in human HeLa and xeroderma pigmentosum cells. The same inability of acrolein DNA adducts to cause miscoding was observed in *E. coli* as well (VanderVeen et al. 2001). Because of the limited number of *in vivo* tests, there is insufficient evidence to predict that acrolein poses a genotoxic threat to humans.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans after inhalation exposure to acrolein. The collection of such data would be problematic, as acrolein is highly reactive with any nucleophilic binding site it encounters during exposure by any route.

Egle (1972) exposed anesthetized dogs to concentrations of acrolein between 172 and 262 ppm for a brief period of time (1–3 minutes) and observed that acrolein uptake by the total respiratory tract at ventilation rates of 6–20 respirations/minute averaged 80–85% of the inhaled dose. Retention was independent of the respiratory rate. The author estimated that only about 20% of the inhaled dose reached the lower respiratory tract. Morris (1996) and Morris et al. (2003) exposed mice to 1.1 ppm and rats to 0.9–9.1 ppm acrolein. In both species, most of the inhaled acrolein was absorbed entirely into the upper respiratory tract. Mice absorbed 92% of 1.1 ppm over 10 minutes. Absorption in the upper respiratory tract of rats

was found to be dose- and breathing-rate related. At a breathing rate of 50 mL/minute, absorption ranged from >90% to approximately 70% for 0.9–9.1 ppm, while approximately 50–30% was absorbed when breathing 300 mL/minute of the same concentrations for 40 minutes.

Exposure of the lower respiratory tract alone resulted in 65–70% concentration-independent retention, but decreased slightly with increases in tidal volume from 100 to 160 mL. Although the study by Egle (1972) does not provide information on the disposition of the retained acrolein or on whether the uptake rates represent steady-state values, it indicates that acrolein at relatively high concentrations is effectively removed from inhaled air by both the upper and lower respiratory tracts.

3.4.1.2 Oral Exposure

No studies were located regarding absorption of acrolein in humans after oral exposure.

Parent et al. (1996a) administered gavage doses of 2.5 or 15 mg/kg [2,3-^{14}C]acrolein to male and female Sprague-Dawley rats. Doses of 2.5 mg/kg were extensively absorbed, as 12–15% of the initial dose was found in the feces. In the high-dose group, 28–31% of the initial dose was found in the feces.

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of acrolein in humans after dermal exposure. In cases of accidental dermal exposure (described in Section 3.2.3), effects were restricted to the exposed region of the body, presumably because of the high reactivity of acrolein.

Limited information is available regarding dermal absorption of acrolein in animals. The percutaneous LD_{50} for rabbits ranged from 160 to 1,000 mg/kg, depending on the acrolein concentration and vehicle (water or mineral spirits) (Albin 1962). LD_{50}values for acrolein administered in mineral spirits are lower than those in which water served as the vehicle, likely because of the greater skin permeability of mineral spirits.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding distribution of acrolein in humans or animals after inhalation exposure.

3.4.2.2 Oral Exposure

No studies were located regarding distribution of acrolein in humans after oral exposure.

In a study conducted by Draminski et al. (1983), the acrolein conjugated metabolite S-carboxyethyl-mercapturic acid was identified in the urine of rats after oral administration of a single dose of 10 mg/kg of acrolein, suggesting distribution of acrolein to the liver and kidney, where conjugation most likely occurred. Parent et al. (1996a) found similar levels of [2,3-^{14}C]acrolein in the kidney, spleen, lungs, blood, liver, fat, adrenals, and ovaries of rats sacrificed 168 hours after dosing.

3.4.2.3 Dermal Exposure

No studies were located regarding distribution of acrolein in humans or animals after dermal exposure.

3.4.2.4 Other Routes of Exposure

Parent et al. (1996a) found [2,3-^{14}C]acrolein in the kidney, spleen, lungs, blood, liver, fat, adrenals, and ovaries of rats administered 2.5 mg/kg [2,3-^{14}C]acrolein intravenously. The [2,3-^{14}C]acrolein were very similar across tissues; however, all tissue measurements were made at 168 hours after dose administration.

3.4.3 Metabolism

There is limited information available regarding the metabolism of acrolein in humans and animals after inhalation, oral, and dermal exposures. The relevant data are presented below.

In non-biological cell-free systems, acrolein forms thiol ethers within seconds when reacted with glutathione or cysteine (Esterbauer et al. 1975, 1976). In cell systems *in vitro*, such as cultured human bronchial cells and isolated cell preparations from rat liver and kidneys, acrolein forms conjugates with glutathione, cysteine, N-acetylcysteine, and/or thioredoxin (Dawson et al. 1984; Dupbukt et al. 1987; Gurtoo et al. 1981b; Yang et al. 2004; Zitting and Heinonen 1980). The formation of these conjugates greatly diminished the cytotoxic effects of acrolein, indicating that conjugation may be an important detoxification mechanism. In addition to the evidence provided by the numerous *in vitro* studies, three reports from the literature (Alarcon 1976; Kaye 1973; Parent et al. 1998) demonstrated that acrolein also

reacts with glutathione *in vivo*. In two of these studies, the acrolein metabolite 3-hydroxypropyl-mercapturic acid was identified in the urine of rats after a subcutaneous dose of acrolein (Alarcon 1976; Kaye 1973). It should be noted that other compounds also metabolize to 3-hydroxypropylmercapturic acid, including allylamine (Boor et al. 1987), allyl halides (Kaye and Young 1972), and allyl alcohol and ester (Kaye 1973). Findings from the third study (Parent et al. 1998) are discussed in Section 3.4.3.2.

Based on experimental results, Patel et al. (1980b) proposed an *in vitro* metabolic scheme for acrolein in rat liver and lung preparations. In this scheme, free acrolein can interact with proteins and nucleic acids, and/or with thiol groups such as glutathione. Acrolein can also be transformed into acrylic acid by liver cytosol or microsomes, or it can be oxidized to glycidaldehyde by lung or liver microsomes. Acrylic acid may be incorporated into amino acids, fatty acids, and sterol. Glycidaldehyde can be metabolized to glyceraldehyde, which then can enter the glycolytic pathways. From the scheme proposed by Patel et al. (1980b), glycidaldehyde appears to be the only chemical that could represent a risk to human health, since it has shown carcinogenic properties in mice and rats when applied dermally (Shamberger et al. 1974; Van Duuren et al. 1967a, 1967b). The metabolic pathway proposed by Patel et al. (1980b) is shown in Figure 3-3.

3.4.3.1 Inhalation Exposure

No studies were located regarding metabolism of acrolein in humans after inhalation exposure.

