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 acrylonitrile. Its purpose is to present levels of significant exposure for acrylonitrile 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 acrylonitrile 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 figures 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 (LOAELS) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

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 extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989a), 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

Table 2-1 and Figure 2-1 summarize quantitative data on the health effects observed in humans and laboratory animals exposed to acrylonitrile by inhalation.

2.2.1.1 Death

In humans, the death of a child (age 3) who was exposed by sleeping in a room that had been fumigated with acrylonitrile has been described by Grunske (1949). Respiratory malfunction, lip cyanosis and tachycardia were among the symptoms described prior to death. Five adults who spent the night in the same room complained only of eye irritation or showed no signs of acrylonitrile poisoning. The concentrations of acrylonitrile in the air were not reported. Several other instances of death in children with only mild irritation in adults were reported by Grunske (1949), but not described in detail.

Data on the NOAELS and LOAELS for death are presented in Table 2-1 for several animal species. The data presented indicate that species differences exist with respect to acute lethal effects. Dogs appear to be the most susceptible species, but this is based on studies involving only a few animals. The cause of death varied among test species. In guinea pigs, death resulted from pulmonary irritation (see

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	4 hr		130		315	Dudley and Neal 1942
2	Gn Pig	4 hr		265		575	Dudley and Neal 1942
3	Rabbit	4 hr		135		260	Dudley and Neal 1942
4	Dog	4 hr		30		65[a]	Dudley and Neal 1942
5	Cat	4 hr		275		600	Dudley and Neal 1942
6	Monkey	4 hr		90			Dudley and Neal 1942
Systemic							
7	Human	20-45 min (occup)	Derm/Oc		16 (skin irritation)		Wilson et al. 1948
8	Rat	5 d 8hr/d	Renal	129			Gut et al. 1984
9	Rat	5 d 8hr/d	Hepatic	125			Gut et al. 1985
10	Rat	12 hr	Hepatic	26			Gut et al. 1984
11	Rats	4 hr	Renal	100	200 (glucosuria, proteinuria)		Rouisse et al. 1986
12	Rat	5 d 8hr/d	Hepatic		129 (lower liver wt.)		Gut et al. 1984
13	Rat	5 d 8hr/d	Resp	129			Gut et al. 1984

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
14	Rat	5 d 8hr/d	Other			125 (unhealthy appearance)	Gut et al. 1985
15	Rat	4 hr	Derm/Oc		315 (skin redness)		Dudley and Neal 1942
16	Gn Pig	4 hr	Derm/Oc	100	575 (irritation)		Dudley and Neal 1942
17	Rabbit	4 hr	Derm/Oc		100 (skin redness)		Dudley and Neal 1942
18	Monkey	4 hr	Derm/Oc	65	90[a] (skin redness)		Dudley and Neal 1942
Neurological							
19	Human	20-45 min (occup)			16 (irritability)		Wilson et al. 1948
20	Human	8 hr		4.6[b]			Jakubowski et al. 1987
21	Dog	4 hr			30[a] (salivation)	100 (paralysis)	Dudley and Neal 1942
22	Cat	4 hr			100 (salivation)	275 (pain)	Dudley and Neal 1942
23	Monkey	4 hr		65	90 (weakness)		Dudley and Neal 1942
Developmental							
24	Rat	10 d Gd6-15 6hr/d		40		80[a] (malformations)	Murray et al. 1978
CHRONIC EXPOSURE							
Death							
25	Rat	2 yr 5d/wk 6hr/d				20[a] (early deaths)	Quast et al 1980a

TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Systemic							
26	Rat	2 yr 5d/wk 6hr/d	Hemato	80			Quast et al 1980a
27	Rat	2 yr 5d/wk 6hr/d	Resp	20	80 (irritation nasal mucosa)		Quast et al 1980a
28	Rat	2 yr 5d/wk 6hr/d	Hepatic	80			Quast et al 1980a
29	Rat	2 yr 5d/wk 6hr/d	Renal	80			Quast et al 1980a
Neurological							
30	Rat	2 yr 5d/wk 6hr/d				80[a] (focal gliosis)	Quast et al 1980a
Cancer							
31	Rat	104 wk 5d/wk 7hr/d				60 CEL (multiple tumors)	Maltoni et al. 1988
32	Rat	2 yr 5d/wk 6hr/d				20 CEL (multiple tumors)	Quast et al 1980a

[a]Presented in Table 1-2.
[b]Used to derive acute inhalation MRL; dose adjusted for intermittent exposure and divided by an uncertainty factor of 10 (for human variability), resulting in an MRL of 0.1 ppm. This MRL is presented in Table 1-1.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; ppm = parts per million; hr = hour; derm/oc = dermal/ocular; min = minute; occup = occupational; d = day; wt = weight; Resp = respiratory; Gd = gestation day; yr = year; hemato = hematological; CEL = cancer effect level.

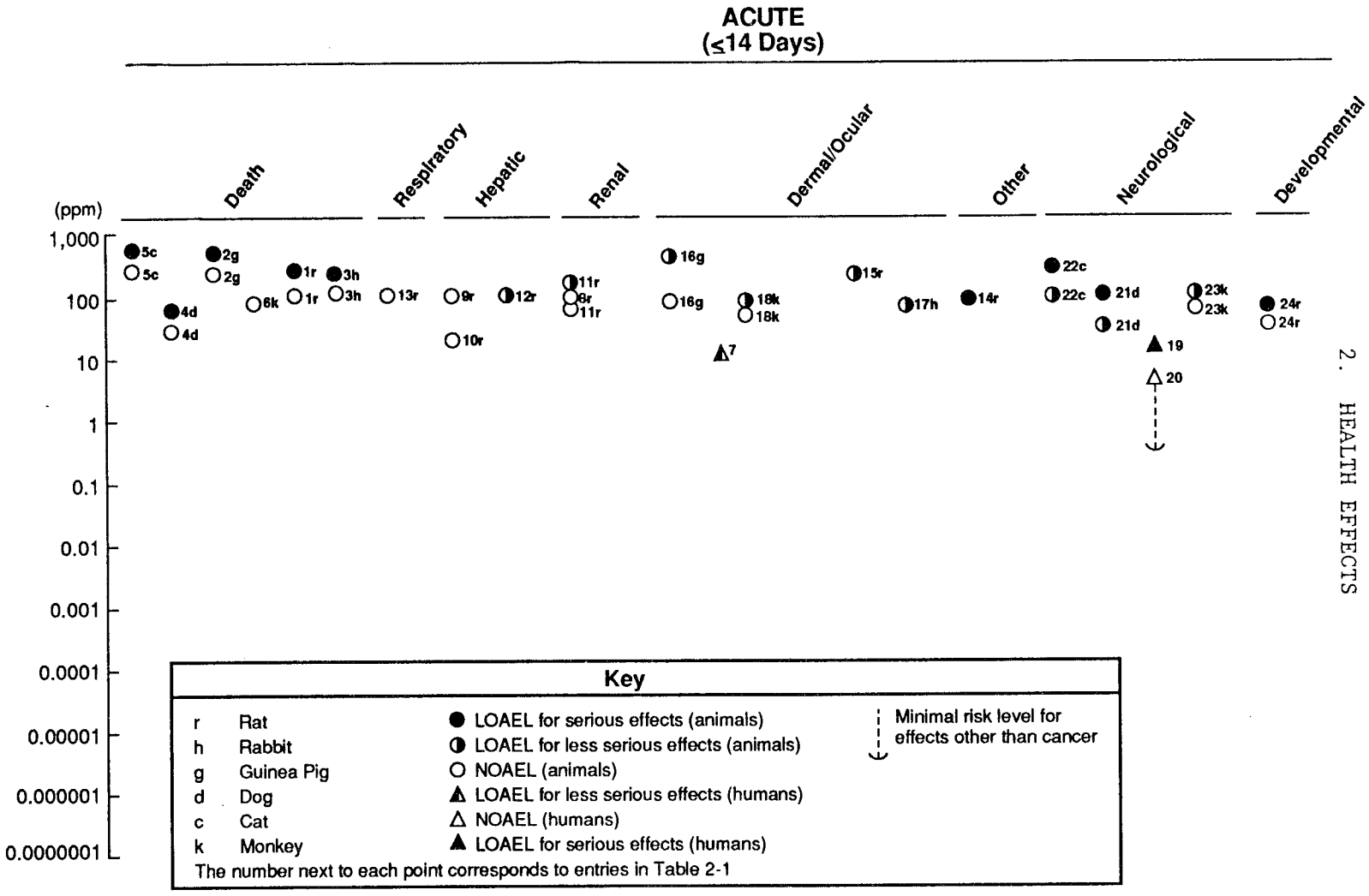

FIGURE 2-1. Levels of Significant Exposure to Acrylonitrile – Inhalation

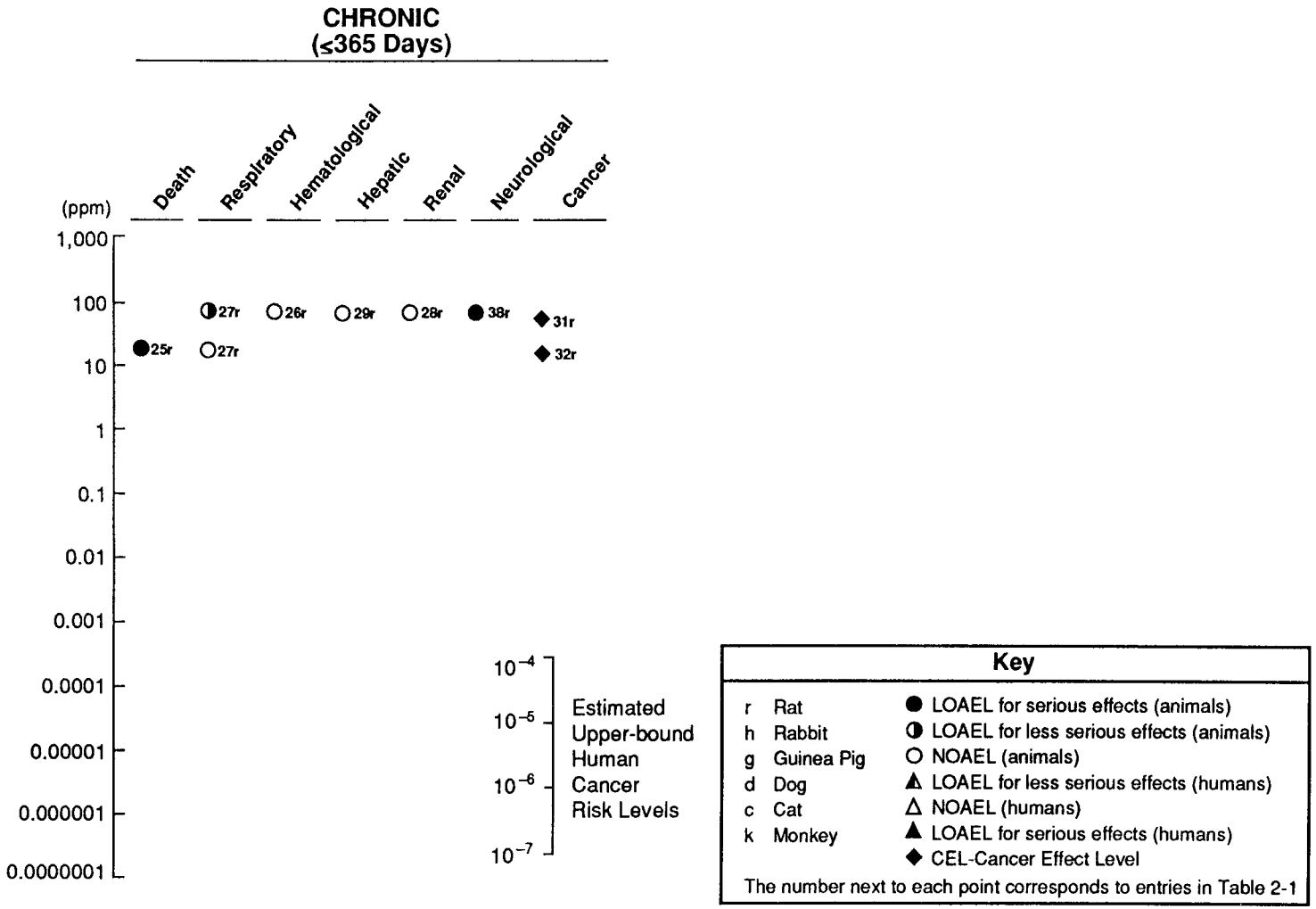

FIGURE 2-1 (Continued)

Section 2.2.1.2) while in the other species convulsions and coma occurred (see Section 2.2.1.4) (Dudley and Neal 1942). It should be noted that this study is based on nominal concentrations without analytical verification.

Chronic exposure to acrylonitrile has been reported to result in early deaths in male and female rats (Quast et al. 1980a). A statistically significant increase in mortality was observed within the first year of a study in which animals were exposed to 80 ppm of acrylonitrile. At 20 ppm, increased deaths were noted in females during the last 10 weeks of the study. The cause of death was not specifically identified.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

Respiratory Effects. In workers exposed to acrylonitrile at concentrations of 16 to 100 ppm for periods of 20 to 45 minutes, irritation of the nose and throat and a feeling of fullness in the chest was reported by Wilson et al. (1948).

