CHAPTER 6. ADEQUACY OF THE DATABASE

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

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 Information on Health Effects

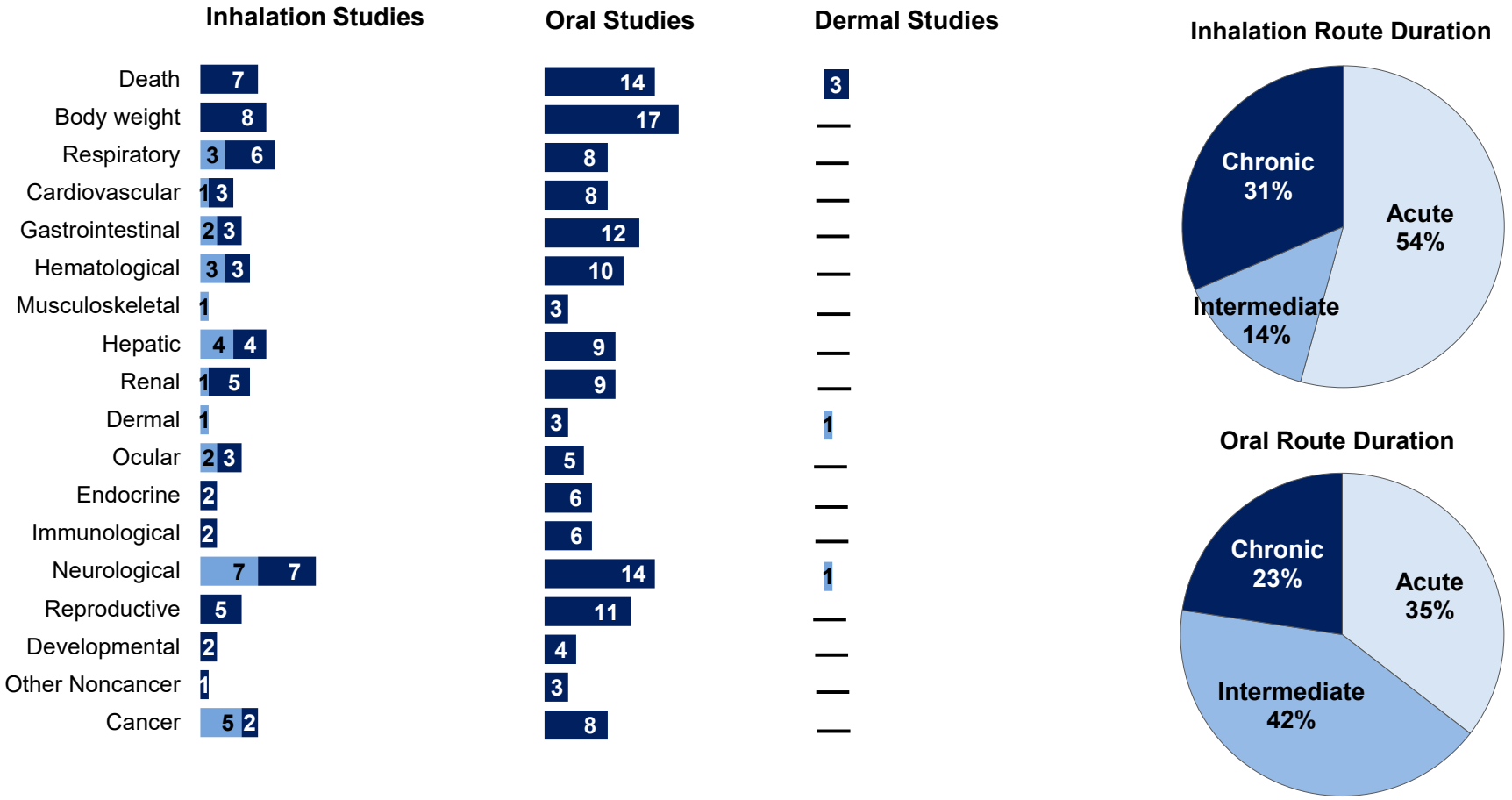
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to acrylonitrile that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of acrylonitrile. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies. Note that some studies examined more than one organ system.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Acrylonitrile by Route and Endpoint*

Potential body weight, liver, and kidney effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

Acute-Duration MRLs. 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 and were not considered adequate for derivation of an acute-duration inhalation MRL. Further studies of humans exposed to low levels of acrylonitrile in the workplace would increase the confidence in derivation of an acute-duration MRL. Reliable studies in animals are needed to identify sensitive targets of toxicity and establish concentration-response relationships. 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 were considered adequate for derivation of an acute-duration oral MRL. Additional studies employing several species and various dose levels would be useful in confirming target tissues and determining thresholds for these effects.

Intermediate-Duration MRLs. No information is available on the effects of intermediate-duration inhalation or oral exposure in humans. Several animal inhalation studies were identified and were considered adequate for derivation of an intermediate-duration inhalation MRL for acrylonitrile. There is information on intermediate-duration oral exposure in animals. Studies revealed decreased hemoglobin, forestomach lesions, and neurological effects in animals. Data in animals were sufficient to derive an intermediate-duration oral MRL. Further studies in animals would be useful in defining thresholds for these effects.

