# 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 NDMA 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 NDMA.

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.

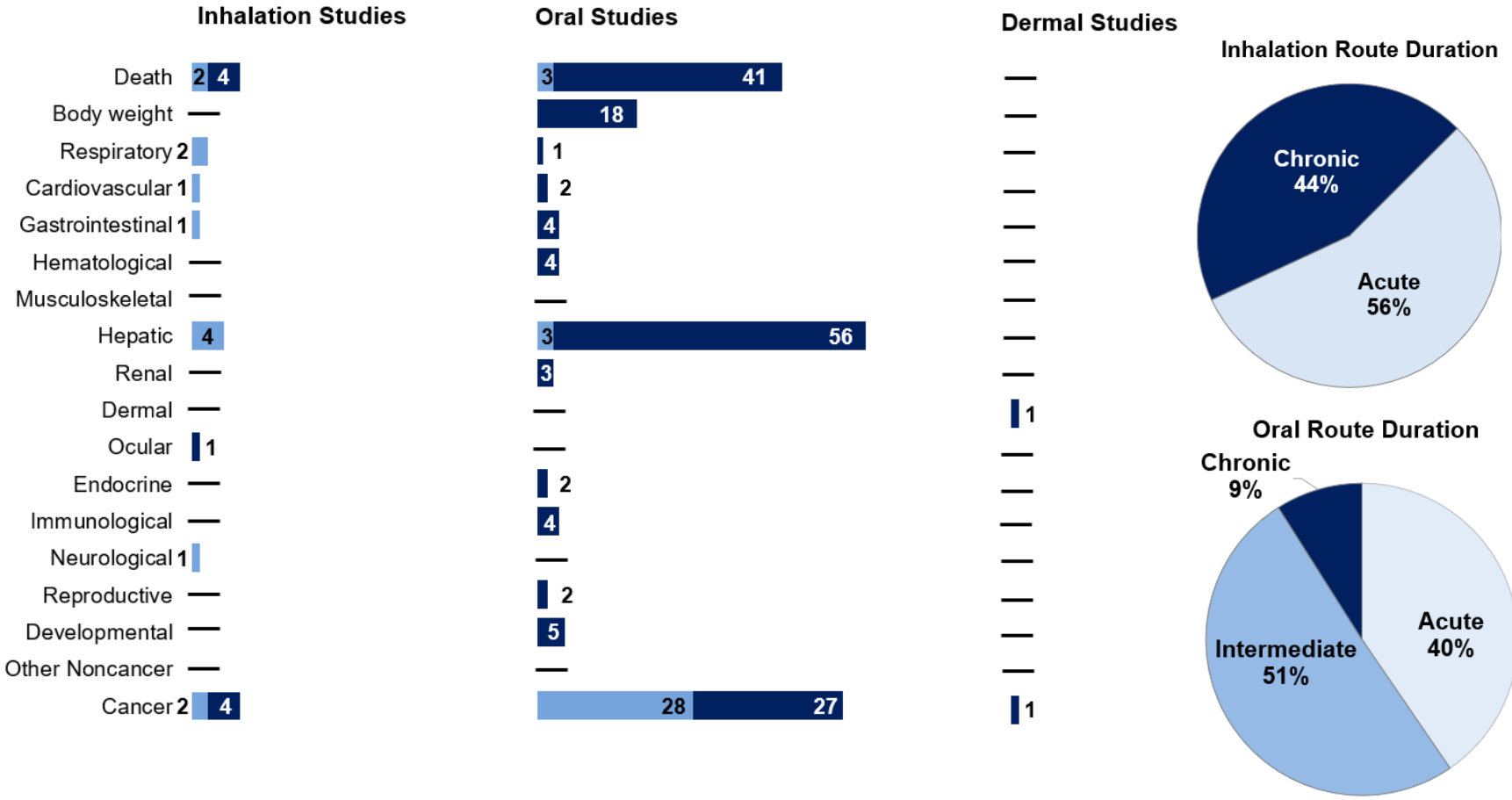
## 6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to NDMA 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 NDMA. 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.

The preponderance of toxicity data on NDMA is derived from studies of animals exposed orally, as demonstrated in Figure 6-1. There are very few inhalation studies. Most of the animal studies examined hepatic toxicity, cancer, and/or survival. Few human studies assessed inhalation exposure to NDMA: most were of oral exposure, which is the most common route of human exposure. As with the animal studies, the available human studies examined limited endpoints (cancer, or death from acute poisoning).

