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 N-nitrosodi-n-propylamine 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 N-nitrosodi-n-propylamine.

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 N-nitrosodi-n-propylamine 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 N-nitrosodi-n-propylamine. 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.

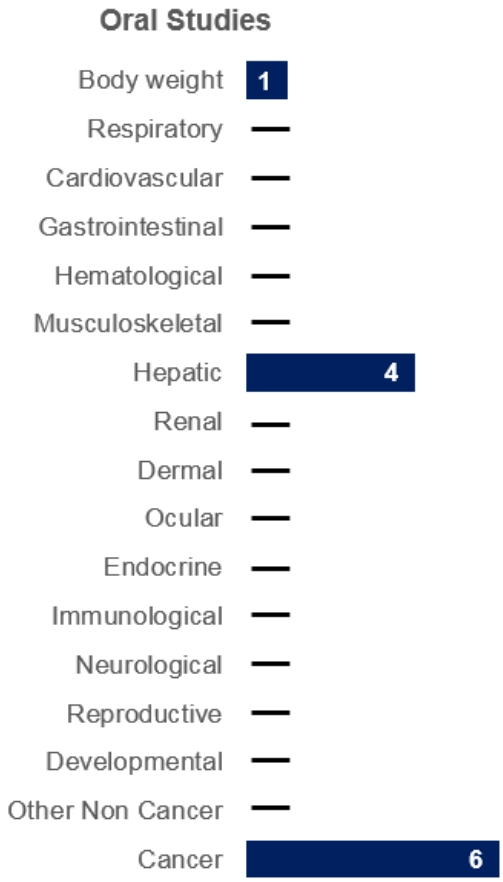
As illustrated in Figure 6-1, all of the data on the toxicity of N-nitrosodi-n-propylamine resulting from exposure via environmentally relevant routes of exposure come from oral studies in laboratory animals. These studies only examined potential liver, body weight, and cancer endpoints. Additional studies are available in laboratory animals receiving intratracheal instillation or injection.

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 N-Nitrosodi-n-Propylamine By Route and Endpoint*

Potential liver, body weight, and cancer effects were the only studied endpoints
All of the studies examined oral exposure in **animals**



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Some studies examined more than 1 endpoint. No inhalation or dermal studies in humans or animals were located. Data are also available for other nonrelevant routes of exposure.

Acute-Duration MRLs. No studies were identified on the acute inhalation toxicity of N-nitrosodi-n-propylamine; studies examining a wide range of possible targets, including the respiratory tract, are needed for derivation of an inhalation MRL. The acute-duration oral database was not considered adequate for derivation of an MRL. The available studies only examined two endpoints and thus, there is uncertainty regarding the critical target organ. Additional studies of a variety of potential endpoints and utilizing multiple dose levels are needed to support whether the liver toxicity is the most sensitive noncancer endpoint and for establishing dose-response relationships.

Intermediate-Duration MRLs. No intermediate-duration inhalation studies were identified for N-nitrosodi-n-propylamine; studies examining a wide range of possible targets, including the respiratory tract, are needed for derivation of an oral MRL. Oral studies provide limited information on the threshold for hepatotoxicity, the critical target in acute-duration oral studies. Several intermediate-duration oral studies with rats, one limited oral study with mice and injection studies with rats, mice, hamsters, and monkeys provide survival data, but no information on effects other than cancer. Additional short-term repeated dose oral studies (e.g., 15–28-day studies) in various species could provide additional information on systemic effects, particularly dose-response characterization of hepatic/hemorrhagic effects.

Chronic-Duration MRLs. No chronic-duration inhalation studies were identified for N-nitrosodi-n-propylamine; studies examining a wide range of possible targets, including the respiratory tract, are needed for derivation of an oral MRL. Chronic oral toxicity data for N-nitrosodi-n-propylamine are not available because treated animals died of cancer within 1 year of treatment. Animals treated with doses lower than those used in the intermediate-duration studies may survive chronic exposure and provide information on nonneoplastic effects and could possibly be used to derive a MRL.

