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*-nitrosodiphenylamine 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*-nitrosodiphenylamine.

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

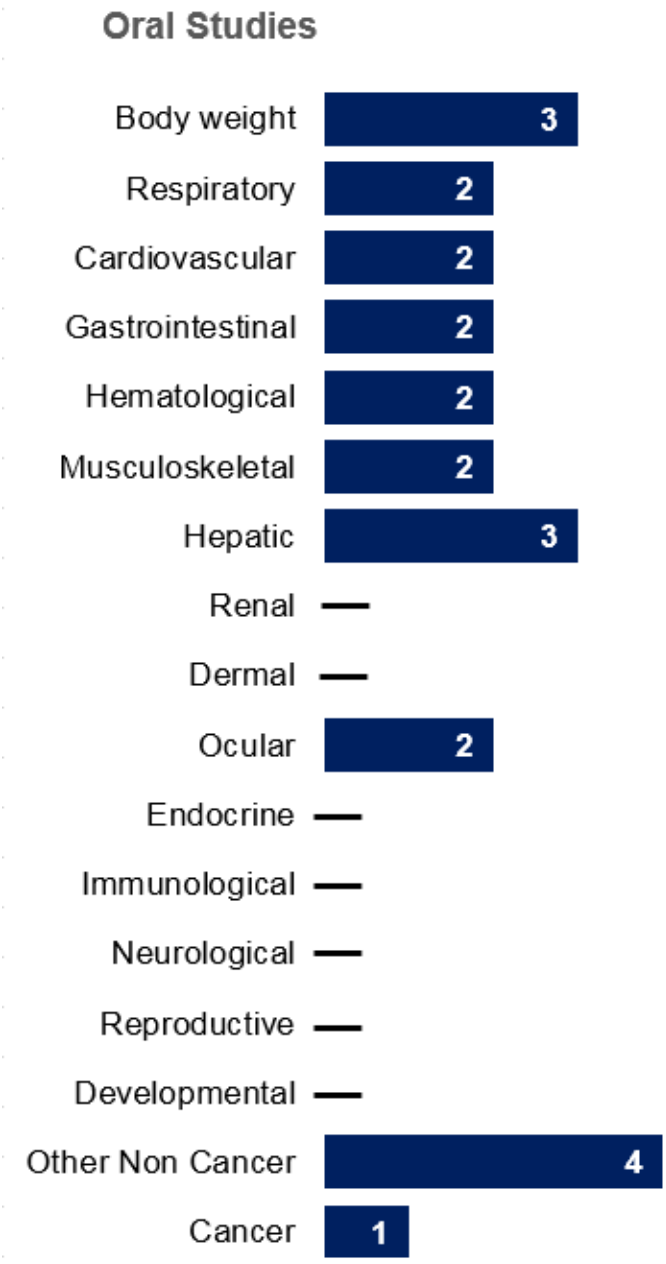
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to *N*-nitrosodiphenylamine that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of *N*-nitrosodiphenylamine. 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 *N*-Nitrosodiphenylamine by Route and Endpoint*

Potential other noncancer, body weight, and liver effects were the most studied endpoints
All studies evaluated health effects in **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.
No dermal or inhalation studies in humans or animals were located.

Acute-Duration MRLs. No cases of accidental or intentional poisonings were available to evaluate acute exposure in humans. There was a paucity of animal data, especially in animals exposed via inhalation or dermal routes. Inhalation studies are needed in order to derive an MRL. A dietary study in female rats provided data on microscopic morphology of the urinary bladder and showed that lesions can develop after 2 weeks of exposure to *N*-nitrosodiphenylamine (Dodd et al. 2013); no other organs or tissues were examined in that study. Insufficient information prevented the derivation of an acute-duration oral MRL.