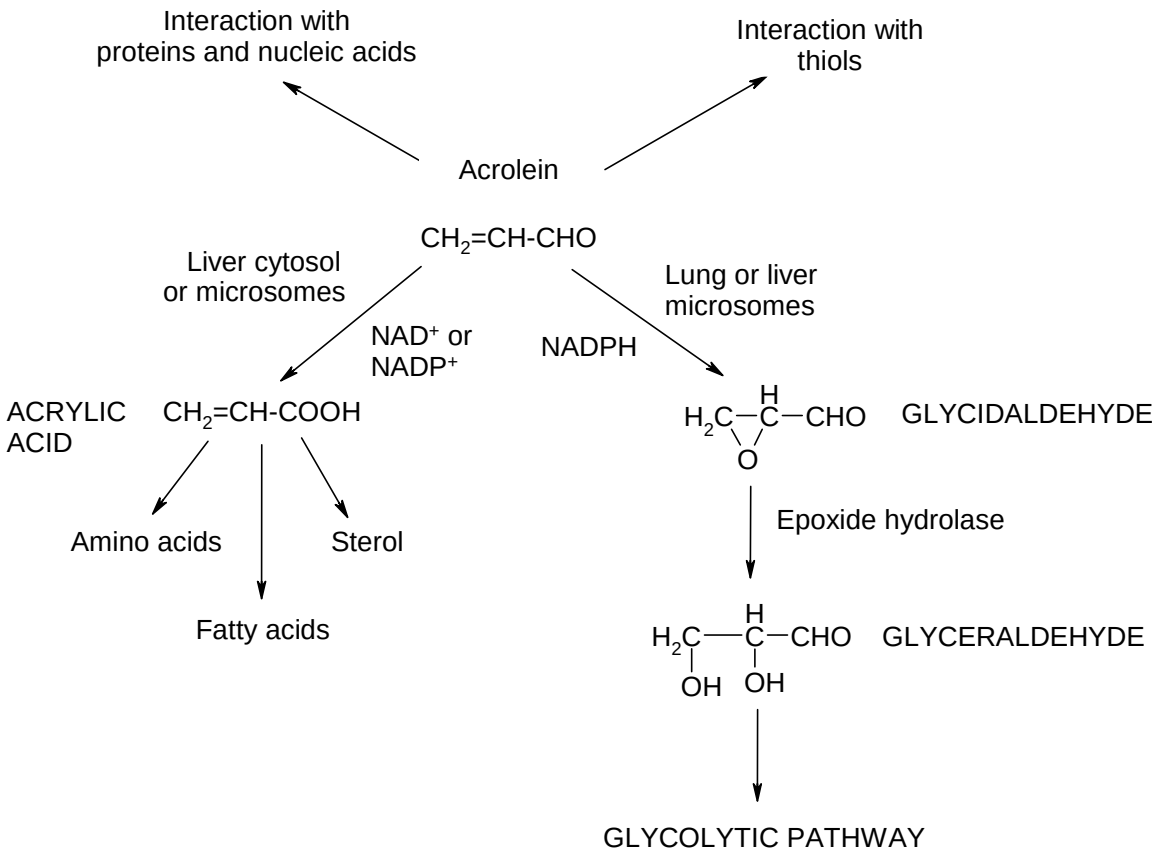
Lam et al. (1985) found a dose-related depletion of glutathione in the nasal respiratory mucosa of rats after exposure to 0.1–2.5 ppm of acrolein for 3 hours. This finding is consistent with a chemical reaction leading to the formation of a glutathione-acrolein adduct.

3.4.3.2 Oral Exposure

No studies were located regarding metabolism of acrolein in humans after oral exposure.

Draminski et al. (1983) administered 10 mg/kg of acrolein as a single oral dose to rats and collected the urine during 3 days. Since the metabolite S-carboxyethylmercapturic acid was found in the urine, but S-hydroxypropylmercapturic acid (which should have been formed if acrolein had reacted with glutathione) was not, an alternative pathway was proposed. In this metabolic scheme, acrolein is first metabolized to acrylic acid with subsequent formation of the methyl ester, which is then conjugated with glutathione to form S-carboxyethylmercapturic acid methyl ester. Both metabolic schemes proposed by

Figure 3-3. Proposed Metabolic Scheme for Acrolein *In Vitro*



Source: Patel et al. 1980

Draminski et al. (1983) and Patel et al. (1980b) involve the hepatic formation of acrylic acid, but differ on the subsequent metabolism of that metabolite. The metabolic pathway postulated by Draminski et al. (1983) is shown in Figure 3-4.

An *in vivo* study in rats identified six metabolites of [2,3-^{14}C]acrolein in urine (Parent et al. 1998) arising from three proposed pathways. The main pathway involves Michael addition of glutathione to acrolein to generate S-3-oxypropylcysteine. Further oxidation or reduction results in two of the mercapturic acids found in urine, N-acetyl-S-2-carboxyethylcysteine and N-acetyl-S-2-hydropropylcysteine. The second pathway involves the epoxidation of acrolein to glycidaldehyde and subsequent attack by glutathione. Further oxidation produced urinary N-acetyl-S-2-hydroxyethylcysteine. Finally, urinary 3-hydroxy-propionic acid, malonic acid, and oxalic acid were proposed to arise from non-enzymatic hydrolysis of acrolein and subsequent oxidation of the aldehyde. No metabolites were found in the feces. The metabolic scheme proposed by Parent et al. (1998) is shown in Figure 3-5.

3.4.3.3 Dermal Exposure

No studies were located regarding metabolism of acrolein in humans or animals after dermal exposure.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

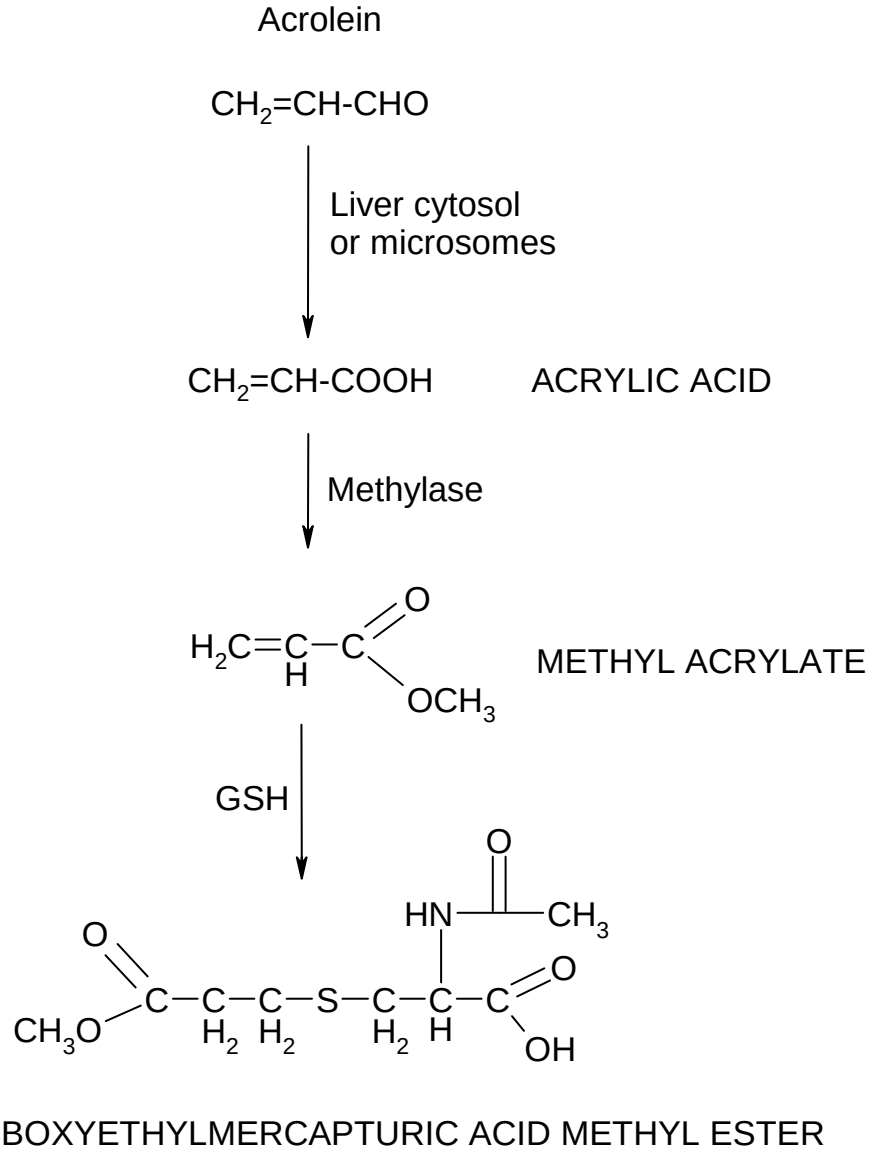
No studies were located regarding excretion of acrolein or metabolites after inhalation exposure.

