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 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine.

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 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine. 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.

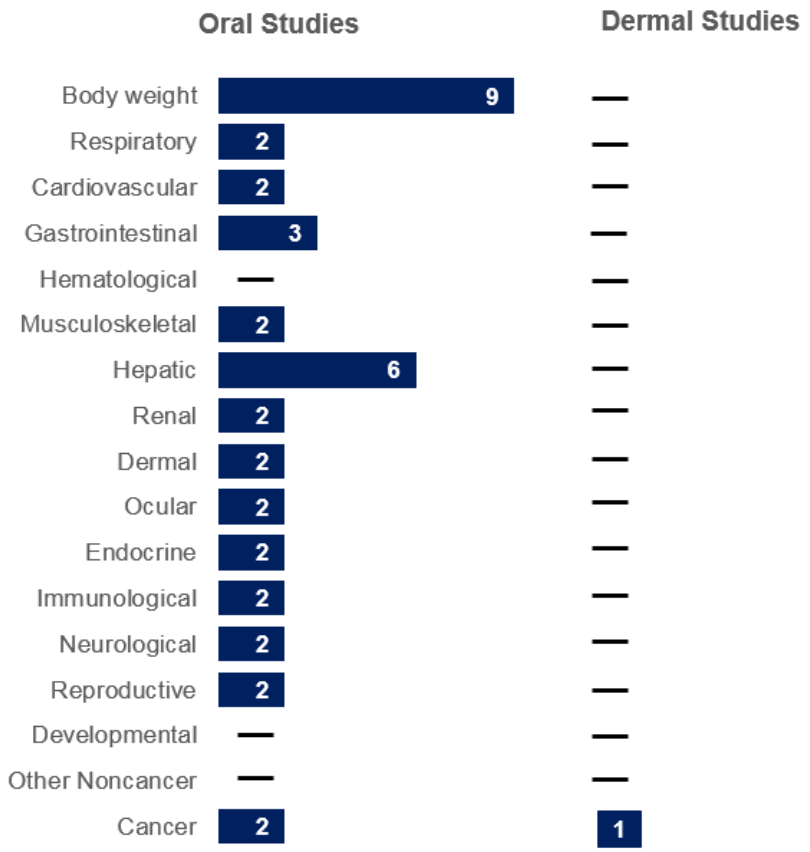
6.2 IDENTIFICATION OF DATA NEEDS

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 1,2-Diphenylhydrazine By Route and Endpoint*

Potential body weight, hepatic, gastrointestinal, and cancer effects were the most studied endpoints

The majority of the studies examined oral exposure in **animals**; no data were identified for **humans**



Acute-Duration MRLs. Information is not available on the health effects of 1,2-diphenylhydrazine resulting from inhalation exposure in humans or animals. Because 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperatures, it is highly unlikely that inhalation exposure to this chemical in the vapor state would occur. However, the possibility of inhalation exposure to dusts of 1,2-diphenyl-hydrazine either free or adsorbed to soil is conceivable. Therefore, acute studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. No studies were located regarding acute oral exposure in humans. The only pertinent acute exposure toxicity studies of 1,2-diphenylhydrazine were conducted in rats; these consist of an oral LD_{50} assay and a repeated-dose study, which did not find adverse hepatic or body weight effects. Additional acute oral exposure studies that could identify the critical targets of toxicity and provide dose-response data are needed for derivation of an acute MRL.

Intermediate-Duration MRLs. No information was located regarding intermediate-duration inhalation exposure to 1,2-diphenylhydrazine in humans or animals. As discussed for acute-duration exposure, 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure to this chemical in the vapor state unlikely. However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine, either free or adsorbed to soil, is conceivable. Therefore, intermediate-duration studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. Data were considered adequate to derive an intermediate-duration oral MRL for 1,2-diphenylhydrazine. However, additional studies examining a wide range of endpoints would support the identification of the liver as the most sensitive target of toxicity.

