

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA (the Comprehensive Environmental Response, Compensation and Liability Act), 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.

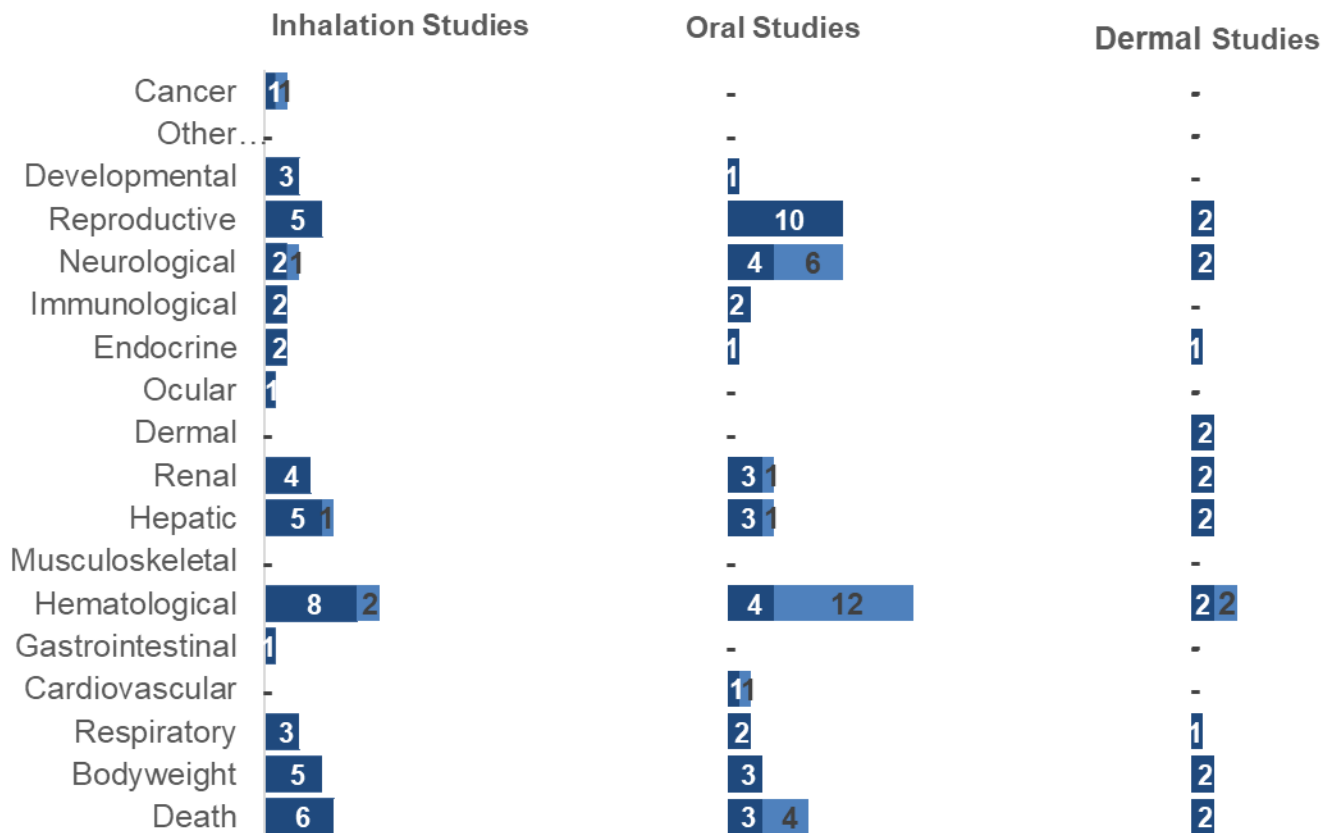
6.1 EXISTING INFORMATION ON HEALTH EFFECTS

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. ADEQUACY OF THE DATABASE

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

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.

Acute-Duration MRLs. The available data was adequate for deriving both an oral and an inhalation MRL. Medinsky and Irons (1985) and Burns et al. (1994) provide full toxicological evaluations for nitrobenzene’s toxicity with acute-duration exposure via inhalation and oral exposure, respectively.

6. ADEQUACY OF THE DATABASE

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

Chronic-Duration MRLs. The data were adequate to derive an MRL for inhalation exposure based on the evidence provided in Cattley et al. (1994). However, no studies were located which 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 fairly comprehensive with full toxicological evaluations conducted on acute and intermediate duration inhalation, oral and dermal studies. However, there are no chronic oral or dermal studies, which could improve the adequacy of the database. The database would benefit from studies that are designed to examine health effects of chronic oral and dermal exposure studies.

Respiratory. The available inhalation studies on nitrobenzene demonstrate the potential for nitrobenzene to cause toxicity in the nasal passage and the lungs. For example, there was a significant increase in the bronchiolization of the alveoli in mice exposed to nitrobenzene and increased pigmentation and degeneration of the olfactory epithelium (Cattley et al., 1994). The significant increase in alveolar bronchiolization in mice at the lowest exposure dose made it difficult to elucidate the dose-response relationship given the high incidence of health effect at the lowest exposure dose. It would be beneficial to understand how nitrobenzene may affect alveolar bronchiolization at doses lower than 5 ppm. Otherwise, the available data on nitrobenzene's toxicity to the respiratory system appears to be adequate.

