

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to acrolein. Its purpose is to present levels of significant exposure for acrolein based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of acrolein and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed.

Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike. Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of

2. HEALTH EFFECTS

extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

The only available information regarding lethal effects in humans after inhalation exposure to acrolein was provided by Gosselin et al. (1979), who described a case of a 4-year-old boy exposed to smoke containing acrolein from an overheated fryer for 2 hours; the boy's 2-year-old brother also died; however, no details were reported. After 24 hours, death occurred by asphyxia. The autopsy revealed massive cellular desquamation of the bronchial lining and miscellaneous debris in the bronchial lumen. Also, multiple pulmonary infarcts were observed. The information provided by this case report must be considered qualitative only, since smoke components other than acrolein may have contributed to the pathology.

Exposure of rats to concentrations of acrolein in the air higher than 7 ppm for short periods of time (<1 hour) caused death in approximately 1-11 days (Ballantyne et al. 1989; Catilina et al. 1966; Crane et al. 1986; Skog 1950). In all cases, death was attributed to severe effects on the respiratory tract including obstruction of trachea and bronchi, and pulmonary edema and hemorrhage. A single exposure to a low concentration of acrolein and repeated exposures to lower concentrations (3-4 ppm) caused death in rats and monkeys before the 10th day of exposure (Carpenter et al. 1949; Kutzman et al. 1984, 1985; Lyon et al. 1970). The cause of death was not reported for the rats, but in monkeys it was attributed to respiratory congestion. The data in experimental animals clearly indicate that the respiratory system is a primary target of acrolein exposure following inhalation and show an inverse relationship between the exposure concentration and the time it takes for death to occur after acute duration exposures. Furthermore, the information provided by animal data regarding cause of death is in good agreement with observations made in humans after accidental exposure (Champeix et al. 1966; Gosselin et al. 1979). Reliable values for lethality in experimental animals after inhalation exposure to acrolein are presented in Table 2-1 and Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to Acrolein - Inhalation

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) | | Reference |
|----------------|---------|---------------------------------|-------------------------|-------------|---|------------------------------|---------------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | |
| ACUTE EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 1 | Rat | 1 d 30 min/d | | | | 130 (LC ₅₀) | Skog 1950 |
| 2 | Rat | 62 d 5 d/wk 6 hr/d | | 1.4 | | 4.0 ^a | Kutzman et al. 1985 |
| 3 | Rat | 1 d 4 h/d | | | | 8 | Carpenter et al. 1949 |
| 4 | Rat | 1 d 10 min/d | | | | 327 (LC ₅₀) | Catilina et al. 1966 |
| 5 | Monkey | 6 wk 5 d/wk 8 hr/d | | 0.7 | | 3.7 ^a | Lyon et al. 1970 |
| Systemic | | | | | | | |
| 6 | Human | 1 d 40 min/d | Derm/Oc Resp Resp | | 0.17 ^{b,c} (eye irrit) 0.26 ^b (nose irrit) 0.43 ^b (throat irrit) | | Weber-Tschopp et al. 1977 |
| 7 | Human | 1 d 5-10 min | Derm/Oc | | 0.81 (eye irrit) | 1.22 (eye irrit) | Sim and Pattle 1957 |
| 8 | Human | 1 d 1 hr/d | Resp Derm/Oc | | 0.3 (decr resp rate) 0.3 (eye irrit) | | Weber-Tschopp et al. 1977 |
| 9 | Rat | 5 d 4 hr/d | Hepatic Other | | 4.0 (decr rel wt) 4.0 (decr body wt) | | Murphy et al. 1964 |
| 10 | Rat | 1 d 10 min/d | Resp | | | 327 (epithelial destruction) | Catilina et al. 1966 |
| 11 | Rat | 9 d 4 hr/d | Hepatic | | 3.9 (decr rel wt) | | Murphy et al. 1964 |

TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) | | Reference |
|---------------|---------|---------------------------------|-----------------|-------------|--------------------------------------|--|-------------------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | |
| Systemic | | | | | | | |
| 12 | Rat | 1 d 4 hr/d | Resp | | 12 (resp irrit) | | Murphy et al. 1964 |
| 13 | Rat | 1 d 30 min/d | Resp Derm/Oc | | | 130 (lung hemorrhage) 130 (sev irrit) | Skog 1950 |
| 14 | Rat | 20-81 hr | Hepatic | 1.0 | 2.1 ^a (incr wt) | | Murphy et al. 1964 |
| 15 | Mouse | 1 d 30 min/d | Resp | | 2.9 (RD ₅₀) | | Nielsen et al. 1984 |
| 16 | Mouse | 1 d 10 min/d | Resp | | 1.41 (RD ₅₀) | | Steinhagen and Barrow 1984 |
| 17 | Mouse | 5 d 6 hr/d | Resp | | 1.7 ^a (RD ₅₀) | | Buckley et al. 1984 |
| 18 | Mouse | 1 d 10 min/d | Resp | | 1.03 (RD ₅₀) | | Steinhagen and Barrow 1984 |
| 19 | Mouse | 4 d 3 hr/d | Resp | | 1.7 (RD ₅₀) | | Kane and Alarie 1977 |
| 20 | Gn pig | 1 d 2 hr/d | Resp | 0.6 | | | Murphy et al. 1963 |
| 21 | Gn Pig | 1 d 60 min/d | Resp | | 17 (decr resp rate) | | Davis et al. 1967 |
| Immunological | | | | | | | |
| 22 | Mouse | 5 d 3 hr/d | | | 0.1 ^a (decr resistance) | | Aranyi et al. 1986 |
| 23 | Mouse | 1 d 8 hr/d | | | 3 (decr resistance) | | Astry and Jakob 1983 |

TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) | | Reference |
|-----------------------|---------|---------------------------------|-----------------------------------|-------------|---|-----------------------|--------------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | |
| INTERMEDIATE EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 24 | Rat | 90 d 7 d/wk 24 hr/d | | 1.8 | | | Lyon et al. 1970 |
| 25 | Mouse | 5 wk 1 hr/d | | 44 | | | Watanabe and Aviado 1974 |
| 26 | Gn Pig | 6 wk 5 d/wk 8 hr/d | | 3.7 | | | Lyon et al. 1970 |
| 27 | Hamster | 13 wk 5 d/wk 6 hr/d | | 4.9 | | | Feron et al. 1978 |
| 28 | Monkey | 90 d 7 d/wk 24 hr/d | | 1.8 | | | Lyon et al. 1970 |
| Systemic | | | | | | | |
| 29 | Rat | 13 wk 5 d/wk 6 hr/d | Resp Cardio Hemato Renal | 1.4 4.9 | 0.4 ^{a,d} (metaplasia) 4.9 (incr hrt wt) 4.9 (incr kdy wt) | 4.9 (lung hemorrhage) | Feron et al. 1978 |
| 30 | Rat | 6 wk 5 d/wk 8 hr/d | Resp Renal Derm/Oc Other | 3.7 3.7 | 0.7 (lung inflammation) 3.7 (decr bw gain) | | Lyon et al. 1970 |
| 31 | Rat | 3 wk 5 d/wk 6 hr/d | Resp Other | | 3.0 (epithelial dysplasia) 3.0 (decr bw gain) | | Leach et al. 1987 |

TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) | | Reference |
|------------|---------|---------------------------------|--|---------------------------------|---|--|------------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | |
| Systemic | | | | | | | |
| 32 | Rat | 62 d 5 d/wk 6 hr/d | Resp Cardio Hepatic Other | 1.4 1.4 | 0.4 (inflammation) 4.0 (incr heart wt) 4.0 (incr liver wt) 4.0 (decr bw gain) | 4.0 ^a (squamous metaplasia) | Kutzman et al. 1984 |
| 33 | Rat | >60<180d 7 d/wk 24 hr/d | Resp Other | | 0.55 (incr lung wt) 0.55 (decr bw gain) | | Bouley et al. 1975 |
| 34 | Rat | 62 d 5 d/wk 6 hr/d | Resp Other | | 1.4 (lung hyperplasia) 4.0 (decr bw gain) | 4.0 (lung edema and decr func) | Costa et al. 1986 |
| 35 | Rat | 62 d 5 d/wk 6 hr/d | Resp Cardio Renal Other | | 1.4 (bronchiolar inflammation) 4.0 (incr heart wt) 4.0 (incr kdy wt) 4.0 (decr bw gain) | 4.0 (bronchiolar necrosis) | Kutzman et al. 1985 |
| 36 | Gn Pig | 90 d 7 d/wk 24 hr/d | Resp Cardio Hepatic | 0.22 1.8 0.22 | 1.0 (lung inflammation) 1.0 (liver inflammation) | | Lyon et al. 1970 |
| 37 | Gn Pig | 6 wk 5 d/wk 8 hr/d | Resp Hemato Renal Derm/Oc Other | | 0.7 ^a (lung inflammation) 3.7 3.7 3.7 3.7 | | Lyon et al. 1970 |
| 38 | Hamster | 13 wk 5 d/wk 6 hr/d | Resp Cardio Hemato Hepatic Renal Derm/Oc Other | 0.4 1.4 4.9 1.4 1.4 | 1.4 (epithelial inflammation) 4.9 (incr hrt wt) 4.9 (incr PCV) 4.9 (incr kdy wt) 4.9 (sens irrit) 4.9 (decr bw gain) | 4.9 (tracheal metaplasia) | Feron et al. 1978 |

TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) | | Reference |
|---------------|---------|---------------------------------|--|--------------------------|--------------------------------------|-----------------------|----------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | |
| Systemic | | | | | | | |
| 39 | Monkey | 6 wk 5 d/wk 8 hr/d | Resp Hemato Hepatic Renal Derm/Oc Other | 3.7 3.7 3.7 0.7 | 0.7 ^a (lung inflammation) | 3.7 (lung hemorrhage) | Lyon et al. 1970 |
| 40 | Monkey | 90 d 7 d/wk 24 hr/d | Resp Cardio Derm/Oc Other | 1.8 1.8 | 1.8 (tracheal hyperplasia) | 1.8 (sev eye irrit) | Lyon et al. 1970 |
| Immunological | | | | | | | |
| 41 | Rat | 3 wk 5 d/wk 6 hr/d | | 3.0 | | | Sherwood et al. 1986 |
| 42 | Rat | 3 wk 5 d/wk 6 hr/d | | 3.0 | | | Leach et al. 1987 |
| Neurological | | | | | | | |
| 43 | Rat | 62 d 5 d/wk 6 hr/d | | | 4.0 (incr brain wt) | | Kutzman et al. 1984 |
| 44 | Rat | 90 d 7 d/wk 24 hr/d | | 1.8 | | | Lyon et al. 1970 |
| 45 | Gn Pig | 90 d 7 d/wk 24 hr/d | | 1.8 | | | Lyon et al. 1970 |
| 46 | Hamster | 13 wk 5 d/wk 6 hr/d | | 4.9 | | | Feron et al. 1978 |

TABLE 2-1 (Continued)

| Figure Key | Species | Exposure Frequency/ Duration | Effect | NOAEL (ppm) | LOAEL (Effect) | | Reference |
|------------------|---------|---------------------------------|---------------|-------------|---|---------------|-------------------------|
| | | | | | Less Serious (ppm) | Serious (ppm) | |
| Neurological | | | | | | | |
| 47 | Monkey | 90 d 7 d/wk 24 hr/d | | 1.8 | | | Lyon et al. 1970 |
| Reproductive | | | | | | | |
| 48 | Rat | >60<180d 7 d/wk 24 hr/d | | 0.55 | | | Bouley et al. 1975 |
| CHRONIC EXPOSURE | | | | | | | |
| Death | | | | | | | |
| 49 | Hamster | 52 wk 5 d/wk 7 hr/d | | 4 | | | Feron and Krusysse 1977 |
| Systemic | | | | | | | |
| 50 | Rat | 10-18 mo 7 d/wk 1 hr/d | Resp Other | 8 | 8 (hyperplasia) | | Le Bouffant et al. 1980 |
| 51 | Hamster | 52 wk 5 d/wk 7 hr/d | Resp Other | | 4 (epithelial metaplasia) 4 (decr bw gain) | | Feron and Krusysse 1977 |

^aPresented in Table 1-2.

^bPresented in Table 1-1.

^cUsed to derive an acute inhalation MRL of 0.00005 ppm, which is presented in Table 1-1; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL).

^dUsed to derive an intermediate inhalation MRL of 0.000009 ppm, which is presented in Table 1-1; dose adjusted for intermittent exposure and divided by an uncertainty factor of 1000 (10 for extrapolation from animals to humans, 10 for human variability, and 10 for use of a LOAEL).

bw = body weight; Cardio = cardiovascular; d = day; decr = decreased; Derm/Oc = dermal/ocular; func = function; Gn Pig = guinea pig; Hemato = hematological; his = histology; hr = hour; hrt = heart; incr = increased; irrit = irritation; kdy = kidney; LC₅₀ = concentration in the air that caused death to 50% of the animals; mo = month; PCV = packed cell volume; RD₅₀ = concentration in the air that caused 50% reduction in respiratory rate; rel = relative; Resp = respiratory; sens = sensory; sev = severe; wk = week; wt = weight.

