Toxicological Profile for N-Nitrosodimethylamine (NDMA)

April 2023

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
April 2023	Final toxicological profile released
January 2022	Draft for public comment toxicological profile released
December 1989	Final toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

N-Nitrosodimethylamine (NDMA) is a volatile nitrosamine that occurs widely in the environment due to its ready formation from commonly found precursors. NDMA is the most well-studied of several volatile N-nitrosamines that exhibit similar toxic properties (including several others that are found in tobacco smoke). For most people, the largest source of exposure to NDMA is through endogenous production (within the body) from precursors (presence of nitrite in foods including drinking water) that occur naturally in the body or in the diet. External sources of NDMA exposure include foods and malt beverages, water, cigarette smoke, and to a lesser extent rubber products, toiletry and cosmetic products, and pesticides. In addition, some people may have had exposures to NDMA through the use of contaminated medications.

NDMA is no longer used in the United States except for research purposes; however, it is readily formed when alkylamines (mainly di- and trimethylamine) come in contact and react with nitrogen oxides, nitrous acid, or nitrite salts, or when trans-nitrosation via nitro or nitroso compounds occurs. Thus, potential exists for release into the environment from industries such as tanneries, pesticide manufacturing plants, rubber and tire manufacturers, alkylamine manufacture/use sites, fish processing industries, foundries and dye manufacturers (Tricker et al. 1989). In air, NDMA may form as a product of the nighttime reaction of dimethylamine with NOx. In water and soil, NDMA forms by the reaction of widely occurring primary, secondary or tertiary amines in the presence of nitrite. NDMA commonly occurs at low levels as a byproduct of disinfection in water treatment plants during the chlorination or chloramination of drinking water and wastewater.

NDMA measurements in ambient air, water, and soil have been reported; however, monitoring data in air and soil are rather scant, and older data may not represent current conditions. An extensive survey in the United States (EPA 2016) showed NDMA detection at parts per trillion levels in a large number of public water systems (PWSs). It occurs primarily due to reactions of disinfectants such as chloramines and ozone with amine-based organic molecules in the water. NDMA has been detected in a variety of other media including foods and beverages, pharmaceutical products, toiletries and cosmetics, tobacco products, rubber products, pesticides, and sewage sludge. NDMA has been found in ground-level fogs (Hutchings et al. 2010) and could be inhaled. NDMA is present at higher concentrations in tobacco smoke than in the tobacco products themselves (Tricker et al. 1991), and elevated NDMA concentrations

in smoke-contaminated rooms suggests that exposure occurs in both smokers and nonsmokers (i.e., involuntary smoking) (IARC 2004). IARC (2004) reported that concentrations of NDMA in sidestream smoke were, on average, 95 times higher than in mainstream smoke.

For most of these media, including foods, the vast majority of published NDMA levels were from samples collected before 1990, and more recent data were not located. NDMA was initially recognized as a contaminant in foods, beverages, and rubber products more than 40 years ago; since that time, producers and manufacturers have modified their processes and techniques to substantially reduce nitrosamine formation. Elimination of NDMA from these products has, however, proved difficult due the abundance of NDMA precursors and the ease with which it is formed. NDMA contamination in prescription and over-the-counter drugs is an active area of U.S. Food and Drug Administration (FDA) investigation; the reader is referred to the FDA website (https://www.fda.gov) for up-to-date information. While many of these medications have been voluntarily recalled, use of previously purchased products containing these medications is possible. Recent data suggest that NDMA is typically not contained in the active pharmaceutical ingredient (API) in drugs like metformin, but rather forms during the manufacture of the final product due to precursors in the excipients (Keire et al. 2022; Zmysłowski et al. 2020).

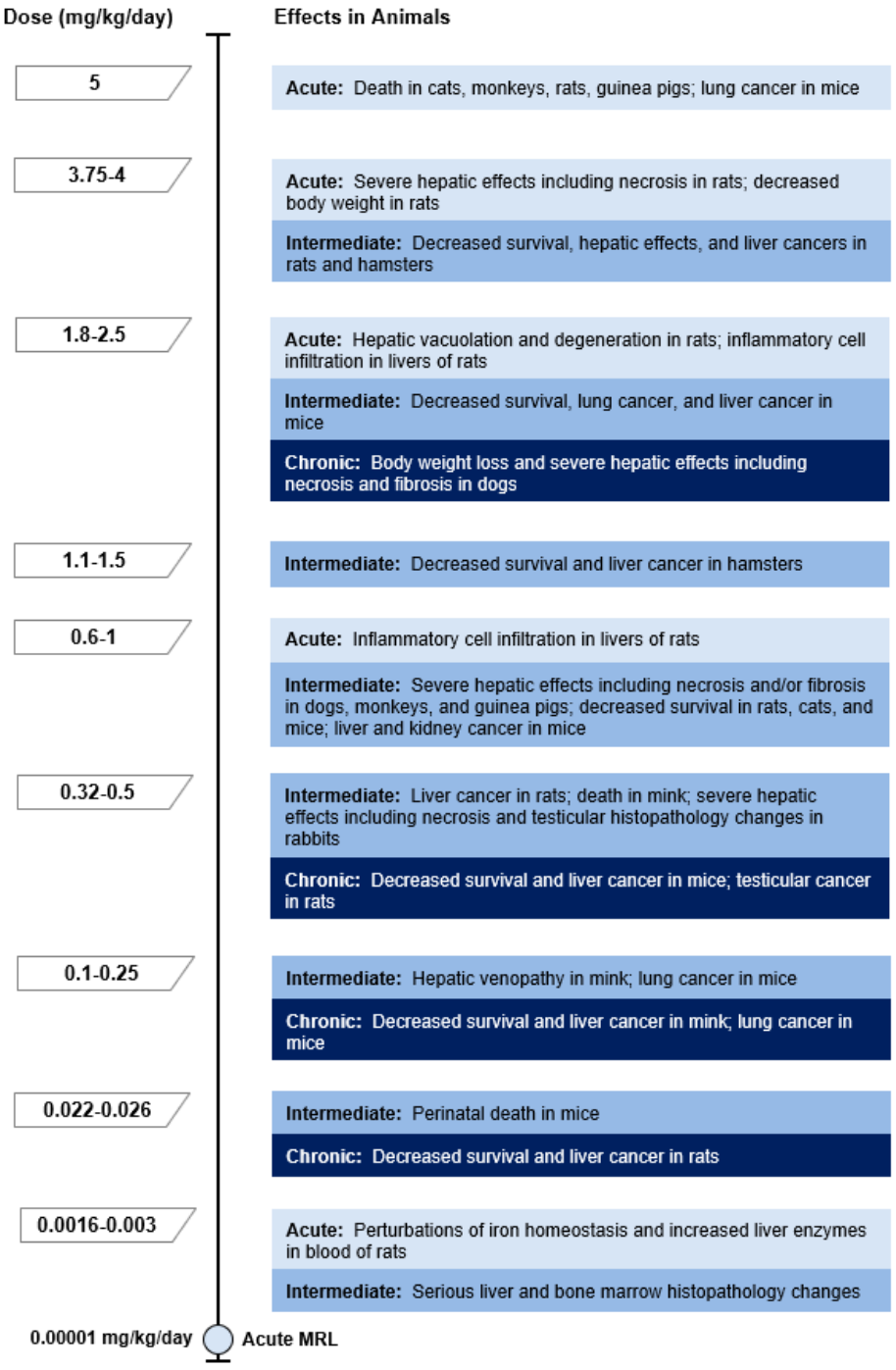
1.2 SUMMARY OF HEALTH EFFECTS

Studies examining the toxicity of NDMA have largely focused on cancers and liver toxicity after oral exposure in animals. A few studies of human noncancer effects associated with occupational exposure to NDMA were located; most of the epidemiological studies examined associations between estimated dietary intake of NDMA and cancers. In the dietary intake studies, exposure to NDMA was assessed using concentrations of NDMA in various foodstuffs combined with food frequency questionnaires administered on a single or a few occasions. As a result, the potential for random misclassification of exposure, which would bias the findings toward the null (no association), is high. A small number of experiments were reviewed in which animals were exposed to NDMA by inhalation for acute or chronic durations; these studies examined only mortality and cancer endpoints. There is a substantial number of studies in which animals were exposed to NDMA by oral administration for acute, intermediate, or chronic durations. However, with few exceptions, these studies have focused on liver effects or cancer, leaving gaps in the data available to assess potential effects on other target organs or systems.