3.4.4.2 Oral Exposure

No studies were located regarding excretion of acrolein or metabolites in humans after oral exposure.

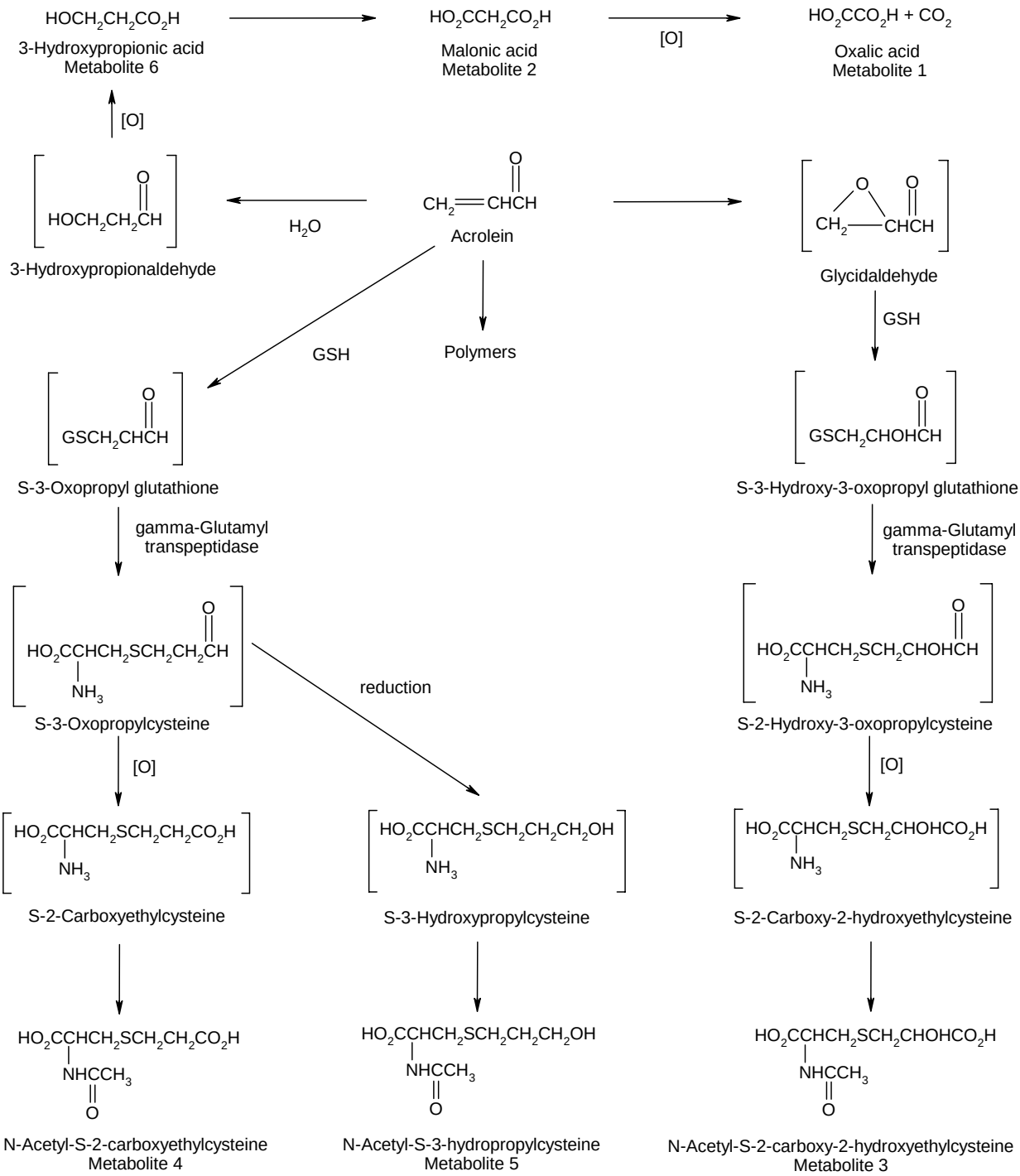
In rats dosed with 2.5 mg/kg [2,3-^{14}C]acrolein via gavage, Parent et al. (1996a) found 27–31% of the initial dose to be expired as CO_2 while 52–63% was found in the urine and 12–15% was found in the feces. Rats dosed with 15 mg/kg [2,3-^{14}C]acrolein exhibited similar expiration of the initial dose as CO_2, but had a higher fraction of the initial dose going to feces (28–31%) and a lower fraction going to urine (37–41%). Six metabolites of [2,3-^{14}C]acrolein were identified in the urinary fraction of the 2.5 mg/kg group: N-acetyl-S-2-carboxyethylcysteine; N-acetyl-S-2-hydropropylcysteine; N-acetyl-S-2-hydroxy-ethylcysteine; 3-hydroxypropionic acid; malonic acid; and oxalic acid (Parent et al. 1998). Draminski et

Figure 3-4. Proposed Metabolic Scheme for Acrolein *In Vivo*



Source: Draminski et al. 1983

Figure 3-5. Proposed Pathway for the Metabolism of Acrolein in Rats*



*The structures in brackets represent postulated intermediates.

Source: Parent et al. 1998

al. (1983) reported the presence of the acrolein metabolite S-carboxyethylmercapturic acid in the urine of rats after administration of a single oral dose of 10 mg/kg of acrolein. The percentage of the dose recovered as the metabolite in the urine was not determined.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of acrolein or metabolites after dermal exposure.

3.4.4.4 Other Routes of Exposure

Rats administered 2.5 mg/kg [2,3-^{14}C]acrolein intravenously expired 26–27% of the initial dose as CO_2, which is lower, but not significantly different from animals orally exposed to the same dose (Parent et al. 1996a). In this study, intravenously administered [2,3-^{14}C]acrolein was predominantly eliminated in the urine (67–69%), with a small fraction found in the feces (1–2%).

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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-6 shows a conceptualized representation of a PBPK model.