Chronic-Duration MRLs. No studies were located regarding chronic inhalation exposure to 1,2-diphenylhydrazine in humans or animals. As discussed for acute- and intermediate-duration exposure, 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure to this chemical in the vapor state unlikely. However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine either free or adsorbed to soil is conceivable. Therefore, chronic-duration studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. The NCI (1978) bioassay of 1,2-diphenylhydrazine provides the only sufficient chronic oral toxicity data for this chemical. This study was not, however, subjected to the peer-review process used for current NTP bioassays, and it inadequately evaluated non-neoplastic effects. Additional studies would be particularly useful for corroborating and more fully characterizing 1,2-diphenylhydrazine-induced systemic toxicity. In particular, more studies could provide information on cause(s) of death due to chronic exposure, and delineate carcinogenic and non-carcinogenic doses.

Health Effects. A small number of studies have evaluated the toxicity of 1,2-diphenylhydrazine. The available studies have found liver, lung, gastrointestinal, and cancer effects following oral exposure. No inhalation studies were identified and the only dermal study was of poor quality and only examined cancer endpoints. Acute-, intermediate-, and chronic-duration inhalation, oral, and dermal studies examining a wide range of potential targets of toxicity are needed to identify the critical targets and effect levels. Additionally, studies are needed to evaluate immune, neurological, and reproductive function and developmental endpoints to assess whether these systems are targets of toxicity.

Epidemiology and Human Dosimetry Studies. Health effects of 1,2-diphenylhydrazine have not been described in humans. As discussed in Chapter 5, the potential for environmental exposure to 1,2-diphenylhydrazine is extremely low. Although dermal exposure to 1,2-diphenylhydrazine could occur at a contaminated waste site, it is highly unlikely that segments of the general population will be exposed to 1,2-diphenylhydrazine.

Biomarkers of Exposure and Effect. No biomarkers are known that are specific for 1,2-diphenylhydrazine exposure. If 1,2-diphenylhydrazine or its metabolites in urine can be correlated with exposure, it may be possible to monitor humans for exposure. No biomarkers of effect have been identified.

Absorption, Distribution, Metabolism, and Excretion. The general metabolic pathways of 1,2-diphenylhydrazine are identifiable based on limited evidence for 1,2-diphenylhydrazine in oral, intratracheal, and injection experiments with rats, metabolism data for azobenzene (which is metabolized to 1,2-diphenylhydrazine), and metabolism data for aniline (an initial metabolite). The relative contribution of the different pathways is not established. Although oral absorption of 1,2-diphenylhydrazine and urinary excretion of 1,2-diphenylhydrazine and its metabolites are apparent, there is no information on the rate and extent of absorption, excretion, or tissue distribution following oral exposure. Investigations of the toxicokinetics of 1,2-diphenylhydrazine following dermal exposure have not been conducted. Additional studies of absorption, distribution, metabolism, and excretion in animals by the oral and dermal routes of exposure would provide information needed for sufficient characterization of the toxicokinetics of 1,2-diphenylhydrazine. Studies addressing differences in metabolism between oral and dermal routes would be particularly informative, as benzidine may be formed by acidity in the stomach.

Comparative Toxicokinetics. No data are available to determine if there are differences in the toxicokinetics of 1,2-diphenylhydrazine among species. Toxicokinetic studies with different species could help explain observed differences in toxicity and carcinogenicity between rats and mice, and help identify the animal species that serves as the best model for extrapolating results to humans.

Children's Susceptibility. No studies have evaluated the toxicity of 1,2-diphenylhydrazine in children or young animals. Studies in young animals would be useful to address potential concerns that children may be more susceptible to the toxicity of 1,2-diphenylhydrazine than adults. As previously noted, developmental toxicity studies are also needed.

Physical and Chemical Properties. Physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Data are available for only a few physical and chemical properties of 1,2-diphenylhydrazine, and most of these have limited experimental descriptions. Therefore, an evaluation of the accuracy of the data is difficult. Specifically, measured solubility, vapor pressure, K_{oc}, pKa, and Henry's Law constant at environmentally significant temperatures would help to remove any doubt concerning the accuracy of the partitioning estimates, especially in circumstances where 1,2-diphenylhydrazine does not oxidize rapidly (such as when high concentrations are present). These data form the basis of much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions, including hazardous waste landfills. In addition, the uncertainty in these measurements can be used to estimate the sensitivity of these properties in determining the overall fate of 1,2-diphenylhydrazine in the environment.