Acute effects on the respiratory tract of animals demonstrate species differences. In guinea pigs exposed to 575 ppm for 4 hours, marked irritation of the respiratory tract was evidenced by coughing and nasal exudate, with delayed death from lung edema (Dudley and Neal 1942). In other species (rats, rabbits, dogs and monkeys), death occurred at lower doses than in guinea pigs, but was not related to respiratory effects. In these animals, mild irritation of the respiratory tract and effects resembling cyanide poisoning were noted. Respiration was initially stimulated, but then followed by rapid shallow breathing (Dudley and Neal 1942).

Reported exposure at lower doses shows no acrylonitrile-related effects on the respiratory system. For example, rats repeatedly exposed for 5 days to 129 ppm of acrylonitrile showed no gross or histological changes in lung tissue (Gut et al. 1984). However, chronic exposure of rats to acrylonitrile appears to cause irritation of the nasal passages. In a 2-year study, histopathological evaluation of tissues of the respiratory system revealed degenerative and inflammatory changes of the nasal turbinates at 80 ppm (Quast et al. 1980a). These effects were not noted at 20 ppm.

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. In humans, tachycardia was among the symptoms described in a child (age 3) who was exposed by sleeping in a room that had been fumigated with acrylonitrile. The child died as a result of the exposure (see Section 2.2.1.1) (Grunske 1949). No studies were located regarding cardiovascular effects in animals following inhalation exposure to acrylonitrile.

Gastrointestinal Effects. Though tumors of the small intestine were noted in a comprehensive and well-conducted study by Quast et al. (1980a) (see Section 2.2.1.8), there were no nonneoplastic histopathologic changes observed in any portion of the gastrointestinal tract of rats at doses up to 80 ppm for 2 years.

Hematological Effects. Humans exposed to acrylonitrile at concentrations where nausea, vomiting and weakness occurred (16 to 100 ppm for 20 to 45 minutes), were also reported to have low grade anemia. However, complete recovery after cessation of exposure was reported (Wilson 1944; Wilson et al. 1948). No adverse hematological effects were detected in Japanese workers exposed to acrylonitrile for 10 to 13 years at exposure levels averaging 2.1 to 14.1 ppm (Sakurai et al. 1978).

In a chronic study in rats (Quast et al. 1980a), some changes in the blood parameters measured were observed at various intervals during the study, but the findings did not occur consistently and were not dose-related. Therefore, the authors concluded that these findings were not direct effects of exposure to acrylonitrile, but rather were a secondary response to other effects such as weight loss, tumor formation, or inflammatory reactions.

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 following inhalation exposure to acrylonitrile.

Hepatic Effects. Acrylonitrile is metabolized in the liver to potentially toxic metabolites (see Section 2.3). There are limited indications that the liver is a target organ for acrylonitrile toxicity.

In humans, mild jaundice lasting several days to 4 weeks has been observed after acute occupational exposure to acrylonitrile vapors at high concentrations (Wilson 1944); however, the concentrations of acrylonitrile to which workers were exposed were not reported. The effects were fully reversible. In factory workers exposed to acrylonitrile for 10 years or more, Sakurai et al. (1978) reported an increase in palpable livers of workers. However, the authors considered these results to be inconclusive because the increase was not statistically significant and subjective judgments were involved. Also, blood chemistry evaluations did not indicate liver damage.

In animals, acrylonitrile does not appear to cause damage to the liver following acute or chronic inhalation exposure, though some biochemical changes are noted. Exposure of rats for 5 days to 129 ppm of acrylonitrile resulted in slightly lower liver weight, but no histopathological changes were found (Gut et al. 1984). Depletion of glutathione and effects on carbohydrate and lipid metabolism were observed (Gut et al. 1984, 1985). These effects would be expected considering the affinity of acrylonitrile for sulfhydryl groups on proteins and the involvement of glutathione in the metabolism of acrylonitrile (see Section 2.6). A 2-year chronic study in rats showed no liver injury as evaluated by serum enzyme activity and histopathological evaluation of the tissue (Quast et al. 1980a).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

Renal Effects. Most studies indicate that inhalation exposure to acrylonitrile does not result in significant kidney injury. For example, physical examination of workers exposed to acrylonitrile vapors in the workplace for 10 or more years provided no indication of renal effects (Sakurai et al. 1978). In animals, no histological or biochemical signs of renal injury were seen following exposure of rats to 129 ppm of acrylonitrile for 5 days (Gut et al. 1984), or to 80 ppm for 2 years (Quast et al. 1980a). Small increases in urinary levels of glucose, gamma-glutamyl transpeptidase, and N-acetyl-glucosaminidase were observed in rats exposed to 200 ppm of acrylonitrile for 4 hours (Rouisse et al. 1986), but this was not accompanied by any significant effect on urinary creatinine or blood urea nitrogen. No significant effects were noted at 100 ppm for this duration of exposure.

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-l.

Dermal/Ocular Effects. In humans, direct skin irritation resulting from exposure to acrylonitrile vapors has been observed (see Section 2.2.3).

A skin redness reported in experimental animals (rats, rabbits, cats and monkeys) after inhalation exposure to acrylonitrile may be due to a vasodilatory effect, rather than a direct irritant action (Ahmed and Patel 1981). Guinea pigs, which do not exhibit the cyanide-type effects of acrylonitrile poisoning (see Section 2.2.1.4), were observed to have nose and eye irritation from the acrylonitrile vapors (Dudley and Neal 1942).

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.

2.2.1.3 Immunological Effects

No studies were located regarding immunologic effects in humans or animals following inhalation exposure to acrylonitrile.

2.2.1.4 Neurological Effects

In humans, acute exposure to acrylonitrile results in characteristics of cyanide-type toxicity. Symptoms in humans associated with acrylonitrile poisoning include limb weakness, labored and irregular breathing, dizziness and impaired judgment, cyanosis, nausea, collapse, and convulsions (Baxter 1979). However, the doses that produce these effects were not clearly defined. Workers exposed to 16 to 100 ppm for 20 to 45 minutes complained of headaches and nausea, apprehension and nervous irritation (Wilson et al. 1948). The workers exposed to acrylonitrile vapors fully recovered. In a study with human volunteers exposed to acrylonitrile at doses of 2.3 and 4.6 ppm, no symptoms attributable to effects on the nervous system were observed (Jakubowski et al. 1987). The dose of 4.6 ppm was used to calculate the acute inhalation MRL of 0.1 ppm, as described in the footnote in Table 2-1.

Animals exposed to acrylonitrile usually display acute neurological symptoms. Dogs appear to be particularly sensitive. Excessive salivation in dogs occurred at concentrations of 30 ppm of acrylonitrile, and paralysis of the hind limbs occurred at 100 ppm. In cats, excessive salivation occurred at 100 ppm; at 275 ppm animals were observed to paw their heads and stomachs and howl as if in pain. In monkeys, "weakness" was reported at 90 ppm, but higher doses were not tested. Guinea pigs showed no measurable signs of neurological effects from acute exposure to acrylonitrile at a dose that caused death

(575 ppm) (Dudley and Neal 1942). It should be noted that this study is based on nominal concentrations with no analytical verification. Therefore, the overall usefulness of the study is limited.

Chronic exposure of rats to 80 ppm acrylonitrile resulted in focal gliosis and perivascular cuffing in the brain (Quast et al. 1980a). The gliosis appeared *to* be a pre-malignant lesion related *to* the formation of brain tumors, and is discussed in more detail in Section 2.2.1.8 (below).

The highest NOAEL values and all reliable LOAEL values for neurological effects are recorded in Table 2-l and plotted Figure 2-l.

2.2.1.5 Developmental Effects

Inhalation exposure to acrylonitrile results in teratogenic effects in rats. Inhalation of 80 ppm acrylonitrile during days 6 to 15 of gestation (the critical period of organogenesis) resulted in a significant increase in fetal malformations. These malformations included short tail, missing vertebrae, short trunk, omphalocele and hemivertebra. In this well-conducted study, mean number of implantations, live fetus and resorptions were not significantly altered by exposure to 40 or 80 ppm of acrylonitrile. No effects on fetal body size were evident. Maternal toxicity was observed at both dose levels tested (40 and 80 ppm), as evidenced by decreased weight gain (Murray et al. 1978).

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following inhalation exposure *to* acrylonitrile.

2.2.1.7 Genotoxic Effects

Factory workers exposed for an average of 15 years to acrylonitrile vapors showed no increase in chromosomal aberrations in the peripheral lymphocytes (Thiess and Fleig 1978). As in most human studies, the actual concentration of acrylonitrile to which these workers were exposed was not reported. However, monitoring data indicated that the average exposure concentration for the workers was 5 ppm for the majority of the exposure period (approximately 10 years); at the time the study was conducted, acrylonitrile levels in the workplace had been reduced to 1.5 ppm.

No studies were located regarding genotoxic effects in animals following inhalation exposure to acrylonitrile.

2.2.1.8 Cancer

A number of epidemiological studies have been conducted to evaluate the association between lung cancer and occupational exposure to acrylonitrile (Collins et al. 1989; Delzell and Monson 1982; Kiesselbach et al. 1979; O'Berg 1980; O'Berg et al. 1985). However, many of the studies suffer from deficiencies such as an insufficient quantification of exposure, short follow-up, small and relatively youthful cohorts or lack of consideration of the effects of smoking, and the results of the studies are often inconsistent.

The most reliable of the epidemiology studies on acrylonitrile is that conducted by O'Berg (1980) in which 1,345 male workers in a textile factory were followed over a period of 25 years. Exposures to acrylonitrile were divided into three groups (low, medium and high), although quantitative estimates of exposure levels were not assigned. O'Berg (1980) concluded that there may be an association between human lung cancer and acrylonitrile inhalation exposure. The incidence of cancer did not increase significantly in exposed workers over the unexposed population. The data from this on-going study were updated by O'Berg et al. (1985) to include an additional 7 years of follow-up. Though an increased incidence of lung cancer in workers exposed to acrylonitrile was observed, the effect was not as pronounced as it had been in the previous report. The authors concluded that continued follow-up was needed.

Statistically significant cancer excesses have been observed in other studies; however, due to limitations in the studies firm conclusions cannot be made. In an analysis of mortality among 327 rubber workers, nine deaths from lung cancer were observed compared to 4.7 to 5.9 expected deaths among the general population and other rubber workers (Delzell and Monson 1982). The observed and expected numbers of death were small and the study did not evaluate cigarette smoking as a confounding factor contributing to excess death.

Another well-designed epidemiology study (Collins et al. 1989) did not find an increased risk of lung cancer from acrylonitrile exposure. In this study, 2,671 males (1,774 with known acrylonitrile exposure) were followed for 32 years. Workers in acrylic fiber manufacturing plants were categorized into four dose ranges (expressed in ppm/year). Smoking histories were taken into consideration. No significant relationship between lung cancer and acrylonitrile exposure was established, although the authors found some evidence in this study of confounding association between smoking status and cumulative exposure to acrylonitrile. In this study, as in the previously discussed studies (O'Berg 1980; O'Berg et al. 1985), the subjects were relatively young,

and only 9% of the cohort had died. Additional follow-up will be necessary to determine whether death can be associated with cancers resulting from acrylonitrile exposure.

Epidemiology studies have also suggested a possible association between acrylonitrile exposure and prostate cancer (Chen et al. 1987; O'Berg et al. 1985), but the data are too limited to warrant any firm conclusion. Collins et al. (1989) found no increase in prostate cancer in acrylonitrile-exposed workers, but again the data are too limited to be meaningful.

Deaths from cancer of the stomach were statistically elevated in one study of six manufacturing plants in the United Kingdom involved in the polymerization of acrylonitrile and the spinning of acrylic fibers (Werner and Carter 1981). No quantitative data on the exposure levels to acrylonitrile were given and the numbers of expected deaths was too small to provide confidence in the results.

In animals, chronic studies provide convincing evidence that acrylonitrile is carcinogenic when administered by the inhalation route of exposure. Tumors in the brain, Zymbal gland and mammary glands in rats exposed to acrylonitrile for 2 years were reported by both Quast et al. (1980a) and Maltoni et al. (1988). Quast et al. (1980a) reported two types of lesions in the central nervous system: astrocytomas and focal or multifocal glial cell proliferation. The glial cell proliferation was considered to be a microscopic change suggestive of early tumorigenesis. Brain tumors were observed in males exposed to 80 ppm of acrylonitrile, and in females at 20 and 80 ppm. In addition, Quast et al. (1980a) reported tumors of the tongue and small intestine in males (80 ppm). Maltoni et al. (1988) noted tumors in the liver (60 ppm).

2.2.2 Oral Exposure

No studies were located regarding health effects in humans associated with the oral ingestion of acrylonitrile. Table 2-2 and Figure 2-2 summarize the health effects observed in experimental animals following oral exposure to acrylonitrile. These effects are discussed below.

2.2.2.1 Death

The acute oral LD_{50} has been estimated to be 93 mg acrylonitrile/kg body weight (mg/kg) in rats (Back et al. 1972) and 27 mg/kg for mice (Ahmed and Pate1 1981). Longer term intake (6 months) in dogs at 16 mg/kg/day resulted in early deaths. Animals lost weight and were described as depressed, lethargic, weak and emaciated prior to death.