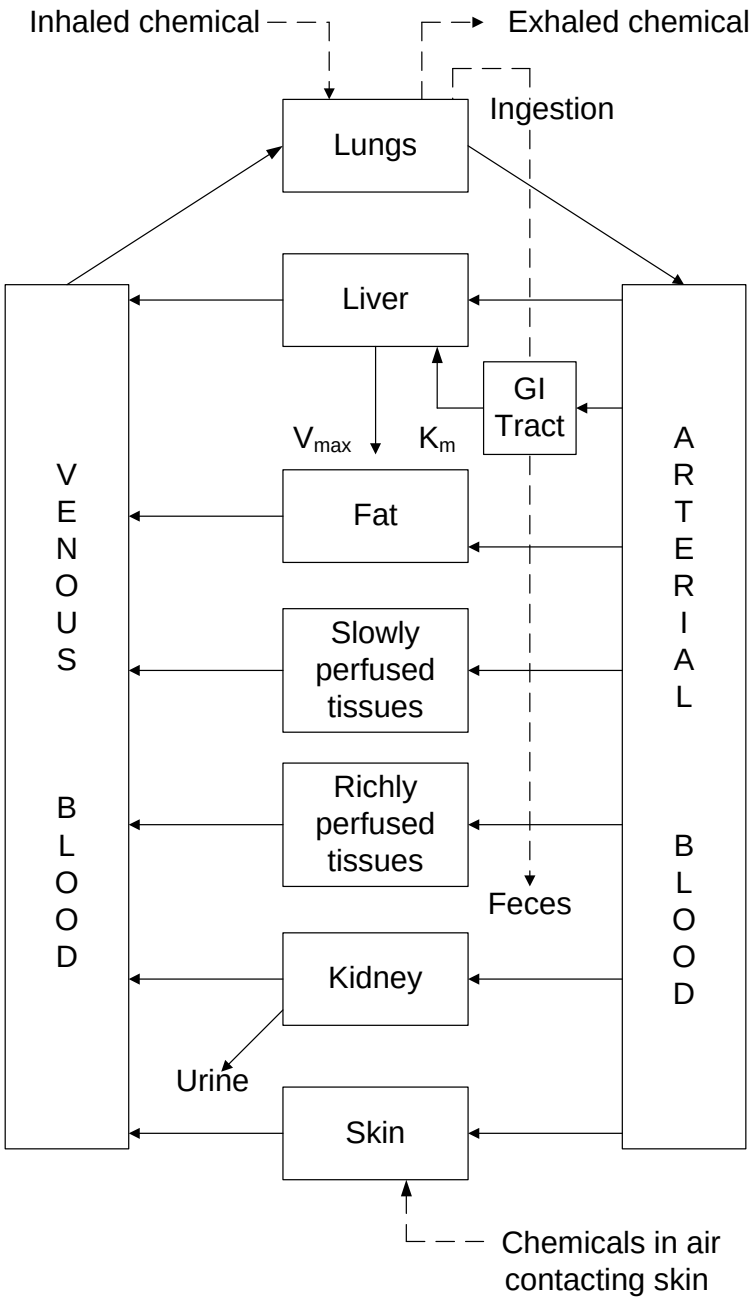
No PBPK models for acrolein were identified in the literature.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

No studies were located for animals or humans that describe observed mechanisms for acrolein absorption across the skin, lung, or gut, metabolism (either through passive adduct formation or enzymatically catalyzed transformation), or excretion. It is not known whether acrolein and its metabolites are transported across cell membranes via passive diffusion or active transport processes. Since acrolein is

Figure 3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

Source: adapted from Krishnan et al. 1994

known to react with any nucleophilic site, including protein thiol moieties, peptide-based active transporters may form adducts with acrolein, which may serve to diminish or inhibit the transporter's functionality.

3.5.2 Mechanisms of Toxicity

As an ethenylic aldehyde, acrolein is a highly reactive compound. In biological systems, it binds extensively to lysine moieties and has the highest affinity for sulfhydryl groups found on many cellular molecules, including most proteins. As such, it binds rapidly and irreversibly to macromolecules to form thiol ethers (Beauchamp et al. 1985). In this fashion, acrolein may bind to structural and biological messenger compounds to produce direct cytotoxic effects or secondary effects from interrupted cell signaling pathways. Perturbation of inflammatory responses in bronchial epithelial cells was demonstrated by direct action of acrolein on IκB kinase, resulting in inhibition of NFκB activation and suppression of IL-8 production (Valacchi et al. 2005). Alarie (1973) hypothesized that rapid binding of acrolein to neural receptors in the corneal and nasal mucosa may result in rapid depolarization of the associated neurons to produce ocular and nasal irritation. Adams and Klaidman (1993) showed acrolein to bind rapidly to glutathione. Depletion of glutathione could be inhibitory to the enzyme glutathione peroxidase, resulting in a lower level of cellular protection against oxygen radical toxicity. Further, the adduction of glutathione resulted in generation of a GS-propionaldehyde, which was shown to produce oxygen and possibly hydroxy radicals via cytosolic aldehyde dehydrogenase. Glutathione depletion and inhibition of caspase-3 activation in human neutrophils was observed to inhibit neutrophil apoptosis, providing a possible mechanism for extended inflammatory responses (Finkelstein et al. 2005). Similarly, activation of caspase-7 and -9 and inhibition of caspase-3 accompanied apoptosis in Chinese hamster ovary cells (Tanel and Averill-Bates 2005). A dose-dependent increase in NO levels and decrease in thioredoxin reductase was correlated with apoptosis of acrolein-treated human umbilical vein endothelial cells (Misonou et al. 2006; Park et al. 2005). Arumugan et al. (1999) exposed rats to 1 and 2 ppm acrolein for 4 hours and measured various markers for lipid peroxidation in lavage fluid from the lung. They were able to correlate changes in peroxidative status on the lungs with gross histological findings of desquamated alveolar endothelium, a metaplastic change in cell structure that has been observed over the entire respiratory tract of animals. They also found diminished glutathione levels in treated animals as well as an increase in superoxide dismutase and decreases in catalase and glutathione peroxidase, indicative of an imbalance in antioxidant defenses that favors oxidative stress. Further, increased levels of conjugated dienes and thiobarbituric acid reactive substances suggest the onset of lipid peroxidation. Reduction of glutathione and aconitase activity was correlated with increased ROS

production and inhibited electron transport in brain and spinal cord mitochondria of guinea pigs (Luo and Shi 2004, 2005) and human PC12 cells (Luo et al. 2005). Beauchamp et al.'s analysis (1985) suggests that depletion of glutathione and other available cellular thiol sources may permit the movement of acrolein at high concentrations past the initial tissue point of contact. While data were not found that correlated gastrointestinal lesions with glutathione content and peroxidative status as was done in the lung (Arumugan et al. 1999), the appearance of endothelial metaplasia in multiple species of animals following oral exposures suggests that gastrointestinal and respiratory toxicity may occur by the same mechanism of action.

Acrolein has been shown to be produced endogenously from hydroxyl-amino acids (Anderson et al. 1997) and as a product of lipid peroxidation (Uchida et al. 1998a, 1998b), which can form protein conjugates that may be significant factors in certain diseases. Acrolein conjugation with lysine residues of low-density lipoproteins has been suggested as a factor in the development of atherosclerosis (Uchida et al. 1998b). Protein-acrolein binding products resulting from lipid peroxidation have been implicated in the formation of neurofibrillary tangles (Calingasan et al. 1999) and induction of protein tau hyperphosphorylation (Gomez-Ramos et al. 2003), both hallmarks of Alzheimer's disease.

3.5.3 Animal-to-Human Extrapolations

The irritant properties of acrolein have been reported in both human and animal studies. *In vivo* studies in animals and *in vitro* studies in human and animal cell cultures have reported the common mechanisms of action of cellular thiol reactivity and glutathione depletion (Arumugan et al. 1999; Beauchamp et al. 1985; Nardini et al. 2002). Acrolein exposure levels were very comparable for the appearance of cellular changes in nasal epithelium of animals (Cassee et al. 1996) and onset of nasal irritation in humans (Weber-Tschopp et al. 1977). Therefore, it is reasonable to extrapolate animal health effects to human health risk resulting from acrolein exposure.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in human or animals after exposure to acrolein. No *in vitro* studies were located regarding endocrine disruption of acrolein. Based on the mechanism of toxicity and data from animal studies (Parent et al. 1991a, 1992a, 1992b), acrolein is not expected to have endocrine-modulating activities.

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).

Since point-of-contact irritation is the principal toxic action of acrolein, children are not likely to be more susceptible to acrolein's effects at the tissue level. Despite uncertainties in age-related differences in lung architecture, surface area, and ventilation rates, simple dosimetry modeling of a category 1 gas, such as acrolein, does not suggest significant differences in early juvenile and adult internal inhalation exposure (Ginsberg et al. 2005). It is not known if there are age-related differences in the pharmacokinetics of acrolein. The amount of ingested acrolein available for gastrointestinal irritation would be the same for children and adults. While children may have a higher inhalation rate (per mass) than adults (NRC 1993), it is unknown whether they would continue to breathe more airborne acrolein than adults. While adults have been shown to reduce their respiration rate by as much as 20% in the presence of airborne acrolein (Weber-Tschopp et al. 1977), it is not known if children will react in the same or similar manner. Animal studies have shown offspring of acrolein-exposed mothers to have reduced body weights and skeletal deformities (King 1982; Parent et al. 1992c). However, these effects occurred at high oral doses that were fatal to the mothers.

