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 nitrobenzene 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 nitrobenzene.

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 nitrobenzene 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 nitrobenzene. 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.

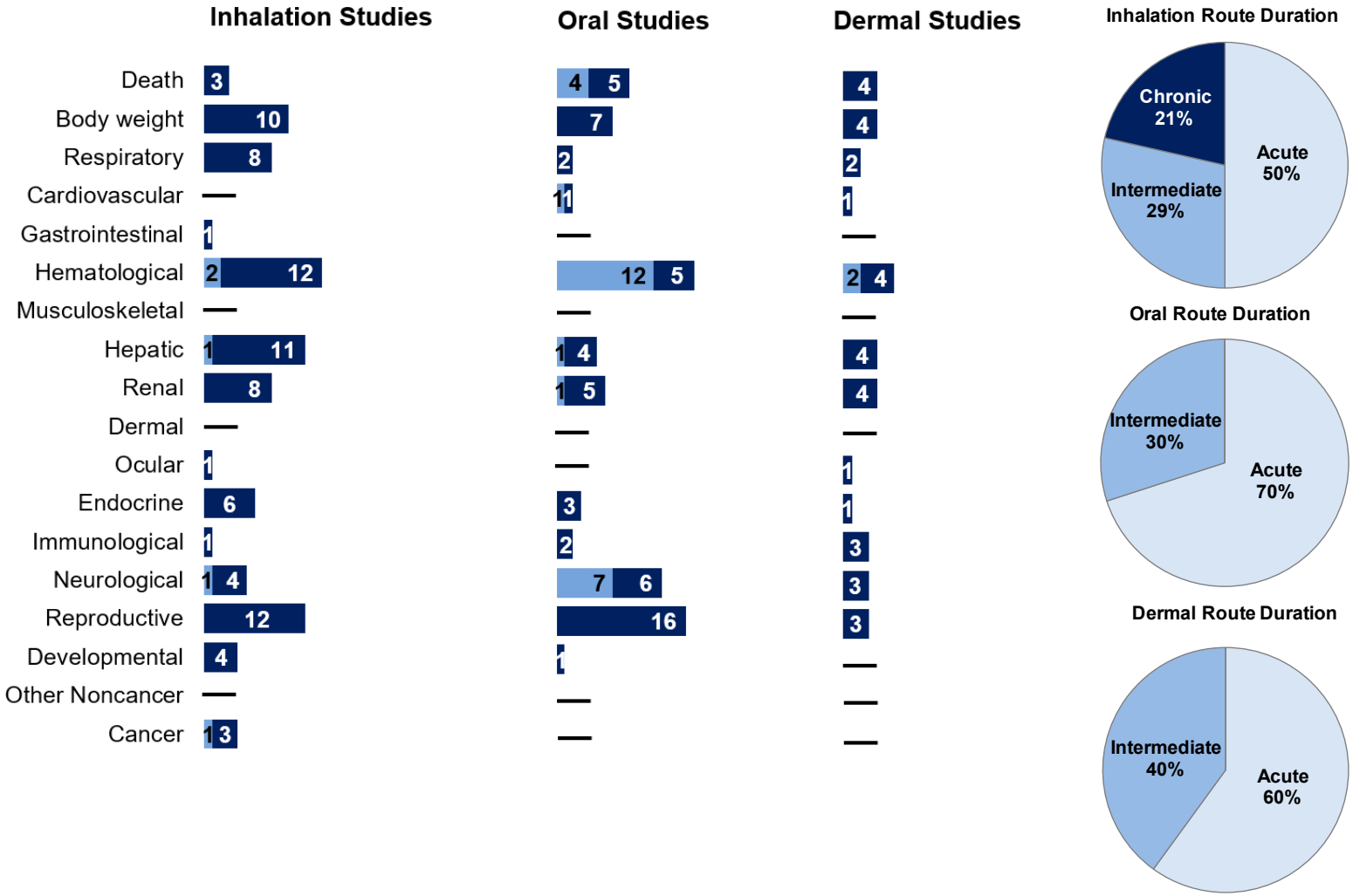
6.2 IDENTIFICATION OF DATA NEEDS

Acute-Duration MRLs. The inhalation database was adequate to derive an inhalation MRL. Medinsky and Irons (1985) provided full toxicological evaluations for nitrobenzene's toxicity with acute-duration via inhalation exposure. The available data were adequate for deriving an oral MRL. Burns et al. (1994) provided full toxicological evaluations for nitrobenzene's toxicity with acute-duration exposure via oral exposure.

Intermediate-Duration MRLs. The data were adequate to derive an intermediate MRL for both inhalation and oral routes of exposure. Hamm et al. (1984) and NTP (1983a) provided comprehensive toxicological evaluations of nitrobenzene's toxicity with intermediate-duration exposure via inhalation and oral exposure, respectively.