Endocrine. Several studies noted endocrine effects after nitrobenzene exposure. Specifically, both Hamm Jr. et al., (1984) and NTP (1983a) observed cellular vacuolization of the zona reticularis in the adrenal gland. Additionally, chronic nitrobenzene inhalation resulted in thyroid follicular cell hyperplasia in Cattley et al. (1994) which may indicate toxicity to the thyroid. 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 papers were located which evaluated developmental outcomes as a result of nitrobenzene exposure (e.g., Tyl et al. 1987 and Dodd et al., 1987). Both authors stated no developmental effects were observed. However, Tyl et al. (1987) did observe an increase of litters with one or more

6. ADEQUACY OF THE DATABASE

Sprague-Dawley rat fetuses with external variations at 40.0 ppm for ecchymosis (discoloration of the skin due to bleeding underneath) on the trunk (but not on the head or extremities). Additionally, the incidence of these malformations increased with increasing doses, however this increase was not statistically significant. In addition, there was a significant increase the number of litters with animals having holes in the parietal skull plate, with 73 percent of litters in the 40 ppm group displaying this anomaly compared to 32 percent in the control group.. Since methemoglobinemia is a biomarker of nitrobenzene exposure, studies that examine the effects of methemoglobinemia on developmental parameters need to be conducted to examine the health effects further.

Cancer. A chronic inhalation study for nitrobenzene has been conducted (Cattley et al. 1994). This study has provided the basis for many cancer classifications. However, it is not known if the effects seen in this study occur in humans after nitrobenzene exposure. In the current profile only one epidemiological study was located, which also included exposure to two other chemicals (aniline and o-toluidine) (Carreón et al. 2014). No chronic oral studies assessing nitrobenzene's carcinogenicity potential were located, which would improve the database for this endpoint. Further, epidemiological studies with chronic oral exposure to nitrobenzene would help learn more about 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 have genotoxic effects. However, there is some evidence that nitrobenzene causes chromosomal aberrations based on the positive comet and micronucleus assays. Additionally, researchers have observed nitrobenzene forming adducts with hepatic DNA (Li et al. 2003a; Li et al. 2003b). Therefore, additional research would be beneficial to understand the potential genotoxic effects of nitrobenzene.

Epidemiology and Human Dosimetry Studies.

Only one relevant epidemiology study was located while developing the profile. Additional epidemiological studies on the toxicity of nitrobenzene would improve the database on this chemical in regard to understanding the relevance of the effects seen in experimental animals for humans.

Biomarkers of Exposure and Effect.

Exposure. Urinary levels of p- nitrophenol and aminophenol reflect recent exposure to nitrobenzene. The limitation of using these metabolites as biomarkers of exposure, however, is that they are non-specific. p- Nitrophenol is a metabolite of not only nitrobenzene, but also of the insecticides such as methyl parathion,

6. ADEQUACY OF THE DATABASE

ethyl parathion, and O-ethyl-O-(4-nitrophenyl) phenylphosphonothioate. A measurement of p-nitrophenol and p-aminophenol, therefore, should not be used to determine the level of nitrobenzene exposure. Nitrobenzene can be biomonitored in urine, but it is only reflective of recent exposure.

Effect. The presence of increased levels of metHb 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.

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 high degree of absorption. In animals, absorption studies using oral and dermal route suggest the 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 concentration was found in the liver, brain, blood and stomach. Delayed rise in the metHb levels in severe methemoglobinemia after antidote administration may be attributed to the release of nitrobenzene stores from the adipose tissue. However, there is 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 understanding 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

6. ADEQUACY OF THE DATABASE

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 inhalation studies using mice and rats. The reason for these differences and the toxicokinetics involved are not understood. Available data suggests dermal absorption of nitrobenzene elicits a more sensitive response in monkeys than in humans. Additional toxicokinetic studies in species other than rodents and attempts to estimate the sensitivity of humans relative to these test species would be valuable aids in interpreting the results of available toxicity studies and in understanding individual differences noted in response to nitrobenzene exposure. 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. 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.

Use. Nitrobenzene is widely used in the workplace to produce raw materials and as a solvent. Information on the uses of nitrobenzene is available in the literature and more information is not needed.

Release. According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 2017,

6. ADEQUACY OF THE DATABASE

became available in 2019. This database is updated yearly and provides a reliable estimate of industrial production and emissions.

Disposal. Because nitrobenzene is listed as a hazardous substance, disposal of waste nitrobenzene is controlled by a number of federal regulations (see CHAPTER 7). Land disposal restrictions (treatment standards) apply to wastes containing nitrobenzene. Data on the amounts of nitrobenzene disposed was not located in the literature.

Regulatory Information. 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 that information on the nature and quantity of plant metabolites would assist assessment of exposure via that route.

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. Because nitrobenzene is a priority pollutant, extensive data are available on its occurrence in surface waters, sediments, and aquatic animals. It would be useful to have data on its presence in soils and groundwater and correlations of measured air concentrations to soil levels and of plant levels to soil concentrations.

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

6. ADEQUACY OF THE DATABASE

need to be performed for local sites and the potentially effected 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

ATSDR is not aware of any ongoing studies related to nitrobenzene toxicity.