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, 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 acrolein 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 acrolein 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 Acrolein

A product of the conjugation of acrolein with glutathione, 3-hydroxypropylmercapturic acid, has been identified in the urine of individuals receiving the drug cyclophosphamide (Alarcon 1976; Kaye and Young 1974). Since the same product was identified in the urine of rats administered acrolein subcutaneously (Alarcon 1976), it was thought that levels of 3-hydroxypropylmercapturic acid in the urine could be used to identify exposure to acrolein. However, Alarcon (1976) found no correlation between the dose of cyclophosphamide administered and the amount of 3-hydroxypropylmercapturic acid in the urine of patients. Parent et al. (1998b) found six urinary metabolites (predominantly mercapturic acids) following oral and intravenous dosing of radiolabled acrolein in rats, but did not correlate metabolite levels with dose. Methods developed to determine levels of acrolein in human tissues and fluids are described in Chapter 7.

3.8.2 Biomarkers Used to Characterize Effects Caused by Acrolein

No studies were located regarding levels of acrolein or its metabolites in human tissues and fluids associated with effects. No biochemical or histological changes specific for acrolein exposure were identified. Results from a toxicokinetic study suggested that acrolein can react with proteins and nucleic acids in the organism (Patel et al. 1980b).

After transformation into acrylic acid, incorporation into amino acids, fatty acids, and sterols can be expected (Patel et al. 1980b). However, specific effects associated with these biochemical reactions are not known.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Ansari et al. (1988a) showed that acrolein enhances the inhibitory effect that certain industrial chemicals, such as styrene and 1,2-dichloroethane, have on the αl-proteinase inhibitor of human plasma *in vitro*. A decrease in the activity of the αl-proteinase inhibitor may result in an increase in the activity of the lung enzyme neutrophil elastase, which can lead to the development of emphysema. Acrolein has also been shown to increase the pentobarbital- and hexobarbital-induced sleeping time in rats (Jaeger and Murphy 1973a). The mechanism, according to the authors, could include changes in the absorption and distribution of the barbiturates. More recent information suggests that the mechanism may involve a covalent reaction between acrolein and cytochrome P-450 leading to inactivation of P-450 resulting in prolonged action of the barbiturates (Lame and Segall 1987).

Acrolein forms adducts with thiols such as glutathione, cysteine, N-acetylcysteine, and others. Such reaction protects tissues and cells from the cytotoxic effects of acrolein or acrolein-releasing substances (Brock et al. 1981b; Chaviano et al. 1985; Dawson et al. 1984; Gurtoo et al. 1983; Ohno and Ormstad 1985; Whitehouse and Beck 1975).

Exposure of mice for 10 minutes to mixtures of sulfur dioxide and acrolein showed that either irritant can alter or block the effect of the other (Kane and Alarie 1979a). Furthermore, when the mice were exposed to mixtures, recovery was much slower than when exposed to the individual chemicals. The authors postulated that a bisulfite-acrolein adduct may be formed. When exposure ceased, this adduct would release acrolein, thus preventing immediate recovery. In addition, Kane and Alarie (1978) exposed mice to mixtures of acrolein and formaldehyde and showed that the respiratory response to mixtures was less

pronounced than the response to either chemical alone. This is consistent with a mechanism in which both chemicals act on the same type of physiological receptor (free nerve endings).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to acrolein than will most persons exposed to the same level of acrolein 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 acrolein, or compromised function of organs affected by acrolein. Populations who are at greater risk due to their unusually high exposure to acrolein are discussed in Section 6.7, Populations with Potentially High Exposures.

In general, individuals whose respiratory function is compromised, such as those with emphysema, or individuals with allergic conditions such as asthma, will be at a higher risk of developing adverse respiratory responses when exposed to a strong respiratory irritant such as acrolein. This was demonstrated in animals in which allergic airway-diseased mice were more responsive than nondiseased mice to acute respiratory irritant effects of 0.3 ppm acrolein (Morris et al. 2003).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to acrolein. 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 acrolein. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to acrolein:

Bronstein AC, Currance PL. 1994. Emergency care for hazardous materials exposure. 2nd ed. St. Louis, MO: Mosby Lifeline.

ITII. 1988. Toxic and hazardous industrial chemicals safety manual. Tokyo, Japan: The International Technical Information Institute.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 2002. Toxicologic emergencies. 7th ed. New York, NY:McGraw-Hill, Medical Publishing Division, 1470.

3.11.1 Reducing Peak Absorption Following Exposure

The mechanisms of absorption of acrolein following inhalation or oral exposures is not known. Since acrolein is a point-of-contact irritant, measures to dilute the concentration at the pulmonary, gastrointestinal, or dermal tissue surfaces may reduce absorption. Emergency treatment for acrolein inhalation exposure includes ventilation and oxygenation. Water may be ingested or used as a rinse to dilute oral or dermal exposures, respectively. Gastric lavage or nasogastric suction may be administered if life-threatening amounts of acrolein are ingested (HSDB 2007).

3.11.2 Reducing Body Burden

Acrolein is not believed to accumulate in the body. With the exception of gastric lavage and nasogastric suction (see Section 3.11.1), no studies or guidelines could be located with procedures for reducing the body burden of acrolein.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Acrolein acts by contact reactivity (i.e., adduction) with nucleophilic sites on macromolecules of biological tissues, including binding to glutathione. There are no clinically-accepted procedures for therapeutically interfering with acrolein's toxic mechanism of action. Several *in vitro* and *in vivo* studies suggest candidates for treatment of acrolein exposure at the cellular level. The anti-hypertensive drug hydrazinophthalazine is effective in trapping reactive acrolein-protein adducts formed following *in vitro* acrolein exposure of mouse hepatocytes (Burcham et al. 2004) and *in vivo* intraperitoneal allyl alcohol (which is metabolized to acrolein) exposure in mice (Kaminskas et al. 2004). Effective *in vitro* and *in vivo* concentrations of hydrazinophthalazine ranged from 2 to 50 μM and from 6 to 18 mg/kg, respectively. Pretreatment of rat A10 aortic smooth muscle cells with 1,2-dithiole-3-thione resulted in induction of cellular glutathione and glutathione-S-transferease (an enzyme that catalyzes the conjugation of reduced glutathione and reactive electrophiles, such as acrolein) and a marked decrease in acrolein cytotoxicity (Cao et al. 2003). Cells treated with 100 μM 1,2-dithiole-3-thione were 90–100% viable after 24 hours of exposure to as much as 40 μM acrolein. The antioxidants α-tocopherol and ascorbic acid served to significantly reduce acrolein-induced apoptosis (25 μM) in cultured human bronchial epithelial cells at levels of 5 and 50 μM, respectively (Nardini et al. 2002). While these studies report a variety of compounds and cellular concentrations capable of interfering with acrolein's toxic mechanism of action, they do not provide data regarding an effective administered dose (by any route) or maximum delay in administration that would provide efficacy against acrolein toxicity in humans or animals.

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 acrolein 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 acrolein.