Chronic-Duration MRLs. Several occupational exposure studies have been identified that examined symptoms, hematological, and serum clinical chemistry parameters. No studies were located evaluating health effects associated with chronic-duration oral or dermal exposure in humans. One animal study evaluated noncancer endpoints following chronic-duration inhalation exposure; this study could not be used to derive an MRL for acrylonitrile because death was observed at the lowest dose level. Additional chronic-duration inhalation studies testing low concentrations would be useful for identifying sensitive target tissues and concentration-response relationships. Several studies have evaluated the chronic oral toxicity of acrylonitrile in rats and mice; these studies were considered adequate to identify a sensitive target of toxicity. Thus, the database was considered adequate for derivation of a chronic-duration oral MRL. Since the MRL is based on a LOAEL (lowest dose tested in the study), additional studies would be useful to establish dose-response relationships in the low dose range.

Health Effects.

Reproductive Toxicity. Information on the potential reproductive toxicity of acrylonitrile is limited to an occupational exposure study and several inhalation or oral exposure studies in animals. Studies in male rats and mice have shown that exposure to acrylonitrile results in increases in sperm aberrations, decreases in sperm motility and concentrations, and increases in sperm head and tail morphological alterations. Testicular tubular degeneration has also been observed. Studies to further evaluate the significance of the testicular effects on reproductive capability in rats, mice, and other species would be very valuable.

Developmental Toxicity. No information is available on developmental effects of acrylonitrile in humans by any route of exposure. Developmental toxicity has been observed in rats both by the oral and inhalation routes of exposure; however, effects have only been observed at maternally toxic doses. Additional studies providing insight into whether the observed effects are due to direct fetal toxicity or are secondary to the maternal toxicity would provide valuable information. Developmental studies on other animal species have not been conducted. Because species differences for acute-duration acrylonitrile toxicity and metabolism have been demonstrated, additional developmental studies in other species using various dose levels would be valuable in evaluating the potential for acrylonitrile to cause developmental effects in humans.

Immunotoxicity. Information on the immunotoxicity of acrylonitrile is limited to intermediate- and chronic-duration studies in rats and mice that examined the tissues in the immune system. No studies examined immune function. Studies evaluating potential functional impairment of the immune system are 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.

Epidemiology and Human Dosimetry Studies. There are studies on the adverse effects of acrylonitrile in humans. Most of these studies evaluated the potential carcinogenicity of acrylonitrile

exposure in workers. 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 estimating the exposure levels associated with adverse effects.

Biomarkers of Exposure and Effect. Several biomarkers of acrylonitrile exposure have been identified. These include thiocyanate and 2CyEMA in urine and the hemoglobin adduct, N-(2-cyanoethyl)valine. Additional studies on 2CyEMA and N-(2-cyanoethyl)valine, which are specific to acrylonitrile, would be useful for assessing acrylonitrile exposure.

Effects produced by exposure to acrylonitrile, particularly after acute-duration 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.

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.

Children's Susceptibility. There are limited data to evaluate potential differences between the toxicity of acrylonitrile in children and adults. One study found differences in corticosterone and

aldosterone between young animals and adult animals; however, the biological significance of these alterations is not known. Additional studies examining a wide range of effects, especially neurological, respiratory, and gastrointestinal would be useful to identify potential age-related differences.

Physical and Chemical Properties. Most of the important physical-chemical properties of acrylonitrile have been determined (see Table 4-2). However, the partitioning of acrylonitrile between the air and water has been evaluated by using an estimated value for a Henry's law constant. This general approach assumes that the concentration of the chemical in water is low. Because acrylonitrile is soluble in water, this approach may not be accurate. Experimental measurement of the partition coefficient for acrylonitrile at water-air interfaces would be useful in refining models on the behavior of acrylonitrile in the environment.

Production, Import/Export, Use, Release, and Disposal. Substantial data exist on production, use, and emissions of acrylonitrile in the United States. Additional studies are not needed at this time because these data are readily available.

Environmental Fate. Laboratory studies indicate that acrylonitrile is biodegraded in aqueous systems promoting microbial growth, but typical degradation rates in lakes or rivers have not been studied in detail. Data on the chemical oxidation, photodegradation, and biodegradation of acrylonitrile in surface and groundwater would be helpful.

Bioavailability from Environmental Media. There are limited data on the bioavailability of acrylonitrile in different environmental media. Data on the bioavailability of acrylonitrile would be valuable.

Food Chain Bioaccumulation. Little data are available on the bioaccumulation of acrylonitrile in the food chain. This is not considered a major limitation, because the available data suggest that acrylonitrile has a relatively low tendency to be bioconcentrated by lower trophic levels.

Exposure Levels in Environmental Media. There are limited data on the levels present in soil and sediment, but because acrylonitrile is not expected to accumulate in these compartments, this may not be a major data limitation. Because higher levels of exposure are most likely near industrial sources or chemical waste sites, additional data on the occurrence of acrylonitrile in the atmosphere, surface water, and groundwater near such sites would be useful.

Exposure Levels in Humans. Human exposure levels to acrylonitrile can only be estimated based on average concentrations in air, food, and water and by measurement of biomarkers of exposure. Direct studies of personal exposure levels for individuals with exposures judged to be average and above average (e.g., people living near industrial sources or hazardous waste sites) would be helpful in improving total dose estimates, and in identifying exposure pathways of concern. More recent data regarding exposure from ingestion of food, as well as data on the potential exposure from contact with consumer products containing acrylonitrile, would useful.

Exposures of Children. Biomonitoring data in children as young as 3 years of age have been reported in the most recent National Report on Human Exposure to Environmental Chemicals (2017–2018). Continued monitoring of children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.