1. RELEVANCE TO PUBLIC HEALTH

Based on the available information and recognizing the limitations in data on other potential target organs, the most sensitive health endpoints observed after oral exposure of animals to NDMA were cancer, and severe noncancer effects on the liver and developing organism, as shown in Figure 1-1.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to N-Nitrosodimethylamine (NDMA)



Hepatic Effects. Hepatic effects of NDMA have been observed in humans after poisoning incidents (Cooper and Kimbrough 1980; Freund 1937; Hamilton and Hardy 1974; Kimbrough 1982), and in at least one case, death was attributed to liver damage from chronic NDMA exposure (Fussgaenger and Ditschuneit 1980; Pedal et al. 1982). The liver effects in animals exposed orally are well known. In every species tested (including rats, mice, hamsters, monkeys, dogs, cats, guinea pigs, and mink), oral exposure to NDMA has induced severe damage to the liver (see, for example, Anderson et al. 1992a; Carter et al. 1969; Khanna and Puri 1966; Maduagwu and Bassir 1980; Nishie 1983; Ungar 1984). The liver effects, mediated by reactive metabolites of NDMA, are typically characterized by hemorrhagic necrosis, followed (if the animal survives) by fibrosis, cirrhosis, and portal hypertension. These effects have been seen after acute-, intermediate-, and chronic-duration exposures. Many of the studies of animals exposed orally to NDMA identified serious lowest-observed-adverse-effect levels (LOAELs) for hepatic effects (a serious LOAEL indicates effects such as system failure that can lead to morbidity or mortality) without no-observed-adverse-effect levels (NOAELs). Little information is available on hepatic effects in animals exposed by inhalation; however, in LC_{50}studies in rats, mice, and dogs, autopsy findings showed hemorrhagic necrosis of the liver (Jacobson et al. 1955).

Developmental Effects. Data pertaining to developmental effects of NDMA are limited but suggest that oral exposure may result in fetal or neonatal mortality after acute- or intermediate-duration exposure in animals (Aleksandrov 1974; Anderson et al. 1978; Bhattacharyya 1965; Napalkov and Alexandrov 1968). The available information on potential teratogenic effects of NDMA is insufficient, as the only studies examining this endpoint (Aleksandrov 1974; Napalkov and Alexandrov 1968) were limited by lack of controls, lack of maternal toxicity data, and/or uncertain treatment schedule.

Cancer. In a study of occupational exposure to NDMA, associations between NDMA exposure and a number of cancer types (including gastric, liver, bladder, and prostate cancers, as well as leukemia and multiple myeloma) were reported (Hidajat et al. 2019a). Epidemiological studies of general population exposure showed associations between dietary intake and cancers of the gastrointestinal tract, especially the stomach (De Stefani et al. 1998; Keszei et al. 2013; Larsson et al. 2006; La Vecchia et al. 1995; Pobel et al. 1995; Song et al. 2015) and colon/rectum (Knekt et al. 1999; Loh et al. 2011; Zhu et al. 2014). No human studies examining the association between oral exposure to NDMA and liver cancer (the primary tumor type seen in laboratory animals exposed to NDMA) were located in the literature reviewed.

The carcinogenicity of NDMA has been established in rats and mice after chronic-duration exposure by inhalation and in numerous studies of animals exposed orally for acute, intermediate, and chronic

durations. Inhalation exposure has resulted in liver, lung, and kidney tumors in rats and mice (Moiseev and Benemanski 1975), and in nasal tumors in rats (Druckrey et al. 1967; Klein et al. 1989, 1991). Oral exposure to NDMA induces several types of liver and lung tumors in rats and mice (Anderson 1988; Anderson et al. 1992a; Arai et al. 1979; Clapp and Toya 1970; Den Engelse et al. 1974; Ito et al. 1982; Keefer et al. 1973; Lijinsky and Kovatch 1989; Lijinsky and Reuber 1984; Magee and Barnes 1956; Peto et al. 1984, 1991a, 1991b; Takahashi et al. 2000; Takayama and Oota 1965; Terracini et al. 1966), and has also induced kidney tumors in these species (Lijinsky and Kovatch 1989; Takayama and Oota 1965; Terracini et al. 1966) and testicular tumors in rats (Terao et al. 1978). Both hamsters and mink also developed liver tumors after oral exposure to NDMA (Bosan et al. 1987; Koppang and Rimeslatten 1976; Ungar 1986). In animals exposed orally, NDMA has induced increased incidences of lung tumors in mice after a single 5 mg/kg dose (Anderson et al. 1992a). In intermediate-duration studies, increased incidences of liver or lung tumors were seen in mice and rats after 1–4 months of exposure to doses of 1.2–1.8 mg/kg/day (Anderson 1988; Anderson et al. 1992a; Clapp and Toya 1970; Den Engelse et al. 1974) or after 7–10 months of exposure to doses ≥0.25 mg/kg/day (Anderson et al. 1992a; Clapp and Toya 1970; Keefer et al. 1973; Lijinsky and Kovatch 1989; Lijinsky and Reuber 1984; Magee and Barnes 1956; Takahashi et al. 2000; Terracini et al. 1966). Chronic exposure to NDMA at doses as low as 0.022 mg/kg/day resulted in decreased survival due to liver tumors in rats (Peto et al. 1984, 1991a, 1991b).

NDMA's carcinogenicity is widely recognized. The U.S. Environmental Protection Agency (EPA) (IRIS 1987) classified NDMA in Group B2 (probable human carcinogen) based on sufficient evidence of carcinogenicity in animals. The International Agency for Research on Cancer (IARC 1987) assigned NDMA to Group 2A (probably carcinogenic to humans) based on inadequate information in humans and sufficient evidence in experimental animals. Likewise, the Department of Health and Human Services (HHS) National Toxicology Program (NTP 2016) Report on Carcinogens concluded that NDMA is "reasonably anticipated to be a human carcinogen," based on sufficient evidence in animals.

1.3 MINIMAL RISK LEVELS (MRLs)

The data on inhalation exposure of humans or animals to NDMA are not adequate to identify target organs. The most sensitive outcomes in the animal studies of oral NDMA were liver, hematological, immune system, and developmental effects, and cancer, as shown in Figure 1-2. The oral database was considered adequate for derivation of an acute-duration MRL but was not sufficient for derivation of

intermediate- or chronic-duration oral MRLs. The MRL values for NDMA are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of N-Nitrosodimethylamine (NDMA) – Oral

Effects in animals at the lowest doses tested include serious effects on the liver; cancer in the liver, lung, and kidneys; and death or decreased survival, including of the developing organism.
Numbers in circles or triangles are the lowest LOAELs for all health effects in animals; all LOAELs are serious LOAELs. No reliable dose-response data were available for humans