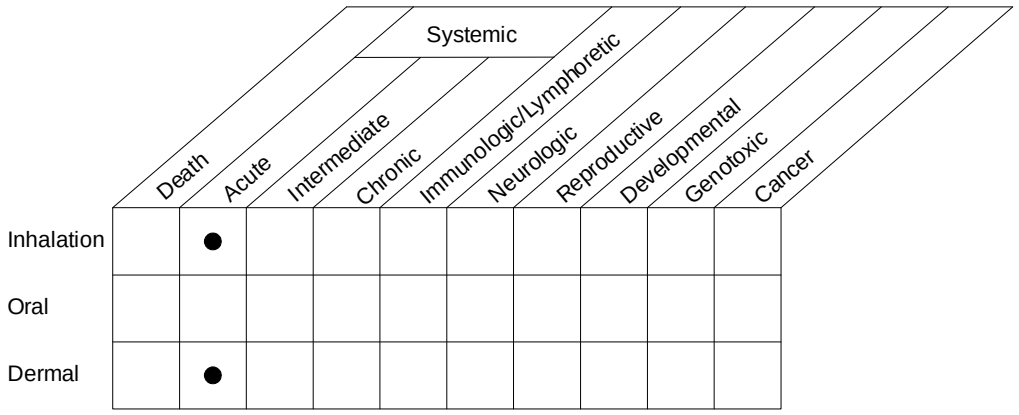
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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 Acrolein

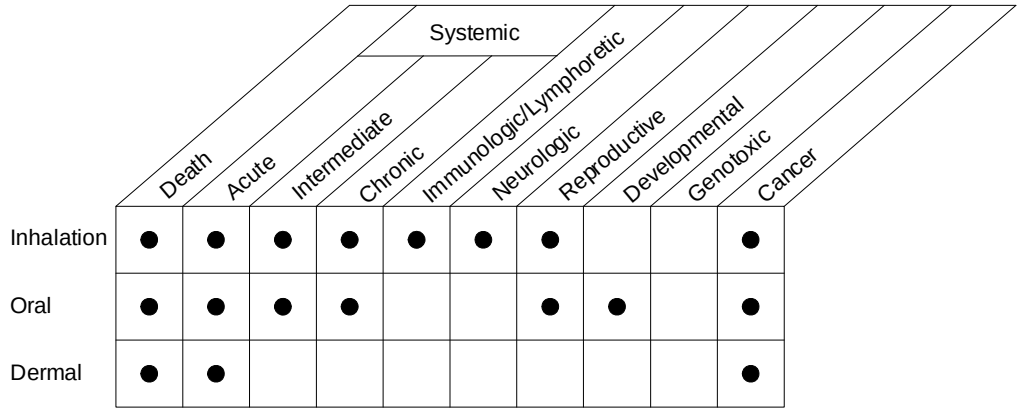
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to acrolein are summarized in Figure 3-7. The purpose of this figure is to illustrate the existing information concerning the health effects of acrolein. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As seen from Figure 3-7, very little information is available regarding the health effects of exposure of humans to acrolein. Experimental studies in humans have attempted to determine the thresholds for eye, nose, and throat irritation. Information on humans accidentally exposed to acrolein also indicates that acrolein irritates the skin, eyes, nose, and throat, and that severe respiratory effects can persist long after exposure occurs.

Figure 3-7. Existing Information on Health Effects of Acrolein



Human



Animal

● Existing Studies

Data are available for acute and intermediate inhalation exposures that resulted in death of animals. For the most part, these exposures also affected the respiratory tract and the immune response to bacterial agents.

An intermediate inhalation exposure study of rats prior to mating and during pregnancy did not result in fetotoxic or teratogenic effects. Limited information is available regarding chronic inhalation exposure.

Data are available for oral doses associated with death and increased mortality in acute, intermediate, and chronic exposure. The developmental and reproductive effects of oral exposure to acrolein have also been investigated. Chronic oral exposure of female rats may have resulted in neoplasms in the adrenal cortex, though the data are equivocal.

Acrolein applied to the skin of animals results in skin irritation and death if applied in high concentration. Acrolein was not carcinogenic when applied to the skin of mice for 10 weeks.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure to acrolein is irritating to the upper respiratory system in humans (Sim and Pattle 1957; Weber-Tschopp et al. 1977) and animals (Cassee et al. 1996). The respiratory tract is the primary target of acrolein toxicity via inhalation exposure. Desquamation of the respiratory epithelium followed by airway occlusion and asphyxiation was the main reason for acrolein-induced mortality in animals (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). An MRL for acute inhalation exposure was derived from human data (Weber-Tschopp et al. 1977) for respiratory effects. No data were located regarding acrolein toxicity in humans after oral exposure. Information regarding acute oral exposure of animals is limited to developmental toxicity studies (King 1982; Parent et al. 1993). The lowest LOAEL between the two studies, 2 mg/kg/day in rabbits, resulted in significant decrement in weight gain followed by a rebound to control values. This transient effect on body weight was not observed in non-pregnant animals. It is not known if pregnancy contributed to the reversal of effect on body weight. Therefore, the acute oral data are not sufficient to derive an MRL. Acute-duration oral exposure studies in non-pregnant animals need to be performed using low doses about which clinical effects have been observed (i.e., vomiting in dogs from 0.5 mg/kg [Parent et al. 1992b]). Histological examination of the gastrointestinal tissues may provide data regarding sensitive irritant effects, such as epithelial metaplasia, that may serve as a basis for an acute MRL.

Skin contact with acrolein caused irritation, burns, and epidermal necrosis in humans (Champeix et al. 1966; Lacroix et al. 1976; Schöning 1966). It is evident, therefore, that the necrotic effects of acrolein occur at the site of primary contact regardless of routes of exposure. Target organs for acrolein toxicity other than at the site of contact, however, were not identified and pharmacokinetic data are insufficient to identify target organs across routes of exposure. Further studies describing the tissue-specific pharmacokinetics of acrolein after exposure via all three routes would be useful. The information is important for populations living near hazardous waste sites that might be exposed to acrolein for brief periods of time.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to acrolein in humans. Inhalation exposure studies in animals (Costa et al. 1986; Feron et al. 1978; Kutzman et al. 1984; Lyon et al. 1970) suggest that the respiratory tract is the most sensitive target of toxicity for inhaled acrolein. The information was sufficient for derivation of an inhalation MRL (Feron et al. 1978). Oral exposure studies in animals (King 1984; NTP 2006; Parent et al. 1992b, 1992c) provide strong evidence that the stomach is the most sensitive target of toxicity. An intermediate-duration oral MRL was based on histological changes in the gastrointestinal tract of mice (NTP 2006). Studies are needed to assess the dermal effects of intermediate-duration exposures. While intermediate-duration data are available for ocular irritation in animals (Lyon et al. 1970), no data are available for the effects of acrolein exposure to skin. Studies examining effects on the skin of intermediate-duration exposures to acrolein would be of limited utility, as acrolein in the environment evaporates rapidly from water and binds significantly to nucleophilic sites in soil-born matter, likely resulting in low bioavailability.

Chronic-Duration Exposure and Cancer. No studies were located regarding toxicity in humans following chronic exposure. Respiratory toxicity was observed in rats and hamsters after inhalation exposure (Feron and Kruysse 1977; Le Bouffant et al. 1980). However, the designs of these inhalation studies were not sufficient for MRL derivation. The studies used short daily exposures that are not indicative of chronic exposure, or had only one exposure level, which would not provide a NOAEL and corresponding LOAEL. Chronic-duration inhalation studies with multiple exposure levels and having extensive daily exposure periods are needed to derive a chronic-duration inhalation MRL. Chronic oral studies were performed in rats, mice, and dogs (Parent et al. 1991a, 1992a, 1992b). Extensive histopathological examination revealed no effects in any organs. Reduced survival of mice and rats (a frank effect level) was observed, although no cause of death could be determined. Chronic-duration oral studies identifying a NOAEL and/or less serious LOAEL are needed to derive a chronic-duration oral

MRL. No studies were located regarding acrolein toxicity after chronic-duration dermal exposure in animals. Studies describing the effects of acrolein associated with chronic, low-level exposure of the skin would be useful.