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

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat		ND				93 (LD50)	Back et al. 1972
2	Mouse	(G)	ND				27[a] (LD50)	Ahmed and Patel 1981
Systemic								
3	Rat	(G)	1x	Gastro		50 (GI bleeding)		Ghanayem and Ahmed 1983
4	Rat	(G)	10 d Gd6-15 1x/d	Hepatic	25	65 (incr. liver wt.)		Murray et al. 1978
5	Rat	(G)	1x	Gastro		46.5 (covalent binding to proteins)		Farooqui and Ahmed 1983
6	Rat	(G)	10 d Gd6-15 1x/d	Gastro	10	25 (stomach effects)		Murray et al. 1978
7	Rat	(G)	1x	Hemato		80 (RBC enzyme alteration)		Farooqui and Ahmed 1983
Neurological								
8	Rat	(G)	1x				93 (CNS effects)	Ahmed and Patel 1981
9	Mouse	(G)	1x				27 (CNS effects)	Ahmed and Patel 1981
Developmental								
10	Rat	(G)	10 d Gd6-15 1x/d		10[b]		25[c] (malformations)	Murray et al. 1978

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE								
Death								
11	Dog	(W)	6 mo		10		16	Quast et al. 1975
Systemic								
12	Rat	(W)	50 wk	Gastro	70			Beliles et al. 1980
13	Rat	(W)	3 wk	Other	14	70 (adrenal atrophy)		Szabo et al. 1984
14	Rat	(W)	21 d	Hepatic	14	70 (incr. GSH)		Szabo et al. 1977
15	Dog	(W)	6 mo	Gastro	10		16[d] (esophageal ulcerations)	Quast et al. 1975
16	Dog	(W)	6 mo	Renal	18			Quast et al. 1975
17	Dog	(W)	6 mo	Hemato	10	16 (decr. RBC)		Quast et al. 1975
Neurological								
18	Rat	(W)	50 wk		70			Beliles et al. 1980
Reproductive								
19	Dog	(W)	6 mo		10		16 (depression, lethargy)	Quast et al. 1975
20	Rat	(W)	220 d		14		70[e] (decr. reproduct. indices)	Beliles et al. 1980
21	Mouse	(G)	60 d 1x/d				10[f] (decr. sperm count, tubular degeneration)	Tandon et al. 1988

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
Cancer								
22	Rat	(W)	50 wk				14 CEL (multiple tumors)	Beliles et al. 1980
CHRONIC EXPOSURE								
Death								
23	Rat	(W)	M:26 mo F:23 mo		4.2		14 (early deaths)	Bio/dynamics 1980b
24	Rat	(G)	20 mo 7d/wk 1x/d		0.1		10 (early deaths)	Bio/dynamics 1980c
25	Rat	(W)	M:22 mo F:19 mo		0.14		14 (early deaths)	Bio/dynamics 1980a
26	Rat	(W)	2 yr				4.4[g] (early deaths)	Quast et al. 1980b
Systemic								
27	Rat	(W)	M:22 mo F:19 mo	Hemato	0.14	14 (decr. red cells)		Bio/dynamics 1980a
28	Rat	(W)	M:26 mo F:23 mo	Hepatic	4.2	14 (incr. liver wt.)		Bio/dynamics 1980b
29	Rat	(W)	M:22 mo F:19 mo	Renal		14 (incr. kidney wt.)		Bio/dynamics 1980a
30	Rat	(W)	M:22 mo F:19 mo	Cardio	14			Bio/dynamics 1980a
31	Rat	(G)	20 mo 7d/wk 1x/d	Hemato		10 (decr. red cells)		Bio/dynamics 1980c

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
32	Rat	(G)	20 mo 7d/wk 1x/d	Hepatic	0.1	10 (incr. liver wt.)		Bio/dynamics 1980c
33	Rat	(G)	20 mo 7d/wk 1x/d	Renal	0.1	10 (incr. kidney wt.)		Bio/dynamics 1980c
34	Rat	(W)	2 yr	Hemato	25			Quast et al. 1980b
35	Rat	(W)	M:26 mo F:23 mo	Renal	4.2	14 (incr. kidney wt.)		Bio/dynamics 1980b
36	Rat	(W)	M:22 mo F:19 mo	Hepatic		14 (incr. liver wt.)		Bio/dynamics 1980a
37	Rat	(W)	2 yr	Renal	25			Quast et al. 1980b
38	Rat	(W)	M:26 mo F:23 mo	Hemato	4.2[h]	14[i] (decr. red cells)		Bio/dynamics 1980b
Neurological								
39	Rat	(W)	18 mo			70 (decr. activity)		Bigner et al. 1986
Reproductive								
40	Rat	(W)	M:22 mo F:19 mo		0.14	14 (incr. testes wt.)		Bio/dynamics 1980a
Cancer								
41	Rat	(W)	95 wk				70 CEL (tumors)	Beliles et al. 1980
42	Rat	(W)	2 yr				28 CEL (zymbal gland)	Gallagher et al. 1988

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
43	Rat	(G)	20 mo 7d/wk 1x/d				10 CEL (multiple tumors)	Bio/dynamics 1980c
44	Rat	(W)	M:26 mo F:23 mo				1.4 CEL (multiple tumors)	Bio/dynamics 1980b
45	Rat	(W)	M:22 mo F:19 mo				14 CEL (multiple tumors)	Bio/dynamics 1980a
46	Rat	(W)	18 mo				70 CEL (brain tumor)	Bigner et al. 1986
47	Rat	(W)	2 yr				3.4 CEL (multiple tumors)	Quast et al. 1980b

[a]Converted to an equivalent concentration of 142 ppm in water for presentation in Table 1-4.
[b]Used to derive acute oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a minimal risk level of 0.1 mg/kg/day. This MRL has been converted to an equivalent concentration in water (3.4 ppm) for presentation in Table 1-3.
[c]Converted to an equivalent concentration of 180 ppm in water for presentation in Table 1-4.
[d]Converted to an equivalent concentration of 200 ppm in water for presentation in Table 1-4.
[e]Converted to an equivalent concentration of 500 ppm in water for presentation in Table 1-4.
[f]Converted to an equivalent concentration of 52 ppm in water for presentation in Table 1-4. Value also used to derive intermediate oral MRL; dose divided by an uncertainty factor of 1,000 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a minimal risk level of 0.01 mg/kg/day.
[g]Converted to an equivalent concentration of 35 ppm in water for presentation in Table 1-4.
[h]Used to derive chronic oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability resulting in a minimal risk level of 0.04 mg/kg/day. This MRL has been converted to an equivalent concentration in water (1.4 ppm) for presentation in Table 1-3.
[i]Converted to an equivalent concentration of 100 ppm in water for presentation in Table 1-4.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg/kg/day = milligram/kilogram/day; ND = no data; (G) = gavage; LD50 = lethal dose, mortality 50%; d = day; Gd = gestation day; 1x = one time; hemato = hematological; gastro = gastrointestinal; RBC = red blood cell; CNS = central nervous system; (W) = water; mo = month; wk = week; cardio = cardiovascular; incr. = increased; GSH = glutathione; decr = decreased; reproduct. = reproductive; histo = histological; CEL = cancer effect level; M = males; F = females; wt. = weight.

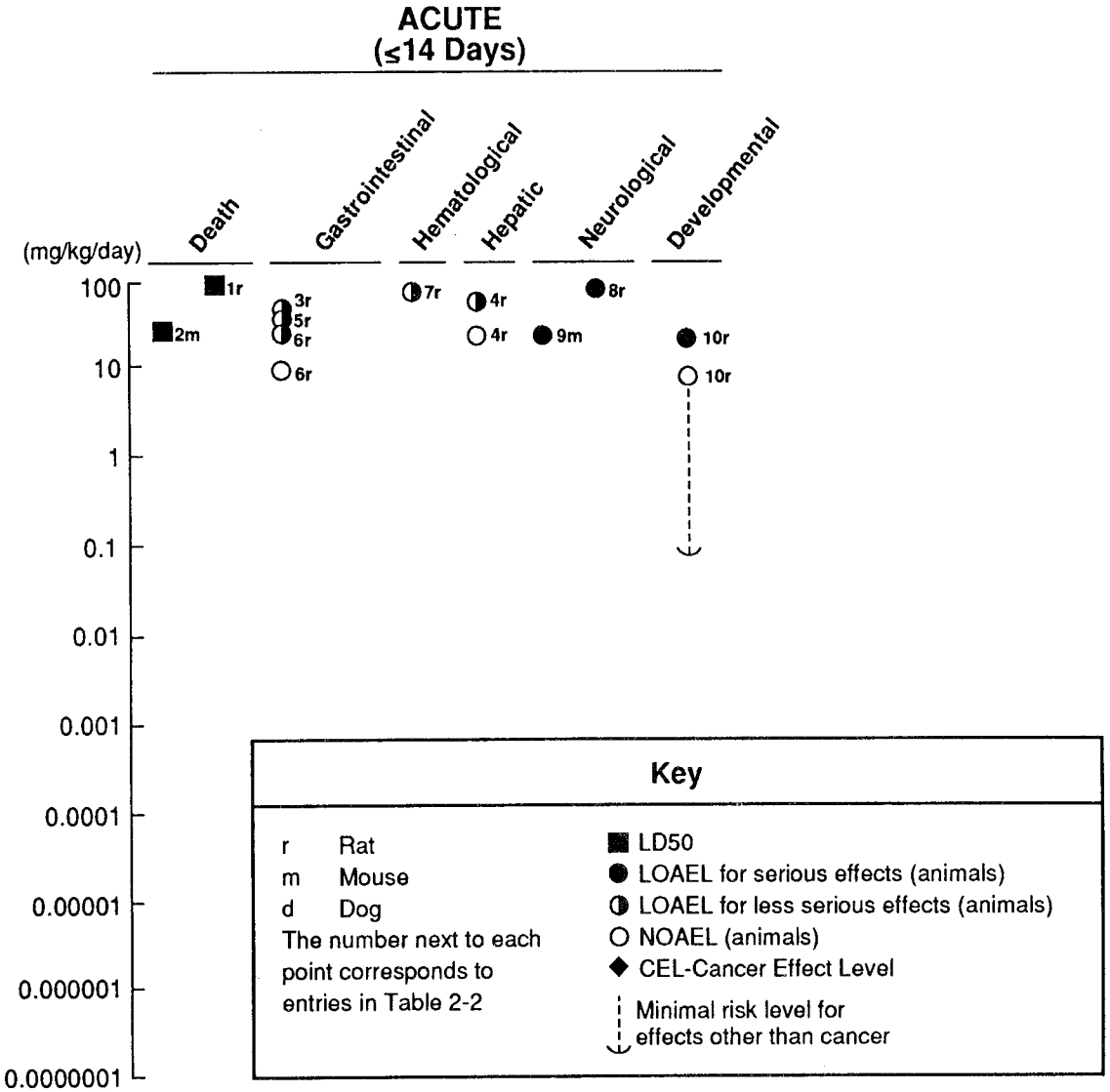

FIGURE 2-2. Levels of Significant Exposure to Acrylonitrile – Oral

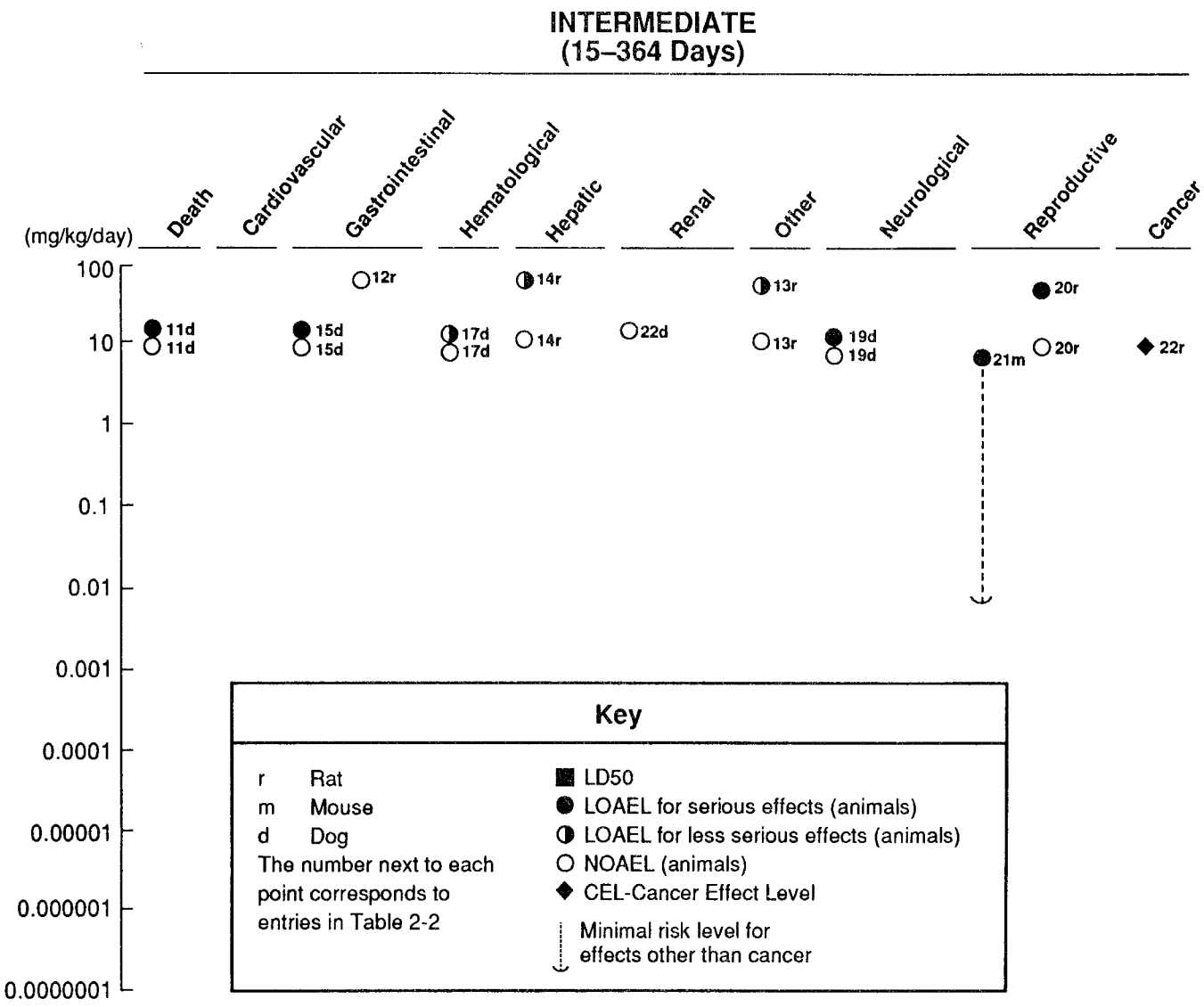

FIGURE 2-2 (Continued)