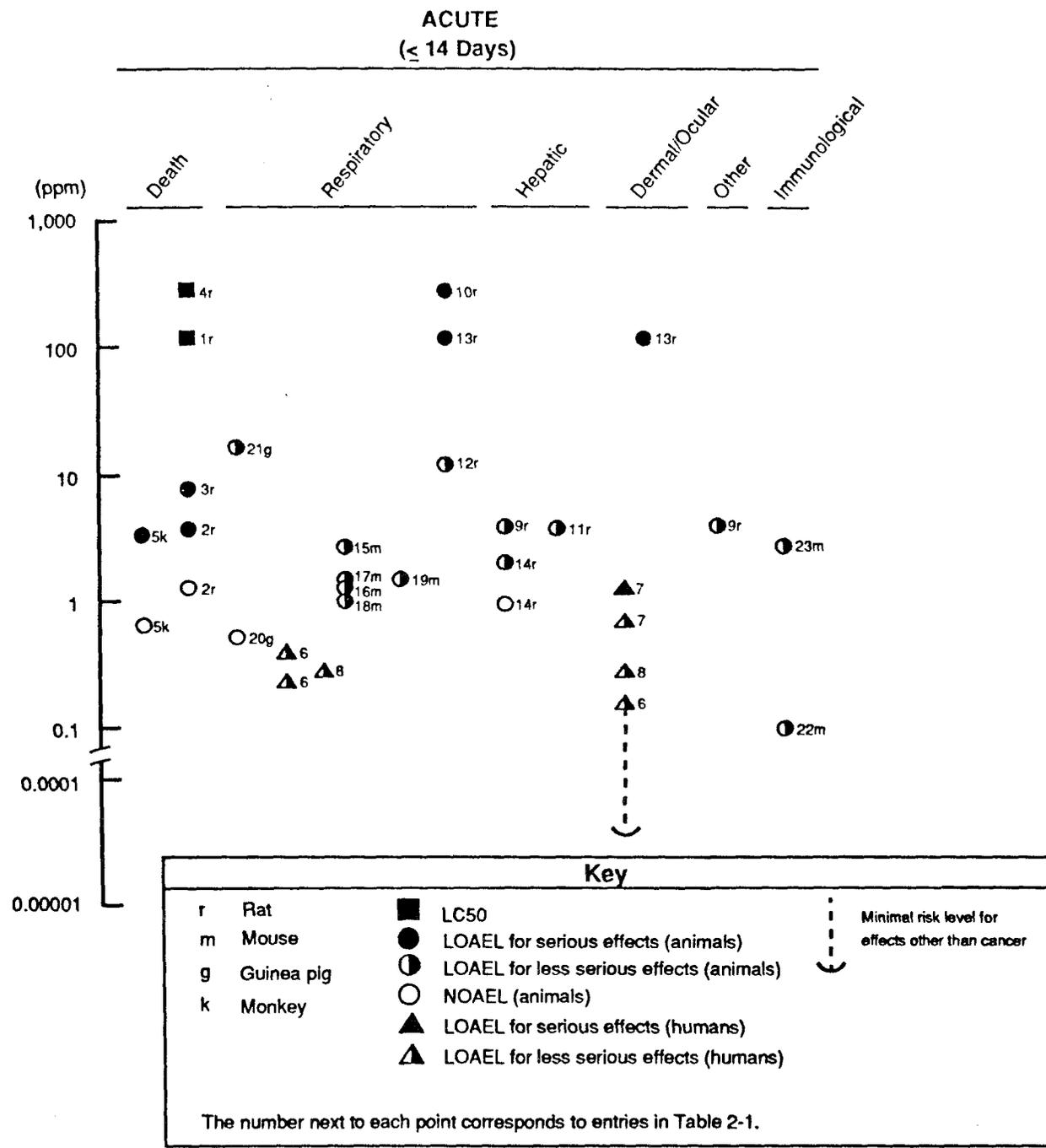


FIGURE 2-1. Levels of Significant Exposure to Acrolein - Inhalation

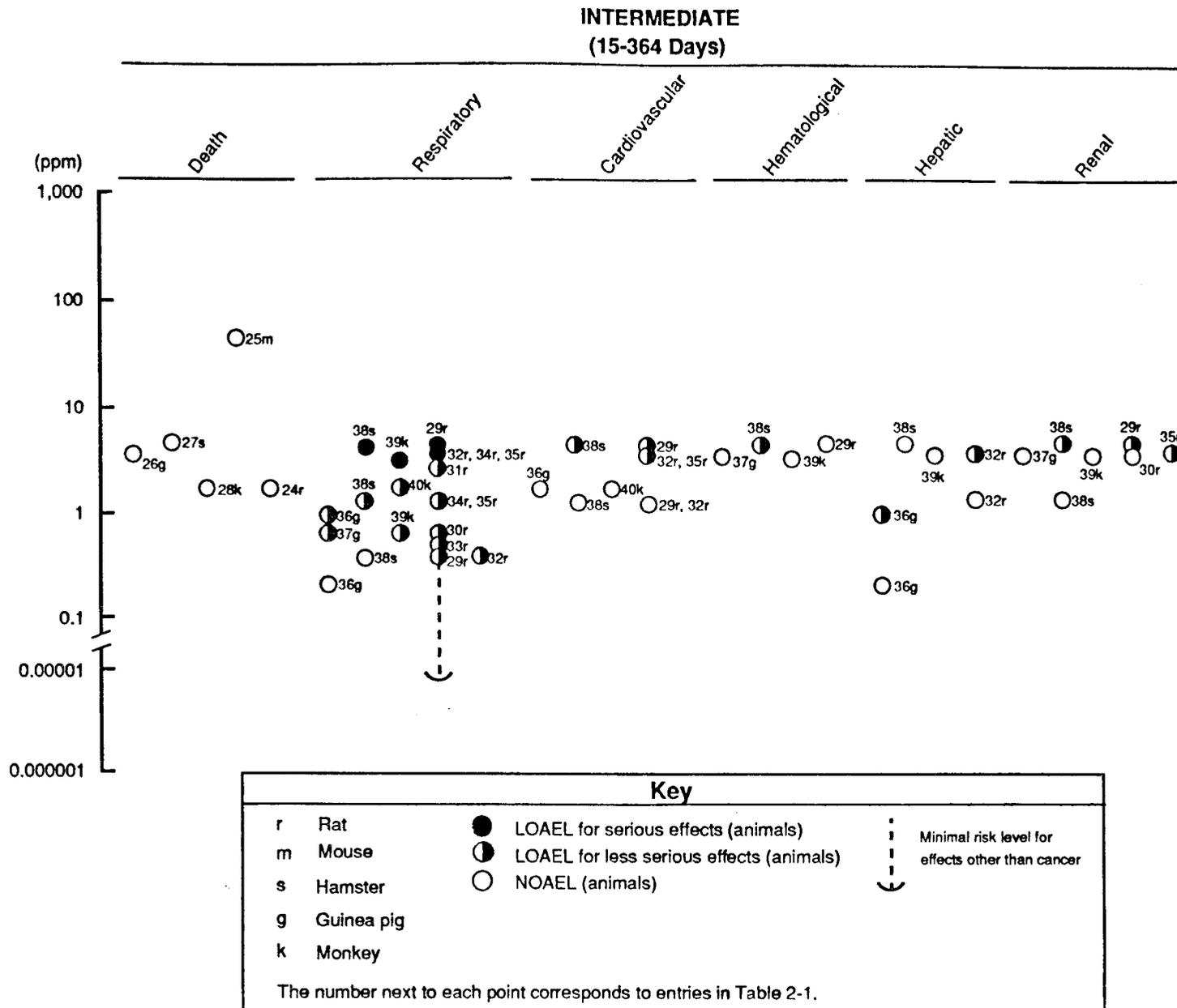
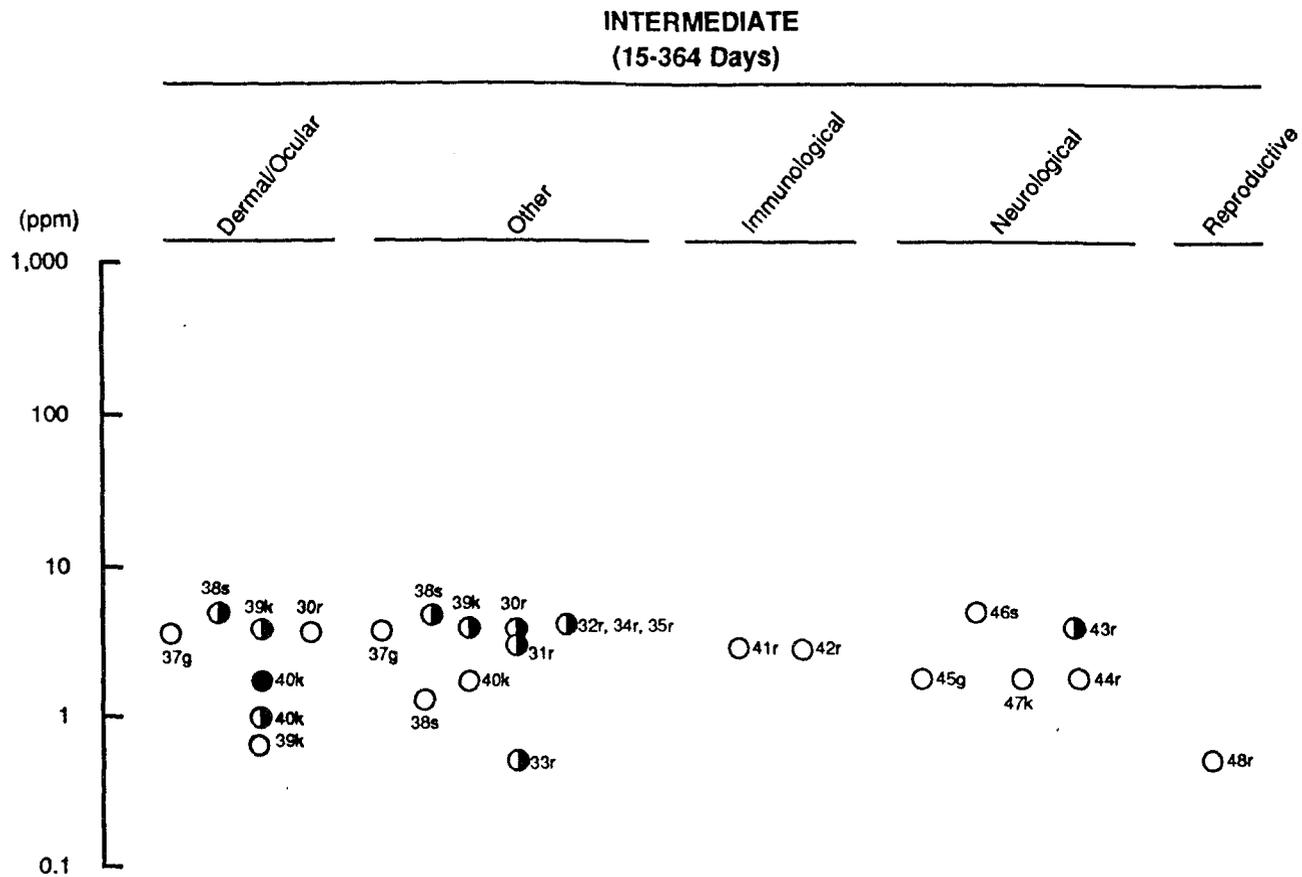


FIGURE 2-1 (Continued)



| Key | | | |
|------------|------------|---|--|
| r | Rat | ● | LOAEL for serious effects (animals) |
| s | Hamster | ◐ | LOAEL for less serious effects (animals) |
| g | Guinea pig | ○ | NOAEL (animals) |
| k | Monkey | | |

The number next to each point corresponds to entries in Table 2-1.

FIGURE 2-1 (Continued)

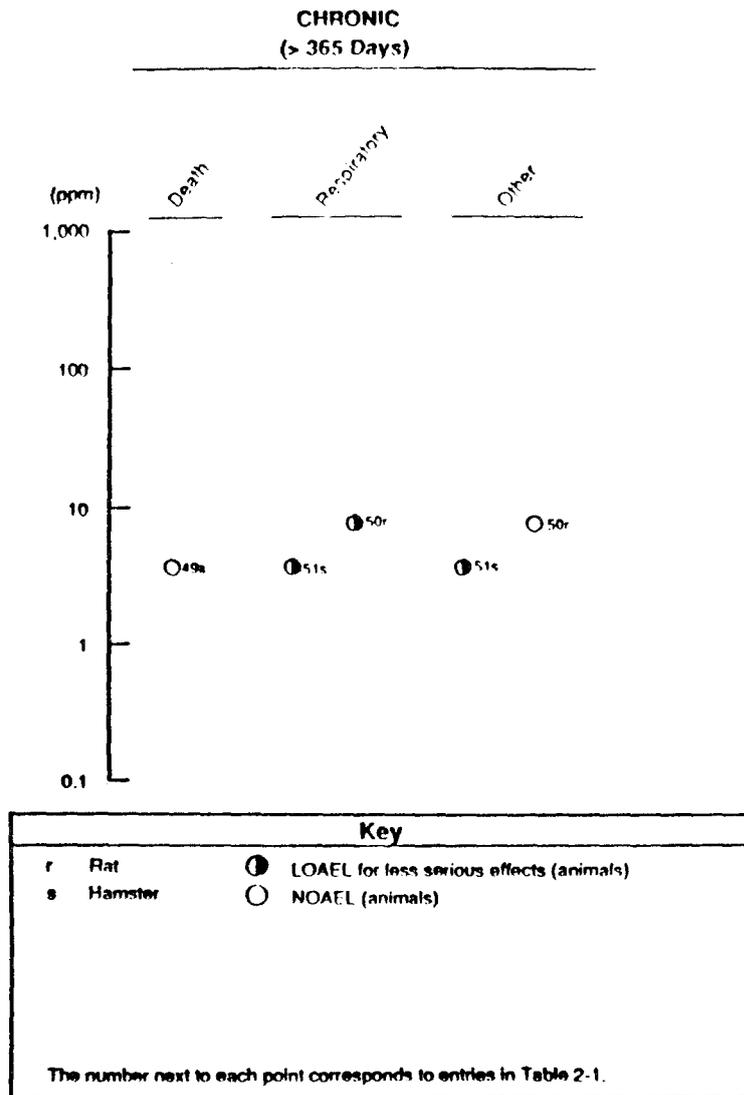


FIGURE 2-1 (Continued)

2. HEALTH EFFECTS

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans after inhalation exposure to acrolein.