No studies were located regarding the carcinogenicity of acrolein in humans. No increase in tumor incidence was observed in two limited, chronic inhalation studies in animals. These studies either had a very short daily exposure of 1 hour (Le Bouffant et al. 1980) or were carried out for less-than-lifetime duration for the study animals (Feron and Kruysse 1977; Le Bouffant et al. 1980). Dermal application of acrolein to mice for ten weeks did not induce cancer (Salaman and Roe 1956). However, the length of the study is considered too short for proper evaluation of carcinogenicity. No carcinogenic effect was found in rats, mice, and dogs following extensive histopathological examinations after chronic oral exposure to acrolein (Parent et al. 1991a, 1992a, 1992b). An increased incidence of adrenocortical adenomas was reported in female rats after oral exposure to acrolein in another study (Lijinsky and Reuber 1987); however, these findings were dismissed by an independent pathology working group (Parent et al. 1992a). Although Parent et al. (1991a, 1992a, 1992b) provided carcinogenicity data in animals receiving lifetime gavage doses of acrolein, lifetime drinking water studies in animals are needed to further assess lack of carcinogenicity reported in the lifetime gavage studies.

Genotoxicity. No studies were located regarding acrolein genotoxicity in humans. Dominant lethality of acrolein was not observed in mice (Epstein et al. 1972). However, *in vitro* data showed weak mutagenic potential of acrolein in bacterial and mammalian cells without metabolic activation (Table 3-4). Further studies in animals would be useful to determine the ability of acrolein to induce chromosomal aberrations after exposure. Cytogenetic analysis of peripheral lymphocytes of workers exposed to acrolein would provide an opportunity to assess its genotoxicity in humans.

Reproductive Toxicity. No studies were located regarding reproductive effects of acrolein in humans. No changes in reproductive organs of rats after intermediate and chronic oral exposures or in mice or dogs after chronic exposures were found during histopathological examination (Parent et al. 1991a, 1992a, 1992b). No reproductive effects were observed in rats after inhalation exposure to acrolein (Bouley et al. 1975). The results of a multi-generation oral exposure study in rats were also negative (King 1984). Although not reproduced in the main study, the statistically-untested results of a pilot dose-range study indicated increased fetal resorptions in rabbits after oral exposure to acrolein (Parent et al. 1993). Furthermore, dominant lethality was induced in mice exposed to acrolein by inhalation. These data indicated possible reproductive effects of acrolein exposure in animals, and further studies would be

useful to support these results. No data were located regarding reproductive effects in animals after dermal exposure, and the pharmacokinetic data are insufficient to draw any conclusion. Further studies of reproductive toxicity following dermal exposure in animals would be useful for extrapolating the results to human exposure.

Developmental Toxicity. No studies were located regarding developmental effects of acrolein in humans by any route of exposure. Increased incidences of skeletal anomalies and delayed ossification were observed in rats (King 1982) receiving oral exposures also resulting in frank toxicity to the dams. Developmental effects were not observed in rabbits exposed to oral dosing levels that did not result in maternal toxicity (Parent et al. 1993). These findings suggest that developmental effects of acrolein may be dependent on frank maternal toxicity. Results from parenteral administration in rats indicate that acrolein may cross the placenta (King 1982). This information is particularly relevant to individuals who are receiving the drug cyclophosphamide, of which acrolein is a metabolite. The developmental effects after inhalation or dermal exposure in animals were not studied. Pharmacokinetic data are insufficient to predict developmental effects after these routes of exposure. Further animal studies providing information on pre- and postnatal developmental toxicity of acrolein after oral, inhalation, and dermal exposure would be useful. The information is important for possible extrapolation of results to human exposure.

Immunotoxicity. Information regarding immunological effects of acrolein in humans is limited to a single case study (Rappaport and Hoffman 1941). No information regarding immunological effects in animals after oral or dermal exposure to acrolein was located. Acute and subchronic inhalation studies indicate that acrolein may increase the risk of bacterial infections in the respiratory tract (Aranyi et al. 1986; Bouley et al. 1975; Sherwood et al. 1986). Studies using a battery of immunotoxicity tests to correlate exposure intensity with specific end points of immune response would provide a more sensitive assessment of possible immunotoxic effects than histological examination of tissues and organs of the immune system. Since a possible case of an allergic response to acrolein derived from cigarette smoke was described in humans (Rappaport and Hoffman 1941), sensitization tests could help identify agents causing allergic responses in individuals exposed to tobacco smoke.

Neurotoxicity. No information was located regarding neurological effects of acrolein in humans. Symptoms of central nervous system depression were observed in rodents after oral exposure to acrolein, but only after lethal concentrations (Sprince et al. 1979). No such effects were observed in animals after inhalation exposure; the animals died from asphyxia caused by epithelial desquamation and,

consequently, respiratory obstruction (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). No behavioral changes were observed in animals exposed to acrolein by any route. Nonspecific histopathological effects on the brains of animals were found in subchronic inhalation studies (Feron et al. 1978; Kutzman et al. 1984, 1985; Lyon et al. 1970). No histopathological changes in neurological tissues were observed after oral exposure (Parent et al. 1991a, 1992a, 1992b). No studies regarding neurotoxicity of acrolein after dermal exposure were located. However, the available data do not indicate that the central nervous system is the major target of acrolein toxicity. No data needs have been identified at this time.

Epidemiological and Human Dosimetry Studies. The only information available concerning effects of acrolein in humans comes from two acute inhalation studies involving volunteers (Sim and Pattle 1957; Weber-Tschopp et al. 1977) and a limited number of cases of accidental inhalation (Bauer et al. 1977; Champeix et al. 1966; Gosselin et al. 1979) and dermal (Schöning 1966) exposures to unknown levels of acrolein (Champeix et al. 1966; Gosselin et al. 1979; Lacroix et al. 1976; Schöning 1966). In these cases, extremes in severity, either quickly reversible eye and respiratory irritation or severe burns of the eyes and respiratory tract mucosa (with some effects persisting for several months), were observed. No epidemiological studies are available. Epidemiology studies correlating the severity of end points such as respiratory and gastrointestinal epithelial metaplasia (obtained by histology of the pulmonary and gastric mucosa) with exposure intensity and duration are needed. Such studies would be useful for identifying effects of long term exposure to tolerable concentrations. This information would be useful for establishing the existence of a dose-response relationship for chronic human exposures and for monitoring individuals near hazardous waste sites for preventive purposes.

Biomarkers of Exposure and Effect.

Exposure. No reliable biomarkers of acrolein exposure have been identified. The finding of 3-hydroxy-propylmercapturic acid in the urine after exposure to acrolein or cyclophosphamide seemed to be promising for use as an exposure identifier (Kaye and Young 1974). However, further studies found no correlation between the amount of 3-hydroxypropylmercapturic acid in the urine and the dose of parent compound administered (Alarcon 1976). Parent et al. (1996a) identified several mercapturic acid metabolites in urine following oral doses in rats. Further identification of acrolein metabolites in the urine and their correlation with levels of exposure would be useful. Iype (1987) presented preliminary results in an abstract regarding the development of an antibody-mediated assay to monitor subjects exposed to acrolein; however, these data are not available in a full, peer-reviewed publication. This assay

exploits the possible formation of acrolein-adducted DNA in cells, or the formation of antibodies against such adducts in serum. Assays for acrolein-adducted DNA, thiols, and lysine could possibly be used to aid in etiology of respiratory diseases such as bronchitis, to which acrolein may be a contributor. Further studies regarding possible biochemical changes after acrolein exposure would be useful.