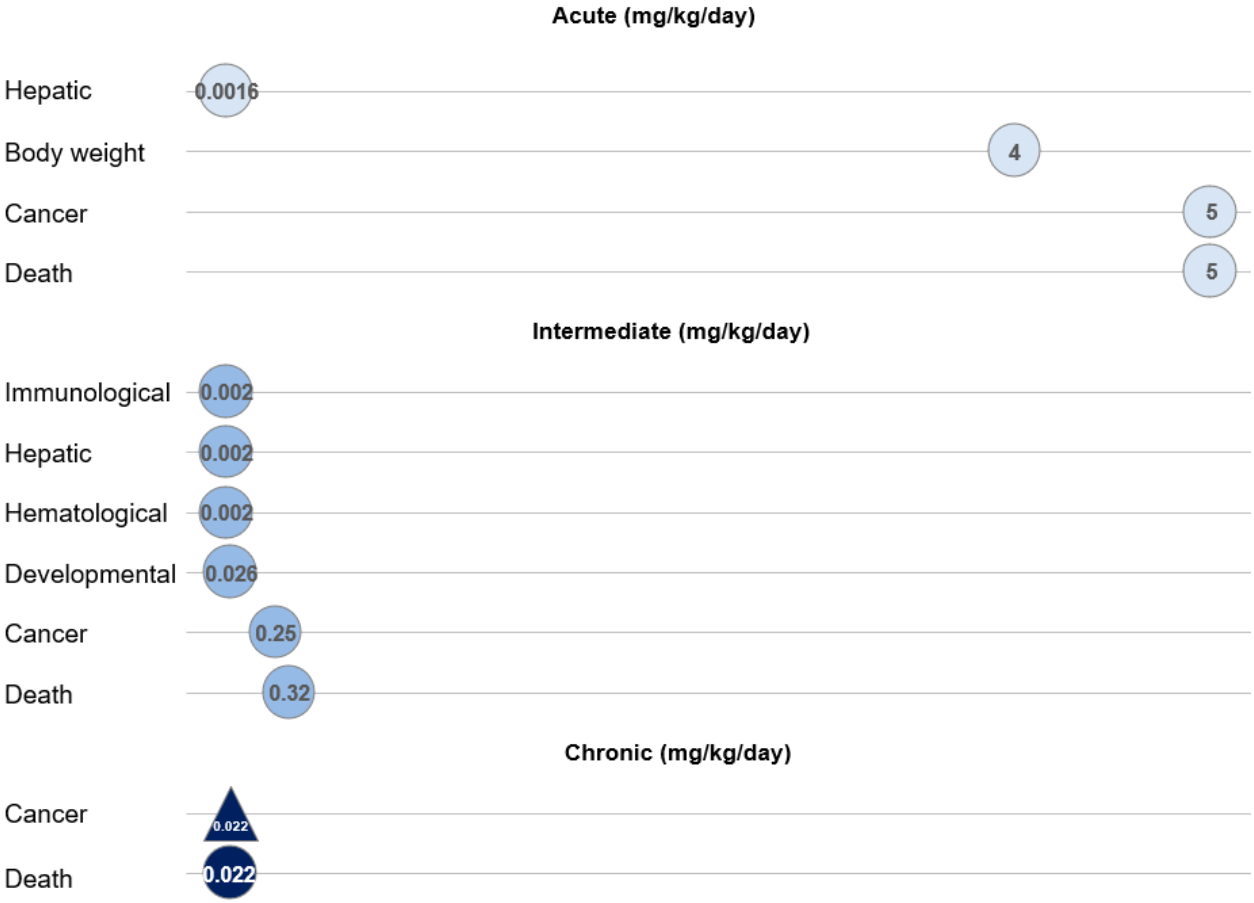


Table 1-1. Minimal Risk Levels (MRLs) for N-Nitrosodimethylamine (NDMA)[a]

Exposure duration	MRL	Critical effect	Point of departure/ Human equivalent concentration	Uncertainty/ modifying factor	Reference
Inhalation exposure (mg/m^3)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	**0.00001** (0.01 µg/kg/day)	Liver effect causing decreased total iron binding capacity in blood	$BMDL_{1SD}$: 0.0014	UF: 100	Moniuszko-Jakoniuk et al. 1999; Roszczenko et al. 1996a, 1996b
Intermediate	Insufficient data for derivation of an MRL				
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

$BMDL_{1SD}$ = 95% lower confidence limit on the BMD associated with 1 SD change from control mean; SD = standard deviation; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of NDMA. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to NDMA, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; no dermal data were identified for NDMA.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an

endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of NDMA are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

A User's Guide has been provided at the end of this profile (see Appendix C]). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Studies examining the health effects of NDMA after inhalation, oral, or dermal exposure and discussed in this profile include 24 human studies and 89 animal studies. Most of the human studies examined associations between dietary intake of NDMA and various cancers. As shown in Figure 2-1, the vast preponderance of the available data consists of studies of animals exposed by oral administration (at doses ranging from 0.0007 to 50 mg/kg/day) in which hepatic effects, cancer, and/or survival were assessed. Very few data are available for other endpoints. A substantial number of studies were identified in which NDMA was administered via intraperitoneal (i.p.) injection in rats as an animal model of liver fibrosis or cirrhosis. However, these studies do not contribute to the understanding of NDMA health effects or dose-response relationships and are thus not discussed in this profile.

- **Hepatic Effects:** Data on the hepatic effects of NDMA are largely limited to studies of animals exposed by oral administration. In these studies, NDMA induced severe liver injury (hemorrhagic necrosis, fibrosis, and/or cirrhosis) in a wide range of species (rats, mice, hamsters, monkeys, dogs, cats, guinea pigs, and mink) after all exposure durations. Human data on the hepatic effects of NDMA are limited to case reports.

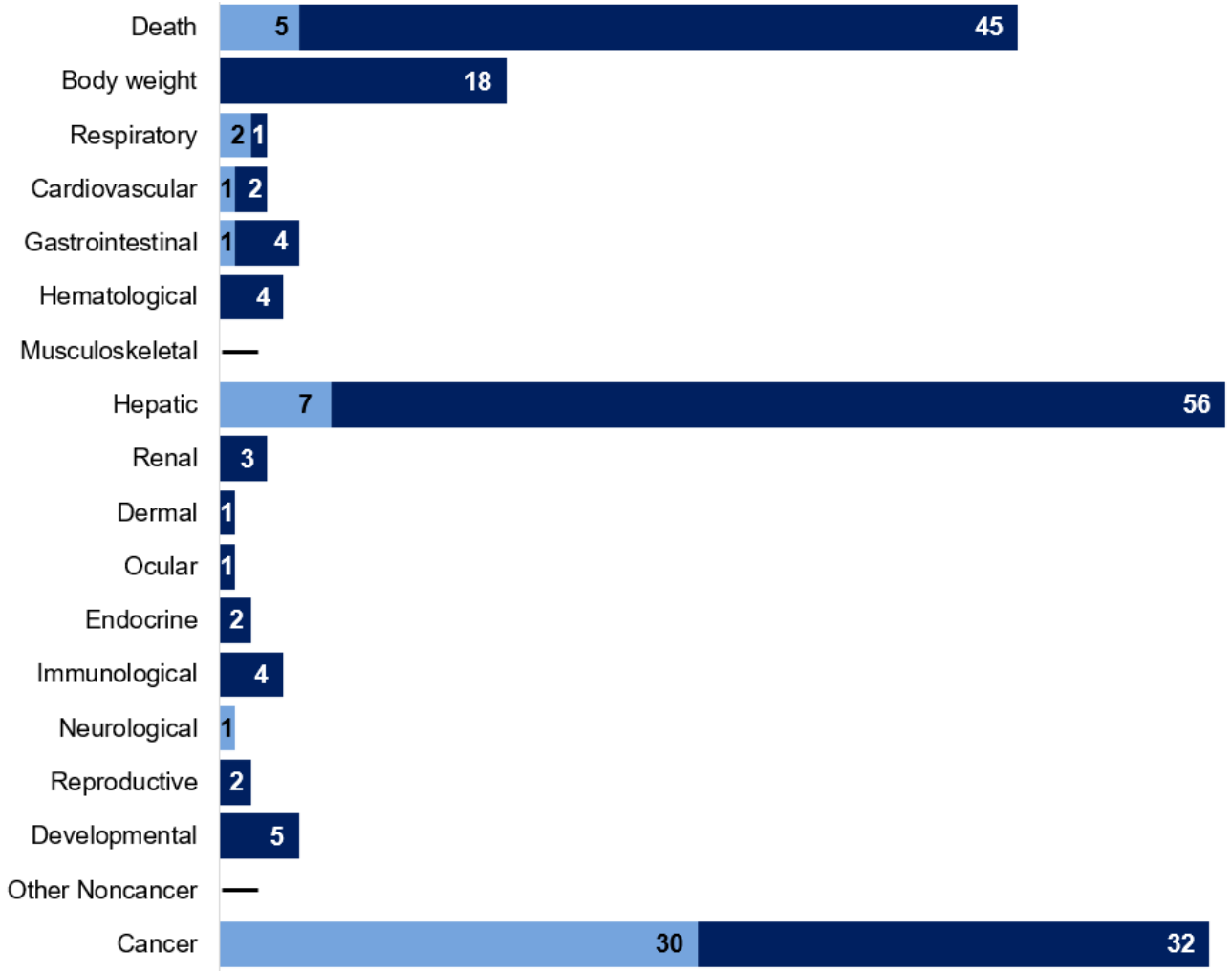
- **Developmental Effects:** Very limited data pertaining to developmental effects of NDMA were located, but the available studies suggest that oral exposure may result in fetal or neonatal mortality after acute- or intermediate-duration exposure in animals. The available information on potential teratogenic effects of NDMA is insufficient, as the only studies examining this endpoint were limited by lack of controls, lack of maternal toxicity data, and/or uncertain treatment schedule.