Respiratory Effects. Champeix et al. (1966) reported that a 36-year old male was accidentally exposed to acrolein vapors in the workplace (duration of exposure was not reported, but is presumed to be less than 1 day). The most relevant signs and symptoms noticed were high fever, dyspnea, coughing, foamy expectoration, cyanosis, and pulmonary edema. Eighteen months after the exposure, the chronic pneumopathy, bronchitis, and emphysema persisted. Similar respiratory effects were observed by Bauer et al. (1977) on a 21-year-old male exposed to smoke from an overheated pan for 6 hours. It was assumed that acrolein was the main component of the smoke, although other components may have contributed to the symptoms.

In a study conducted with volunteers, a 20% decrease in respiratory rate was seen after an acute exposure to a low-level concentration of acrolein; throat irritation occurred after 10 minutes (Weber-Tschopp et al. 1977). In the same study, the concentration of acrolein in the air was gradually increased from 0 to 0.6 ppm during 35 minutes and was kept at that level for an additional 5 minutes. In this case, there was a 25% decrease in respiratory rate at 0.6 ppm, and throat irritation was noticed at 0.43 ppm. 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). In the case reported by Gosselin et al. (1979), death was presumably caused by inhalation of acrolein from an overheated fryer. Cellular desquamation of the bronchial lining and miscellaneous debris in the bronchial lumen were observed.

Several studies reported acute effects of acrolein in experimental animals; generally, the results confirm information provided by the lethality studies that acrolein is a highly selective respiratory toxicant. Exposure of rodents to low concentrations of acrolein for several minutes induced a reflex decrease in respiratory rate by activation of the sensory nerve endings in the nasal mucosa (Alarie 1973; Davis et al. 1967; Kane and Alarie 1977; Nielsen et al. 1984; Steinhagen and Barrow 1984). In all species examined (mice, rats, guinea pigs, hamsters, and dogs), exposure to concentrations of 1.7 ppm or more induced moderate to severe histological alterations of the respiratory epithelium (Buckley et al. 1984; Catilina et al. 1966; Dahlgren et al. 1972; Feron et al. 1978; Hales et al. 1988; Kilburn and Mackenzie 1978; Murphy et al. 1964; Skog 1950). In addition, low levels of exposure to 0.1-2.5 ppm caused biochemical alterations in the nasal respiratory mucosa of rats, but the toxicological significance of this finding is unclear (Lam et al. 1985). Bronchial responsiveness, assessed by changes in pulmonary resistance, was increased in guinea pigs exposed to

2. HEALTH EFFECTS

0.3-1.3 ppm acrolein for 2 hours (Leikauf et al. 1989). This increase, however, was not accompanied by a simultaneous increase in neutrophil infiltration, which the authors took to suggest that cells other than neutrophils are responsible for the increase in bronchial responsiveness.

Studies regarding respiratory effects after intermediate duration exposure of humans to acrolein were not located in the available literature. In experimental animals, histological alterations in the respiratory tract appear to be common. Repeated exposures to acrolein concentrations between 0.2 and 5.0 ppm for up to 180 days caused moderate to severe epithelial damage in the bronchi and lungs of rats (Costa et al. 1986; Kutzman et al. 1984, 1985; Lyon et al. 1970), monkeys, guinea pigs, and dogs (Lyon et al. 1970), and rabbits and hamsters (Feron et al. 1978). In general, as indicated in Table 2-1 and Figure 2-1, the severity of the effects increased as the concentration of acrolein increased. An intermediate MRL was derived from the less serious LOAEL identified in the Feron et al. (1978) study.

Studies regarding the respiratory effects of chronic exposure to acrolein in humans were not located in the literature. In the chronic exposure study in rats (Le Bouffant et al. 1980), occasional emphysematous areas were seen in the alveoli after 18 months of exposure to 8 ppm acrolein; however, the animals were only exposed to acrolein vapors for 1 hour/day, 7 days/week. Hamsters exposed to 4.0 ppm acrolein 7 hours/day, 5 days/week for 52 weeks developed inflammation and epithelial metaplasia in the nasal cavity, with a few animals exhibiting exudation in the lumen (Feron and Krusysse 1977). Approximately 20% of the animals killed at week 81, after a recovery period of about 6 months, still showed treatment-related effects in the nasal cavity.

The overall evidence from acute, intermediate, and chronic duration studies in experimental animals indicates that the respiratory system is a target for acrolein. These results agree with the clinical picture observed in a case of accidental human exposure to acrolein, in which the respiratory effects were prevalent and persisted for several months after exposure (Champeix et al. 1966). Furthermore, from the animal data available, no species appears to be especially sensitive to acrolein since similar effects were seen in all species tested with comparable acrolein concentrations. The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Cardiovascular Effects. As previously indicated, studies regarding cardiovascular effects in humans after intentional inhalation exposure to acrolein were not located in the literature. No cardiovascular effects were observed in a case of accidental exposure to acrolein vapors (the concentration of acrolein or the duration of exposure was not reported) (Champeix et al. 1966).

2. HEALTH EFFECTS

In experimental animals, the cardiovascular system does not appear to be a target for acrolein. Nonspecific inflammatory lesions in the heart were reported in rats, dogs, monkeys, and guinea pigs after intermediate duration exposure to similar concentrations of acrolein (Lyon et al. 1970). Also, an increase in relative heart weight was observed in hamsters and rats exposed to 4.9 ppm of acrolein (Feron et al. 1978).

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

Hematological Effects. As previously mentioned, no studies regarding hematological effects in humans after inhalation exposure to acrolein were located in the literature. No remarkable hematological alterations were described in a case of accidental exposure to acrolein vapors (Champeix et al. 1966).

The weight of evidence indicates that the hematological system is not asensitive indicator of acrolein toxicity in laboratory animals. In general, intermediate duration exposure had no adverse hematological effects in rats, guinea pigs, dogs, male hamsters, and monkeys (Feron et al. 1978; Lyon et al. 1970). Increased numbers of erythrocytes, hemoglobin, and lymphocytes were observed in female hamsters exposed at 4.9 ppm (Feron et al. 1978). No acute or chronic studies were located regarding hematological effects of acrolein. The highest NOAEL values and all reliable LOAEL values for hematological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

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

Hepatic Effects. No studies regarding hepatic effects in humans after inhalation exposure to acrolein were located in the literature. No hepatic alterations were described in a case of accidental exposure to acrolein vapors (Champeix et al. 1966).

In general, the liver does not appear to be a target organ for acrolein in experimental animals. Effects reported in rats after acute exposure to low concentrations (4-8 ppm) of acrolein consisted of increases in enzyme activities and changes in liver/body weight ratio; however, these changes could represent adaptive responses (Murphy 1965; Murphy et al. 1964). One report was found describing liver necrosis (minute foci without a specific pattern) in 3 of 9 rats after intermediate duration exposure to 1.0 ppm acrolein, but this effect was not noticed at a higher concentration (Lyon et al. 1970). As seen in Table 2-1 and Figure 2-1, no adverse liver effects were seen in hamsters, rabbits, monkeys, dogs, and guinea pigs exposed to 4.9 ppm acrolein or less. The highest NOAEL values and all reliable LOAEL

2. HEALTH EFFECTS

values for hepatic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Renal Effects. No studies regarding renal effects in humans after inhalation exposure to acrolein were located in the literature. A normal urinalysis was reported in a case of accidental exposure to acrolein vapors (Champeix et al. 1966).

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. The overall evidence suggests that the kidney is not a target for acrolein. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Dermal/Ocular Effects. Volunteers had eye irritation after exposure to 0.6 ppm acrolein for 7.5 minutes or to 0.17 ppm for approximately 1 hour (Weber-Tschopp et al. 1977). 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 that 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. Reliable LOAELs for dermal/ocular effects in humans are presented in Table 2-1 and Figure 2-1. Data from the Weber-Tschopp et al. (1977) study were used as a basis for an acute inhalation MRL.

The dermal/ocular effects observed in experimental animals are qualitatively similar to those described in humans. Concentrations of acrolein higher than 1.0 ppm (1.8-3.7 ppm) caused eye irritation in dogs and monkeys, 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 discharges are commonly seen (Murphy et al. 1964; Skog 1950). The highest NOAEL values and all reliable LOAEL values for dermal/ocular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Other Systemic Effects. Data regarding other systemic effects in humans after inhalation exposure to acrolein were not located in the literature. Decreased body weights and increased adrenal weights after acute exposures were reported in rats (Murphy et al. 1964). In intermediate duration studies, depressed body weight gains were reported in rats, hamsters, monkeys, and rabbits (Bouley et al. 1975; Feron et al. 1978; Kutzman et al. 1985; Leach et al. 1987; Lyon et al. 1970). In the absence of information regarding food intake, the significance of these findings is unclear.

2. HEALTH EFFECTS

2.2.1.3 Immunological 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; Astry and Jakab 1983; Bouley et al. 1975). It is conceivable, however, that this is not a true immunological effect but results from the destruction by acrolein of the respiratory epithelium and its inherent defense mechanisms. The immunotoxicity of acrolein after inhalation exposure was tested in rats using several immunoassays (Leach et al. 1987; Sharwood et al. 1986). Negative results were obtained with exposures up to 3 ppm for 3 weeks in both studies. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

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

Concentrations of acrolein between 22 and 249 ppm for 10 minutes induced a dose-related decrease in substance P 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. Springall et al. (1990) indicate that acrolein may induced release of peptides that could play a role in the physiological response to irritants.

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 noticed in rats, guinea pigs, dogs, and monkeys at comparable concentrations of acrolein. Based on the evidence available, it does not appear that the nervous system is a target for acrolein.

2.2.1.5 Developmental Effects

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

2.2.1.6 Reproductive Effects

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

2. HEALTH EFFECTS

A single study was 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 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 diminishes the impact of the reproductive assessment derived from this study.

2.2.1.7 Genotoxic Effects

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

2.2.1.8 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 Krusysse (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. Le Bouffant et al. (1980) exposed rats for 10-18 months to 8 ppm acrolein for 1 hour/day, 7 days/week and reported no evidence of tumors in the respiratory tract or in other tissues and organs.

2.2.2 Oral Exposure

2.2.2.1 Death

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

The oral LD₅₀ 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/d and in rabbits treated with 4 mg/kg/d during gestational days 7-19 (Hoberman 1987; King 1982). In contrast, no increase in deaths was observed in a two-generation reproductive study, in which rats were treated by gavage with 7.2 mg/kg/d (King 1984). Similarly, the overall survival rate was not affected in rats chronically exposed to 2.5 mg/kg/d and in dogs exposed to 2 mg/kg/d (Long 1987; Long and Johnson 1988). Decreased survival was, however, reported in

2. HEALTH EFFECTS

male mice chronically treated with 4.5 mg/kg/d acrolein by gavage (Long and Johnson 1989). Chronic exposure of rats to 36 mg/kg/d or less of acrolein via the drinking water did not affect mortality (Lijinsky and Reuber 1987). From these limited data, presented in Table 2-2 and Figure 2-2, it appears that acrolein is more lethal if administered via gavage than via drinking water. This is probably the result of the dose being administered all at once rather than throughout the day. although intubation errors or aspiration of the injected bolus cannot be ruled out. Another factor that must be considered is the stability of acrolein in drinking water.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular effects in humans after oral exposure to acrolein. However, studies were located regarding these endpoints 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 2-2 and plotted in Figure 2-2.

Respiratory Effects. No histopathological changes were observed in the respiratory systems of rats after intermediate-duration exposure to 7.2 mg/kg/d (King 1984). Similarly, no changes were observed during histopathological examination of respiratory tract tissues from rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) chronically exposed to 2.5, 4.5, or 2 mg/kg/d, respectively.

Cardiovascular Effects. Histopathological examination of the cardiovascular system revealed no effects after intermediate-duration exposure to acrolein in rats or after chronic exposure in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987).

Gastrointestinal Effects. Rats administered a single gavage dose of 25 mg/kg of acrolein in saline showed severe gastrointestinal effects that included multifocal ulceration of the forestomach and glandular stomach 48 hours after dosing. The areas of ulceration showed severe inflammation, focal hemorrhage, and edema (Sakata et al. 1989). Gastric mucosa ulcerations were also observed in rabbits exposed to 4 mg/kg/d during gestational days 7-19 (Hoberman 1987). Similar findings were reported in rats after an intermediate-duration exposure to 5.4 mg/kg/d (King 1984). No significant gastrointestinal effects of acrolein exposure, however, were reported in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after chronic dosing with 2.5, 4.5, or 2 mg/kg/d, respectively.