Intermediate-Duration MRLs. There is no information on repeated exposure to *N*-nitrosodiphenylamine in humans. Rats showed body weight depression in an 8–11-week feeding study (NCI 1979). A low incidence of pigmentation of Kupffer's cells occurred in mice fed a diet containing a high concentration of *N*-nitrosodiphenylamine, but the effect was not considered adverse (NCI 1979). A study provided information on the effects of *N*-nitrosodiphenylamine on the urinary bladder of rats after 4 and 13 weeks of exposure (Dodd et al. 2013). It appeared that preneoplastic lesions had already formed after 4 weeks of exposure. Well-conducted intermediate-duration inhalation and dermal studies would be useful in determining whether adverse effects occur via these exposure routes. Additional intermediate-duration oral studies that examine major organs and tissues in several different animal species would be very helpful in determining potential adverse health effects in humans.

Chronic-Duration MRLs. Chronic oral studies in rats have shown decreased body weight and bladder effects in the form of squamous metaplasia and submucosal inflammation (Cardy et al. 1979; NCI 1979). The only other noncancer health effect of *N*-nitrosodiphenylamine was cornea1 opacity in the high-dose male rats and low-dose female rats (Cardy et al. 1979; NCI 1979). These data indicate that the bladder is the target for chronic oral exposure to this chemical. A chronic oral MRL was not derived for *N*-nitrosodiphenylamine because the bladder effects were considered preneoplastic. Long-term animal studies via the inhalation and dermal routes would be valuable for determining whether similar chronic effects would occur, and if exposures via these routes could cause toxicity in populations exposed to *N*-nitrosodiphenylamine near hazardous waste sites for extended periods.

Health Effects.

Genotoxicity. Data from *in vitro* assays suggest that *N*-nitrosodiphenylamine and/or one or more of its metabolites may damage DNA in mammalian liver cells (McQueen et al. 1983). However, *in vivo* studies of this type are lacking. In addition, oral, and perhaps even dermal, exposure *in vivo* studies in animals would be useful since these are the routes of exposure

pertinent to humans. Additional studies that investigate chromosome/chromatid effects in different animals and tissue/organ systems would help confirm or refute the inconclusive evidence (Abe and Sasaki 1977; Ishidate and Odashima 1977; McFee et al. 1981; Salamone et al. 1981) regarding this compound's clastogenicity. Genotoxicity assays in humans exposed to *N*-nitrosodiphenylamine would help to determine this chemical's status as a human genotoxin following *in vivo* exposure. Additional data on the metabolism of this compound would be very useful in assessing the inconsistencies of the available information.

Reproductive Toxicity. No human data and limited animal data were available regarding reproductive effects of *N*-nitrosodiphenylamine. Given the lack of reproductive information, any studies investigating adverse reproductive effects using different species and different routes of administration would be useful. Long-term oral studies in rats and mice did not find gross or microscopis alterations in the reproductive organs, but none examined fertility. A 2-generation reproductive toxicity study would provide valuable information regarding potential reproductive and developmental effects of *N*-nitrosodiphenylamine.

Developmental Toxicity. There were no studies evaluating developmental effects in humans or animals. As mentioned under *Reproductive Toxicity* above, a 2-generation reproductive toxicity study would provide valuable information regarding potential reproductive and developmental effects of *N*-nitrosodiphenylamine. A standard developmental toxicity study may also be warranted to determine potential effects in the offspring caused by maternal exposure during gestation.

Immunotoxicity. No studies were found that specifically investigated the immunotoxicity of *N*-nitrosodiphenylamine in either humans or animals. Studies specifically addressing the immune system responses in mammalian species would be valuable in assessing possible long-term health effects in humans that might reflect subtle changes in the immune system. Dermal studies may also provide useful information on the potential for allergic responses since skin contact by humans can occur in the workplace and via soil and water near hazardous waste sites.

Neurotoxicity. There were no human data and limited animal data evaluating the neurotoxicity of *N*-nitrosodiphenylamine. Given the lack of any information regarding neurotoxicity and the paucity of data concerning the mechanism of action of *N*-nitrosodiphenylamine, well-conducted

acute, intermediate, and chronic studies across all exposure routes investigating neurological effects of *N*-nitrosodiphenylamine exposure would be useful.