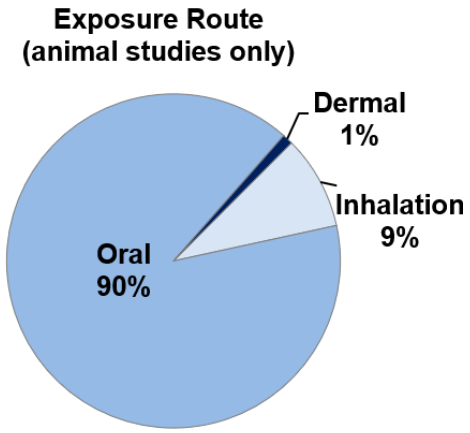
- **Cancer Effects:** In a study of occupational exposure by inhalation, cumulative NDMA exposure was associated with higher risks of gastric, liver, bladder, and prostate cancers, and also with increased risks of leukemia and multiple myeloma. Epidemiological studies have reported associations between NDMA exposure in the diet and gastric and colorectal cancers. In animals exposed by inhalation, NDMA has induced liver, lung, and kidney tumors in rats and mice, and nasal tumors in rats. Oral exposure to NDMA primarily induces liver and lung tumors in rats and mice and has also induced kidney tumors in these species and testicular tumors in rats. Increased incidences of liver tumors were also observed in hamsters and mink after oral exposure to NDMA.

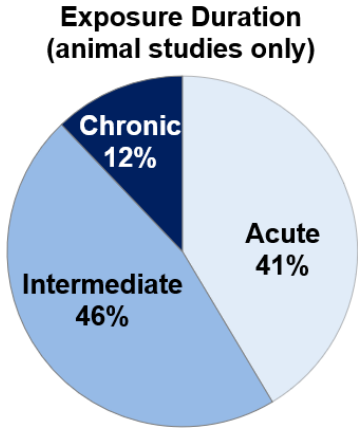
Figure 2-1. Overview of the Number of Studies Examining N-Nitrosodimethylamine (NDMA) Health Effects*

Most studies examined the potential carcinogenicity, hepatic effects, and lethality of NDMA

Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 113 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to N-Nitrosodimethylamine – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
1	Rat (NS) 10 M	4 hours, once	41–188	CS,GN	Death			78	LC_{50}
					Hepatic			78	Hemorrhagic necrosis
Jacobson et al. 1955									
2	Mouse (NS) 10 F	4 hours, once	39–67	CS,GN	Death			57	LC_{50}
					Hepatic			57	Hemorrhagic necrosis
Jacobson et al. 1955									
3	Dog (beagle) 3 M	4 hours, once	16–144	BC, CS, OF GN, HP, HE	Death			16	2/3 died; all died at higher exposures
					Hepatic			16	Hemorrhagic necrosis
Jacobson et al. 1955									
CHRONIC EXPOSURE									
4	Rat (BD) 6–12 NR	Lifetime, 2 days/week, 0.5 hours/day	50, 100	HP	Cancer			50	CEL: nasal tumors
Druckrey et al. 1967									
5	Rat (Sprague-Dawley) 36 F	At least 52 weeks, 5 days/week, 4 hours/day	0, 0.04, 0.2, 1	LE, BW, HP	Death			1	Reduced survival (median survival 9 months less than controls)
					Bd wt	0.2		1	>20% decrease in body weight at the end of exposure
					Cancer			0.04	CEL: nasal tumors
Klein et al. 1989, 1991									
6	Rat (Wistar) 36–51 M, F	25 months, continuous	0, 0.002, 0.07	HP	Cancer			0.07	CEL: liver, lung, kidney tumors
Moiseev and Benemanski 1975									

Table 2-1. Levels of Significant Exposure to N-Nitrosodimethylamine – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
7	Mouse (BALB/c) 30–68 M, F	17 months, continuous	0, 0.002, 0.07	HP	Cancer	0.002		0.07	CEL: liver, lung, kidney tumors
Moiseev and Benemanski 1975									

BC = blood chemistry; Bd wt or BW = body weight; CEL = cancer effect level; CS = clinical signs; F = female(s); GN = gross necropsy; HE = hematology; HP = histopathology; LC_{50} = concentration producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; m = male(s); NOAEL = no-observed-adverse-effect level; NR = not reported; OF = organ function

Figure 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Inhalation
Acute (≤14 days)