Hematological Effects. No hematological effects were observed in rats after intermediate-duration exposure to 7.2 mg/kg/d acrolein (King 1984). In contrast, hematocrit values were decreased in rats exposed to 0.05 mg/kg/d acrolein or more for 6 months (Long and Johnson 1988). The values

TABLE 2-2. Levels of Significant Exposure to Acrolein - Oral

| Figure Key | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/d) | LOAEL (Effect) | | Reference |
|----------------|---------|-------|---------------------------------|-----------------|--------------------|---------------------------------|---|------------------------|
| | | | | | | Less Serious (mg/kg/d) | Serious (mg/kg/d) | |
| ACUTE EXPOSURE | | | | | | | | |
| Death | | | | | | | | |
| 1 | Rat | (G) | Gd 7-19 1x/d | | 6 | | 10 (14/40 died) | King 1982 |
| 2 | Rat | (W) | ND | | | | 46 (LD ₅₀) | Smyth et al. 1951 |
| 3 | Rat | (G) | 1x | | | | 11.2 ^a | Sprince et al. 1979 |
| 4 | Rat | (G) | 1x | | | | 25 | Sakata et al. 1989 |
| 5 | Rabbit | (G) | Gd 7-19 1x/d | | 2 | | 4 | Hoberman 1987 |
| Systemic | | | | | | | | |
| 6 | Rat | (G) | 1x | Gastro | | | 25 (stomach ulceration) | Sakata et al. 1989 |
| 7 | Rat | (G) | Gd 7-19 1x/d | Other | 3.6 | 6 (decreased body wt gain) | | King 1982 |
| 8 | Rabbit | (G) | Gd 7-19 1x/d | Gastro Other | 2 | 0.5 (decreased body wt gain) | 4 ^b (gastric ulceration) | Hoberman 1987 |
| Developmental | | | | | | | | |
| 9 | Rat | (G) | Gd 7-19 1x/d | | 6 | | 10 ^c (decreased litter wt, increased skeletal anomalies) | King 1982 |
| 10 | Rabbit | (G) | Gd 7-19 1x/d | | 0.5 | | 1 (fetal resorptions) | Hoberman 1987 |

TABLE 2-2 (Continued)

| Figure Key | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/d) | LOAEL (Effect) | | Reference |
|-----------------------|---------|-------|---------------------------------|---|--|--|------------------------------------|-----------------------------|
| | | | | | | Less Serious (mg/kg/d) | Serious (mg/kg/d) | |
| Reproductive | | | | | | | | |
| 11 | Rat | (G) | Gd 7-19 1x/d | | 10 | | | King 1982 |
| 12 | Rabbit | (G) | Gd 7-19 1x/d | | 0.5 | | 1 ^d (fetal resorptions) | Hoberman 1987 |
| INTERMEDIATE EXPOSURE | | | | | | | | |
| Death | | | | | | | | |
| 13 | Rat | (G) | 115 d 1x/d | | 7.2 | | | King 1984 |
| Systemic | | | | | | | | |
| 14 | Rat | (G) | 115 d 1x/d | Resp Cardio Gastro | 7.2 7.2 4 | 5.4 (stomach ulcerations) | | King 1984 |
| | | | | Hemato Musc/skel Hepatic Renal Derm/Oc Other | 7.2 7.2 7.2 7.2 7.2 5.4 | 7.2 (decreased body wt in F ₀ generation) | | |
| Reproductive | | | | | | | | |
| 15 | Rat | (G) | 115 d 1x/d | | 7.2 | | | King 1984 |
| CHRONIC EXPOSURE | | | | | | | | |
| Death | | | | | | | | |
| 16 | Rat | (W) | 104-124 wk 5 d/wk | | 36 | | | Lijinsky and Reuber 1987 |

TABLE 2-2 (Continued)

| Figure Key | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/d) | LOAEL (Effect) | | Reference |
|------------|---------|-------|---------------------------------|---|---|---|----------------------|-----------------------|
| | | | | | | Less Serious (mg/kg/d) | Serious (mg/kg/d) | |
| Death | | | | | | | | |
| 17 | Rat | (G) | 24 mo 7d/wk 1x/d | | 2.5 | | | Long and Johnson 1988 |
| 18 | Mouse | (G) | 18 mo 7d/wk 1x/d | | 2.0 | | 4.5 ^e | Long and Johnson 1989 |
| 19 | Dog | (C) | 12 mo 7d/wk 1x/d | | 2.0 | | | Long 1987 |
| Systemic | | | | | | | | |
| 20 | Rat | (G) | 24 mo 7d/wk 1x/d | Resp Cardio Gastro Hemato | 2.5 2.5 2.5 0.05 ^f | 0.5 ^g (decreased monocytes in females) | | Long and Johnson 1988 |
| | | | | Musc/skel Hepatic Renal Derm/Oc Other | 2.5 2.5 2.5 2.5 2.5 | | | |
| 21 | Mouse | (G) | 18 mo 7d/wk 1x/d | Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/Oc Other | 4.5 4.5 4.5 4.5 4.5 4.5 4.5 4.5 0.5 | 2.0 (decreased body wt gain) | | Long and Johnson 1989 |

TABLE 2-2 (Continued)

| Figure Key | Species | Route | Exposure Frequency/ Duration | Effect | NOAEL (mg/kg/d) | LOAEL (Effect) | | Reference |
|--------------|---------|-------|---------------------------------|-----------|--------------------|---------------------------|----------------------|-----------------------------|
| | | | | | | Less Serious (mg/kg/d) | Serious (mg/kg/d) | |
| 22 | Dog | (C) | 12 mo 7d/wk 1x/d | Resp | 2.0 | | | Long 1987 |
| | | | | Cardio | 2.0 | | | |
| | | | | Gastro | 2.0 | | | |
| | | | | Hemato | 2.0 | | | |
| | | | | Musc/skel | 2.0 | | | |
| | | | | Hepatic | 2.0 | | | |
| | | | | Renal | 2.0 | | | |
| | | | | Derm/Oc | 2.0 | | | |
| | | | | Other | 2.0 | | | |
| Reproductive | | | | | | | | |
| 23 | Rat | (G) | 24 mo 7d/wk 1x/d | | 2.5 | | | Long and Johnson 1988 |
| 24 | Mouse | (G) | 18 mo 7d/wk 1x/d | | 4.5 | | | Long and Johnson 1989 |
| 25 | Dog | (C) | 12 mo 7d/wk 1x/d | | 2.0 | | | Long 1987 |
| Cancer | | | | | | | | |
| 26 | Rat | (W) | 104-124 wk 5d/wk | | | | 36 (CEL) | Lijinsky and Reuber 1987 |

^aConverted to an equivalent concentration of 80 ppm in water for presentation in Table 1-4.

^bConverted to an equivalent concentration of 36 ppm in water for presentation in Table 1-4.

^cConverted to an equivalent concentration of 72 ppm in water for presentation in Table 1-4.

^dConverted to an equivalent concentration of 9 ppm in water for presentation in Table 1-4.

^eConverted to an equivalent concentration of 24 ppm in water for presentation in Table 1-4.

^fUsed to derive a chronic oral Minimal Risk Level (MRL) of 0.0005 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability). This MRL has been converted to an equivalent concentration in water (0.02 ppm) for presentation in Table 1-3.

^gConverted to an equivalent concentration of 4 ppm in water for presentation in Table 1-4.

(C) = capsule; Cardio = cardiological; CEL = cancer effect level; d = day; Derm/oc = dermal/ocular; (G) = gavage; Gastro = gastrological; Gd = gestation day; Hemato = hematological; mo = month; Musc/skel = musculoskeletal; ND = no data; Resp = respiratory; (W) = water; wk = week.

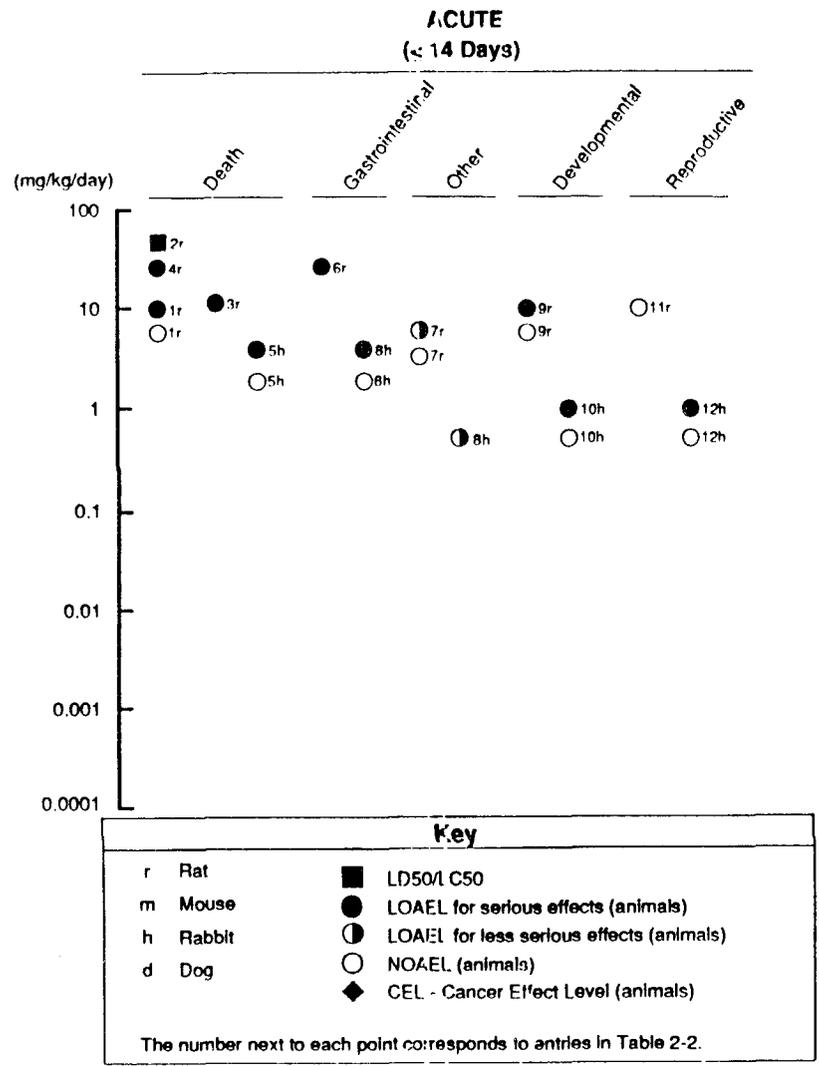


FIGURE 2-2. Levels of Significant Exposure to Acrolein - Oral

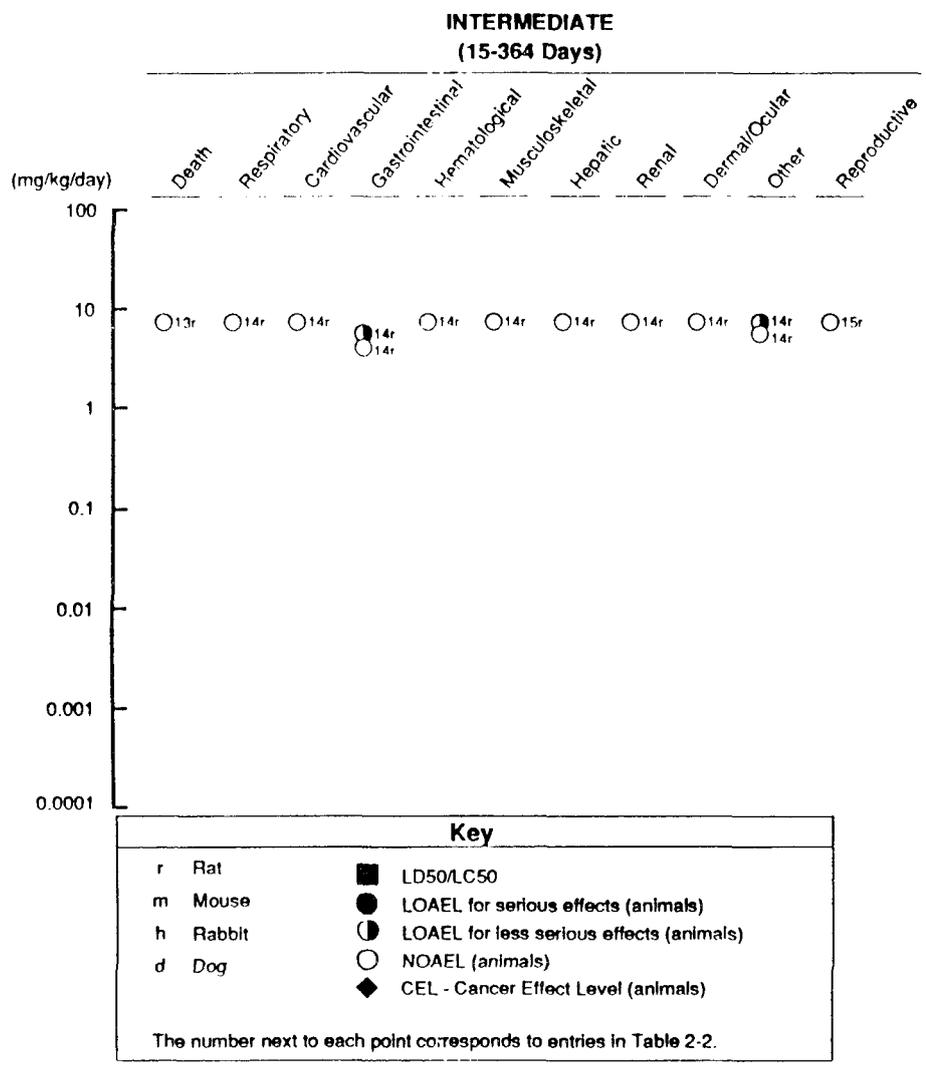


FIGURE 2-2 (Continued)