Epidemiology and Human Dosimetry Studies. Populations that may potentially be exposed to *N*-nitrosodiphenylamine would include workers in the rubber industry, those residing near hazardous waste sites, or workers involved in the clean-up of wastes. A study of German workers in the rubber industry reported that exposure to nitrosamines was associated with increased risk of cancer of the prostate and the oral cavity and pharynx (Straif et al. 2000); however, the role of *N*-nitrosamine, if any, could not be determined. No further relevant humans studies were located. Additional studies of rubber workers with better characterization of exposures could help confirm or refute the findings of Straif et al. (2000), although the generally low levels of the chemical that have been measured in the occupational air space would make quantifying this relationship difficult. Yet, this type of epidemiological study may help determine whether bladder toxicity may occur in humans as in animals.

Biomarkers of Exposure and Effect. Currently, there are no biomarkers identified for human exposure to *N*-nitrosodiphenylamine. The chemical and some of its metabolites have been measured in the blood, serum, and urine of animals (Pylypiw and Harrington 1981). Monitoring data in humans with suspected occupational exposure to *N*-nitrosodiphenylamine would be useful.

Currently, there are no human biomarkers of effect identified for *N*-nitrosodiphenylamine. There are so few data available on the chemical that it is difficult to associate specific symptoms with exposure to *N*-nitrosodiphenylamine. The determination of the target organ in humans would be valuable for identifying possible effects to monitor in populations with high risk of exposure to the chemical, such as workers in the rubber industry. Furthermore, animal and epidemiological studies that correlate adverse health effects with levels in tissues would help researchers to devise more sensitive and more specific biomarkers of disease.

Absorption, Distribution, Metabolism, and Excretion. There was no information available on relative rates and extent of absorption, distribution, metabolism, and excretion for inhalation, oral, or dermal exposure in humans or animals. Although there are no quantitative data on absorption, animal studies provided indirect evidence that *N*-nitrosodiphenylamine was absorbed following administration of a single oral dose (Appel et al. 1984; Tatsumi et al. 1983) and during longer-term oral exposure (Cardy et al. 1979; Dodd et al. 2013; NCI 1979). Absorption rate data for all three exposure routes would be useful in estimating absorption characteristics in humans.

No studies on the distribution pattern and rates of *N*-nitrosodiphenylamine were available for humans or animals. Intermediate and chronic oral studies have reported alterations in specific organs in animals (Cardy et al. 1979; Dodd et al. 2013; NCI 1979); however, *N*-nitrosodiphenylamine levels in these tissues were not provided. Additional studies on distribution would assist in the evaluation of target organ toxicity of *N*-nitrosodiphenylamine. Metabolism of *N*-nitrosodiphenylamine was studied in rats (Appel et al. 1984) and guinea pigs (Tatsumi et al. 1983) exposed to a single oral dose. No inhalation or dermal studies were available. Additional studies are needed to assess whether differences in rate and extent of metabolism exist across the three routes of exposure and to predict the metabolism pattern of the chemical in humans.

No human data and limited animal data were available on excretion. Rapid excretion occurs in rats after acute oral exposure (Appel et al. 1984). Studies on excretion following exposure via all routes would be useful for determining the variation in elimination pattern with route, and also the variation in excretion among species.

Neither the mechanism of absorption of *N*-nitrosodiphenylamine, nor the mechanism of distribution in the body are known, although indirect evidence from animal studies indicates that orally administered *N*-nitrosodiphenylamine is absorbed (Appel et al. 1984; Cardy et al. 1979; Dodd et al. 2013; NCI 1979; Tatsumi et al. 1983). Information regarding these mechanisms would be useful in developing methods to reduce peak absorption. There are no established methods for reducing the body burden of this compound or any toxic metabolite(s), but the existing data suggest that *N*-nitrosodiphenylamine has a low potential for bioaccumulation (see Section 5.4.1). There is little actual experience in treating persons exposed to *N*-nitrosodiphenylamine. The mechanism of toxic action is not known, although possible carcinogenic mechanisms have been proposed (NCI 1979; Preussmann and Stewart 1984; Raineri et al. 1981; Wakabayashi et al. 1982). Information regarding the nephrotoxic and possible carcinogenic mechanisms of *N*-nitrosodiphenylamine would be useful in developing methods to block its toxic effects.