Production, Import/Export, Use, Release, and Disposal. Production methods for 1,2-diphenyl-hydrazine are well described in the literature (including the patent literature); there does not appear to be a need for further information in this area. Uses of 1,2-diphenylhydrazine are documented, but no recent production figures or detailed descriptions of uses are available. This information is useful for estimating the potential for environmental releases from manufacturing and use industries as well as the potential environmental burden, but it is difficult to obtain in the detail desired since it is considered confidential business information for those industries that manufacture 1,2-diphenylhydrazine. Release information is similar to use information in that it is not obtained easily and can be used to estimate environmental burdens and potentially exposed populations. TRI will provide some of this information in the future. Disposal information is useful for determining environmental burden and potential concentrations where environmental exposures may be high. Data on different disposal methods for 1,2-diphenylhydrazine are lacking.

Environmental Fate. The environmental fate and transport of 1,2-diphenylhydrazine are influenced by its rapid oxidation under aerobic conditions. Direct photolysis and biodegradation studies are lacking, but are not likely important due to the rapid rate of oxidation. A data need exists to study the fate of 1,2-diphenylhydrazine under anaerobic conditions, which may be found in anoxic layers of sediment or groundwater.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of 1,2-diphenylhydrazine from environmental media, but lack of these data does not necessarily indicate a lack of bioavailability. As exposure to 1,2-diphenylhydrazine could occur at waste sites by dermal

contact with contaminated soil or by ingestion of contaminated soil, it would be useful to know if dermal or oral absorption of 1,2-diphenylhydrazine from environmental media could occur. Information on dermal absorption of 1,2-diphenylhydrazine from other media is not available, but qualitative evidence indicates that 1,2-diphenylhydrazine in diet or oil media is absorbed from the gastrointestinal tract.

Food Chain Bioaccumulation. 1,2-Diphenylhydrazine reacts rapidly in water to form azobenzene and other oxidation products (the half-life in waste water is 60 minutes). Because of this and based upon the log octanol/water partition coefficient, no bioaccumulation is expected in any aquatic organism.

Exposure Levels in Environmental Media. Environmental monitoring data are not available or are of questionable accuracy for water, soil, and air. These data would be helpful in determining the ambient concentrations of 1,2-diphenylhydrazine so that exposure estimates for the general population could be made as well as 1,2-diphenylhydrazine exposure estimates for terrestrial and aquatic organisms.

Exposure Levels in Humans. The database for exposure levels in humans is very limited, and it is unclear if an exposed population exists given the rapid disappearance of 1,2-diphenylhydrazine from the environment. While a more complete database would be helpful in determining the current exposure levels and thereby estimating the average daily dose associated with various scenarios (e.g., living near a hazardous waste site), a number of factors limit establishing such a program, including the lack of appropriate analytical methods.

Exposures of Children. No data were located on exposures in children. See the previous section for issues relating to collecting monitoring data.

Analytical Methods. No adequate methods are available for the analysis of 1,2-diphenylhydrazine in biological materials. If this information were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used in toxicological studies. Furthermore, the ready availability of tested analytical methods, including sample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans. Adequate methods appear to be available for the analysis of 1,2-diphenyl-hydrazine metabolites in biological materials. Metabolites include azobenzene and aniline, both of which appear to be amenable to analysis by standard methods. 1,2-Diphenylhydrazine and its metabolites, however, have not been established as a quantitative biomarker of exposure to 1,2-diphenylhydrazine.

While analytical methods appear to be available for the analysis of 1,2-diphenylhydrazine, no methods were found for the preservation of 1,2-diphenylhydrazine in ambient air, water, or soil samples. Since 1,2-diphenylhydrazine is rapidly oxidized to azobenzene and has been previously reported to decompose instantaneously to azobenzene when introduced to the GC injection port (Riggin and Howard 1979), most GC analysis of 1,2-diphenylhydrazine are calibrated using azobenzene and the results are reported as a combination of both of these compounds.

6.3 ONGOING STUDIES

No ongoing studies were identified by the National Institutes of Health (NIH) (RePORTER 2020).