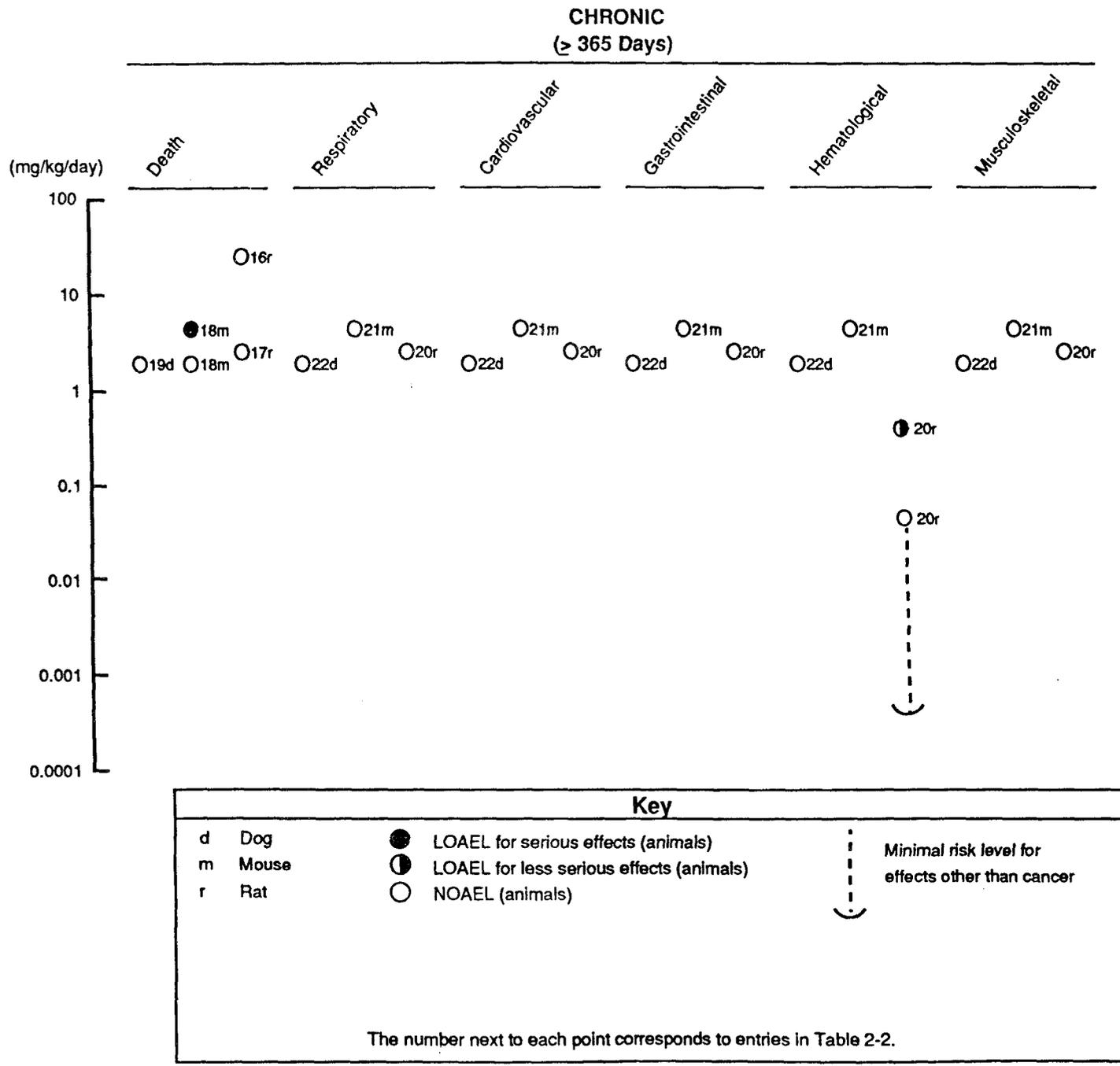


FIGURE 2-2 (Continued)

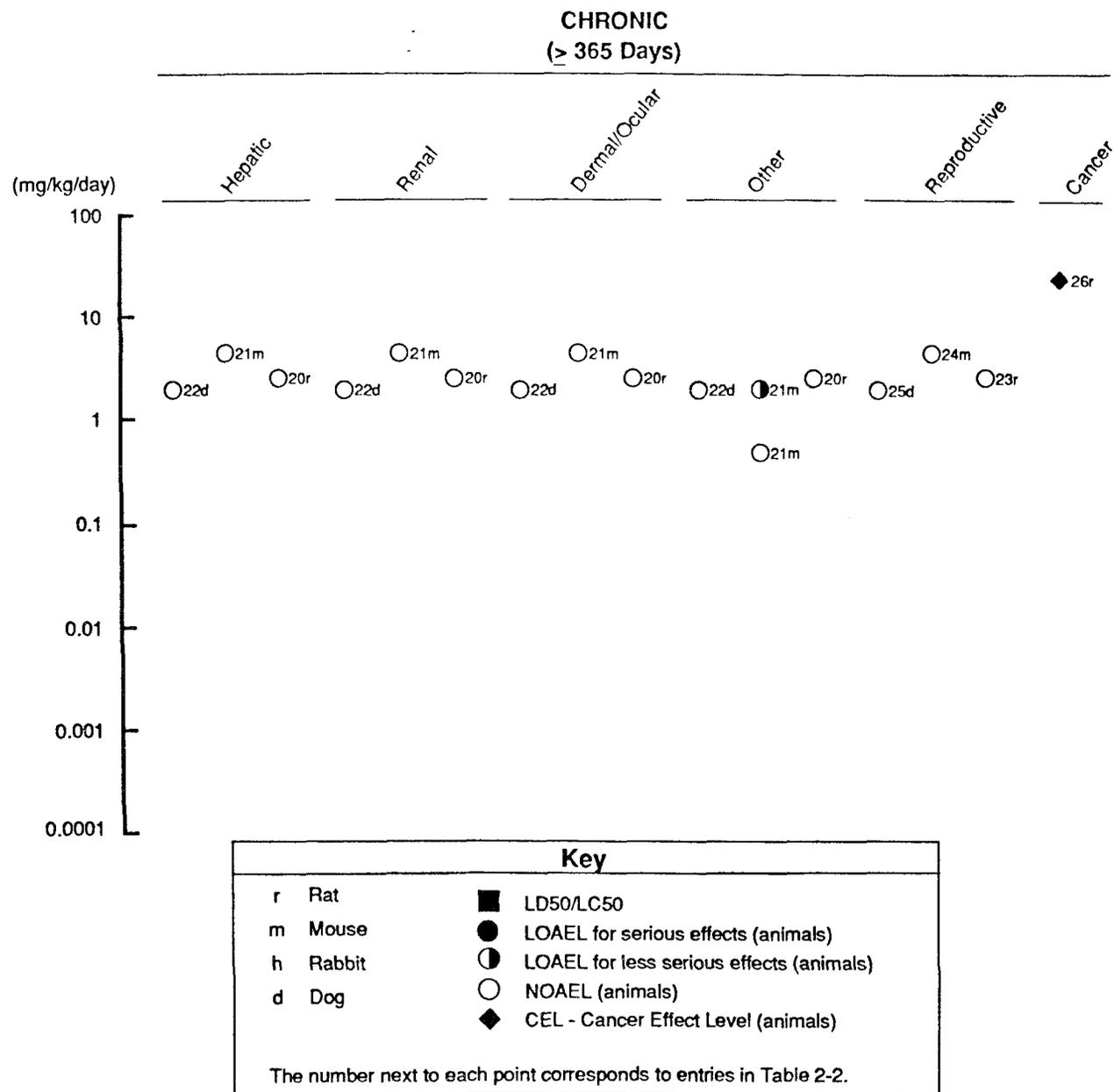


FIGURE 2-2 (Continued)

2. HEALTH EFFECTS

returned to normal at 24 months when the study was terminated. Furthermore, decreased monocytes were reported in female rats after 24 months of exposure to 0.5 mg/kg/d acrolein. The NOAEL value was 0.05 mg/kg/d and was used for the derivation of a chronic oral MRL of 0.0005 mg/kg/d as described in the footnote to Table 2-2. No pathological changes were found after hematological analysis of blood from mice or dogs chronically exposed to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively (Long and Johnson 1988, 1989).

Musculoskeletal Effects. Extensive histopathological examination in rats after intermediate-duration exposure also included the musculoskeletal system (King 1984). No changes were found. Similar results were obtained in rats (Long and Johnson 1988), mice (Long and Johnson 1989), and dogs (Long 1987) chronically exposed to acrolein.

Hepatic Effects. Smyth et al. (1951) administered acrolein to rats in drinking water at concentrations ranging between 0.17 and 1.5 ppm for 30 days. The authors reported that altered liver or kidney weights occurred with all concentrations of acrolein; however, the investigators did not indicate whether the alterations were increases or decreases. Furthermore, it is unclear if the altered organ weight occurred in the liver and/or kidneys. No liver effects were observed upon gross pathological or histological examinations in rats after intermediate-duration exposure to 7.2 mg/kg/d acrolein (King 1984). Similarly, no changes were found in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after chronic exposure to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively.

Renal Effects. Altered kidney weights were reported by Smyth et al. (1951) in rats given acrolein in doses that ranged between 0.17 and 1.5 ppm in the drinking water. It is unclear from the report whether there was an alteration in kidney weight or liver weight or both. The investigators did not indicate whether the effects were increases or decreases in organ weights. No histopathological changes were reported in kidneys of rats after intermediate-duration exposure to 7.2 mg/kg/d (King 1984) or in rats (Long and Johnson 1988), mice (Long and Johnson 1989), and dogs (Long 1987) after chronic exposure to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively. Negative results were also obtained from the urinalysis of exposed animals.

Dermal/Ocular Effects. No treatment-related dermal/ocular effects were reported in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) chronically exposed to acrolein.

Other Systemic Effects. Decreased body weight gains were reported in rats treated with 6 mg/kg/d (King 1982) and in rabbits treated with 4 mg/kg/d acrolein during gestation days 7-19 (Hoberman 1987). In a preliminary study, decreased body weight gain was also observed in rabbits treated with 0.5 mg/kg/d acrolein.

2. HEALTH EFFECTS

Statistically significant decreases in total serum protein, albumin, and calcium were observed in dogs given 2 mg/kg/d acrolein for 12 months (Long 1987). However, the toxicological significance of this finding is not clear, since no effects were observed in any organs or tissues upon gross pathological or histological examination.

2.2.2.3 Immunological Effects

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

2.2.2.4 Neurological Effects

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

Slow response to stimuli, body sag, loss of elevation reflexes, and poor body tone were observed in rats exposed to a single oral dose of 11.2 mg/kg acrolein (Sprince et al. 1979). The usefulness of this study in assessing the neurotoxic effects of oral exposure to acrolein is limited. It is difficult to determine whether these observed effects are direct toxicological effects attributed to acrolein treatment or nonspecific responses of animals in extremis.

2.2.2.5 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. 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/d (King 1982). This dosage, however, was toxic to the dams, resulting in maternal deaths. In a preliminary dose-range finding study, exposure of rabbits to 1 mg/kg/d or more resulted in dose-related increased incidences of fetal resorption (Hoberman 1987); however, fetal mortality was not affected in the primary study, in which rabbits were exposed to 2 mg/kg/d or less during gestation. No explanation for the discrepancy was provided. The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Reproductive Effects

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

Exposure of rats to 10 mg/kg/d acrolein during pregnancy had no effect on the number of implantations or resorptions or on the ratio of live/dead

2. HEALTH EFFECTS

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/d for 100-120 days prior to mating and then for 15 days during mating (King 1984). Similarly, no effects on fertility were found in rabbits exposed to 2 mg/kg/d acrolein during pregnancy (Hoberman 1987). However, in the preliminary dose-range study, a dose-related increase in embryonal resorptions was observed after exposure of dams to 1 mg/kg/d or more. No explanation for this discrepancy was given in the study. No fetuses were alive in the litters of dams that were administered 4 mg/kg/d acrolein. The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

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

2.2.2.8 Cancer

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

Limited evidence of the carcinogenicity of acrolein in animals is provided by the long-term study of Lijinsky and Reuber (1987). In this study, groups of male rats were given acrolein in the drinking water at concentrations that provided doses of 0, 5.6, 14, or 36 mg/kg/day, 5 days/week for 104-124 weeks. A control group of females was also kept. 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 female rats. Five of 20 rats treated with the highest acrolein dose had adenomas and two had hyperplastic nodules of the adrenal cortex. According to the authors, this type of tumor is rare in untreated female rats of the strain used (F344); the historical incidence is approximately 5% (there was one reported in concurrent controls). The increased incidence of adrenocortical tumors was only marginally significant as judged by the Fisher Exact Test. Because only 20 rats per group were used, this study cannot be considered a definitive bioassay for carcinogenicity, but the results do suggest a carcinogenic potential. Extensive histopathological examination did not reveal any carcinogenic effects in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after oral exposure to 2.5, 4.5, or 2 mg/kg/d acrolein, respectively, for 12-24 months. However, it must be mentioned that the duration of two of these studies, 18 months in mice and 12 months in dogs, may have precluded the development of neoplasms. It should also be noted that the doses used in these three studies are considerably smaller than those used by Lijinsky and Reuber (1987). The dose of 36 mg/kg/d is presented as a tentative CEL in Table 2-2 and Figure 2-2.