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

Potential hematological, reproductive, and neurological effects were the most studied endpoints.
The majority of studies examined oral exposure in **animals** (versus **humans**)



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

Chronic-Duration MRLs. The data were adequate to derive an MRL for inhalation exposure based on the data provided in Cattley et al. (1994, 1995; CIIT 1993). However, no studies were located that evaluated the chronic effects of nitrobenzene exposure after oral exposure. Therefore, a chronic-duration oral exposure study is needed to have an adequate database to derive an MRL.

Health Effects. Overall, the database for nitrobenzene is relatively complete, with comprehensive toxicological evaluations in rats and mice exposed for acute and intermediate durations via inhalation, oral, and dermal studies. However, there are no chronic-duration oral or dermal studies, which could improve the completeness of the database. In addition, studies designed to evaluate the health effects of acute-duration inhalation at low exposure concentrations would improve the database.

Hematology. Available animal studies on nitrobenzene provide abundant evidence for hematological toxicity through all exposure routes. However, none of the available studies identified a NOAEL for this endpoint. Additional testing at lower doses would be useful for determining no-effect levels for hematologic effects.

Respiratory. The available inhalation studies on nitrobenzene demonstrate the potential for nitrobenzene to cause toxicity in the nasal passages and lungs. As with the hematology changes, the available studies did not identify NOAELs, as effects were seen at all exposure concentrations. Otherwise, the available data on nitrobenzene toxicity to the respiratory system appear to be adequate.

Endocrine. Several studies noted effects on the adrenal and thyroid glands after nitrobenzene exposure. Both Hamm et al. (1984) and NTP (1983a) observed cellular vacuolization of the zona reticularis in the adrenal gland. Additionally, chronic-duration nitrobenzene inhalation resulted in thyroid follicular cell hyperplasia. Additional studies that explore the endocrine effects of nitrobenzene exposure would be helpful to better understand the potential implications of an altered endocrine system.

Developmental. Two studies were located that evaluated developmental outcomes as a result of nitrobenzene exposure via inhalation. The potential developmental effects of nitrobenzene would be better understood if oral and/or dermal developmental toxicity studies were available.

Cancer. A chronic-duration inhalation study of nitrobenzene identified carcinogenic effects in rats and mice. No chronic-duration oral studies assessing nitrobenzene's carcinogenic potential were located; such studies would improve the database for this endpoint. Further, epidemiological studies on cancer in humans exposed to nitrobenzene would better delineate the carcinogenic potential of nitrobenzene in humans.

Genotoxicity. No studies were located regarding genotoxic effects in humans after inhalation, dermal, or oral exposure to nitrobenzene. However, many studies have been published evaluating nitrobenzene's mutagenicity/genotoxicity potential *in vitro* (see Table 2-4), some using human cells, and *in vivo* using experimental animals (see Table 2-5). The evidence is fairly conclusive that nitrobenzene does not induce mutations in bacteria. However, there is some evidence that nitrobenzene may causes chromosomal aberrations, micronuclei, and DNA damage and/or adducts. Additional research on these endpoints, particularly in relevant tissues (lung, liver, kidney, and mammary glands) from animals exposed *in vivo*, would serve to better characterize the potential genotoxic effects of nitrobenzene.

Epidemiology and Human Dosimetry Studies. Only one relevant epidemiology study was located. Additional epidemiological studies on the toxicity of nitrobenzene would improve the database on this chemical regarding understanding the relevance of the effects seen in experimental animals for humans.

Biomarkers of Exposure and Effect. Urinary levels of p-nitrophenol and p-aminophenol reflect recent exposure to nitrobenzene. The limitation of using these metabolites as biomarkers of exposure, however, is that they are nonspecific. p-Nitrophenol is a metabolite of not only nitrobenzene, but also of insecticides such as methyl parathion, ethyl parathion, and O-ethyl-O-(4-nitrophenyl) phenylphosphonothioate. A measurement of p-nitrophenol and p-aminophenol, therefore, should not be used to confirm or quantify nitrobenzene exposure. Nitrobenzene can be biomonitored in urine, but it is only reflective of recent exposure.

The presence of increased levels of methemoglobin may indicate exposure to nitrobenzene. However, it is an effect that is common to several other toxic substances. Therefore, methemoglobinemia by itself would not serve as a satisfactory biomarker of effect for nitrobenzene. Further study in this area does not appear to be potentially useful.

Absorption, Distribution, Metabolism, and Excretion. Nitrobenzene is readily absorbed following exposure by any route. Absorption data for humans exposed to nitrobenzene via inhalation and the dermal route indicate that it is efficiently absorbed by these routes. Although absorption studies using the oral route have not been located for humans, the available case studies suggest that it can also be absorbed via ingestion. The lipophilicity of nitrobenzene suggests a high degree of absorption. In animals, absorption studies using oral and dermal routes suggest extensive absorption. No quantitative absorption studies using inhalation exposure are available, but the available toxicity data suggest that absorption does take place. This does not appear to be a priority area for further research.