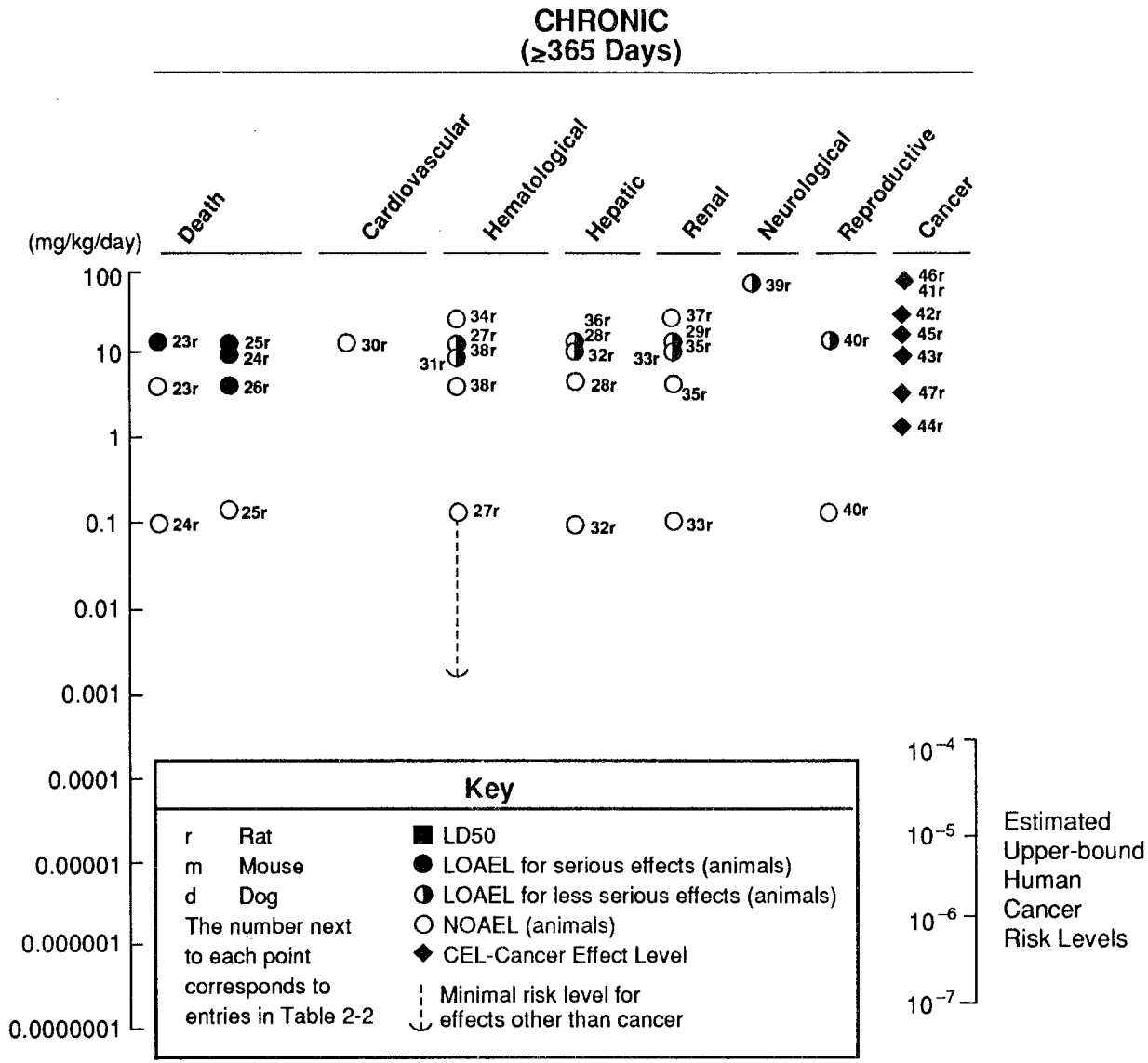

FIGURE 2-2 (Continued)

Chronic studies in rats indicate that lifetime exposure to doses of 4.4 mg acrylonitrile/kg body weight/day (mg/kg/day) or higher may result in premature death (Bio/dynamics 1980a, 1980b, 1980c; Gallagher et al. 1988; Quast et al. 1980b). The cause of death was not specifically identified.

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Respiratory Effects. Chronic oral exposure of animals to low levels of acrylonitrile has not been found to result in damage to the lungs. Histopathological evaluation of lung tissues from rats showed no lung injury at doses up to 25 mg/kg/day for 2 years (Bio/dynamics 1980a, 1980b, 1980c; Quast et al. 1980b).

Cardiovascular Effects. No injury to the cardiovascular system has been detected in studies in animals. No effects were seen in dogs exposed to 18 mg/kg/day in drinking water for 6 months (Quast et al. 1975). In chronic studies in rats exposed to 14 mg/kg/day in drinking water (Bio/dynamics 1980b) or by gavage (Bio/dynamics 198Oc), an increased heart-to-body-weight ratio was observed. However, the effects were not seen in other studies where acrylonitrile was given to rats in drinking water (Bio/dynamics 1980a; Quast et al. 1980b). No histopathological changes were reported in heart tissues in any of the chronic studies (Bio/dynamics 1980a, 1980b, 1980c; Quast et al. 1980b).

The highest NOAEL values and all reliable LOAEL values for cardiovascular effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Gastrointestinal Effects. Studies in animals suggest that oral exposure to acrylonitrile is irritating to the esophagus and stomach. An acute oral dose of acrylonitrile resulted in hemorrhagic necrosis of the forestomach of rats (Szabo et al. 1984). In dogs given acrylonitrile in drinking water for 6 months at 16 mg/kg/day, gross and microscopic evaluation showed focal erosions and ulcerations in the esophagus (Quast et al. 1975). The authors considered these lesions to be due to irritation to the mucous membranes, No esophageal lesions were present at 10 mg/kg/day. Rats given acrylonitrile in drinking water for 50 weeks at doses up to 70 mg/kg/day showed no effects on the gastrointestinal tract (Beliles et al. 1980), indicating that rats are less sensitive to this effect than dogs. Rats exposed to acrylonitrile in drinking water for 2 years developed papillomatous proliferations of the epithelium of the forestomach at a dose of 28 mg/kg/day, but not at

7.1 mg/kg/day (Gallagher et al. 1988). This effect is discussed under Section 2.2.2.8 below. Nonproliferative effects on the stomach were not reported.

The method by which an oral dose is administered may also determine whether gastrointestinal effects occur. While no effects were observed in rats given acrylonitrile in drinking water at doses up to 70 mg/kg/day for 50 weeks (Beliles et al. 1980), administration by gavage of 25 mg/kg/day acrylonitrile to rats for 10 days resulted in thickening of the nonglandular portion of the stomach (Murray et al. 1978). A single gavage dose of 50 mg/kg to rats was reported to cause gastrointestinal bleeding, as measured by increased heme content in the gastrointestinal tract (Ghanayem and Ahmed 1983).

The highest NOAEL values and all reliable LOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Hematological Effects. Decreased red blood cell counts, hematocrit, and hemoglobin content have been reported following acute, intermediate and chronic oral studies in animals (Bio/dynamics 1980a, 1980b, 198Oc; Farooqui and Ahmed 1983a; Quast et al. 1975). Although the mechanism of these hemotoxic effects is not clear, Farooqui and Ahmed (1983) found that acrylonitrile bound covalently both to red blood cell membranes and to hemoglobin. In dogs administered acrylonitrile at doses up to 18 mg/kg/day for 6 months, decreased red cell counts, hematocrit, and hemoglobin content were seen only in animals that died (Quast et al. 1975). In chronic studies in rats, lower red cell parameters were seen at 14 mg/kg/day, but these effects were not specifically identified with animals that died during the study (Bio/dynamics 1980a, 1980b, 1980c). In another chronic study in rats at doses up to 25 mg/kg/day for 2 years, no effects on red cell parameters were observed, though early deaths were observed in the study (Quast et al. 1980b). Based on lower red cell parameters (Bio/dynamics 1982a), a chronic oral MRL of 0.04 mg/kg/day was calculated as described in the footnote in Table 2-2.

The highest NOAEL values and all reliable LOAEL values for hematological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following oral exposure to acrylonitrile.

Hepatic Effects. Although acrylonitrile is metabolized by the liver to potentially toxic metabolites (see Section 2.3.3), the liver does not appear to be an important target organ for acrylonitrile toxicity (Silver et al. 1982). In chronic studies in rats, microscopic examination of liver tissue showed no damage after 2 years of exposure to acrylonitrile at doses up to 25 mg/kg/day (Bio/dynamics 1980a, 1980b, 198Oc; Quast et al. 1980b).

Some effects in the liver have been reported, but they may be adaptive changes related to increased metabolic activity. Increased glutathione levels were reported at doses of 70 mg/kg/day for 21 days (Szabo et al. 1977). Because the metabolism of acrylonitrile includes pathways that utilize glutathione (see Section 2.3.3), the higher glutathione levels in the liver may be due to increased demand for glutathione for the metabolism of acrylonitrile.

A consistent observation in rats exposed to acrylonitrile was increased liver weight, both in acute studies at 65 mg/kg/day (Murray et al. 1978) and chronic studies at 10 mg/kg/day (Bio/dynamics 1980a, 1980b, 1980c). Again, this may be an adaptive change related to increased metabolic activity by the liver due to the presence of acrylonitrile in the body.

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Renal Effects. No adverse effects on the renal system have been reported in animals administered acrylonitrile via the oral route. In chronic studies in rats, increased kidney weights relative to body weight were observed (Bio/dynamics 1980a, 1980b, 1980c). However, the significance of this observation, if any, is not known, because no histopathological, blood chemistry, or urinalysis findings suggestive of kidney injury were observed in intermediate and chronic studies in rats or dogs (Bio/dynamics 1980a, 1980b, 1980c; Quast et al. 1975, 1980b).

The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans or animals following oral exposure to acrylonitrile.

Other Systemic Effects. Decreased adrenal weight, adrenal atrophy, and decreased aldosterone and corticosterone levels in plasma were observed in rats administered acrylonitrile in drinking water for 3 weeks at 70 mg/kg/day (Szabo et al. 1984). Similar effects were observed when the dosing period was extended to 60 days (Szabo et al. 1984). However, no effects on adrenal weight or histopathology of the adrenals were observed in several chronic studies in which doses were similar to the 21- and 60-day studies by Szabo et al. (1984) (Bio/dynamics 1980a, 1980b, 198Oc; Quast et al. 1980b).

The highest NOAEL values and all reliable LOAEL values for other systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.3 Immunological Effects

No studies were located regarding immunologic effects in humans or animals following oral exposure to acrylonitrile.

2.2.2.4 Neurological Effects

Exposure to acrylonitrile caused effects similar to those of cyanide poisoning. Intermediate and chronic exposure of animals to acrylonitrile resulted in decreased activity and depression (Beliles et al. 1980; Bigner et al. 1986; Quast et al. 1975). Species differences are apparent, dogs being more susceptible than rats. In dogs administered acrylonitrile for 6 months at 16 mg/kg/day, depression and lethargy were reported, with the majority of the experimental groups animals dying before the end of the study period (Quast et al. 1975). In rats, acute exposure results in a transient cholinomimetic stimulatory phase (salivation, diarrhea, lachrymation, vasodilation), followed by a central nervous system depression (Ahmed and Farooqui 1982; Ahmed and Pate1 1981). In rats exposed for 1 to 2 years at 70 mg/kg/day, decreased activity, abnormal gait, and prostration were noted but no deaths were reported (Beliles et al. 1980; Bigner et al. 1986). No histopathological changes in the nervous system were reported except those related to tumor formation (see Section 2.2.2.8) (Beliles et al. 1980).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Developmental Effects

Oral exposure to acrylonitrile has been shown to result in teratogenic effects in rats (Murray et al. 1978). Oral administration of 25 mg/kg/day of acrylonitrile during days 6 to 15 of gestation resulted in an increased incidence of malformations. Although the incidence of malformations at 25 mg/kg/day was not statistically significant, the authors considered them related to the administration of acrylonitrile. At a higher dose (65 mg/kg/day), the increase in malformations was statistically significant, and the same malformations were seen at both doses. Statistically significant lowered fetal body weight and shorter crown-rump length also were observed at 65 mg/kg/day. The number of live pups and resorption per litter were not affected by the administration of acrylonitrile. In this study a NOAEL of 10 mg/kg/day was established. Based on this value an acute oral MRL of 0.1 mg/kg/day was calculated as described in the footnote in Table 2-2.