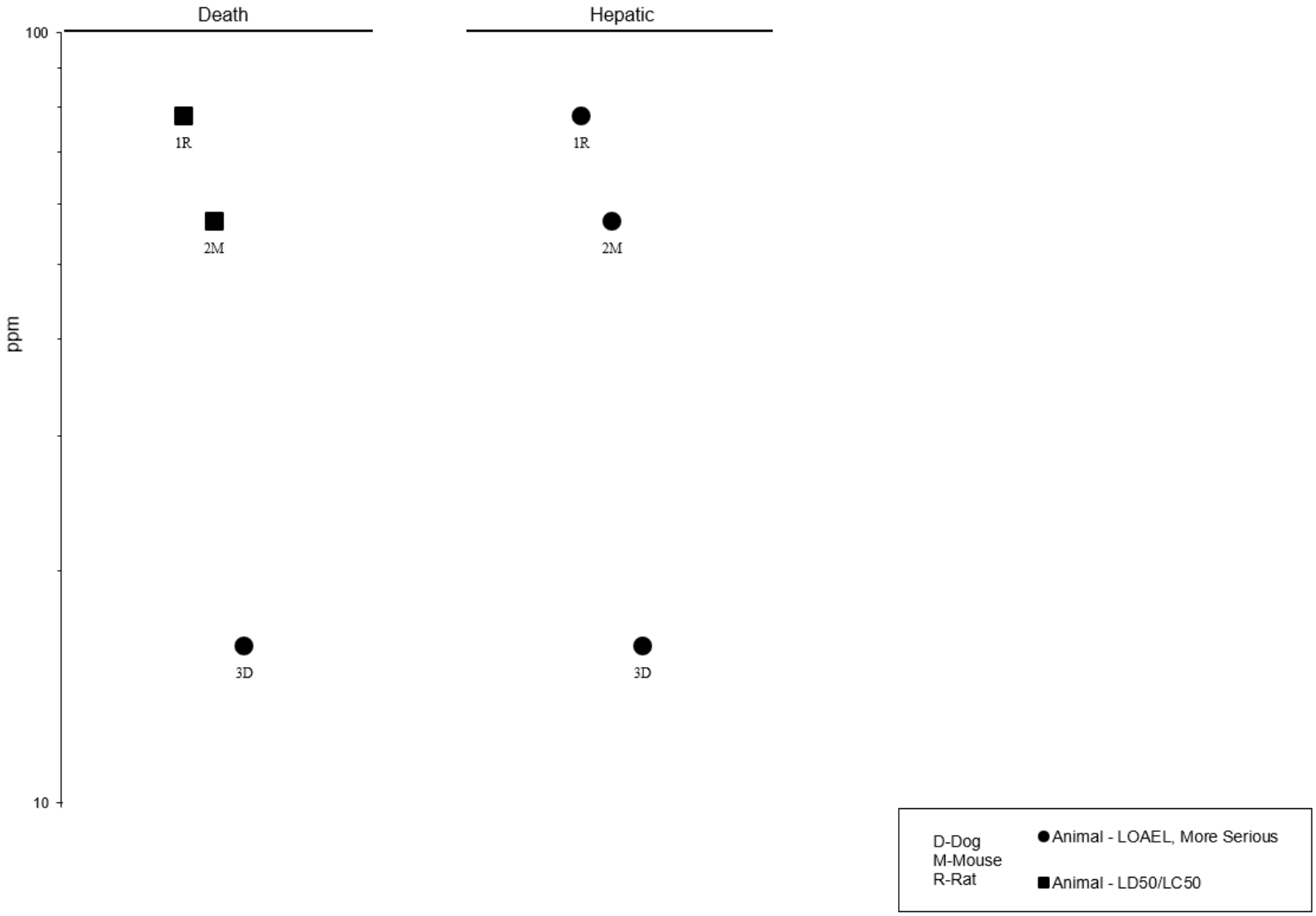
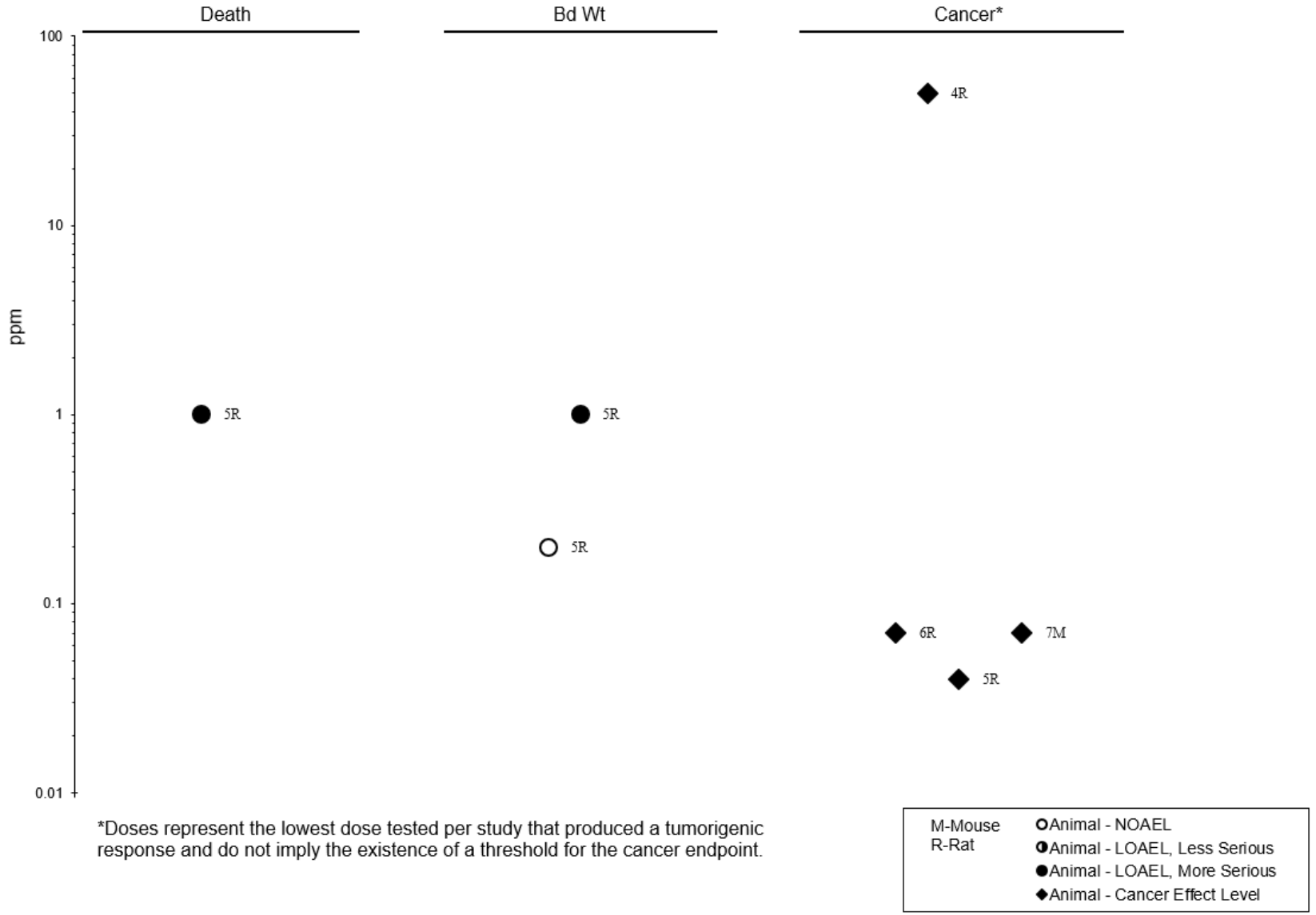