2. HEALTH EFFECTS

2.2.3 Dermal/Ocular Exposure

2.2.3.1 Death

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

In rabbits administered several dilutions of acrolein percutaneously, the LD₅₀s ranged from 160-1000 mg/kg body weight, depending on the vehicle and concentration (Albin 1962). 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.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to acrolein.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to acrolein. When applied locally 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/Ocular Effects. Schonning (1966) described a case of a 57-year-old man who accidentally spilled acrolein over his genital area. Swelling of the penis and scrotum occurred, and after 15 days the genital area was deeply ulcerated and gangrenous. No follow-up information was provided. Lacroix et al. (1976) applied a solution of 10% acrolein in ethanol to 12 volunteers; the skin was biopsied 48 hours later. All subjects exhibited irritation and had papillary edema, and 11 had polymorphonuclear infiltrates. In addition, five cases of epidermal necrosis occurred. No further information was provided.

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

Effects such as eye and nose irritation produced by exposure to acrolein vapors are discussed in Section 2.2.1.2.

2.2.3.3 Immunological 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 from the cigarette.

2. HEALTH EFFECTS

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:

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 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.

Levels of significant exposure by the dermal route associated with effects are presented in Table 2-3.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans after inhalation exposure to acrolein.

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 ventilatory rates of 6-20 respirations/minute averaged 80-85X 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. 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

TABLE 2-3. Levels of Significant Exposure to Acrolein - Dermal

| Species | Exposure Frequency/ Duration | Effect | NOAEL | LOAEL (Effect) | | Reference |
|-----------------------|------------------------------------|---------|------------|----------------|------------------------------|-------------------------|
| | | | | Less Serious | Serious | |
| ACUTE EXPOSURE | | | | | | |
| Systemic | | | | | | |
| Human | 1 d | Derm/Oc | | | 10% (severe skin irritation) | Lacroix et al. 1976 |
| INTERMEDIATE EXPOSURE | | | | | | |
| Death | | | | | | |
| Mouse | 10 wk 1 d/wk | | 42 mg/kg/d | | | Salaman and Roe 1956 |

d = day; Derm/Oc = dermal/ocular; wk = week.

2. HEALTH EFFECTS

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.

2.3.1.2 Oral Exposure

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

Very little information is known about the absorption of acrolein following oral exposure. Based on toxicological effects observed after oral administration of acrolein, it is assumed to be absorbed through the gastrointestinal tract. However, the rate and extent of absorption are not known.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to acrolein. In cases of accidental dermal exposure (described in Section 2.2.3), 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 LD₅₀ for rabbits ranged from 160 to 1000 mg/kg, depending on the vehicle (Albin 1962). From these limited data, it appears that acrolein is more efficiently absorbed when mineral spirits are used as a vehicle, rather than water.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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

2.3.2.2 Oral Exposure

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

In a study conducted by Draminski et al. (1983), the acrolein conjugated metabolite S-carboxyethylmercapturic acid was identified in the urine of rats after oral administration of a single dose of 10 mg/kg of acrolein. This study provides indirect evidence of distribution of acrolein to the liver or kidney, where conjugation most likely occurred.

2. HEALTH EFFECTS

2.3.2.3 Dermal Exposure

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

2.3.3 Metabolism

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

In nonbiological cell-free systems, acrolein has been shown to form 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 has been shown to form conjugates with glutathione, cysteine, and/or N-acetylcysteine (Dawson et al. 1984; Dupbukt et al. 1987; Gurtoo et al. 1981; Zitting and Heinonen 1980). The formation of these conjugates greatly diminished the cytotoxic effects of acrolein, indicating that conjugation may be an important detoxication mechanism. In addition to the evidence provided by the numerous in vitro studies, two reports from the literature demonstrated that acrolein also reacts with glutathione in vivo. In these studies, the acrolein metabolite 3-hydroxymercapturic acid was identified in the urine of rats after a subcutaneous dose of acrolein (Alarcon 1976; Kaye 1973).

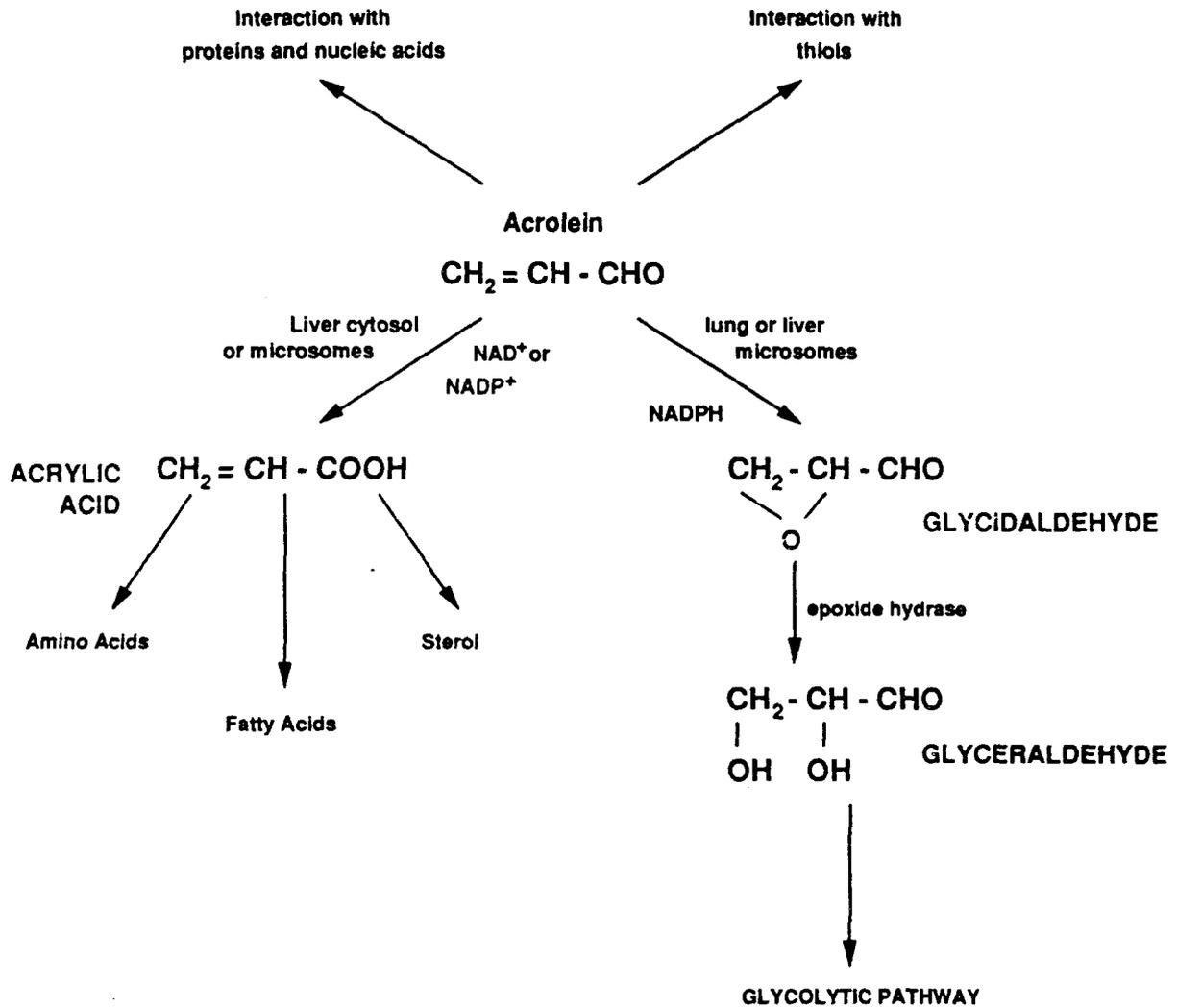
Based on experimental results, Patel et al. (1980) proposed an in vitro metabolic scheme for acrolein in rat liver and lung preparations. In this scheme, free acrolein can interact with proteins and nucleic acids, and/or with thiol groups such as glutathione. Acrolein can also be transformed into acrylic 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 glycolitic pathways. From the scheme proposed by Patel et al. (1980), 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 1974; Van Duuren 1967a, 1967b). The metabolic pathway proposed by Patel et al. (1980) is shown in Figure 2-3.

2.3.3.1 Inhalation Exposure

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

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.

2. HEALTH EFFECTS

FIGURE 2-3. Proposed Metabolic Scheme for Acrolein In Vitro

Source: Patel et al. 1980

2. HEALTH EFFECTS

2.3.3.2 Oral Exposure

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

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. The metabolic pathway postulated by Draminski et al. (1983) is shown in Figure 2-4.

2.3.3.3 Dermal Exposure

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

2.3.4. Excretion

2.3.4-1 Inhalation Exposure

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

2.3.4.2 Oral Exposure

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

Draminski et 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.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to acrolein.

2.4 RELEVANCE TO PUBLIC HEALTH

The clinical signs common to humans and animals following acute inhalation exposure to acrolein (e.g., lacrimation, upper respiratory tract

2. HEALTH EFFECTS

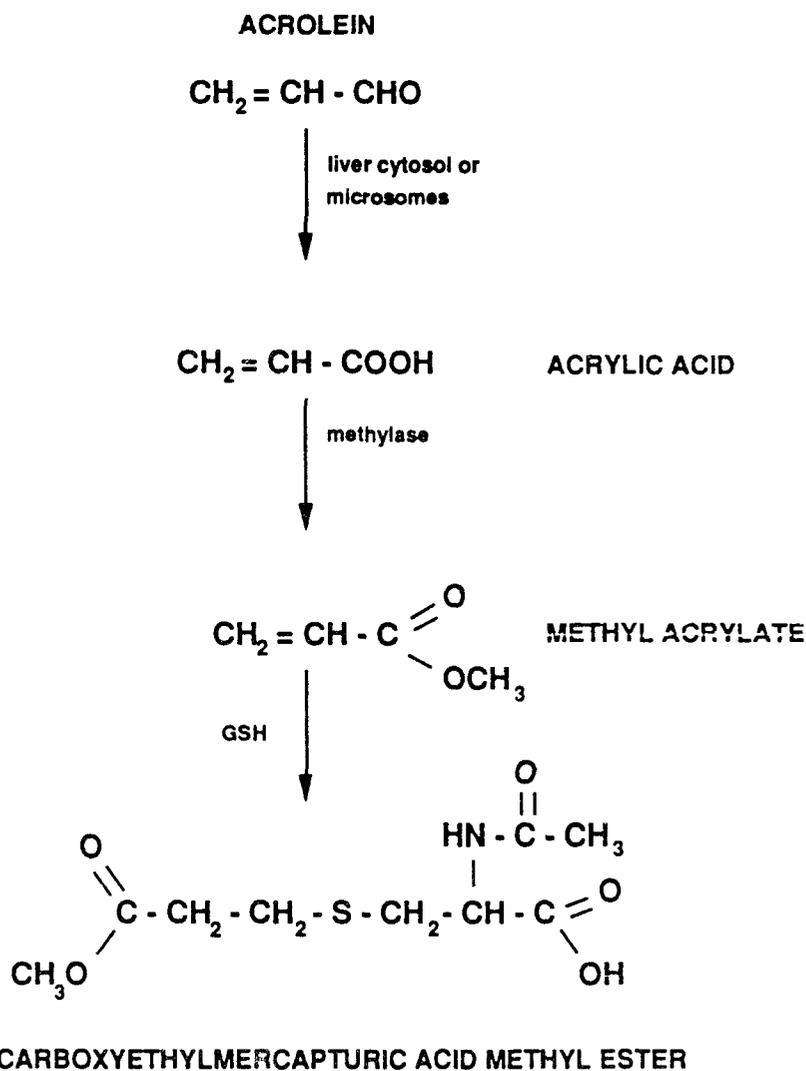


FIGURE 2-4. Proposed Metabolic Scheme for Acrolein In Vivo
 Source: Draminski et al. 1983

2. HEALTH EFFECTS

irritation and congestion, airway occlusion, and death by asphyxiation) point to the respiratory system as the major target of toxicity. Even if death is prevented, some respiratory effects may persist for months. The respiratory systems of animals are also affected following longer-term exposure. Animal data do not suggest that acrolein may have immunological effects; however, exposure to acrolein vapors may result in a decrease in bactericidal activity. No other systems or organs have yet been identified as targets for acrolein, although nonspecific effects have been identified in the livers, kidneys, and brains of animals.

Death. No human fatality due specifically to inhalation of acrolein has been reported. However, based on results obtained with experimental animals, it is reasonable to assume that exposure to relatively high doses of acrolein vapors is lethal to humans. Death has been observed in animals after inhalation, oral, and dermal exposure to acrolein. The cause of death in experimental animals seemed to be respiratory failure caused by the formation of cellular debris, which blocked the tracheal and bronchial lumen and led to asphyxiation. The concentration of acrolein necessary to induce death in animals is inversely related to the duration of exposure (see Table 2-1). The irritative properties of acrolein in the eyes and upper respiratory tract, seen in both humans and animals, will most likely serve as warning long before lethal concentrations can be reached.