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

In a three-generation reproduction study in rats, Beliles et al. (1980) found that exposure of animals to acrylonitrile in drinking water at 70 mg/kg/day resulted in reduced viability and lactation indices in all generations. The authors considered the reduced pup indices to be the result of maternal toxicity, possibly related to reduced milk production due to decreased water intake by the dams. Fostering of pups on untreated dams lessened pup mortality. Measurement of acrylonitrile in the pups was not performed.

Animal studies suggest possible effects of acrylonitrile on the male reproductive system. Tandon et al. (1988) observed histological and biochemical evidence of degenerative changes in testicular tubules of mice exposed to 10 mg/kg/day of acrylonitrile for 60 days. These changes were accompanied by a 45% decrease in sperm count. Whether the tubular changes or the decreased sperm count have an effect on fertility is not known because no studies have been conducted to evaluate the effects of acrylonitrile on the reproductive capability of treated mice. Based on the reduced sperm count and the degenerative changes in testicular tubules, an intermediate oral MRL of 0.01 mg/kg/day was calculated as described in the footnote in Table 2-2.

There appear to be significant inter-species differences with respect to histopathological effects of acrylonitrile on the male reproductive system. Histological examination did not reveal testicular degeneration in rats or dogs given acrylonitrile for 2 years (Bio/dynamics 1980a, 1980b, 198Oc; Quast et al. 1975, 1980b), although

an increase in testicular weight was observed in rats given acrylonitrile in drinking water at doses of 14 mg/kg/day for 2 years (Bio/dynamics 1980a). The biological significance of this effect is not clear, because this was observed in only one chronic drinking water study in rats, and was not observed in a gavage study in the same strain of rat (Spartan) or at comparable doses in Fisher 344 rats (Bio/dynamics 1980b, 1980c).

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

In vivo studies in animals suggest that oral exposure to acrylonitrile has limited genotoxic potential. Acrylonitrile produced no significant increase in chromosomal aberrations in bone marrow cells from rats administered up to 21 mg/kg/day (Rabello-Gay and Ahmed 1980), and no significant effect in a dominant lethal assay in rats at doses up to 60 mg/kg/day (Working et al. 1987). Studies on unscheduled DNA synthesis in liver and brain of rats exposed to doses of 50 mg/kg showed increased DNA synthesis in the liver but not in the brain, suggesting limited potential for acrylonitrile to be genotoxic (Hogy and Guengerich 1986). However, unscheduled DNA synthesis was not observed in an in vivo spermatocyte assay in rats exposed to 60 mg/kg/day (Hurtt et al. 1987).

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to acrylonitrile.

Chronic studies in rats provide convincing evidence that acrylonitrile is carcinogenic to animals when administered orally (Beliles et al. 1980; Bigner et al. 1986; Bio/dynamics 1980a, 1980b, 198Oc; Gallagher et al. 1988; Quast et al. 1980a). Tumors of the central nervous system and Zymbal gland were identified in most studies at doses of 1.4 mg/kg/day and higher. Tumors of the gastrointestinal tract (forestomach, intestines) and mammary gland (in females) were also common at doses of 3.4 mg/kg/day or higher (Bigner et al. 1986; Bio/dynamics 1980a, 198Oc; Maltoni et al. 1977; Quast et al. 1980b). Gallagher et al. (1988) noted a dose-dependent decrease in the number of rats with pituitary tumors (mainly prolactinomas) following chronic oral exposure to acrylonitrile in drinking water.

2.2.3 Dermal Exposure

2.2.3.1 Death

The death of a 10-year-old girl following dermal exposure to acrylonitrile was reported by Lorz (1950). An acrylonitrile preparation had been applied to the scalp of the child as a treatment for head lice. The child experienced nausea, headache and dizziness. Death occurred 4 hours after application. The concentration was not specified in this case report.

In guinea pigs, the dermal LD_{50} was reported to be 370 mg/kg (Roudabush et al. 1965). Values of 226 to 250 mg/kg have been noted in rabbits (Back et al. 1972; Roudabush et al. 1965).

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in animals following dermal exposure to acrylonitrile.

In humans, one study of a worker accidentally sprayed with acrylonitrile indicated that transient injury to liver and muscle may have occurred, but the data are too limited to draw any firm conclusions (Vogel and Kirkendall 1984).

Workers exposed to acrylonitrile vapors at 16 to 100 ppm for 20 to 45 minutes complained of intolerable itching of the skin, but no dermatitis was observed (Wilson et al. 1948). This is presumably a direct irritant effect of acrylonitrile on the skin.

In a study of Japanese workers exposed to acrylonitrile, irritation of the conjunctiva and upper respiratory tract was reported. Workers who may have been exposed to particularly high concentrations (inside polymerization tanks) experienced transient irritation of the scrotal skin. No concentrations of acrylonitrile were specified (Sakurai et al. 1978).

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following dermal exposure to acrylonitrile.

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

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/day)	LOAEL (Effect) Less Serious (mg/kg/day)	LOAEL (Effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE							
Death							
1	Gn Pig	ND				370 (LD50)	Roudabush et al. 1965
2	Rabbit	ND				250 (LD50)	Back et al. 1972
3	Rabbit	ND				226 (LD50)	Roudabush et al. 1965

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg/kg/day = milligram/kilogram/day; ND = no data; LD50 = lethal dose, mortality 50%.

2.2.3.4 Neurological Effects

Signs of cyanide poisoning were exhibited by a man accidentally sprayed with acrylonitrile. Dizziness, redness, nausea, vomiting and hallucinations were reported (Vogel and Kirkendall 1984). The symptoms persisted for 3 days.

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

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

In a well-controlled and conducted study with human volunteers, Jakubowski et al. (1987) reported that an average of 52% of the inhaled dose of acrylonitrile (5 or 10 mg/m^3) is absorbed by the lungs. Similar results were reported by Rogaczewska and Piotrowski (1968), who found that 46% of inhaled acrylonitrile is retained by the lungs of humans.

Pilon et al. (1988b) demonstrated in rats exposed to 4 mg/kg acrylonitrile (2,3-^{14}C) in a closed-circuit inhalation chamber that the absorption of acrylonitrile was biphasic, characterized by a rapid dose-dependent phase that was followed by a slower dose-independent phase.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to acrylonitrile.

Results of studies in laboratory animals with ^{14}C-acrylonitrile indicate acrylonitrile is rapidly and extensively absorbed by the oral route. Radiolabeled acrylonitrile is detected in blood within 30 minutes after administration of an oral dose and peak plasma concentrations are reached 6 hours after administration (Farooqui and Ahmed 1982). Extensive absorption is indicated by the fact that only 2 to 10% of administered radioactivity is recovered in the feces (Ahmed et al. 1982, 1983; Farooqui and Ahmed 1982; Young et al. 1977).

2.3.1.3 Dermal Exposure

In studies in human volunteers conducted by Rogaczewska and Piotrowski (1968), absorption by skin was estimated to be 0.6 mg/cm^2/hr. Though no quantitative estimates of dermal absorption could be made, absorption of acrylonitrile via the dermal route by humans was demonstrated in a case study by Vogel and Kirkendall (1984). Accidental spraying of a man with acrylonitrile resulted in marked symptoms of acrylonitrile toxicity, indicating that significant amounts of acrylonitrile had been absorbed, primarily through the skin.

No studies were located regarding absorption in animals following dermal exposure to acrylonitrile.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution of acrylonitrile in humans following inhalation exposure to acrylonitrile.

Acrylonitrile is rapidly distributed throughout the body after inhalation exposure. Measurable amounts of acrylonitrile derived radiolabel were present in the brain, stomach, liver, kidney, lung and blood within 1 hour of initiation of exposure (Pilon et al. 1988b).

2.3.2.2 Oral Exposure

Tissue distribution of radioactivity in rats after a single oral dose of ^{14}C-acrylonitrile indicates that acrylonitrile and its metabolites are rapidly distributed to all tissues (Ahmed et al. 1982, 1983; Silver et al. 1987; Young et al. 1977). Species differences are apparent. In mice, cyanide levels in the blood peaked at 1 hour, while in rats peak levels were not reached until 3 hours after administration (Ahmed and Pate1 1981). The highest levels of radioactivity were recovered in the gastrointestinal tract, in particular in the stomach. The retention of acrylonitrile and its metabolites in the stomach appears to be due, at least in part, to covalent binding (Ahmed et al. 1982; Silver et al. 1987). Young et al. (1977) noted that label accumulated in the stomach following intravenous as well as oral exposure to ^{14}C-acrylonitrile, suggesting that enterogastric circulation may be important in the preferential retention in the stomach.

Distribution studies by whole-body autoradiography in rats and monkeys revealed accumulation of radiolabel in the liver, kidney, lung, adrenal cortex and stomach. In fetuses exposed in utero, only the eye lens accumulated radiolabel at a higher concentration than that observed in maternal blood (Sandberg and Slanina 1980).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals following dermal exposure to acrylonitrile.

2.3.3 Metabolism

Proposed pathways for the metabolism of acrylonitrile are presented in Figure 2-3 (Ahmed et al. 1983; EPA 1980a; Langvardt et al. 1980; Linhart et al. 1988; Muller et al. 1987; Pilon et al. 1988a; Roberts et al. 1989). Studies indicate that the metabolism of acrylonitrile in animals proceeds by the same pathways whether exposure is by the oral (Ahmed et al. 1983; Langvardt et al. 1980; Pilon et al. 1988a) or the inhalation route (Gut et al. 1985; Muller et al. 1987; Tardif et al. 1987). No data were located regarding the metabolism of acrylonitrile following dermal exposure.

Both enzymatic and nonenzymatic biotransformation of acrylonitrile occurs. Acrylonitrile is capable of covalently binding to proteins and other macromolecules such as lipids or nucleic acids, or acrylonitrile can also be directly conjugated to glutathione and excreted in urine as cyanoethylmercapturic acid.

Alternatively, acrylonitrile is metabolized to 2-cyanoethylene oxide by the microsomal enzyme system. 2-Cyanoethylene oxide can react directly with tissue macromolecules or it can be further metabolized to oxidation products that release cyanide. Cyanide is converted to thiocyanate and excreted in the urine. 2-Cyanoethylene oxide is also conjugated with glutathione and metabolized to 2-hydroxyethylmercapturic acid which is excreted in the urine.

Acrylonitrile is also metabolized to CO_2 which is eliminated through the lungs. Carbon dioxide is produced when acrylonitrile is metabolized to ethylene oxide and degraded to oxidation products and cyanide via the epoxide hydratase pathways (Farooqui and Ahmed 1982; Young et al. 1977).

Studies indicate that acrylonitrile conjugation with glutathione is the preferred pathway for metabolism (Ghanayem and Ahmed 1982; Miller and Villaume 1978; Pilon et al. 1988a). However, if glutathione is depleted or the pathway is overloaded (as may be the case at high doses), metabolism to the thiocyanate via 2-cyanoethylene oxide is increased. Increased thiocyanate excretion with glutathione depletion or increased dose was demonstrated by Pilon et al. (1988a). Glutathione