Figure 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Inhalation
Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
1	Monkey (African green) 6 M	Once (G)	0, 50	LE, BW, OW, GN, HP, BC, CS	Bd wt	50			No difference in body weight gain
					Hepatic		50		Enlarged, cherry-red liver
Maduagwu and Bassir 1980									
2	Monkey (African green) 6 M	5–11 days, 1 time/day (G)	0, 5	LE, BW, OW, GN, HP, BC, CS	Death			5	3/6 died
					Bd wt	5			No difference in body weight gain
					Hepatic			5	Necrosis
Maduagwu and Bassir 1980									
3	Rat (F344/ Du Crj) 3 M	Once (G)	0, 20	BC, HP	Hepatic			20	2–7-fold increases in serum AST and ALT and focal necrosis 1–2 days after dosing
Asakura et al. 1998									
4	Rat (F344/ Du Crj) 3 M	14 days, 1 time/day (G)	0, 4	BC, HP	Hepatic			4	Focal necrosis
Asakura et al. 1998									
5	Rat (BD) NS	Once (G)	40	LE, CS	Death			40	LD_{50}
Druckrey et al. 1967									
6	Rat (Fischer-344) 3–5 M	Once (G)	37, 48.1, 62.5, 81.3	LE, GN, HP	Death			48.1	4/5 died at 48.1 mg/kg
Frank et al. 1990									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
7	Rat (NS) 7–8 NS	Once	0, 10	BC	Hepatic		10		6-fold increase in serum ALT
Garland et al. 1988									
8	Rat (Crl:CD [SD]) 5 M	14 days (GW)	0, 1, 2, 4	LE, BW, OW, HP	Bd wt	2	4		14% lower body weight at termination
					Hepatic		1		Inflammatory cell infiltration
Hamada et al. 2015; Takashima et al. 2015									
9	Rat (albino) 25 NS	1 or 2 weeks, 7 days/week (F)	0, 3.75	HP	Hepatic			3.75	Hemorrhagic necrosis
Khanna and Puri 1966									
10	Rat (Sprague-Dawley) 7–9 M	Once (G)	0, 0.3, 0.7, 1.9, 5.1, 13.7, 37.0, 100	OW, HP, BC, BI	Hepatic	0.7	1.9	13.7	LOAEL: vacuolation Serious LOAEL: necrosis
Korsrud et al. 1973									
11	Rat (Wistar) 10 M	Once (G)	0, 50	BW, OW, GN, HP, BC, CS	Bd wt			50	16% body weight loss (compared to 10% gain in controls)
					Hepatic			50	Necrosis with hemorrhage into peritoneum
Maduagwu and Bassir 1980									
12	Rat (Wistar) 10 M	5–11 days, 1 time/day (G)	0, 5	LE, BW, OW, GN, HP, BC, CS	Death			5	3/10 died
					Bd wt			5	41% body weight loss (compared to 32% gain in controls)
					Hepatic			5	Necrosis
Maduagwu and Bassir 1980									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
13	Rat (Wistar) 8 M	10 days, 7 days/week (W)	0, 0.002, 0.003	BI, HP	Hemato	0.003			No changes in bone marrow histopathology
					Hepatic	0.003			No changes in liver histopathology
					Immuno	0.003			No changes in spleen histopathology
Moniuszko-Jakoniuk et al. 1999									
14	Rat (Holtzman) 17–32 F	Once on GD 18 (GO)	0, 15, 20	LE, CS	Death			15	3/32 pregnant rats died at 15 mg/kg
Nishie 1983									
15	Rat (Holtzman) 21 F	Once (GO)	0, 15, 20	BW, BC, BI, OW, HP	Bd wt	20			
					Hepatic			15	Necrosis, glycogen depletion
					Endocrine	20			No change in thyroid weight or histopathology
Nishie 1983									
16	Rat (Holtzman) 6–22 F	Once on GDs 9, 12, 14, and 15 (20 mg/kg) or GD 16, 18, or 20 (15 or 20 mg/kg) (GO)	0, 15, 20	BW, BC, BI, OW, HP	Hepatic			15	Severe centrilobular damage (necrosis and glycogen depletion) in dams
					Endocrine	20			No change in thyroid weight or histopathology in dams
Nishie 1983									
17	Rat (Holtzman) 6–22 F	Once on GD 15 or 20 (GO)	0, 20	DX	Develop			20	12–18% decrease in mean fetal weight
Nishie 1983									
18	Rat (Wistar) 7 M	10 days, 7 days/week (W)	0, 0.002	BC	Hepatic		0.002		≥2-fold increases in serum AST, ALT, ALP, and GGT
Roszczenko et al. 1996a									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
19	Rat (Wistar) 7 M	10 days, 7 days/week (W)	0, 0.0007, 0.0016, 0.0035	HE, BC, BI	Hepatic	0.0007[b]	0.0016		Decreased serum total and latent iron binding capacity; $BMDL_{1sd}$=0.0014.
Roszczenko et al. 1996b									
20	Rat (Wistar) 12–20 M	Once (G)	0, 8, 9, 10	HP, BC	Hepatic			8	Necrosis; serum ALT and AST increased 15- and 22-fold (respectively) in germ-free rats and 1.7- and 1.9-fold (respectively) in conventional rats
Sumi and Miyakawa 1983									
21	Rat (Wistar) 5–20 M	Once (G)	0, 40	OF	Death			40	All rats died by day 21
Waynforth and Magee 1974									
22	Mouse (A/JNCr) 50 M	Once (GW)	0, 1, 5	BW, WI, GN, HP	Bd wt	5			
					Cancer			5	CEL: lung tumors (at sacrifice 16 weeks after dosing)
Anderson et al. 1992a									
23	Mouse (CD-1) 3 M	2 weeks, 7 days/week (GW)	0, 2, 4, 7, 10	LE, BC, BI	Death			7	All animals died within 6 days
					Hepatic	2	4		2-fold increases in serum ALT and AST
Doolittle et al. 1987									
24	Mouse (Swiss) 18 M, 13 F	1 week, 7 days/week (W)	0, 10	LE, CS, HP	Death			10	Decreased survival (survival at week 10: 0/13 males and 12/18 females treated versus and 32/33 male and 36/36 female controls)
					Cancer			10 F	CEL: kidney and lung tumors
Terracini et al. 1966									
25	Guinea pig (Hartley) 10M	Once (G)	0, 50	LE, BW, OW, GN, HP, BC, CS	Bd wt			50	10% body weight loss (compared to 8% gain in controls)
					Hepatic			50	Hemorrhagic centrilobular necrosis
Maduagwu and Bassir 1980									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
26	Guinea pig (Hartley) 10 M	5–11 days, 1 time/day (G)	0, 5	LE, BW, OW, GN, HP, BC, CS	Death			5	4/10 died
					Bd wt			5	14% body weight loss (compared to 17% gain in controls)
					Hepatic			5	Necrosis
Maduagwu and Bassir 1980									
27	Hamster (Golden) 5–20 M	1–14 days, 7 days/week (W)	0, 4	CS, GN, HP	Hepatic		4		Portal venopathy
Ungar 1984									
28	Cat (domestic) 6 M	5–11 days, 1 time/day (G)	0, 5	LE, BW, OW, GN, HP, BC, CS	Death			5	4/6 died
					Bd wt			5	21% body weight loss (compared to 13% gain in controls)
					Hepatic			5	Necrosis
Maduagwu and Bassir 1980									
29	Cat (domestic) 6 M	Once (G)	0, 50	LE, BW, OW, GN, HP, BC, CS	Death			50	2/6 died
					Bd wt			50	13% body weight loss (compared to 4% gain in controls)
					Hepatic			50	Ascites; severe hemorrhage into peritoneum
Maduagwu and Bassir 1980									
INTERMEDIATE EXPOSURE									
30	Monkey (African green) 6 M	30 days, 1 time/day (G)	0, 1	LE, BW, OW, GN, HP, BC, CS	Hepatic			1	Necrosis
Maduagwu and Bassir 1980									
31	Rat (albino) 6 NS	34–110 days, 7 days/week (F)	0, 5, 10, 20	BW, FI, GN, HP	Death			10	6/6 died between days 62 and 95; at 20 mg/kg/day, 6/6 died between days 34 and 37
					Bd wt			10	35% decrease in body weight
					Gastro			20	Hemorrhage