Health Effects. A small number of studies have evaluated the toxicity/carcinogenicity of N-nitrosodi-n-propylamine. These studies involved oral, intratracheal, or parenteral exposure; no inhalation or dermal exposure studies were identified. Additionally, no human health effect studies were identified. The oral studies were limited in scope on examining lethality, liver endpoints, and cancer effects; injection studies also examined immune and developmental endpoints. Acute-, intermediate-, and chronic-duration inhalation and oral studies examining a wide-range of potential targets of toxicity are needed to identify the critical targets and effect levels. In addition to general toxicity studies, oral exposure studies addressing the potential immune, reproductive, and developmental toxicity of N-nitrosodi-n-propylamine are needed.

Epidemiology and Human Dosimetry Studies. Health effects of N-nitrosodi-n-propylamine have not been described in humans. Effects in treated animals, however, include hepatotoxicity and cancer. As discussed in Chapter 5, the potential for environmental exposure to N-nitrosodi-n-propylamine is very low, and segments of the general population with potentially high or specific exposure to N-nitrosodi-n-propylamine have not been identified. N-nitrosodi-n-propylamine has been detected in rubber manufacturing facilities, but concentrations are low and exposure is complicated by the presence of other nitrosamines and additional chemicals.

If N-nitrosodi-n-propylamine or its metabolites in urine can be correlated with exposure in humans, it may be possible to monitor humans for exposure. If toxic effects of N-nitrosodi-n-propylamine are identified in humans, it may then be possible to correlate urinary levels of N-nitrosodi-n-propylamine or one its metabolites with systemic effects.

Biomarkers of Exposure and Effect. No biomarkers of exposure to N-nitrosodi-n-propylamine were located. Studies evaluating whether the levels of N-nitrosodi-n-propylamine or one of its metabolites in biological fluids are reflective of exposure levels would be useful.

Absorption, Distribution, Metabolism, and Excretion. The general metabolic pathways of N-nitrosodi-n-propylamine in animals have been identified, but the relative contribution of the pathways *in vivo*, particularly following exposure by natural routes, is inadequately characterized. The identity of the alkylating agent(s) associated with carcinogenesis is unclear. Information is not available regarding absorption and distribution of N-nitrosodi-n-propylamine. Evidence from studies of other nitrosamines indicates that a number of factors (e.g., species, route of exposure, dosing schedule) appear to determine the organ specificity and the severity of the effects induced by these compounds. Therefore, to fully characterize the pharmacokinetics of N-nitrosodi-n-propylamine, studies of absorption, distribution, metabolism, and excretion in animals following exposure by all three routes are needed. Studies measuring the time-course of metabolite excretion would be useful for estimating the rates of metabolism and excretion.

Comparative Toxicokinetics. The toxic and carcinogenic effects of N-nitrosodi-n-propylamine are attributable to activity of metabolites, but no data are available to determine if there are quantitative differences in metabolism among species. Information from studies of other nitrosamines suggests that there are species-characteristic tumors induced by nitrosamines. This seems to be the reflection of

differences in metabolic activities (and also repair mechanisms) existing among animal species; therefore, caution must be exercised when extrapolating possible effects to humans. Additional studies examining potential species differences are needed.

Children's Susceptibility. No studies have evaluated the toxicity of N-nitrosodi-n-propylamine 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 N-nitrosodi-n-propylamine than adults.

Physical and Chemical Properties. Physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Many physical and chemical properties are available for N-nitrosodi-n- propylamine, but most do not have extensive experimental descriptions accompanying the data so that an evaluation of the accuracy of the data is difficult. Specifically, measured water solubility, vapor pressure, K_{oc}, and Henry's Law constant would be helpful in removing any doubt concerning the accuracy of the data as well as in providing information concerning the uncertainty of these types of data. These data form the basis for much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions including those at hazardous waste landfills.

Production, Import/Export, Use, Release, and Disposal. Uses, methods of synthesis, and methods of disposal are described in the literature, and there does not appear to be a need for further information in these topics. Lack of information pertaining to the import of this compound is to be expected, since this compound has no commercial significance. It is doubtful that research quantities would be imported rather than prepared by laboratories in the United States. Data regarding the amount of N-nitrosodi-n-propylamine released to air, water, and soil are needed in order to establish potential sources of exposure and levels of exposure from environmental media. In particular, releases from hazardous waste landfills and industries in which this compound is inadvertently formed should be established, in order to determine whether people living in the vicinity of these sites are exposed to elevated levels of this compound.