Systemic Effects. The only known effects of acrolein exposure in humans are general respiratory congestion and eye, nose, and throat irritation. Studies in humans have shown that eye irritation occurs with concentrations slightly lower than those that produce either nose or throat irritation (Weber-Tschopp et al. 1977). Amooore and Hautala (1983) calculated an odor safety factor for acrolein of 0.61. This value was derived by dividing the threshold limit value (TLV) (0.1 ppm) by the odor threshold (0.16 ppm), and means that approximately 50% of attentive persons can detect the TLV concentration in the air. These irritative effects of acrolein, also observed in animals (Lyon et al. 1970; Murphy et al. 1964; Skog 1950), are temporary and disappear rapidly when exposure ceases. Acrolein stimulates free nerve endings in the corneal and nasal epithelium, triggering the reflex response of reduction in the respiratory rate (Alarie 1973). This response is particularly prominent in rodents and is aimed at decreasing the intake of the chemical irritant. The respiratory congestion observed in animals following acute inhalation exposure to acrolein (Catilina et al. 1966) probably results from its irritating properties on mucous membranes. Since acrolein is known to be irritating to mucous membranes of humans, inhalation exposure would probably result in pulmonary congestion in humans. In fact, the case described by Champeix et al. (1966) clearly supports that view. In addition, it shows that serious respiratory alterations, such as emphysema, can persist for several months after the accidental exposure.

No information is available regarding cardiovascular effects in humans following inhalation, oral, or dermal exposure to acrolein. Changes in

2. HEALTH EFFECTS

blood pressure and heart rate reported in rats (Egle and Hudgins 1974) were shown to be sympathetic-mediated, with pressor effects occurring at lower intravenous doses (0.25 mg/kg), whereas vagal-mediated cardioinhibitory and depressor effects were seen at higher intravenous doses (5 mg/kg). In contrast, no cardiovascular effects were observed in rats after intermediate-duration oral exposure to acrolein (King 1984). Furthermore, no effects were reported after chronic oral exposure in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987). No information was located regarding cardiovascular effects in animals following dermal exposure to acrolein. In the absence of further information, no inference can be made regarding possible cardiovascular effects in humans.

No information is available regarding gastrointestinal effects in humans following inhalation, oral, or dermal exposure to acrolein. A recent report by Sakata et al. (1989) showed that in rats acrolein causes severe gastrointestinal damage when administered by gavage. This effect is due to the strong irritant properties of acrolein on mucosal membranes, and is in complete agreement with the effects produced by acrolein in the respiratory tract when inhaled. This result is supported by similar findings in rabbits treated orally during pregnancy (Hoberman 1987) and in rats after intermediate-duration exposure (King 1984). In contrast, no changes in the gastric mucosa were reported in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987) after chronic exposure to lower concentrations of acrolein. It is reasonable to assume that if acrolein is ingested by humans, it would cause severe gastrointestinal effects.

No studies were located regarding hematological effects in humans after acrolein exposure. Mostly negative results were obtained in experimental animals after inhalation and oral exposures to acrolein. The only hematological changes were recorded in female rats (increased number of erythrocytes, lymphocytes) after inhalation exposure, but not in males in the same exposure group (Feron et al. 1978). Similarly, female rats had an increased number of monocytes after chronic oral exposure (Long and Johnson 1988). No such changes were found in males. The reason for the apparent sex-related difference is not clear.

No data were located regarding hepatic effects in humans following inhalation, oral, or dermal exposure to acrolein. No serious dose-related effects were noticed in animals exposed to acrolein in the air. Similarly, no toxic effects were observed in the livers of orally exposed animals (King 1984; Long 1987; Long and Johnson 1988, 1989). Furthermore, no data were located regarding hepatic effects in animals following dermal exposure to acrolein. There are insufficient data to predict whether acrolein is hepatotoxic in humans.

Cases of accidental dermal contact with acrolein and studies with volunteers clearly indicate that acrolein is a strong dermal irritant,

2. HEALTH EFFECTS

causing skin burns. A 10% solution in ethanol applied to the skin caused epidermal necrosis.

Whether systemic effects, other than respiratory, caused by acrolein in animals will occur in humans is difficult to ascertain. It is clear that because of its high chemical reactivity, acrolein will cause damage to all tissues that come in contact with it. However, because the most relevant route of exposure is by inhalation, and because of the strong irritant odor, systemic effects other than respiratory are not likely to be observed in humans.

Immunological Effects. No data were located regarding immunological effects in humans following inhalation, oral, or dermal exposure to acrolein. In experimental animals, the effects of acrolein on the immune system have been evaluated by determining the lethality of bacterial agents to acrolein-exposed animals. The effects have varied, depending on the concentration of acrolein, duration of exposure, and species used. Although the mechanism by which acrolein alters the immune response is not known, the general view is that it decreases the bactericidal activity of the respiratory epithelium by destroying mucosal layers that contain defense mechanisms. Acrolein destroyed ciliated cells in the respiratory tract of rats (Catilina et al. 1966), guinea pigs (Dahlgren et al. 1972), and hamsters (Kilburn and McKenzie 1978). This effect was also induced in rabbit tracheas by tobacco smoke, and acrolein was identified as one of the agents having ciliary-depressant activity (Kensler and Battista 1963). Acrolein suppressed protein synthesis 50% in rabbit alveolar macrophages in vitro (Leffingwell and Low 1979). Increased mortality due to bacterial infection was reported in mice (Astry and Jakab 1983) and rats (Bouley et al. 1975) after exposure to acrolein for 8 hours and 3 weeks, respectively. However, in the study by Bouley et al. (1975), no difference was seen between control and treated animals after 63 days of exposure to acrolein, which probably indicates that immunity can develop after the initial infection; this should be considered in intermediate- and longduration studies. Administration of 5.6 mg/kg acrolein intravenously in mice prior to sensitization with sheep erythrocytes resulted in enhancement of the delayed-type hypersensitivity and antibody forming cells response to the sheep erythrocytes (Kawabata and White 1988). The authors suggest that enhancement of the immune response was produced by acrolein binding to the sulfhydryl groups of cells required for the generation of suppressor T-cells. Based on studies in experimental animals, it is likely that humans accidentally exposed to high concentrations of acrolein by inhalation will have an increased risk of contracting respiratory infections. The effects of long-term exposure to low concentrations of acrolein on the human immune system are not known.

Neurological Effects. No information was identified regarding neurological effects in humans following exposure to acrolein. The only data available in experimental animals described nonspecific brain inflammation after exposure to acrolein in the air (Lyon et al. 1970). In

2. HEALTH EFFECTS

the absence of further information, no inference regarding possible effects in humans can be made. However, levels in the ambient environment or in air, water, and soil surrounding waste sites are probably not high enough to warrant concern for severe neurological effects.

Developmental Effects. No evidence exists to indicate that acrolein causes developmental effects in humans. However, several studies have been conducted regarding the teratogenic and embryotoxic properties of acrolein in animals. An increased incidence of skeletal anomalies was reported in the offspring of rats that were exposed to 10 mg/kg/d acrolein by gavage during gestation (King 1982) but not in rabbits that were exposed to 2 mg/kg/d during gestation (Hoberman 1987). Increased fetal resorptions were, however, reported in a preliminary dose-range study in rabbits exposed orally during pregnancy, and no live fetuses were found in the group exposed to 4 mg/kg/d acrolein (Hoberman 1987). Acrolein was embryo-lethal when injected intravenously to pregnant rabbits at doses that had toxic effects in the maternal animals (Claussen et al. 1980). When injected into the yolk sac, acrolein was embryo-lethal and teratogenic, but at doses considerably higher than intravenous doses. Acrolein induced malformations when injected into the amniotic fluid of pregnant rats (Hales 1982; Slott and Hales 1985). However, when rat embryos were cultured in vitro, acrolein did not induce malformations (Mirkes et al. 1984), but it delayed growth (Schmid et al. 1981). Similar results were found with mouse limb buds cultured in vitro (Stahlmann et al. 1985). Slott and Hales (1986), however, found that acrolein was teratogenic to rat embryos cultured in vitro. Since the range of concentrations used by Slott and Hales (1986) was similar to that used by Schmid et al. (1981), the difference in the results is difficult to interpret but is probably related to differences in incubation procedures or the presence of serum at the time of exposure (Curren et al. 1988; Smith et al. 1990). Although it is not known whether acrolein causes developmental effects in humans, it is possible that, if free acrolein reaches the human embryo, teratogenic effects may develop.

Reproductive Effects. It is not known whether acrolein could cause reproductive effects in humans. A single study was identified regarding the reproductive effects of inhaled acrolein in animals. In this study (Bouley et al. 1975), exposure of rats to acrolein prior to mating did not affect the number of pregnancies or number and weight of the fetuses. Acrolein treatment during pregnancy did not affect the reproductive ability of rats (King 1982). Similarly, no reproductive effects were found in a two-generation oral exposure study in this species (King 1984). Increased fetal resorptions were reported in rabbits exposed orally to 1 mg/kg/d during pregnancy, but no live fetuses were found in the group exposed to 4 mg/kg/d acrolein (Hoberman 1987). Therefore, the potential of acrolein to cause reproductive effects in humans cannot be ruled out.

Genotoxic Effects. 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

2. HEALTH EFFECTS

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 2-4, indicates that acrolein is weakly mutagenic without activating systems and nonmutagenic in the presence of activating systems in Salmonella tyohimurium and Escherichia coli. In the yeast, Saccharomyces cerevisiae, acrolein was not mutagenic without activating systems. In mammalian cells, acrolein gave positive results without activating systems. Acrolein inhibited the activity of DNA polymerase as well as DNA and RNA synthesis in rat liver cell nuclei. 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 O⁶-methylguanine-DNA methyl transferase. 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 1N²-propanodeoxyguanine (Chung et al. 1984; Foiles et al. 1989) and 1N⁶-propanodeoxyadenine (Smith et al. 1990). Because of the limited number of in vivo tests, there is insufficient evidence to predict that acrolein poses a genotoxic threat to humans.

Cancer. Acrolein administered in the water for 104 weeks induced neoplasms in the adrenal cortex of female rats (Lijinsky and Reuber 1987). This type of tumor is rare in untreated rats. The increased incidence over controls was only marginally significant according to the Fisher Exact Test. This study cannot be considered a definitive positive or negative bioassay for carcinogenicity. Long-duration inhalation studies provided no evidence of carcinogenicity in hamsters or rats (Feron and Krusysse 1977; Le Bouffant et al. 1980). Furthermore, no neoplastic effects of chronic oral exposure to acrolein were observed in rats (Long and Johnson 1988), mice (Long and Johnson 1989), or dogs (Long 1987). The same results were found with dermal application and subcutaneous injections of acrolein (Salaman and Roe 1956; Steiner et al. 1943). However, several classes of chemicals structurally or functionally related to acrolein, such as aldehydes and dienes, are alkylating agents and have shown evidence of being animal carcinogens. There is some evidence that glycidaldehyde, a proposed acrolein metabolite, induces skin cancer in mice and rats (Shamberger 1974; Van Duuren 1967a,b). Based on the above and on the lack of epidemiological data, acrolein is considered to have limited animal evidence for carcinogenicity. Based on the overall available evidence, the EPA has classified acrolein as a Group C substance: a possible human carcinogen (EPA 1987c). IARC (1987) has classified acrolein as a Group 3 substance, i.e., a chemical for which there is inadequate evidence for carcinogenicity in humans and animals.

TABLE 2-4. Genotoxicity of Acrolein In Vitro

| End Point | Species (Test System) | Result | | Reference |
|---------------------------|---|-----------------|--------------------|-------------------------------|
| | | With Activation | Without Activation | |
| Prokaryotic organisms: | | | | |
| Gene mutation | | | | |
| | <u>Salmonella typhimurium</u> (plate incorporation) | - | - | Andersen et al. 1972 |
| | <u>S. typhimurium</u> (plate incorporation) | - | - | Florin et al. 1980 |
| | <u>S. typhimurium</u> (plate incorporation) | - | - | Loquet et al. 1981 |
| | <u>S. typhimurium</u> (plate incorporation) | - | - | Bignami et al. 1977 |
| | <u>S. typhimurium</u> (plate incorporation) | - | (+) | Lijinsky and Andrews 1980 |
| | <u>S. typhimurium</u> (plate incorporation) | - | + | Lutz et al. 1982 |
| | <u>S. typhimurium</u> (plate incorporation) | - | + | Eder et al. 1982 |
| | <u>S. typhimurium</u> (plate incorporation) | - | - | Basu and Marnett 1984 |
| | <u>S. typhimurium</u> (plate incorporation) | ND | - | Bartsch et al. 1980 |
| | <u>S. typhimurium</u> (plate incorporation) | ND | (+) | Khudoley et al. 1987 |
| | <u>S. typhimurium</u> (liquid preincubation test) | ND | + | Marnett et al. 1985 |
| | <u>S. typhimurium</u> (liquid incubation method) | ND | + | Foiles et al. 1989 |
| | <u>S. typhimurium</u> (liquid incubation method) | - | (+) | Waegemaekers and Bensink 1984 |
| | <u>Escherichia coli</u> PQ37 (SOS chromotest) | - | - | Von der Hude et al. 1988 |
| | <u>E. coli</u> K-12/343/113 (plate incorporation) | - | ND | Ellenberger and Mohn 1977 |
| | <u>E. coli</u> WPuvrA (plate incorporation) | ND | (+) | Hemminki et al. 1980 |
| | <u>E. coli</u> DNA polymerase deficiency (plate incorporation) | ND | + | Bilimoria 1975 |
| Eukaryotic organisms: | | | | |
| Fungi: | | | | |
| Gene mutation | | | | |
| | <u>Saccharomyces cerevisiae</u> (plate incorporation) N123, S211, S138 | ND | - | Izard 1973 |
| Chromosomal aberrations | | | | |
| | <u>S. cerevisiae</u> MB1072-2B (plate incorporation) | ND | - | Fleer and Brendel 1982 |
| Mammalian cells: | | | | |
| DNA, RNA synthesis | | | | |
| | Rat liver cell nuclei | ND | + | Moule et al. 1971 |
| DNA polymerase activity | | | | |
| | Rat liver | ND | + | 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 |
| DNA damage | | | | |
| | Human myeloid cells K562 | ND | + | Crook et al. 1986 |
| DNA damage | | | | |
| | Human bronchial cells (culture) | ND | + | Grafstrom et al. 1988 |
| DNA repair | | | | |
| | Human bronchial cells (culture) | ND | + | Krokan et al. 1985 |
| DNA repair | | | | |
| | Human fibroblasts (culture) | ND | - | Curren et al. 1988 |
| DNA repair | | | | |
| | Human fibroblasts (xeroderma pigmentation) | ND | + | Curren et al. 1988 |
| Gene mutation | | | | |
| | Chinese hamster V79 cells | ND | + | Smith et al. 1990 |

+ = positive result; - = negative result; (+) = positive or marginal result; ND = no data.