## Figure 6-1. Summary of Existing Health Effects Studies on N-Nitrosodimethylamine (NDMA) by Route and Endpoint*

**Potential carcinogenicity, hepatic effects, and lethality were the most studied endpoints**
The majority of the studies examined oral exposure in **animals** (versus **humans**)



## 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.** Data pertaining to health effects in humans exposed to NDMA via acute-duration inhalation and oral exposure are limited to case reports of fatalities (Cooper and Kimbrough 1980; Freund 1937; Fussgaenger and Ditschuneit 1980; Hamilton and Hardy 1974; Kimbrough 1982). Animal studies of acute-duration inhalation exposure only examined lethality; thus, the data were not adequate for derivation of an acute-duration inhalation MRL. Studies examining a wide range of potential health effects, including the liver, in animals exposed by inhalation would facilitate the identification of target organs and concentration-response relationships. Adequate data were available for derivation of an acute-duration oral MRL.

**Intermediate-Duration MRLs.** No studies were located in which humans or animals were exposed to NDMA by inhalation for intermediate durations; thus, no data were available for derivation of an intermediate-duration inhalation MRL. Intermediate-duration studies in humans exposed orally were also not located. There are many intermediate-duration studies of oral exposure to NDMA in animals. However, like the acute-duration oral studies, these experiments were largely focused on evaluating liver effects or cancer and identified freestanding serious LOAELs. A single developmental toxicity study reported perinatal mortality at the only dose tested (Anderson et al. 1978) and did not evaluate potential teratogenicity. The few other studies of this endpoint were not considered reliable due to lack of controls, lack of maternal toxicity data, and/or uncertain treatment schedule. Likewise, a single study in rabbits identified serious effects on the male reproductive tract at a dose that also induced serious liver effects (Sheweita et al. 2017). Studies examining comprehensive endpoints, including sensitive measures of developmental and reproductive toxicity, and using lower doses (<10 μg/kg/day) might provide dose-response information enabling derivation of an intermediate-duration oral MRL.

**Chronic-Duration MRLs.** One chronic study of humans exposed by inhalation to NDMA in an occupational setting was identified (Hidajat et al. 2019a); this study examined only cancer endpoints. Chronic-duration inhalation studies of NDMA in animals also examined cancer endpoints with little to no

information on nonneoplastic changes. Therefore, the data were inadequate for derivation of a chronic-duration inhalation MRL. Reliable epidemiological studies examining associations between oral intake of NDMA and noncancer endpoints were not located. Chronic oral exposure in animals was tested in a small number of studies; with one exception, these studies also focused on cancer endpoints. In the one study evaluating noncancer effects, dogs exhibited anorexia and severe hepatotoxicity at the only dose tested (Butler-Howe et al. 1993). In the absence of data on less serious noncancer effects, the data were not considered adequate for derivation of a chronic-duration oral MRL. Chronic-duration animal studies of oral exposure to very low doses of NDMA with evaluation of comprehensive noncancer endpoints are needed to identify dose-response information for MRL derivation.

## Health Effects.

***Hepatic.*** The hepatic effects of NDMA in animals and their mode of action are well-established after oral exposure. There remains a data gap with respect to hepatic effects in animals after inhalation exposure. In addition, the lack of studies in animals exposed to very low doses and examining sensitive and/or precursor events precludes identification of less-serious LOAELs or NOAELs.

***Immunological.*** Suppression of both humoral and cellular immunity was observed in mice exposed to NDMA in drinking water (Desjardins et al. 1992). Although sensitive measures of liver toxicity were not evaluated, ascites was evident in mice exposed to higher doses of NDMA in this study, indicating that the mice had severe liver injury. Thus, available data are not adequate to determine whether immune suppression is a sensitive endpoint; additional studies of immune system function would inform this question.

***Reproductive.*** Serious effects on the male reproductive tract were reported in rabbits exposed to NDMA in drinking water (Sheweita et al. 2017). The rabbits exhibited severe liver toxicity in this study at the same dose (only dose tested). Further evaluation of reproductive toxicity, including a multigeneration study, could provide useful information if doses were low enough to prevent serious effects on the liver and/or cancer were used.