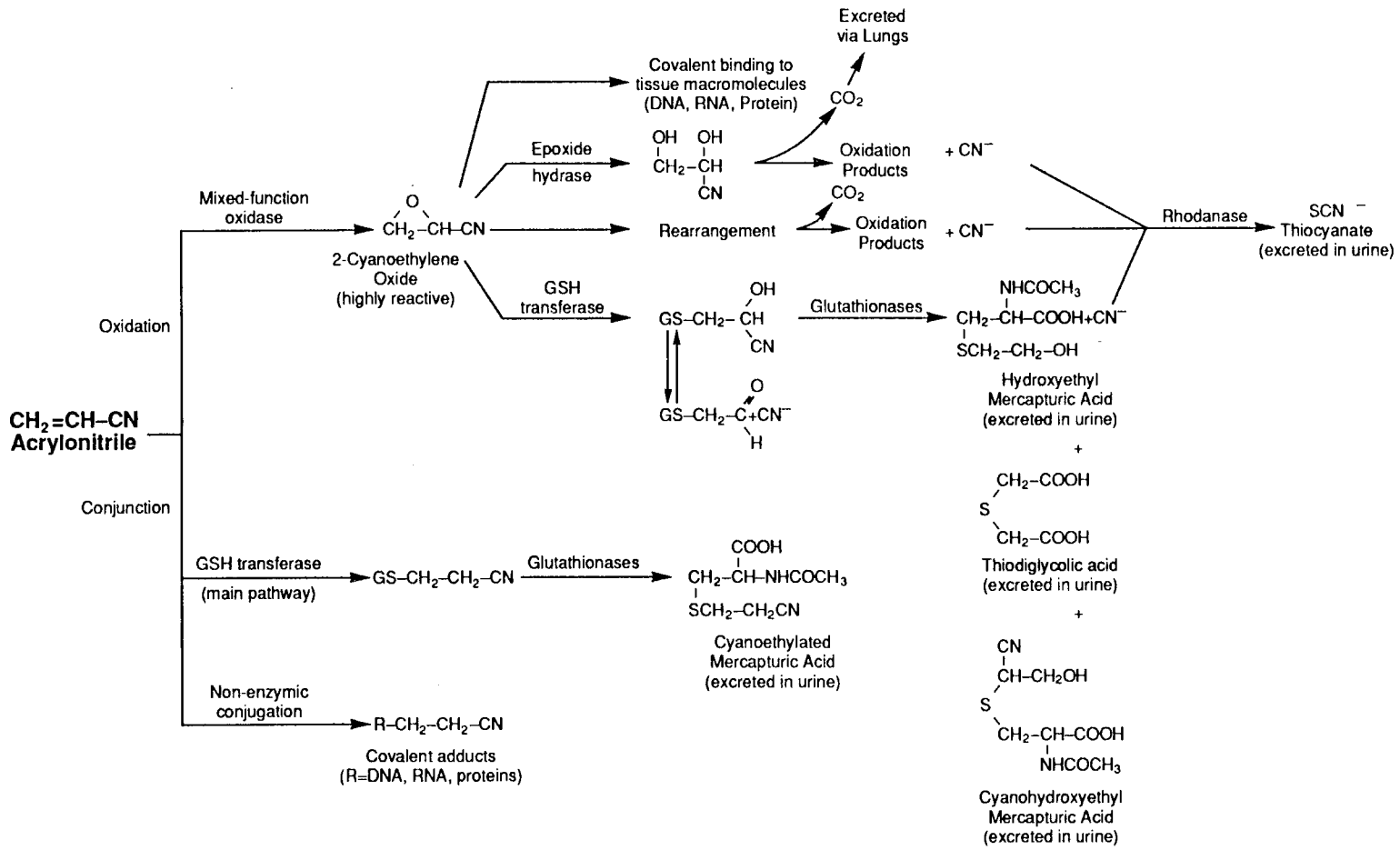

FIGURE 2-3. Proposed Metabolic Scheme for Acrylonitrole

Adapted from Ahmed et al. 1983, Linhart et al. 1988, Muller et al. 1987, Roberts et al. 1989

depleted rats excreted 58% of an orally administered dose as thiocyanate, while normal rats given the same dose (4 mg/kg) of acrylonitrile excreted only 23% as thiocyanate. Normal rats given acrylonitrile at 4 or 10 mg/kg excreted 16% and 23% of the dose as thiocyanate, respectively.

The increased metabolism of acrylonitrile to 2-cyanoethylene oxide has significant implications in acrylonitrile toxicity. 2-Cyanoethylene oxide has been shown to react with cell macromolecules (including nucleic acids) both in vivo and in vitro (Guengerich et al. 1981; Hogy and Guengerich 1986). This metabolite may be responsible for the carcinogenic effects of acrylonitrile.

Urinary excretion patterns of thiocyanate suggest that there are quantitative species differences in acrylonitrile metabolism (Ahmed and Patel 1981). Thiocyanate was identified as a metabolite in rats, mice, rabbits and Chinese hamsters. About 20 to 23% of the administered dose was excreted as thiocyanate in rats, rabbits and Chinese hamsters, while 35% was excreted as thiocyanate in mice (Gut et al. 1975). It has also been observed that mice metabolize acrylonitrile more rapidly than rats (Ahmed and Patel 1981; Gut et al. 1975). Maximum blood cyanide concentrations were observed 1 hour after dosing in mice, but 3 hours after dosing in rats (Ahmed and Patel 1981). In mice, thiocyanate was present in the urine within 4 hours of dosing, while in rats, thiocyanate was present in urine only at time intervals longer than 4 hours (Gut et al, 1975).

In humans, metabolites of acrylonitrile have been identified in urine following occupational exposure (assumed to be by the inhalation route), and also in controlled exposure studies. Metabolites identified in humans were the same as those in animals (Jakubowski et al. 1987; Sakurai et al. 1978). Acrylonitrile and thiocyanate were quantified in urine of workers exposed to acrylonitrile. Dose-related increases in thiocyanate were observed, indicating that cyanide is liberated with the metabolism of acrylonitrile. In a study with human volunteers under controlled conditions, 2-cyanoethylmercapturic acid (CMA) was monitored in urine as an indication of exposure. On average, 22% of the absorbed acrylonitrile was metabolized to CMA; however, considerable individual variability was observed. The CMA excretion ranged from 13% to 39% of the absorbed dose (Jakubowski et al. 1987).

In a case study of a human male accidentally sprayed with acrylonitrile, recurring signs of cyanide poisoning were seen over a 3 day period (Vogel and Kirkendall 1984). This indicates that acrylonitrile is also metabolized to cyanide following predominantly dermal exposure.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

Studies on workers in an occupational setting showed a dose-response relationship between the concentration of acrylonitrile of inspired air and the recovery of metabolites in the urine (Houthuijs et al. 1982; Sakurai et al. 1978). In a controlled study using human volunteers, urinary metabolite data suggested that the elimination of acrylonitrile followed first-order kinetics, with a half-life of seven to eight hours (Jakubowski et al. 1987).

The predominant route of excretion in rats is via urine (Gut et al. 1985; Tardif et al. 1987; Young et al. 1977). In rats exposed to 5 ppm of 1-^{14}C-acrylonitrile for 6 hours, 68% of the absorbed radioactivity was excreted in the urine within 220 hours, with 3.9% in the feces, 6.1% in expired air as $^{14}CO_2$, and 18% of the radioactivity being retained in the body tissues. Following exposure to a higher concentration (100 mm), a larger fraction of the dose was recovered in urine (82%) and a smaller fraction (2.6%) was retained in the body (Young et al. 1977), indicating that urinary excretion is dose-dependent. Percent fecal excretion was similar at both doses.

2.3.4.2 Oral Exposure

Following oral exposure, the major route of excretion of acrylonitrile in rats is via the urine, either as thiocyanate or as other products of conjugation. Within the first 24 hours of a single oral dose, 40% to 60% was recovered in the urine (Ahmed et al. 1983). Farooqui and Ahmed (1982) reported that 10 days after the administration of a single dose, 61% of the dose had been accounted for in the urine, 3% in feces and 13% in the expired air. Approximately 25% was retained in the body covalently bound to tissues (see Section 2.3.3).

A study by Young et al. (1977) showed that retention and excretion of acrylonitrile are not directly proportional to dose. The data suggest a saturation process, perhaps due to covalent binding to tissue macromolecules. Seventy-two hours after administration of single oral doses of either 0.1 or 10 mg/kg, the proportion of the dose retained in the carcass was 37% at the low dose (0.1 mg/kg) and 27% at the high dose (10 mg/kg).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to acrylonitrile.

2.4 RELEVANCE TO PUBLIC HEALTH

Acrylonitrile is a common industrial chemical, and humans may be exposed to acrylonitrile around factories where it is made or used, or near chemical waste sites where it has been improperly stored or disposed of. The two most likely exposure pathways are breathing acrylonitrile that has evaporated into air (it is readily volatile), or drinking water that has been contaminated (acrylonitrile is highly soluble and stable in water). However, data describing acrylonitrile levels in drinking water are currently lacking. The low odor threshold of acrylonitrile in water (19 ppm) could limit exposure to this substance through contaminated drinking water.

Short exposures at high concentrations show cyanide-type toxicity. In humans, symptoms include headaches, feelings of nausea, irritability, and apprehension. These symptoms are reversible. However, prolonged exposure can result in death. Limited data suggest that children may be more susceptible to acrylonitrile toxicity than adults. However, current data are not significant to draw firm conclusions. In animals, acrylonitrile has been shown to result in teratogenic effects when administered by either the inhalation or oral routes of exposure. Impaired reproductive capability has also been demonstrated in mice. Exposures high enough to cause neurological, developmental, or reproductive effects in humans are rather unlikely to occur except in cases of spills or accidents.

Epidemiologic studies have associated acrylonitrile exposure in the workplace with increased incidence of lung cancer and possibly prostate cancer. Because only six cases of prostate cancer were observed and all were found in workers at ages when the incidence rate increases, firm conclusions cannot be made about the potential for acrylonitrile to cause prostate cancer. In animals, acrylonitrile has been demonstrated to cause tumors at multiple sites, including the nervous system, gastrointestinal tract, Zymbal gland and mammary gland. Because of this clear carcinogenic potential, chronic low-level exposure to acrylonitrile is of special concern.

Death. Several cases of death in children following inhalation or dermal exposure to acrylonitrile has been reported (Grunske 1949; Lorz 1950). Children seem to be more susceptible to the lethal effect of acrylonitrile than adults. However, current data are not sufficient to draw firm conclusions regarding risk. In the case studies where children had died after sleeping in rooms fumigated with acrylonitrile, the adults that shared the quarters reported few, if any, effects.

In animals, deaths from acrylonitrile have been reported in several species following inhalation, oral or dermal exposure. In most species, death appears to be related to cyanide poisoning. That the cyanide moiety is involved in human toxicity of acrylonitrile has been reported in a case study in which a human male was sprayed with acrylonitrile when a valve burst (Vogel and Kirkendall 1984). This individual suffered symptoms characteristic of cyanide poisoning, and treatments designed to reduce cyanide levels in the blood were required in order to save his life.

Systemic Effects. Humans exposed to high levels of acrylonitrile in the workplace have complained of nasal irritation and an oppressive feeling in the upper respiratory passages (Wilson 1944; Wilson et al. 1948). Acute exposure of guinea pigs to acrylonitrile has resulted in severe pulmonary irritation and lung edema. In other species, only mild pulmonary irritation has been reported (Dudley and Neal 1942). Chronic exposure to acrylonitrile via inhalation has resulted in degenerative and inflammatory changes in the nasal passages in rats (Quast et al. 1980a). The concentrations at which these effects have been seen in animals are irritating to the respiratory tract of humans.

The gastrointestinal tract does not appear to be a target organ of acrylonitrile toxicity in humans. In animals, noncarcinogenic lesions in the esophagus and stomach suggest an irritational effect on the gastrointestinal tract (Murray et al. 1978; Quast et al. 1975). However, several investigators (Cote et al. 1984; Ghanayem and Ahmed 1983; Ghanayem et al. 1985; Szabo et al. 1983) have demonstrated that gastrointestinal bleeding and duodenal ulcers may occur even when rats were given acrylonitrile by routes other than oral, suggesting that the effects on the gastrointestinal tract may not be due exclusively to irritation. More study is needed in this area before any conclusions about the relevance to human health can be drawn.

In humans, severe cases of acrylonitrile poisoning have resulted in low grade anemia (Wilson 1944; Wilson et al. 1948), but complete recovery was reported. Chronic occupational exposure to low levels of acrylonitrile has not resulted in detectable effects on the hematological system (Sakurai et al. 1978). In intermediate and chronic studies in animals, decreased red cell count, hemoglobin concentration and hematocyte were observed (Bio/dynamics 1980a, 1980b, 198Oc; Quast et al. 1975; 198Oa). However, it is not certain if these effects are due to acrylonitrile binding to red blood cell membranes and proteins (Farooqui and Ahmed 1982), or are secondary effects related to the poor physical condition which develops in the exposed animals.

Some liver damage has been reported in humans after acute exposure to high doses. In workers exposed to high levels of acrylonitrile vapors, mild jaundice was diagnosed (Wilson 1944). In a case of an accidental dermal exposure of a man, enzyme levels in the blood suggestive of liver injury were reported for several days (Vogel and Kirkendall 1984). These effects appeared to be fully reversible.

The liver has been reported to be the primary site of acrylonitrile metabolism. Metabolism studies indicate that a toxic metabolite (2-cyanoethylene oxide) is formed that covalently binds to liver tissue. However, the liver has not been indicated as a target organ for intermediate or chronic exposure in humans or animals. In factory workers exposed to acrylonitrile for 10 or more years, no liver damage has been observed (Sakurai et al. 1978). In animal studies, microscopic examination of liver tissue has revealed no hepatic damage after 90 days to 2 years of exposure by the inhalation or oral routes (Bio/dynamics 1980a, 1980b, 198Oc; Humiston et al. 1975; Quast 1975, 1980a, 1980b).

Some effects seen in the livers of animals may suggest that adaptive changes occur as a response to increased metabolic activity. These include increased glutathione levels, possibly due to an increased demand for glutathione for the metabolism of acrylonitrile. Increased liver weights have also been observed in both acute and chronic oral studies (Bio/dynamics 1980a, 1980b, 198Oc; Murray et al. 1978).

Skin irritation results from direct contact with liquid or gaseous acrylonitrile. Workers exposed to high levels of acrylonitrile in air have complained of itching, but no dermatitis was observed (Wilson et al. 1948). Also, transient irritation of scrotal skin has been noted by workers after entering areas with high ambient acrylonitrile concentrations. Direct contact of acrylonitrile with the skin has resulted in erythema, desquamation and slow healing (Dudley and Neal 1942). In both humans and animals, skin redness has been reported subsequent to acute exposures (Dudley and Neal 1942; Vogel and Kirkendall 1984).

Immunological Effects. Immunological effects of acrylonitrile have not been studied in humans or animals.