Effect. As with biomarkers for exposure, no studies were located for animals or humans that correlated the concentration of acrolein or its metabolites with toxic effects in target tissues. No biochemical or histological changes specific to acrolein exposure have been identified in humans or animals. Although transformation, and subsequent incorporation into macromolecules, of acrolein to acrylic acid has been identified (Patel et al. 1980b), no specific health effects of these reactions are known. Studies designed to correlate the appearance of adduction products and metabolites with increasingly severe acrolein-induced lesions may be useful in identifying "fingerprints" of metabolites to serve as biomarkers of effect.

Absorption, Distribution, Metabolism, and Excretion. There are no data available sufficient to derive the rates of acrolein absorption, distribution, metabolism, or excretion. Toxicokinetic data of acrolein are from the *in vivo* absorption study in dogs (Egle 1972) and rats (Morris 1996) and the oral exposure study in rats by Draminski et al. (1983) and Parent et al. (1996a), from which a possible metabolic pathways were proposed. However, dermal and inhalation exposures may very different absorption rates and lead to different metabolic pathways and patterns of distribution and excretion, which could account for differences in the degree of toxicity exhibited by different routes of exposure. The metabolism of acrolein *in vitro* seems to be well understood, including the reaction with glutathione (Patel et al. 1980b). This reaction represents an important mechanism for the protection of cells and tissues from the cytotoxic effects of acrolein. Determining the urinary excretion of acrolein conjugates in control volunteers and in individuals known to have been exposed to polluted environments could provide information concerning absorption and excretion of the xenobiotic. The use of human cell lines in culture might be considered a useful alternative to studying the metabolic fate of acrolein.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of acrolein *in vivo*. Differences in the toxicokinetics of a chemical among species may account for differences in toxic responses. Though similar inhalation effects have been observed in rats and humans (Cassee et al. 1996; Weber-Tschopp et al. 1977) at comparable exposure levels, the animal species that serves as the best model for extrapolating results to humans remains unknown. Although virtually no information is available regarding the toxicokinetics of acrolein in humans, analysis of the urine of

individuals occupationally exposed to the chemical would provide valuable information on absorption and excretion rates, provided that exposure to acrolein could be reasonably estimated.

Methods for Reducing Toxic Effects. Acrolein is known to react rapidly with nucleophilic groups in every type of tissue (Beauchamp et al. 1985). While systemic metabolism of acrolein to toxic metabolites has been proposed, animal studies (Morris 1996; Morris et al. 2003) and human case reports (Champeix et al. 1966; Gosselin et al. 1979) suggest that point-of-contact toxicity dominates the onset of adverse health effects. For this reason, simple dilution of acrolein at the point of tissue contact may provide the best protection against acrolein-induced injury and obviate the need for data concerning the reduction of toxic effects. Indeed, the standard treatments for inhalation, oral, and dermal acrolein exposures are provision of fresh air, ingestion of water, and copious rinsing with water, respectively (HSDB 2007). No data needs have been identified at this time.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

Although no data are available describing age-related differences in acrolein toxicity, acrolein is expected to affect children by the same mechanisms through which it affects adults. However, data are needed to determine if tissue-specific, age-related differences exist for glutathione levels, possibly resulting in an increased sensitivity to acrolein, particularly for respiratory effects. Children with asthma and reactive airway dysfunction may exhibit effects at levels different than adults with similar sensitivities.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A. Bhatnagar, University of Louisville, Louisville, Kentucky, is identifying and defining the cardiovascular effects (an example of subtle, low-dose effects) of environmental aldehydes and pollutants that generate aldehydes (FEDRIP 2006). The project will integrate molecular and cellular aspects of aldehyde toxicity, delineate the contribution of individual pathways involved in the detoxification of the aldehydes, and elucidate how aldehydes affect atherosclerosis, platelet and endothelial activation, and

myocardial function. Acrolein and trans-2-hexanal will be studied as model aldehydes most prevalent in the environment.

D. Dorman and H. Clewell, Chemical Industry Institute of Toxicology, are exposing rats subchronically to inhaled acrolein to characterize the dose-response for nasal pathology and nasal cell proliferation and evaluate the uptake of inhaled acrolein into nasal tissues (FEDRIP 2006). The results of these studies will be used to develop a computational fluid dynamic model, coupled to a PBPK model, to predict regional dosimetry and perform benchmark dose modeling using internal dosimetric predictions of the models.

D. Horohov and colleagues, Louisiana State University, are measuring immune responses of the respiratory tract in mice receiving intermediate-duration inhalation exposures to tobacco smoke or acrolein. Specifically, they will characterize the dose-response for allergic/asthmatic reactions, changes in pulmonary function, and changes in T-cell differentiation in the lung.

S. Hecht, University of Minnesota Medical School, will study a number of biomarkers of harm in blood and urine from tobacco exposure, including the mercapturic acids of acrolein (FEDRIP 2006). The findings will be used to design further studies aimed at developing harm reduction methods for tobacco-related cancer.

A. Van Der Vliet, University of Vermont, will investigate the effect of aldehydes, including acrolein, on neutrophil regulation pathways, particularly with regard to apoptosis and neutrophil-mediated phagocytic clearance and granule component release (FEDRIP 2006). Cultures of human neutrophils and a mouse pulmonary inflammation model will be utilized to identify specific cellular targets and acrolein-mediated protein modifications to cellular effects.

A. Bhatnagar, University of Louisville, Louisville, Kentucky, will expose low-density lipoprotein receptor-null mice to inhalation and dietary exposures of acrolein to determine the extent of atherogenecity and correlation with hypercholestremia (FEDRIP 2006). Acrolein-specific lipoprotein changes will be investigated and their atherogenic properties will be quantified.

B. Freed, University of Colorado at Denver, will identify the molecular mechanisms involved with smoking-induced immune suppression by studying the effects of acrolein on NFκB and AP-1 induction and interaction with their respective target promoters (CRISP 2006). Human peripheral blood and lymph node lymphocyte will be used in these studies.

S. D'Souza, University of Louisville, proposed that acrolein exposure may influence platelet and blood vessel endothelium interactions (CRISP 2006). Studies will be performed to evaluate processes involved with acrolein-induced platelet toxicity and the associated changes in platelet/endothelium interactions, including measurement of acrolein metabolite production. Specific changes in platelet activation and endothelium function will be investigated.

G. Liekauf, University of Cincinnati, will study the ability of acrolein to induce mucus hypersecretion (a common feature of COPD) in the murine lung (CRISP 2006). Research will include development of a mouse model acrolein-induced COPD, elucidating the role of neutrophil or macrophage/monocyte induction on mucus hypersecretion, and determination of genetic bases of individual susceptibility.

P. Russell, University of Louisville, will investigate the metabolism of acrolein and trans-2-hexanal in cardiovascular tissues of mice (CRISP 2006). The hypothesis that GST-mediated conjugation is the key metabolic pathway will be tested by identifying glutathione depletion, metabolite formation, and protein-acrolein adduct formation following oral or inhalation exposures to acrolein. The effects on acrolein metabolism from specific GST isoforms and hypercholestemia will be studied as well.

S. Prabhu, University of Louisville, will study the mechanisms underlying acrolein-induced changes to cardiac function and cardiac ischemic injury. Acute effects will be observed, including changes to contractile function and excitation-contraction coupling in isolated cardiac myocytes. Changes of acrolein-induced ischemic injury will be studied by observing the severity of myocardial infarction and changes in cardioprotective signaling associated with delayed ischemic preconditioning. Experiments to assess chronic myocardial inflammation will measure changes in NFκB activity and cytokine expression.