***Developmental.*** In a limited study of developmental toxicity in mice exposed orally, perinatal mortality was observed at the only dose tested (Anderson et al. 1978). The few studies examining potential teratogenicity were not considered reliable due to lack of controls, lack of maternal

toxicity data, and/or uncertain treatment schedule. Thus, the available data on developmental toxicity are not adequate to evaluate potential developmental toxicity of NDMA.

***Other Noncancer Effects.*** Because none of the available animal studies examined comprehensive endpoints, the data are inadequate to confirm that the liver is the most sensitive target organ. Toxicokinetic studies have shown that greater amounts of unchanged NDMA escapes first-pass metabolism and reaches systemic circulation in larger species such as dogs, pigs, and monkeys than in rats and mice (Gombar et al. 1987, 1988, 1990; Hino et al. 2000; Mico et al. 1985; Streeter et al. 1990a, 1990b), suggesting that in humans and other large animals, organs and tissues other than the liver may receive larger doses and/or exhibit significant toxicity. Thus, the lack of comprehensive toxicity studies in larger species is a significant data gap.

**Epidemiology and Human Dosimetry Studies.** The only information available concerning effects of NDMA in humans exposed for acute durations comes from cases of acute poisoning and recovery or subsequent death. In these cases, hemorrhagic and necrotic alterations and cirrhosis of the liver were observed. Studies of chronic exposure in humans include an occupational study of presumed inhalation exposure, and studies estimating dietary intake based on food frequency questionnaires and literature estimates of NDMA concentrations in foods. All of these studies focused on cancer endpoints. Studies of hepatic and other non-hepatic effects in occupationally exposed humans for whom reliable exposure estimates are available could inform dose-response assessment and identify additional target organs in humans.

**Biomarkers of Exposure and Effect.** $O^6$-methylguanine DNA adducts have been used as a biomarker of exposure to NDMA, although exposures to other compounds can also produce these adducts. A number of candidate biomarkers for liver fibrosis have been investigated in animals exposed to NDMA, including plasma levels of protein C, MCP-1, and MCP-3, M-CSF, circulating neutrophils, soluble intracellular-adhesion-molecule -1 (sICAM-1), hyaluronic acid, and hyaluronidase (George and Stern 2004; Saha et al. 2007). Evaluation of the validity of these biomarkers in humans and as early predictors of liver toxicity induced by NDMA would improve biomonitoring of workers exposed to this chemical.

**Absorption, Distribution, Metabolism, and Excretion.** Toxicokinetic data with regard to dermal and inhalation exposure of NDMA are clearly lacking. Information on toxicokinetic behavior of NDMA after oral exposure are relatively robust, but studies of the tissue distribution of NDMA and its

metabolites in larger mammals are warranted by the observed differences in systemic availability of unmetabolized NDMA (see Section 3.1.1).

**Comparative Toxicokinetics.** The comparative toxicokinetics of orally administered NDMA have been examined in whole animal studies using rats, mice, beagles, swine, and patas monkeys (Anderson et al. 1992b; Gombar et al. 1987, 1988, 1990; Hino et al. 2000; Hinuma et al. 1990; Mico et al. 1985; Streeter et al. 1990a, 1990b); limited information is also available in ferrets (Wishnok et al. 1987). These studies showed species differences in the amount of NDMA that bypasses first-pass metabolism in the liver and reaches systemic circulation. Missing from the available data are studies comparing tissue levels of NDMA metabolites or NDMA-derived radioactivity across species to determine the extent to which reactive metabolites are formed in tissues other than the liver.

**Children's Susceptibility.** Additional studies of developmental toxicity and/or toxicity studies in infant or young animals would provide information on potential susceptibility of children; available data are very limited.

**Physical and Chemical Properties.** Physical and chemical properties are essential for estimating the partitioning of a chemical among environmental media. Many physical and chemical properties are available for NDMA; however, a measured value for $K_{oc}$ at ambient temperature is not available. Methods for estimating these properties appear to provide relatively close estimates of $K_{oc}$ and Henry's Law constant. Nevertheless, measured values at environmentally significant temperatures would assist in accurately predicting the fate of this compound in the environment.