2. HEALTH EFFECTS

2.5 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).

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 or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid 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 (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 biologic 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 2.5.1.

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 often not 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 2.5.2.

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. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2. HEALTH EFFECTS

2.5.1 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. Methods developed to determine levels of acrolein in human tissues and fluids are described in Chapter 6.

2.5.2 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. 1980). After transformation into acrylic acid, incorporation into amino acids, fatty acids, and sterols can be expected. However, specific effects associated with these biochemical reactions are not known.

2.6 INTERACTIONS WITH OTHER CHEMICALS

Ansari et al. (1988) showed that acrolein enhances the inhibitory effect that certain industrial chemicals, such as styrene and 1,2-dichloroethane, have on the α -1-proteinase inhibitor of human plasma in vitro. A decrease in the activity of the α -1-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 1973). 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 Seggall 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. 1981; 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

2. HEALTH EFFECTS

other (Kane and Alarie 1979). 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).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

In general, individuals whose ventilatory 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.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 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 2-5. 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 imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

As seen from Figure 2-5, very little information is available regarding the health effects of exposure of humans to acrolein. Experimental studies

2. HEALTH EFFECTS

| | Death | SYSTEMIC | | | Immunologic | Neurologic | Developmental | Reproductive | Genotoxic | Cancer |
|------------|-------|----------|-----------|---------|-------------|------------|---------------|--------------|-----------|--------|
| | | Acute | Intermed. | Chronic | | | | | | |
| Inhalation | ● | | | | | | | | | |
| Oral | | | | | | | | | | |
| Dermal | ● | | | | | | | | | |

HUMAN

| | Death | SYSTEMIC | | | Immunologic | Neurologic | Developmental | Reproductive | Genotoxic | Cancer |
|------------|-------|----------|-----------|---------|-------------|------------|---------------|--------------|-----------|--------|
| | | Acute | Intermed. | Chronic | | | | | | |
| Inhalation | ● | ● | ● | ● | ● | | ● | | ● | |
| Oral | ● | ● | ● | ● | | ● | ● | | ● | |
| Dermal | ● | ● | | | | | | | ● | |

ANIMAL

● Existing Studies

FIGURE 2-5. Existing Information on Health Effects of Acrolein

2. HEALTH EFFECTS

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.

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 resulted in neoplasms in the adrenal cortex.

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.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure to acrolein is irritating to the upper respiratory system and eyes in humans and animals. 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. An MRL for acute inhalation exposure was derived from human data 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. These studies have found decreased body weight gain and gastric ulceration in maternal animals, but endpoints of acute oral exposure in nonpregnant animals have not been identified. Therefore, the acute oral data are not sufficient to derive an MRL. Skin contact with acrolein caused irritation, burns, and epidermal necrosis in humans. It is evident, therefore, that the necrotic effects of acrolein occur at the site of primary contact regardless of routes of exposure. The acute lethal levels of acrolein were established after inhalation and oral exposure in rats. 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 in this direction after exposure via all three routes would be useful. The information is important for populations living near hazardous waste sites who might be exposed to acrolein for brief periods of time.

2. HEALTH EFFECTS

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to acrolein in humans. Inhalation exposure studies in animals provided information on doses and treatment schedules that are lethal and that produce respiratory tract toxicity. The information was sufficient for derivation of an inhalation MRL. Two intermediate-duration oral studies were conducted in rats. One of the studies was limited in size and scope, the other one (two-generation reproductive study) has shown some differences between the first and second generation in clinical signs of acrolein toxicity. Furthermore, the mortality, though attributed to injuries from gavaging, was increased in all exposure groups. The study seemed, therefore, unreliable for MRL derivation. No systemic toxicity was reported in mice after intermediate duration dermal exposure to acrolein. The pharmacokinetic data were insufficient to identify the target organs of acrolein toxicity. Further studies regarding acrolein toxicity especially after oral and dermal routes would be useful. The results would be useful for possible extrapolation to humans and protection of populations around hazardous waste sites who might be exposed to acrolein for prolonged periods of time.

Chronic-Duration Exposure and Cancer. No studies were located regarding toxicity in humans following chronic exposure by any route of exposure. Respiratory toxicity was observed in rats and hamsters after inhalation exposure. However, the design of these inhalation studies was poor (short daily exposure or only one exposure level used), and the data were insufficient for MRL derivation. Chronic oral studies were performed in rats, mice, and dogs. Extensive histopathological examination revealed no effects in any organs, and a chronic oral MRL was derived from the results of hematological analysis in rats. No studies were located regarding acrolein toxicity after dermal exposure in animals. The pharmacokinetic data are insufficient to speculate on possible target organs of acrolein toxicity across routes of exposure. Acrolein has been selected for a general toxicology study by the National Toxicology Program (NTP 1990). This study could provide important information that is needed for the evaluation of health hazards of populations living near hazardous waste sites for a long period of time.

No studies were located regarding the carcinogenicity of acrolein in humans. No carcinogenicity of acrolein was observed in two limited (see above) chronic inhalation studies in animals. Dermal application of acrolein to mice for ten weeks did not induce cancer. However, the length of the study is considered too short for proper evaluation. No carcinogenic effect was found in rats, mice, and dogs following extensive histopathological examinations after chronic oral exposure to acrolein. An increased incidence of adrenocortical adenomas was observed in female rats after oral exposure to acrolein in another study. However, the study was limited in the number of exposed animals and the use of only one dose in exposed females. The carcinogenic potential of acrolein will be evaluated in the NTP study (NTP 1990).

2. HEALTH EFFECTS

Genotoxicity. No studies were located regarding acrolein genotoxicity in humans. Dominant lethality of acrolein observed in mice indicated a genotoxic potential in mammals. The result is supported by in vitro data that showed mutagenic potential of acrolein in bacterial and mammalian cells without metabolic activation. 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. Conflicting results were obtained in reproductive toxicity studies in animals. No reproductive effects were observed in rats after inhalation exposure or in rats after oral exposure to acrolein. The results of a multigeneration oral exposure study in rats were also negative. Although not reproduced in the main study, the results of a pilot dose-range study indicated increased fetal resorptions in rabbits after oral exposure to acrolein. 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 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 after any route of exposure. The developmental toxicity of acrolein was studied after oral exposure in rats and rabbits. Increased incidences of skeletal anomalies and delayed ossification were observed in rats, and increased fetal resorptions were found in rabbits. Furthermore, the results from parenteral administration indicate that acrolein can cross the placenta, causing malformations and embryoletality in experimental animals. 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 studies regarding information on developmental toxicity of acrolein after 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 not available. Acute and subchronic inhalation studies indicate that acrolein may increase the risk of bacterial infections in the respiratory tract, but a battery of immunotoxicity tests has not been

2. HEALTH EFFECTS

performed. Such tests provide a more sensitive assessment of possible immunotoxic effects than does histological examination of tissues and organs of the immune system. Since a case of an allergic response to acrolein derived from cigarette smoke was described in humans, sensitization tests could help identify agents causing allergic responses in individuals exposed to tobacco smoke. No information regarding immunological effects in animals after oral or dermal exposure to acrolein were located.

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. No such effects were observed in animals after inhalation exposure; the animals died from asphyxia caused by epithelial desquamation and, consequently, respiratory obstruction. 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. No histopathological changes were observed after oral exposure. 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.

Epidemiological and Human Dosimetry Studies. The only information available concerning effects of acrolein in humans comes from a limited number of cases of accidental exposure by the inhalation and dermal routes. In these cases, severe effects were observed in the eyes and respiratory tract mucosa, some effects persisting for several months after the exposure occurred. However, epidemiological studies are not available. Chronic human exposure is not likely to occur because of the strong irritating effects of acrolein. This means that individuals exposed to acrolein would most likely leave the polluted area before acrolein reaches a dangerous concentration. Amoores and Hautala (1983) calculated that the odor safety factor for acrolein is such that 10-50% of attentive persons can detect the TLV concentration (0.1 ppm) in the air. Nevertheless, epidemiology studies of individuals who live in areas where acrolein has been detected, such as polluted urban centers and of workers occupationally exposed to acrolein, even at low doses, would provide information regarding the effects of longterm exposure to tolerable concentrations. This information would be useful for monitoring individuals near hazardous waste sites for preventive purposes.

Biomarkers of Exposure and Effect. No reliable biomarkers of acrolein exposure have been identified. The finding of 3-hydroxypropylmercapturic acid in the urine after exposure to acrolein or cyclophosphamide seemed to be promising for use as an exposure identifier. However, further studies found no correlation between the amount of 3-hydroxypropylmercapturic acid in the urine and the dose of parent compound administered. Further identification of acrolein metabolites in the urine and their correlation with levels of exposure would be useful. Recently, Iype et al. (1987)

2. HEALTH EFFECTS

presented preliminary results in an abstract regarding the development of an antibody-mediated assay to monitor subjects exposed to acrolein. This assay exploits the possible formation of acrolein-adducted DNA in cells, or the formation of antibodies against such adducts in serum. Such assays could eventually be used for the early detection of respiratory diseases such as emphysema, to which acrolein may be a contributor. Further studies regarding possible biochemical changes after acrolein exposure would be useful.

It has been proposed that acrolein can be transformed metabolically into acrylic acid, which may be incorporated into amino acids, fatty acids, and sterol. However, specific biomarkers of effect for acrolein have not been identified. Studies regarding identification of these biomarkers would be useful.

Absorption, Distribution, Metabolism, Excretion. The only toxicokinetic data of acrolein are from the in vivo absorption study in dogs by Egle (1972) and the oral exposure study in rats by Draminski et al. (1983), from which a possible metabolic pathway was proposed. However, dermal and inhalation exposures may 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, especially the reaction with thiol groups. 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 systems 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. The potential for acrolein to produce toxic effects has been investigated in rats, mice, dogs, guinea pigs, hamsters, rabbits, and monkeys, but 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 accidentally exposed to the chemical or living in polluted urban areas would provide valuable information on absorption and excretion rates if the exposure to acrolein was known.

2.8.3 On-going Studies

Several on-going studies regarding acrolein have been identified from the National Technical Information Service (NTIS 1988).

2. HEALTH EFFECTS

S. Cohen and R. Smith, University of Nebraska, Omaha, NE, are investigating the mechanism by which acrolein induces damage in the bladder epithelium of rats, in vivo and in vitro. Their studies include short-term and long-term bioassays. Similar studies are being performed by C. Irving and co-workers, Veterans Administration Medical Center, Memphis, TN. At Massachusetts General Hospital, Boston, MA, C. Hales is conducting research on the mechanism by which acrolein produces pulmonary edema and how it interacts with skin burns to induce lung injuries. The experimental animals include dogs and sheep.

At the American Health Foundation, New York, NY, P. Foiles and S. Hecht, sponsored by the NCI, are attempting to develop sensitive immunoassays in mice for the detection of acrolein-DNA adducts in animals and eventually in humans exposed to the chemical. Dr. Foiles and his collaborators are pursuing 32 P post-labeling methods for the detection of acrolein modified DNA. C. Sevilla, Proteins International, Rochester, MN, is attempting to develop monoclonal antibodies for acrolein-DNA adducts. These antibodies will be used in clinical and research monitoring of levels of the adduct in human DNA samples.

P. Mirkes, University of Washington, Seattle, WA, is continuing his investigation on the teratogenic properties of the metabolites of the drug cyclophosphamide, of which acrolein is one. The studies are being performed in rat embryos cultured in vitro. R. Okita, Medical College of Wisconsin, Milwaukee, WI, is studying the effects of acrolein on the activity of the enzyme NAD⁺-dependent prostaglandin dehydrogenase in the lungs of rabbits and guinea pigs. His studies are aimed to better characterize this enzyme and the function of prostaglandins and other eicosanoid derivatives in pulmonary function. Acrolein has been selected for a general toxicology study by the National Toxicology Program (NTP 1990).