Environmental Fate. Data are available to establish, in general, the environmental fate of N-nitrosodi-n-propylamine. It has been predicted that in surface waters, beyond the reach of sunlight, N-nitrosodi-n-propylamine would be subject to slow microbial degradation; however, data are needed to determine its degradation rate in unlit surface water under aerobic or anaerobic conditions. Natural water grab sample biodegradation studies and soil metabolism studies carried out in the dark under both aerobic and anaerobic conditions would be useful in establishing the persistence of N-nitrosodi-n-propylamine in the

environment. The dominant removal mechanisms for N-nitrosodi-n-propylamine in air are expected to be photolysis and reaction with photochemically generated hydroxyl radicals; however, no data are available concerning the reaction pathway and the products of these types of reactions. These types of data would be useful in establishing what happens to this compound when it is released to the environment.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of N-nitrosodi-n-propylamine from environmental media. The lack of data concerning levels in human tissues and fluids does not necessarily indicate a lack of bioavailability since the monitoring literature reports that N-nitrosodi-n-propylamine is present in some foods, water, beverages, and workroom air. It is therefore important to determine if N-nitrosodi-n-propylamine can be absorbed by humans from environmental samples. An understanding of the bioavailability of N-nitrosodi-n-propylamine from environmental media may be obtained by studying the biological fluids of individuals exposed to N-nitrosodi-n-propylamine in the workplace or through the ingestion of N-nitrosodi-n-propylamine-containing foods and beverages such as cheeses, cured meats, and whiskey. Limited information is available regarding absorption parameters of N-nitrosodi-n-propylamine in experimental animals. However, it can be assumed, based on data obtained with other nitrosamines, that N-nitrosodi-n-propylamine would be readily absorbed from the gastrointestinal tract if ingested in contaminated soil.

Food Chain Bioaccumulation. No studies were available concerning food chain bioaccumulation of N-nitrosodi-n-propylamine from environmental media. The monitoring literature indicates that N-nitrosodi-n-propylamine has been detected in samples of cooked fish and meat; however, occurrence of N-nitrosodi-n-propylamine in these samples was not the result of bioaccumulation, but was the result of formation resulting from preservation and/or cooking. Various studies have also shown that N-nitrosamines, such as N-nitrosodi-n-propylamine, form in the gastrointestinal tract during digestion of foods containing secondary amines. Estimation techniques have been used to determine that N-nitrosodi-n-propylamine would not bioaccumulate in lipids of fish (see Section 5.4.1, Transport and Partitioning). Based on this limited amount of information it is speculated that human exposure to N-nitrosodi-n-propylamine through diet is not the result of food chain bioaccumulation. Monitoring for the accumulation of N-nitrosodi-n-propylamine in organisms from several trophic levels could be used to support this conclusion.

Exposure Levels in Environmental Media. Data are needed to relate the levels of N-nitrosodi-n-propylamine found at hazardous waste landfills to levels of exposure resulting from its occurrence at these sites. Studies in which air monitoring (ambient and personal air) in the vicinity of contaminated

sites and water sampling (groundwater and drinking water) at locations where contamination from the site is most likely to occur would be useful in establishing the extent of human exposure from contaminated sites. As N-nitrosodi-n-propylamine has been detected on a few occasions in some sodium nitrite-treated foods and alcoholic beverages, ingestion appears to be a potential route of exposure. Recent comprehensive data regarding the occurrence of N-nitrosodi-n-propylamine in foods were not available. A comprehensive survey of those food items in which N-nitrosodi-n-propylamine may occur, including cheese, cured meats and fish, and alcoholic beverages, would be useful in understanding the potential for human exposure to N-nitrosodi-n-propylamine and other nitrosamines. Only one study was available regarding the occurrence of N-nitrosodi-n-propylamine in cigarette smoke. Results of this study do not provide conclusive evidence for occurrence of measurable levels of N-nitrosodi-n-propylamine in cigarette smoke, so further studies need to be carried out before any conclusions can be made.

Exposure Levels in Humans. Limited data were available regarding human exposure to N-nitrosodi-n-propylamine. It appears that the general population may be exposed to N-nitrosodi-n-propylamine through various foodstuffs, some alcoholic beverages, and possibly cigarette smoke; however, data are needed to predict with certainty the frequency and level of exposure. A few broad-based monitoring studies of air, water, and typical diets would be useful in deriving estimates of typical exposure levels of humans.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults. Studies examining potential exposure sources for children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified for N-nitrosodi-n-propylamine.