**Production, Import/Export, Use, Release, and Disposal.** Uses, methods of synthesis, and methods of disposal for NDMA are described in the literature and there does not appear to be a need for further information on these topics. Lack of information pertaining to the import of this compound is not surprising since this compound has no commercial applications. Data regarding the amount of NDMA released to air, water, and soil would be useful in order to establish potential sources of exposure and levels of exposure from environmental media. In particular, information on releases from hazardous waste landfills and industries in which this compound is inadvertently formed may help determine whether people living in the vicinity of these sites are exposed to elevated levels of this compound.

**Environmental Fate.** Sufficient data are available to develop a general understanding of the environmental fate of NDMA, although the data were obtained 40 or more years ago. Kinetic data

regarding photolysis in water and on soil surfaces, biodegradation in water under aerobic and anaerobic conditions, and biodegradation in soil under anaerobic conditions are limited. Natural water grab sample biodegradation studies and soil metabolism studies carried out in the dark under aerobic and anaerobic conditions would be useful in establishing the persistence of NDMA in the environment. Photolysis studies carried out under simulated environmental conditions in water and soil would be useful in establishing the rate of photolytic degradation, the significance of this process as a removal mechanism, and the products of this reaction in these media.

**Bioavailability from Environmental Media.** No studies were located regarding the bioavailability of NDMA from environmental media. Since NDMA has been detected in ambient air, water, and soil (ppb levels), it is important to determine if NDMA can be absorbed by humans from environmental samples. It must be noted that NDMA has been found in trace amounts in some foods and beverages and that endogenous formation of NDMA has been found to occur from the nitrosation of amines in the gastrointestinal tract. An understanding of the bioavailability of NDMA from environmental media may be obtained by studying the biological fluids of individuals exposed in the workplace or through the ingestion of NDMA-containing foods and beverages. The limited information available regarding absorption parameters of NDMA in experimental animals indicates that NDMA is rapidly absorbed from the gastrointestinal tract; therefore, one can assume that if water or soil contaminated with NDMA are ingested, NDMA will be readily absorbed.

**Food Chain Bioaccumulation.** No studies were available concerning food chain bioaccumulation of NDMA from environmental sources. NDMA has been detected in samples of cooked fish and meat. However, the occurrence of NDMA in these samples is not the result of bioaccumulation, but of formation during preservation and/or cooking (Scanlan 1983). Estimation techniques have been used to determine that NDMA would not bioaccumulate in lipids of fish. Based on this information and the physical-chemical properties of NDMA, it is expected that human exposure to NDMA through diet is not the result of food chain bioaccumulation and no data needs are identified at this time.

**Exposure Levels in Environmental Media.** Limited data suggest that NDMA may be found in urban air, but recent monitoring data pertaining to the detection of NDMA in ambient air are needed to establish this fact. Occurrence of NDMA in air has been associated with cigarette smoke, rubber products, and leather products; however, most of these data are more than 40 years old and may not reflect current manufacturing processes. Studies pertaining to the monitoring of NDMA in indoor air are needed to determine NDMA levels in indoor air under current conditions.

**Exposure Levels in Humans.** Although numerous studies are available concerning the detection of NDMA in various foods, the vast majority of data are 30–40 years old. Thus, a market basket study is needed to provide a reliable estimate of the average daily dietary intake of NDMA associated with current food and beverage production methods. In addition, further research to refine estimates of endogenous NDMA production in infants, children, and adults would provide more reliable information on overall exposures. More work is needed to improve estimates of the contribution of NDMA in drinking water to human exposure, relative to other sources, and the contribution of dermal exposure in swimming pools or bathing activities. Additional information related to the impact of nitrate in drinking water on endogenous NDMA formation in humans (including children) is needed. The presence of NDMA in various pharmaceutical products and human exposure from these products requires continued investigation. Moreover, reliable analytical techniques must be used to distinguish NDMA levels in these products from interfering substances.

**Exposures of Children.** Children are exposed to NDMA by pathways similar to adults, with the exception of consumption of malt liquors and direct use of tobacco products; thus, data needs identified for adults also pertain to childhood exposures. Data on NDMA levels in human breast milk are limited to two studies conducted in 1996 and 1984; more recent data are desirable. In addition, no studies of NDMA levels in infant formula were located, but it is expected that low levels may exist in formulas made from cow's milk (Hrudey et al. 2013). No information was located on NDMA migrating from rubber baby bottle nipples sold in the United States since the FDA action level was established in 1985. Such data are needed to confirm that levels are below the action level.

## 6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institutes of Health (NIH) RePORTER (2022) database, which tracks projects funded by NIH.