Neurological Effects. Acute effects have been described as being a cyanide-type poisoning (Dudley and Neal 1942; Vogel and Kirkendall 1984). These observations are consistent with results from studies in animals where it has been shown that the major metabolic pathways include cyanide and thiocyanate as products of acrylonitrile metabolism (Ahmed et al. 1983; EPA 1980a; Langvardt et al. 1980; Pilon et al. 1988a). The formation of cyanide following oral exposure is greater than inhalation or subcutaneous exposure (Gut et al. 1975), indicating

that the amount of acrylonitrile reaching the liver in free form (i.e., not covalently bound) may determine the amount of cyanide formed. Symptoms which have been associated with acrylonitrile poisoning in humans include limb weakness, labored and irregular breathing, dizziness and impaired judgment, cyanosis and nausea, collapse, and convulsions (Baxter 1979). Case studies of occupational exposure to acrylonitrile suggest that the acute nonlethal effects in humans may be fully reversible (Vogel and Kirkendall 1984; Wilson 1944; Wilson et al. 1948).

Acute exposure of several species of animals has been reported to lead to convulsions and coma (Dudley and Neal 1942). Exposure of animals for 6 months or more at 16 mg of acrylonitrile per kilogram body weight per day (mg/kg/day) results in neurological effects characterized by decreased activity and depression (Bigner et al. 1986; Beliles et al. 1980; Quast et al. 1975). However, the only histopathological changes seen in the nervous system have been those associated with the formation of tumors (Bio/dynamics 1980a, 1980b, 1980c; Quast et al. 1975, 1980a, 1980b).

Developmental Effects. There are no data available on developmental effects of acrylonitrile in humans; however, two well-conducted studies in rats have shown that acrylonitrile is teratogenic in animals by both inhalation and oral exposure (Murray et al. 1978). Fetal malformations occurred in a dose-related manner. When administered orally, malformations were present even at doses in which no maternal or fetal toxicity was apparent.

Reproductive Effects. There are no data available on the reproductive effects in humans. However, a three-generation reproduction study in rats showed that acrylonitrile has an effect on reproduction. In all three generations, viability and lactation indices were affected by 'the presence of acrylonitrile in the drinking water (Beliles et al. 1980). Species differences were observed with respect to the effects of acrylonitrile on male reproductive organs. In mice, adverse effects on male reproductive organs were demonstrated at 10 mg/kg/day in a 60-day study (Tandon et al. 1988). In rats, no effects on male reproductive organs were seen even when exposure was at 14 mg/kg/day for 2 years (Bio/dynamics 1980a, 1980b, 198Oc; Quast et al. 1980a, 1980b).

Genotoxic Effects. The genotoxicity of acrylonitrile in vitro has been extensively studied (Table 2-4). Although the results are not entirely consistent, positive results have been observed for all end points evaluated: gene mutations, chromosomal aberrations, DNA damage, and cell transformation. However, in vivo genotoxicity studies have generally been negative in mammalian systems, including humans (Table 2-5). Tests in Drosonhila melanozaster suggest that

TABLE 2-4. Genotoxicity of Acrylonitrile In Vitro

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	Salmonella typhirmurium (plate incorporation)	+	+	Khudoley et al. 1987
	S. typhimurium (plate incorporation)	+	-	Lijinsky and Andrews 1980
	S. typhimurium (plate incorporation)	-	+	Baker and Bonin 1985
	S. typhimurium (liquid preincubation)	+	+	Zeiger and Haworth 1985
	S. typhimurium (liquid preincubation)	-	-	Matsushima et al. 1985
	S. typhimurium (gas exposure)	+	-	DeMeester et al. 1978
	Escherichia coli	No data	+	Venitt et al. 1977
Eukaryotic organisms:				
Fungi:				
Gene conversion	Saccharomyces cerevisia D7	-	+	Arni 1985
	S. cerevisiae JD1	+	-	Brooks et al. 1985
Mammalian cells:				
Gene mutation	Mouse lymphoma L5178Y thymidine kinase locus	No data	+	Myhr et al. 1985
	Mouse lymphoma L5178Y thymidine kinase locus	+	+	Amacher and Turner 1985
	Mouse lymphoma L5178Y thymidine kinase locus	+	+	Lee and Webber 1985
	Mouse lymphoma L5178Y ouabain resistance	-	-	Garner and Campbell 1985
	Mouse lymphoma L5178Y 6-thioguanine resistance	+	+	Garner and Campbell 1985

TABLE 2-4 (Continued)

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
	Chinese hamster V79/HGPT	-	-	Lee and Webber 1985
	Mouse lymphoma P388F thymidine kinase locus	+	-	Anderson and Cross 1985
	Human lymphoblasts AHH-1 TK6	+	-	Crespi et al. 1985
	Human lymphoblastoid TK6	+	-	Recio and Skopek 1988
	Human lymphoblasts	NA	+	Crespi et al. 1985
Sister chromatid exchange	Rat liver RL4	NA	-	Priston and Dean 1985
	Human lymphocytes	-	-	Obe et al. 1985
	Human lymphocytes	+	-	Perocco et al. 1982
	Chinese hamster ovary	+	-	Brat and Williams 1982
DNA Synthesis	Hepatocyte primary cultures	NA	+	Williams et al. 1985
	Hepatocyte primary cultures	NA	+	Glauert et al. 1985
	Hepatocyte primary cultures	NA	-	Probst and Hill 1985
Cell transformation	Syrian hamster embryo cells	NA	+	Sanner and Rivedal 1985; Parent and Casto 1979
	Balb/C-3T3	+	-	Matthews et al. 1985
	C3H/10T1/2	+	-	Lawrence and McGregor 1985
	C3H/10T1/2	NA	+	Banerjee and Segal 1986
	NIH/3T3	NA	+	Banerjee and Segal 1986

+ = positive result; - = negative result; NA = not applicable.

TABLE 2-5. Genotoxicity of Acrylonitrile *In Vivo*

End Point	Species (Test System)	Results	Reference
Mammalian systems:			
Chromosomal aberrations	Mouse bone marrow	-	Leonard et al. 1981
	Mouse bone marrow	-	Sharief et al. 1986
	Mouse bone marrow	-	Rabello-Gay 1980; Ahmed 1980
Micronuclei	Mouse bone marrow	-	Leonard et al. 1981
Dominant lethals	Mouse	-	Leonard et al. 1981
Host medicated assays:			
Gene mutations	*S. typhimuriam* (mouse host mediated)	-	Lambotte-Vandepaer et al. 1980
	S. typhimuriam (rat host mediated)	-	Lambotte-Vandepaer et al. 1980, 1981
Non-mammalian systems:			
Gene mutations	*Drosophila melanogaster*	+	Fujikawa et al. 1985; Vogel 1985; Wurgler et al. 1985

- = negative result; + = positive result.

acrylonitrile may have potential for genotoxicity in vivo. Acrylonitrile and its metabolites have been shown to bind to nucleic acids both in vivo and in vitro suggesting that acrylonitrile does have potential for genetic damage.

Cancer. Studies in rats by inhalation and oral exposure have all demonstrated that acrylonitrile is carcinogenic. Multiple tumor sites have been identified (Bio/dynamics 1980a, 1980b, 1980c; Quast et al. 1980a, 1980b). There is limited evidence that acrylonitrile is a human carcinogen. Some epidemiology studies indicate that occupational exposure to acrylonitrile results in an increased incidence of lung cancer (O'Berg 1980; O'Berg et al. 1985). However, other studies have not reached this conclusion (Collins et al. 1989; Kiesselbach et al. 1979). There is also a suggestion that acrylonitrile exposure may result in an increased incidence of prostate cancer (Chen et al. 1987; O'Berg et al. 1985). Limitations of these studies do not allow firm conclusions about the potential for acrylonitrile to cause prostate cancer. EPA has classified acrylonitrile as a probable human carcinogen (IRIS 1988). There is sufficient evidence in animals that acrylonitrile is carcinogenic, but the human evidence is limited.

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 biomarkers of exposure, biomarkers of effect, and biomarkers 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 acrylonitrile 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 epithelium 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 acrylonitrile 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."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Acrylonitrile

Parent acrylonitrile molecule and its metabolites have been measured in blood and urine, but, except for measurement of thiocyanate, methods have not been developed for routine monitoring of exposed humans.

Factory workers exposed to an average of 0.1, 0.5 and 4.2 ppm of acrylonitrile in the air during an 8-hour work day averaged 3.9, 19.7, and 360 μg/L acrylonitrile in the urine, respectively, and 4.5, 5.78, and 11.4 mg/L thiocyanate in the urine, respectively (Sakurai et al. 1978). No acrylonitrile was detected in the urine of a control group, but an average of 4.00 mg/L of thiocyanate was found in the urine. The presence of thiocyanate in the urine of workers not exposed to acrylonitrile has been related to cigarette smoking (Houthuijs et al. 1882; Sakuria et al. 1978). Houthuijs et al. (1982) reported post-shift acrylonitrile values of 39 μg/L when the mean acrylonitrile concentration in the air was 0.13 ppm.

2.5.2 Biomarkers Used to Characterize Effects Caused by Acrylonitrile

A variety of effects have been demonstrated following acrylonitrile exposure in humans and animals. These effects show a close similarity to an underlying cyanide effect, particularly for acute exposures. Effects can be detected in groups of exposed individuals by monitoring

signs and symptoms such as increased salivation, dizziness, and labored and irregular breathing. In some cases convulsions and coma may occur. Because the release of cyanide for producing toxic effects is common for other compounds, measuring these effects is not specific for acrylonitrile exposure. These effects do identify potential health impairment. It should be noted that the toxicity of acrylonitrile resides not only in the cyanide radical but in the entire molecule. The latter structure explains various chronic effects such as cancer that result from acrylonitrile, as opposed to cyanide whose effects are more relevant for acute toxicity. Studies that identify subtle physiological changes that can be used to detect or predict risk of disease following long-term exposure to acrylonitrile are not available.

2.6 INTERACTIONS WITH OTHER CHEMICALS

The interaction between acrylonitrile and other chemicals has not been thoroughly studied. O'Berg (1980) noted that out of 8 workers exposed to acrylonitrile who developed lung cancer, 7 were smokers (smoking history was not available for the eighth individual). This suggests that smoking might increase lung cancer risk from acrylonitrile, but the data are too limited to draw any firm conclusions on this point.

Radimer et al. (1974) described four cases of severe epidermal necrolysis in individuals who had been exposed to the residual fumes of a mixture of acrylonitrile and carbon tetrachloride used to fumigate their homes. Three of the people died. The authors thought this was most likely due to the effects of acrylonitrile, but noted that an interaction between carbon tetrachloride and acrylonitrile was possible.

In animals, the hemorrhagic effects of acrylonitrile exposure on the adrenals may be reduced by prior exposure of the animals to adrenergic blockers or chemicals that deplete the adrenal cortex of catecholamines (Silver et al. 1987; Szabo et al. 1980). It is difficult to judge whether adrenergic antagonists would have a similar protective effect in humans, because effects of acrylonitrile on the adrenal have not been described in humans.

Acrylonitrile alone has little tendency to produce duodenal ulcers in animals, but pretreatment with phenobarbital or Aroclor results in a marked increase in the incidence of such ulcers (Szabo et al. 1983, 1984). Although the mechanism of the ulcerogenic effect is not obvious, these data indicate that agents which enhanced mixed-function oxidase activity may also increase the toxicity of acrylonitrile.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Case studies of acrylonitrile poisoning in humans following fumigation of living quarters in post-World War II Germany suggest that children are more susceptible to acrylonitrile than adults (Grunske 1949). Children died after sleeping in rooms recently fumigated with acrylonitrile for lice and bed bugs, while adults sharing the same quarters reported few, if any, effects (skin or eye irritation).

Studies in animals indicate that acrylonitrile can produce teratogenic effects at doses that have little maternal toxicity, suggesting that pregnant women may also be susceptible. It also seems likely that individuals in poor health or with respiratory problems might be particularly susceptible to acrylonitrile, but there are no data on this point.

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 acrylonitrile 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 acrylonitrile.

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 the Health Effects of Acrylonitrile

Figure 2-4 summarizes areas concerning the health effects of acrylonitrile where studies have and have not been performed. There are some data available on the effects in humans following acute or chronic exposure to acrylonitrile via the inhalation route of exposure. The target organ for acute toxicity is the nervous system. Chronic exposure to acrylonitrile has been associated with cancer. However, many of the available reports lack quantitative information on exposure levels. In humans, there are no data on oral exposure to acrylonitrile and a very limited amount of acute data on dermal exposure. In animals, there are data available on inhalation and oral exposure and limited dermal exposure data.