Following accidental ingestion of nitrobenzene in humans, the highest concentrations were found in the liver, brain, blood, and stomach. Delayed rise in the methemoglobin levels in severe methemoglobinemia after antidote administration may be attributed to the release of nitrobenzene stores from the adipose tissue. However, there is a lack of supportive evidence of significant accumulation of nitrobenzene or its metabolites in the body. Data in animals are limited to oral studies in rats and mice that indicate that there is some distribution to the blood, liver, brain, kidney, and lung. Not all tissues have been analyzed in these studies. No data on distribution of nitrobenzene are available for humans or animals after inhalation and dermal exposure. Additionally, some of the crucial studies that examine absorption of nitrobenzene are older, and newer studies that leverage current technology to quantify the absorption of nitrobenzene in humans and/or animals would be relevant to better understand the toxicokinetics of nitrobenzene. Comprehensive distribution studies for nitrobenzene administered to mice and rats via all three routes would be very helpful in predicting the organ systems at potential risk in exposed humans. PBPK models help quantitatively predict the internal dosimetry of nitrobenzene and its metabolites in a target tissue and their delayed retention.

Metabolism data available for nitrobenzene suggest that species and/or strain differences in toxicity may be related to the metabolic activities of intestinal bacteria that convert it to its toxic metabolite, aniline. This is an area in which further study may be helpful in making comparisons of human sensitivity with that of other animals, and thus may aid in the interpretation of the currently available animal studies and their relevance to humans.

Excretion data are available for humans exposed to nitrobenzene via the inhalation, oral, and dermal routes. The available animal studies have used the oral route. Urine appears to be the major route of excretion, although this has not been clearly established, especially after inhalation and dermal exposure. There is no apparent need for further studies in this area.

Comparative Toxicokinetics. Species and strain differences in response to nitrobenzene exposure have been noted in studies using mice and rats. The reasons for these differences and the toxicokinetics involved are not understood. Additional toxicokinetic studies comparing metabolism of nitrobenzene in rats, mice, and humans would strengthen the available understanding. In addition, the development of a PBPK/PD model for nitrobenzene would also be useful, in order to reduce the uncertainty in extrapolating dose and effect information from animals to humans.

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

Physical and Chemical Properties. No specific data needs are identified for these properties. Available values are generally accepted and can be used to estimate nitrobenzene's environmental fate.

Production, Import/Export, Use, Release, and Disposal. Production methods for nitrobenzene are well-described in the literature, and there does not appear to be a need for further information. Available data indicate that most nitrobenzene produced in the United States is consumed in the production of aniline. Nitrobenzene is widely used in the workplace to produce raw materials (especially aniline) and as a solvent. Information on the uses of nitrobenzene is available in the literature and more information is not needed. Because nitrobenzene is listed as a hazardous substance, disposal of waste nitrobenzene is controlled by a number of federal regulations. Land disposal restrictions (treatment standards) apply to wastes containing nitrobenzene. Data on the amounts of nitrobenzene disposed was not located in the literature. Nitrobenzene is regulated under EPCRA, the Clean Air Act, the Clean Water Act, and RCRA. Several regulations govern disposal of nitrobenzene. Additional regulatory information is not needed.

Environmental Fate. The environmental fate of nitrobenzene is fairly well understood within the context of recognition of the importance of conditions in estimating or modelling environmental concentrations. The most critical condition is the presence/absence of a viable, competent, and functioning population of microorganisms for biodegradation. The next most critical factor is the amount of sunlight. For exposure assessment modelling accuracy, more data are needed on fate in soil, both in the root zone where plants are exposed and in the saturated and unsaturated zones where groundwater may become contaminated. Metabolism in plants is poorly characterized to date, so information on the

nature and quantity of plant metabolites would assist in the assessment of exposure via ingestion of plants.

Bioavailability from Environmental Media. The available information indicates that nitrobenzene is well absorbed following inhalation, oral, or dermal exposure. It is expected to be well-absorbed by persons breathing or having dermal contact with contaminated air or ingesting water, soil, plants, or any environmental materials that contain it. It would be useful to have information on its absorption after dermal contact with contaminated soil or plant material.

Food Chain Bioaccumulation. Uptake and accumulation of nitrobenzene through food chains are well-understood regarding animal tissues, especially fish. However, more information about plant tissues would be helpful.

Exposure Levels in Environmental Media. Data are available on nitrobenzene occurrence in air, surface waters, soil, sediments, and aquatic animals. However, much of these data are from studies performed decades ago and more current monitoring data is needed to identify current exposure risks.

Exposure Levels in Humans. There is very little information on human exposure to nitrobenzene outside of the workplace. More detailed exposure analyses that take transformation pathways into account can be performed for local sites and the potentially affected populations. Further, it would be useful to know more about the relationship of the organoleptic properties of nitrobenzene with respect to tolerable exposures. For example, it would be useful to know whether its taste and aroma are deterrents to high levels of human exposure.

6.3 ONGOING STUDIES

No relevant ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2022) database.