Comparative Toxicokinetics. No toxicokinetic information was available for humans. Pharmacokinetic data in animals, which could be used in the understanding of species differences in sensitivity and mechanism of toxicity to this chemical, are very limited (Appel et al. 1984; Atawodi and Maduagwu 1990; Ohshima et al. 1982). Additional toxicokinetic studies in a variety of species would be useful in determining the best animal model for evaluating *N*-nitrosodiphenylamine pharmacokinetic characteristics in humans. More toxicokinetic data would be helpful in assessing the potential for long-

term health effects following chronic exposures, which are most likely to occur in residents living near hazardous waste sites.

Children's Susceptibility. There are no studies of children or young animals exposed to *N*-nitrosodiphenylamine. The specific enzymes involved in the metabolism of *N*-nitrosodiphenylamine have not been identified, so it is not known if there would be toxicodynamic differences between children and adults that might influence susceptibility. Studies in young animals and/or children would be useful to address these concerns.

Physical and Chemical Properties. The physical and chemical properties of *N*-nitrosodiphenylamine are sufficiently well defined to allow assessments of the environmental fate of the compound to be made. No additional information is needed.

Production, Import/Export, Use, Release, and Disposal. The general population does not appear to be exposed to any background levels. However, the available data do not permit a confident assessment of the background levels in air, drinking water, or foods. Disposal methods are well documented in the literature (HSDB 1990). More information on current production would be useful in estimating potential exposure to *N*-nitrosodiphenylamine. Further research on the possible production of *N*-nitrosodiphenylamine from diphenylamine by microorganisms would be useful in determining the potential for environmental contamination from this source.

Environmental Fate. *N*-Nitrosodiphenylamine is transported and partitioned in the air, water, and soil. It will sorb to soil and sediment (Swann et al. 1983). It is subject to photolysis in air and biodegradation in water and soil (EPA 1979; Sharma et al. 1986). Additional information regarding hydrolysis and oxidation and the half-lives for these processes would be helpful in determining the persistence of *N*-nitrosodiphenylamine at hazardous waste sites or at production sites where past or current levels might be high.

Bioavailability from Environmental Media. Limited available pharmacokinetic data in animals indicate that *N*-nitrosodiphenylamine is absorbed following oral exposure (Appel et al. 1984; Cardy et al. 1979; NCI 1979; Tatsumi et al. 1983). Additional information on the absorption of this compound by these routes would be useful in evaluating the importance of the various routes of exposure to populations living in the vicinity of hazardous waste sites or near a production facility.

Food Chain Bioaccumulation. *N*-Nitrosodiphenylamine is bioconcentrated in aquatic organisms to a limited extent (Barrows et al. 1980). Biomagnification in the aquatic food chain is not a major environmental fate process (Barrows et al. 1980). No data were located regarding bioaccumulation in terrestrial organisms. Since *N*-nitrosodiphenylamine might be found in soil under certain conditions, additional information would be helpful in determining the potential for biomagnification in the terrestrial food chain.

Exposure Levels in Environmental Media. Current monitoring data were not located regarding levels of *N*-nitrosodiphenylamine in air, water, soil, or food. This information would be useful in determining the risk of exposure for populations living near hazardous waste sites or near a production facility. It would also aid in determining if contamination due to production of *N*-nitrosodiphenylamine by microorganisms is of environmental concern.

Exposure Levels in Humans. *N*-Nitrosodiphenylamine has been detected in the blood and urine of experimental animals (Pylypiw and Harrington 1981); however, there are no monitoring studies of human populations. Current human studies that monitor *N*-nitrosodiphenylamine in these fluids would be helpful in assessing the potential exposure of individuals who might be exposed through their work or of populations living in the vicinity of a production facility or a hazardous waste site.

Exposures of Children. There are no data regarding levels of *N*-nitrosodiphenylamine in air, drinking water, or food. Any information in this regard would help characterize potential exposures of children.

Analytical Methods. Development of analytical methods for detection of *N*-nitrosodiphenylamine in environmental and biological media would be useful.

6.3 Ongoing Studies

No ongoing studies were identified for *N*-nitrosodiphenylamine.