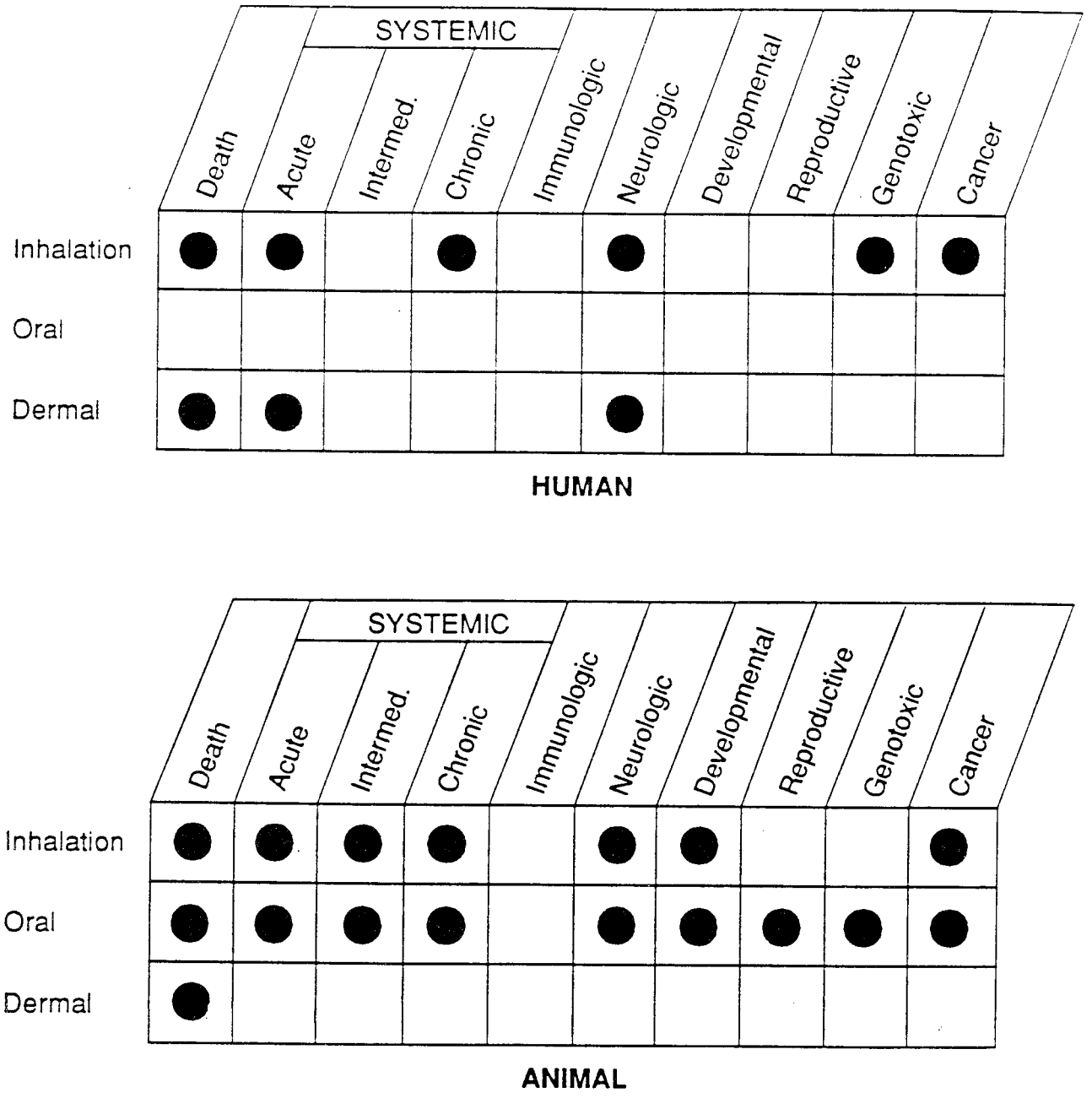

FIGURE 2-4. Existing Information on Health Effects of Acrylonitrile

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Information is available regarding the effects of acute-duration inhalation exposure of humans to acrylonitrile and the effects are characteristic of cyanide-type toxicity. Quantitative data are limited but are sufficient to derive an acute inhalation MRL. Further studies of humans exposed to low levels of acrylonitrile in the workplace would increase the confidence of the acute MRL. Studies in animals support and confirm these findings. No studies are available on the effects of acute-duration oral exposure in humans; however, exposure to acrylonitrile reveals neurological disturbances characteristic of cyanide-type toxicity and lethal effects in rats and mice. Rats also develop birth defects. Animal data are sufficient to derive an acute oral MRL. Additional studies employing other species and various dose levels would be useful in confirming target tissues and determining thresholds for these effects. In humans, acrylonitrile causes irritation of the skin and eyes. No data are available on acute dermal exposures in animals.

Intermediate-Duration Exposure. No information is available on the effects of intermediate-duration inhalation, oral, or dermal exposure in humans or inhalation and dermal exposures in animals. There is information on intermediate-duration oral exposure in animals. Studies revealed decreased reproductive indices, decreased sperm count and tubular degeneration in rats and mice. Blood cell counts were low in rats and there was evidence of ulcerogenic effects in dogs. Acrylonitrile was also lethal in dogs. Data in animals were sufficient to derive an intermediate-duration oral MRL. Further studies in animals would be useful in defining threshold for these effects.

Chronic-Duration Exposure and Cancer. No studies were located evaluating chronic effects associated with acrylonitrile exposure in humans by any route of exposure. There is evidence of hematological effects and alterations in organ weights (kidney, liver) in rats following oral exposure. Additional chronic-duration studies in other species by inhalation and oral exposures would be useful in determining other target organs and thresholds for these effects. There are studies of humans chronically exposed to acrylonitrile in workplace air. These studies link acrylonitrile exposure to lung cancer and it has been suggested that the chemical may have the potential to cause prostate cancer. Due to limitations of these studies, firm conclusions cannot be made. Additional studies providing quantitative exposure data and evaluating confounding associations would be useful in clarifying potential risk.

Genotoxicity. Microbiol and mammalian assays are available on the genotoxic effects of acrylonitrile. Results of in vitro tests evaluating gene mutation in prokaryotic and eukaryotic cell types are variable. Similarly, results were mixed for in vitro mammalian assays evaluating gene mutation, chromosomal aberration and DNA repair and damage. In vivo tests evaluating chromosomal aberrations were negative. Additional investigations evaluating structural and numerical chromosomal aberrations in humans exposed in the workplace would be useful in determining the significance of effects found in animal assays.

Reproductive Toxicity. No studies have been conducted in humans regarding reproductive toxicity of acrylonitrile after inhalation, oral, or dermal exposure or inhalation and dermal exposures in animals. Studies in male mice have shown that exposure to acrylonitrile in drinking water affects sperm count and results in tubular degeneration. No effects on male reproductive organs have been reported in rats. Studies to further evaluate the significance of the testicular effects on reproductive capability in mice and other species would be very valuable. Studies on reproduction via the inhalation route would be valuable in determining whether the effects seen in oral studies are unique to that route of exposure.

Developmental Toxicity. No information is available on developmental effects of acrylonitrile in humans by any route of exposure. Acrylonitrile is teratogenic and embryotoxic in rats both by the oral and inhalation routes of exposure. Developmental studies on other animal species have not been conducted. Because species differences for acute acrylonitrile toxicity and metabolism have been demonstrated, additional developmental studies in other species using various dose leve.ls would be valuable in evaluating the potential for acrylonitrile to cause developmental effects in humans. Because the available oral study was conducted by gavage, additional studies are needed to determine if these effects will occur following ingestion of drinking water or food.

Immunotoxicity. No information was found on the immunological effects of acrylonitrile in humans or animals by any route of exposure. Because no immunopathological effects have been reported in subchronic and chronic studies involving multiple species, additional studies employing a more specific testing battery are not warranted at this time.

Neurotoxicity. Clinical signs indicative of disturbances of the nervous system in exposed humans have been well documented in short-term studies at high doses and appear to be reversible. These effects are characteristic of cyanide toxicity. Animal studies confirm findings in

humans. In longer-term studies, effects on the nervous system have also been reported, but it is not certain if these effects are permanent or reversible following termination of acrylonitrile exposure.

Epidemiological and Human Dosimetry Studies. There are studies on the adverse effects of acrylonitrile in humans. These studies link acrylonitrile exposure and lung cancer. It has also been suggested that acrylonitrile may have the potential to cause prostate cancer. Many of the studies have major limitations including insufficient quantification of exposure, short follow-up, small study population, and inadequate evaluation of confounding associations. Additional studies would be useful in clarifying the cancer risk and estimating the exposure levels that lead to these effects.

Biomarkers of Exposure and Effect. The presence of thiocyanate and 2-cyanoethyl mercapturic acid have been monitored in urine as indicators of acrylonitrile exposure.

Effects produced by exposure to acrylonitrile, particularly after acute exposures, are characteristic of cyanide toxicity. These effects can be detected in people exposed by evaluating signs and symptoms such as limb weakness, labored and irregular breathing, dizziness and impaired judgement, cyanosis and convulsions. While tests are not specific for acrylonitrile-induced toxicity, they do identify potential health impairment. Studies to develop more specific biomarkers of acrylonitrile-induced effects would be useful in assessing the potential health risk of acrylonitrile near hazardous waste sites.

Absorption, Distribution, Metabolism, and Excretion. Metabolism and excretion in animals exposed to acrylonitrile by the inhalation and oral routes have been studied extensively. However, only limited data on absorption and distribution are available. Some data on humans exposed by inhalation are available. No data are available on the toxicokinetics of acrylonitrile when the exposure route is dermal. More extensive information on absorption and distribution of acrylonitrile would be valuable to fully understand the toxicokinetics of acrylonitrile. Some data on the toxicokinetics of acrylonitrile by the dermal route would be valuable in order to determine if metabolism of acrylonitrile differs by route of exposure. Development of physiologically-based toxicokinetic models would also be valuable in extrapolation of animal data to humans.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of acrylonitrile in rats has been studied. Limited work in other species suggests that important species

differences do exist. Further evaluation of these differences, and comparison of metabolic patterns in humans with those of animals would assist in determining the most appropriate animal species for evaluating the hazard and risk of human exposure to acrylonitrile.

2.8.3 On-going Studies

A number of research projects in progress are investigating the mechanism of toxicity and tumor formation of acrylonitrile. The projects are summarized in Table 2-6.

A number of on-going epidemiology studies are evaluating the effects of occupational exposure to acrylonitrile. Independent investigations are being conducted by Dr. R. D. Jones of the Employment Medical Advisory Service of the United Kingdom; Dr. L.J. Lucas of American Cyanamid Company; and Dr. L. I. Glass of SRA Technologies, Inc.

TABLE 2-6. On-going Studies on Acrylonitrile

Investigator	Affiliation	Research Description	Sponsor
D.D. Bigner	Duke University	Immunological and histological studies on brain tumors following acrylonitrile exposure	NCI
F.P. Guengerich	Vanderbilt University	Bioactivation and covalent binding	NIEHS
A. Segal	New York University	Tumor induction by acrylonitrile and its epoxide	NIEHS
-	CIIT	Comparative studies of the metabolism and pharmacokinetics of acrylonitrile and cyano-ethylene oxide in mice and rats	BP
T.R. Fennell, J.P. MacNeela, M.J. Turner, et al.	CIIT	Hemoglobin adducts formed on administration of acrylonitrile (AN) to rats	BP
-	CIIT	Molecular studies of the mutagenic effects of acrylonitrile metabolites and investigation of the formation of DNA adducts	BP
T.R. Fennell, S.C. Sumner, S.D. Held, et al.	CIIT	Detection of eight urinary metabolites of [1,2,3-^{13}C] acrylonitrile in the rat and mouse using ^{13}C nuclear magnetic resonance spectroscopy	-
G.L. Kedderis S.D. Held, R. Batru, et al.	CIIT	Dose-dependent urinary excretion of four acrylonitrile (ACN) metabolites in F-344 rats and B6C3F1 mice	-

Table 2-6 (Continued)

Investigator	Affiliation	Research Description	Sponsor
D.E. Rickert, A.E. Roberts, D. Pilon, et al.	CIIT	Distribution of acrylonitrile (ACN) in tissues of control and glutathione (GSH) depleted B6C3F1 mice	-
M.L. Gargas, G.L. Kedderis, T.R. Fennell, et al.	CIIT	A physiologically-based pharmacokinetic (PB-PK) model for acrylonitrile (ACN) in the rat	-
G.M.H. Swaen	University of Limburg, Netherlands	Mortality study with quantitative exposure assessment of 3,000 Dutch workers exposed to acrylonitrile until 1987 and 4,000 employed controls	-
-	CIIT	Mechanisms of acrylonitrile carcinogenicity in experimental test systems	BP
D.D. Bigner	Duke University	Tumor transplantation to determine whether acrylonitrile is genotoxic in the rat	-
C.H. Tamburro	University of Louisville	Health surveillance systems and molecular dosimetry	-
-	CIIT	Studies on the binding of acrylonitrile and its metabolites to hemoglobin for use as a biomarker	BP
-	CIIT	Development of a physiologically-based dosimetry model for acrylonitrile and cyanoethylene oxide	-

Table 2-6 (Continued)

Investigator	Affiliation	Research Description	Sponsor
C.H. Tamburro	University of Louisville	Development and implementation of prospective medical surveillance system for cancer control involving 1,200 active employees, 5,500 previous employees and 3,500 family members of employees from 1974	-
M. Dosemeci	National Cancer Institute	Case control epidemiology study concerning occupational exposure and cancer risk in Turkey in workers exposed between 1978 and 1984	-
L.M. Pottern	National Cancer Institute	Mortality study of 25,316 workers potentially exposed to acrylonitrile in eight U.S. facilities between 1952 and 1965	NCI/NIOSH
P.A. Stewart	National Cancer Institute	Assessment of historic exposures of acrylonitrile in eight U.S. facilities between 1952 and 1965	NCI/NIOSH

BP = British Petroleum America; CIIT = Chemical Industry Institute of Toxicology; NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Sciences; NIOSH = National Institute for Occupational Safety and Health.