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hepatic	5		10	Necrosis
Barnes and Magee 1954									
32	Rat (Fischer-344) 89–91 M	16 weeks, 7 day/week (W)	0, 0.000075, 0.00075, 0.0075, 0.075, 0.75	BW, BI, OW, GN	Bd wt	0.75			
					Hepatic	0.75			No change in absolute or relative liver weight
Fukushima et al. 2005									
33	Rat (Crl:CD [SD]) 5 M	28 days (GW)	0, 0.5, 1, 2	LE, BW, OW, HP	BW	2			
					Hepatic	1	2		Inflammatory cell infiltration
Hamada et al. 2015; Takashima et al. 2015									
34	Rat (Fischer-344) 12–19 M	8 weeks, 7 days/week (W)	0, 3.9	BW, OW, HP	Bd wt	3.9			
					Hepatic		3.9		Eosinophilic or mixed cell foci and hepatocellular nodules
Jang et al. 1990									
35	Rat (MRC) 15–30 M	30 weeks, 5 days/week (W)	0, 0.4, 2	HP	Cancer			0.4	CEL: liver tumors
Keefer et al. 1973									
36	Rat (albino) 25 NS	4, 8, or 12 weeks, 7 days/week (F)	0, 7.2	HP	Hepatic			7.2	Hemorrhagic necrosis
Khanna and Puri 1966									
37	Rat (Fischer-344) NS M and F	20–30 weeks, 2 days/week (GO)	0, 11.1 (M); 8.1, 13.2 (F)	LE, GN, HP	Death			13.2 F	Some (NS) animals died in 6th week
					Cancer			8.1 F 11.1 M	CEL: liver, lung, and kidney tumors
Lijinsky and Kovatch 1989									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
38	Rat (Fischer-344) 20 F	30 weeks, 5 days/week (W)	0, 0.75, 1.8	HP	Death			0.75	Decreased survival
					Cancer			0.75	CEL: liver tumors
Lijinsky and Reuber 1984									
39	Rat (Wistar) 10 M	30 days, 1 time/day (G)	0, 1	LE, BW, OW, GN, HP, BC, CS	Hepatic		1		Vacuolation and congestion
Maduagwu and Bassir 1980									
40	Rat (albino) 5–10 M, 5–10 F	Up to 40 weeks, 7 days/week (F)	0, 3.9	BW, FI, GN, HP	Death			3.9	Decreased survival
					Hepatic			3.9	Hemorrhagic necrosis
					Cancer			3.9	CEL: liver tumors in 19/20
Magee and Barnes 1956									
41	Rat (Wistar) 8 M	30 or 90 days, 7 days/week (W)	0, 0.002, 0.003	BI, HP	Hemato			0.002	Bone marrow histopathology changes: focal necrosis; edema, degeneration; decrease in megakaryocytes and migration to vascular sinus; myelosclerosis after 90 days
					Hepatic			0.002	Degeneration, argyrophilic and collagenic fibers, and inflammatory infiltrations near portal biliary tract after 30 days; steatosis and parenchymatosis after 90 days
					Immuno		0.002		Splenic histopathology changes: megakaryocytes in red pulp; enhanced lymphatic "texture" after 90 days
Moniuszko-Jakoniuk et al. 1999									
42	Rat (SD) 6 M	15 days (GW)	0, 0.5, 2, 4	BW, BC, HE, HP	Hepatic	0.5		2	Centrilobular hepatocyte degeneration and fibrosis; inflammation of central vein and subscapular region
Rothfuss et al. 2010									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
43	Rat (Wistar) 10–12 M	30 weeks, 7 days/week (W)	0, 1.5, 3.7	LE, BW, OW, HP	Death			1.5	8/12 died at 1.5 mg/kg/day and 6/12 died at 3.7 mg/kg/day
					Bd wt		3.7		10% decrease in terminal body weight
					Cancer			1.5	CEL: liver tumors
Takahashi et al. 2000									
44	Mouse (A/JNCr) 39–50 M	16 weeks, 7 days/week (W)	0, 0.12, 0.25, 1.2	HP, BW, WI	Bd wt	1.2			
					Cancer			1.2	CEL: lung tumors
Anderson 1988									
45	Mouse (CD-1) 10 F	≥100 days total (75 days premating, through Gestation and possibly lactation) (W)	0, 0.026	CS, GN, DX	Develop			0.026	Increased perinatal deaths (stillborn and neonatal)
Anderson et al. 1978									
46	Mouse (Swiss Cr:NIH(s)) 10–20 F	1–4 weeks, 7 days/week (W)	0, 5	BW, WI, GN, BI, HP	Hepatic			5	Hemorrhage (mild to moderate centrilobular) at all time points (1, 2, and 4 weeks)
Anderson et al. 1986									
47	Mouse (A/JNCr) 50 M	4 weeks, 7 days/week (W)	0, 1.2	BW, WI, GN, HP	Bd wt	1.2			
					Cancer			1.2	CEL: lung tumors
Anderson et al. 1992a									
48	Mouse (A/JNCr) 50 M	16–48 weeks, 7 days/week (W)	0, 0.25	BW, WI, GN, HP	Bd wt	0.25			
					Cancer			0.25	CEL: increased incidence or number of lung tumors after 32 or 48 weeks
Anderson et al. 1992a									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
49	Mouse (RF/Un) 83–262 M	49 days, 7 days/week (W)	0, 1.8	CS, GN, HP	Death			1.8	Decreased survival (mean 15 versus 20.5 months in controls)
					Cancer			1.8	CEL: liver and lung tumors
Clapp and Toya 1970									
50	Mouse (RF/Un) 17–262 M	224 days, 7 days/week (W)	0, 0.40	CS, GN, HP	Cancer			0.4	CEL: lung tumors
Clapp and Toya 1970									
51	Mouse (RF/Un) 94–262 M	Lifetime (average 266 days), 7 days/week (W)	0, 0.91	CS, GN, HP	Death			0.91	Decreased survival (mean 12 months versus 20.5 months in controls)
					Cancer			0.91	CEL: liver and lung tumors
Clapp and Toya 1970									
52	Mouse (C3Hf) 17 M, 20 F	13 weeks, 7 days/week (W)	0, 1.2	HP	Death			1.2	Decreased survival
					Cancer			1.2	CEL: liver, lung
Den Engelse et al. 1974									
53	Mouse (CD-1) 15 F	4–17 weeks, 7 days/week (W)	0, 0.26, 1.3, 2.6, 5.3	HE, HP, BC, BW, GN, WI	Death			2.6	1/15 exposed to 2.6 mg/kg/day and 3/15 exposed to 5.3 mg/kg/day
					Hepatic			2.6	Ascites (10/13 between 30 and 120 days of exposure at 2.6 mg/kg/day and 14/14 by exposure day 30 at 5.3 mg/kg/day)
					Immuno	0.26	1.3		Markedly reduced humoral response to sheep red blood cells and inhibition of alloantigenic response of T-cells.
Desjardins et al. 1992									
54	Mouse (C3H/) 30 M	5 months, 7 days/week (F)	0, 5.26	HP	Death			5.26	Decreased survival
					Hepatic			5.26	Hemorrhage/necrosis
					Cancer			5.26	CEL: liver, lung, and kidney tumors
Takayama and Oota 1965									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
55	Mouse (Swiss) 26 M, 19 F	38 weeks, 7 days/week (W)	0, 1	CS, HP	Death			1	Decreased survival (respective male and female survival to 30 weeks: 69 and 53% versus 94 and 89% in controls)
					Cancer			1	CEL: liver, lung, and kidney tumors
Terracini et al. 1966									
56	Guinea pig (Hartley) 10 M	30 days, 1 time/day (G)	0, 1	BW, OW, GN, HP, BC, CS	Hepatic			1	Necrosis
Maduagwu and Bassir 1980									
57	Hamster (Syrian Golden) 30–31 M	Up to 7 months 7 days/week (W)	0, 1.1	BW, WI, GN, HP	Death			1.1	3/30 died within 6 months and 27/30 died within 7 months
					Cancer			1.1	CEL: liver tumors
Bosan et al. 1987									
58	Hamster (Golden) 5–10 M	28 days, 7 days/week (W)	0, 4	GN, HP, CS	Hepatic		4		Portal venopathy
Ungar 1984									
59	Hamster (Golden) 4–13 M	8, 12, or 16 weeks, 7 days/week (W)	0, 4	GN, HP, CS	Death			4	Three animals died prior to week 8
					Hepatic		4		Portal venopathy after 8 weeks
					Cancer			4	CEL: liver tumors after 16 weeks
Ungar 1986									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
60	Dog (Beagle) 6 or 8 M, F	24 weeks, 2 consecutive days/week (C)	0, 2	LE, BW, CS, BC, UR, HE, OW, GN, HP	Bd wt		2		Weight loss (up to 18%)
					Hepatic			2	Severe hepatic effects including increased serum enzymes (AST, ALT, ALP, GGT), bile acids, and bilirubin; histopathology (necrosis, inflammation, cholestasis, vacuolation, lobular collapse, fibrosis and biliary hyperplasia); ascites; hepatic encephalopathy; secondary effects on clotting parameters
Boothe et al. 1992									
61	Dog (Mongrel) 5–8 NS	4 weeks, 2 consecutive days/week (C)	0, 2.51	BC, HP	Hepatic			2.51	Hepatic necrosis, stromal collapse, fibrous structure; increased serum AST, ALT, and LDH (80, 220, and 94% compared to controls)
Hashimoto et al. 1989									
62	Dog (Mongrel) 9–11 NS	4 weeks, 2 consecutive days/week (C)	0, 2.51	BC, HP	Death			2.51	1/9 died of acute liver failure 2 weeks after dosing ended
					Hepatic			2.51	Extensive necrosis, stromal collapse, destruction of lobular architecture, inflammation, cirrhosis; increased serum ALP, AST, and bilirubin; ascites
Madden et al. 1970									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
63	Cat (domestic) 6 M	30 days, 1 time/day (G)	0, 1	LE, BW, OW, GN, HP, BC, CS	Death			1	3/6 died between days 25 and 30
					Bd wt			1	28% body weight loss (compared to 26% gain in controls).
					Hepatic			1	Necrosis
Maduagwu and Bassir 1980									
64	Rabbit (New Zealand) 5 M	12 weeks, 7 days/week (GW) 0, 0.5		BC, BI, HP	Hepatic			0.5	Hepatocytic infiltration in portal areas, central vein congestion, red blood cell hemolysis, vacuolar degeneration
					Repro			0.5	Markedly reduced (96% less than controls) serum testosterone; increased serum estradiol; testicular histopathology (disorganized seminiferous tubules; interstitial edema; degeneration of germinal epithelium in seminiferous tubules and Sertoli cells; exfoliation of cells in lumen of tubules; blood vessel congestion; proliferation of Leydig cells)
Sheweita et al. 2017									
65	Mink ("pastel") 3 M	23–34 days, 7 days/week (F)	0, 0.32, 0.63	LE, BW, FI, HP, CS	Death			0.32	Decreased survival
					Hepatic			0.32	Necrosis
Carter et al. 1969									
66	Mink (NS) 12 M, 12 F	122 days, 7 days/week (F)	0, 0.04, 0.05, 0.06, 0.08, 0.13, 0.17	GN, CS, HP	Hepatic	0.08	0.13		Venopathy
Koppang and Rimeslatten 1976									

Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
67	Rat (Wistar) 24 M, 24 F	96 weeks, 7 days/week (F)	0, 0.013, 0.13, 1.3	BW, OW, FI, WI, HE, BC, HP	Bd wt	1.3			
					Hepatic	0.013	0.13		Nodular hyperplasia
					Renal	1.3			
					Cancer			1.3	CEL: liver (both sexes);leukemia (females)
Arai et al. 1979; Ito et al. 1982									
68	Rat (Wistar) 60 M, 60 F treated, 240 M, 240 F control	1, 1.5, or 3.5 years, 7 days/week (W)	M: 0, 0.001, 0.003, 0.005, 0.011, 0.022, 0.044, 0.065, 0.087, 0.109, 0.131, 0.174, 0.218, 0.261, 0.348, 0.697 F: 0, 0.002, 0.005, 0.010, 0.019, 0.038, 0.076, 0.115, 0.153, 0.191, 0.229, 0.306, 0.382, 0.459, 0.612, 1.224	GN, LE, HP	Death			0.022 M 0.038 F	Decreased survival
					Cancer			0.022 M 0.038 F	CEL: liver tumors
Peto et al. 1984, 1991a, 1991b									
69	Rat (Wistar) 15 M	54 weeks, 7 days/week (F)	0, 0.5	HP	Hepatic	0.5			
					Cancer			0.5	CEL: testicular tumors
Terao et al. 1978									
70	Mouse (A/JNCr) 47–48 M	72 weeks, 7 days/week (W)	0, 0.24	BW, WI, GN, HP	Bd wt	0.24			
					Cancer			0.24	CEL: lung tumors
Anderson et al. 1992a									

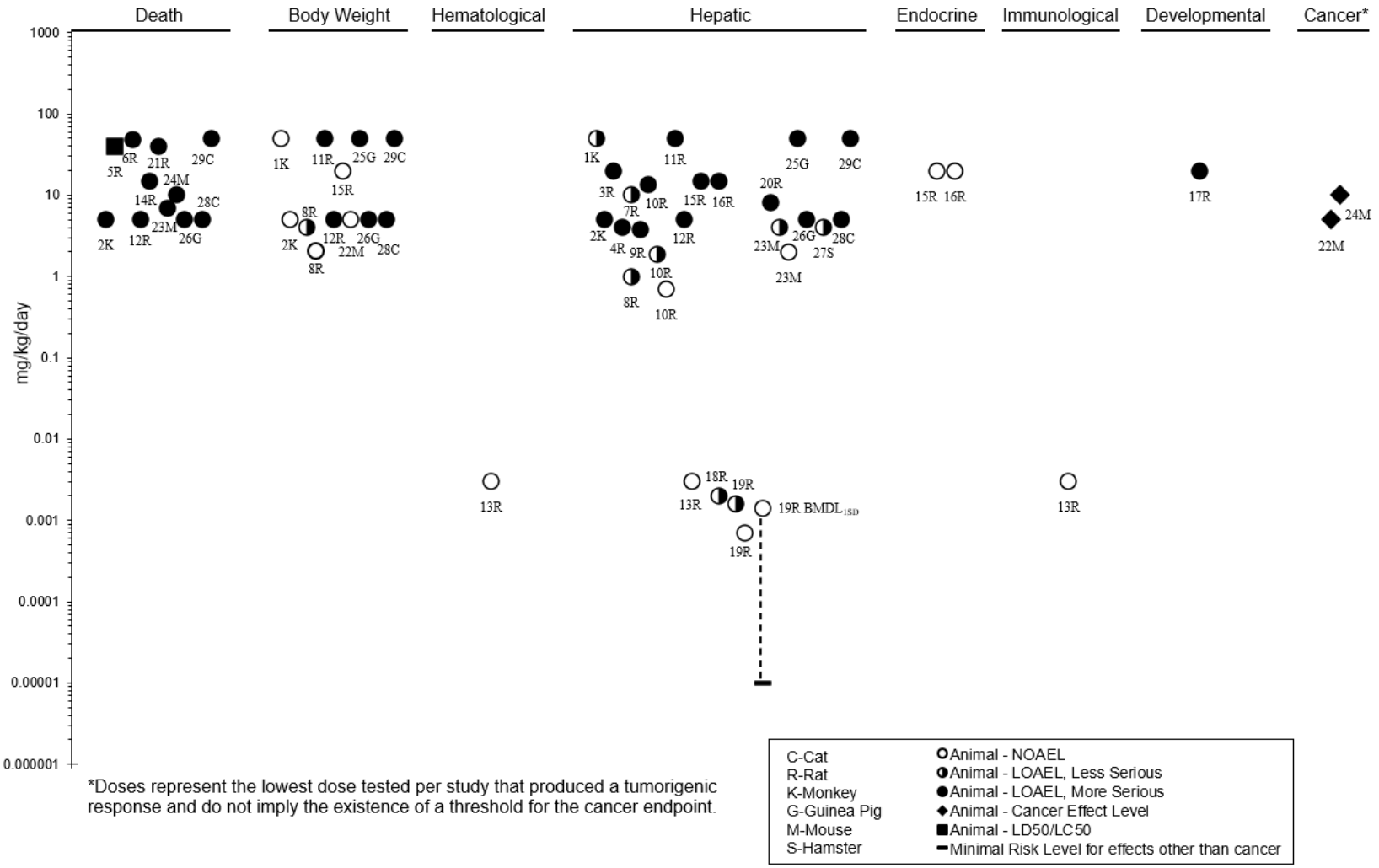
Table 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
71	Mouse (RF/Un) 47 M	Lifetime (average 406 days), 7 days/week (W)	0, 0.43	CS, GN, HP	Death			0.43	Decreased survival (mean 17 versus 20.5 months in controls)
					Cancer			0.43	CEL: liver and lung tumors
Clapp and Toya 1970									
72	Dog (mongrel) 6–10 M and F (number per sex NS)	56 weeks, 2 days/week (C)	0, 2	CS, OF, GN, HP	Bd wt			2	Intermittent anorexia and weight loss (2–15% of body weight).
					Hepatic			2	Fibrosis, centrilobular necrosis, cirrhosis, ascites; 13–54-fold increase in serum bile acids; 20–40-fold increase in sulfobromophthalein retention time
Butler-Howe et al. 1993									
73	Mink (NS) 6 M, 14 F	321–670 days, 7 days/week (F)	0, 0.1–0.13	GN, HP, CS	Death			0.1	Decreased survival
					Hepatic			0.1	Venopathy, focal necrosis
					Cancer			0.1	CEL: liver tumors
Koppang and Rimeslatten 1976									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration oral minimal risk level (MRL) calculated using benchmark dose analysis. The $BMDL_{1SD}$ of 0.0014 mg/kg/day was divided by an uncertainty factor of 100 (10 for human variability and 10 for animal to human extrapolation), resulting in an MRL of 0.00001 mg/kg/day ($1x10^{-5}$ mg/kg/day).

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; $BMDL_{1SD}$ = 95% lower confidence limit on the BMD associated with 1 SD change from control mean; (C) = capsule; CEL = cancer effect level; CS = clinical signs; DX = developmental toxicity; (F) = feed; F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GD = gestation day; GGT = gamma-glutamyl transferase; GN = gross necropsy; HE = hematology; HP = histopathological; Immuno = immunological; LD_{50} = dose producing 50% deaths; LDH = lactate dehydrogenase; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; SD = standard deviation; UR = urinalysis; (W) = drinking water; WI = water intake

Figure 2-3. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral
Acute (≤14 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

Figure 2-3. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral
Intermediate (15–364 days)

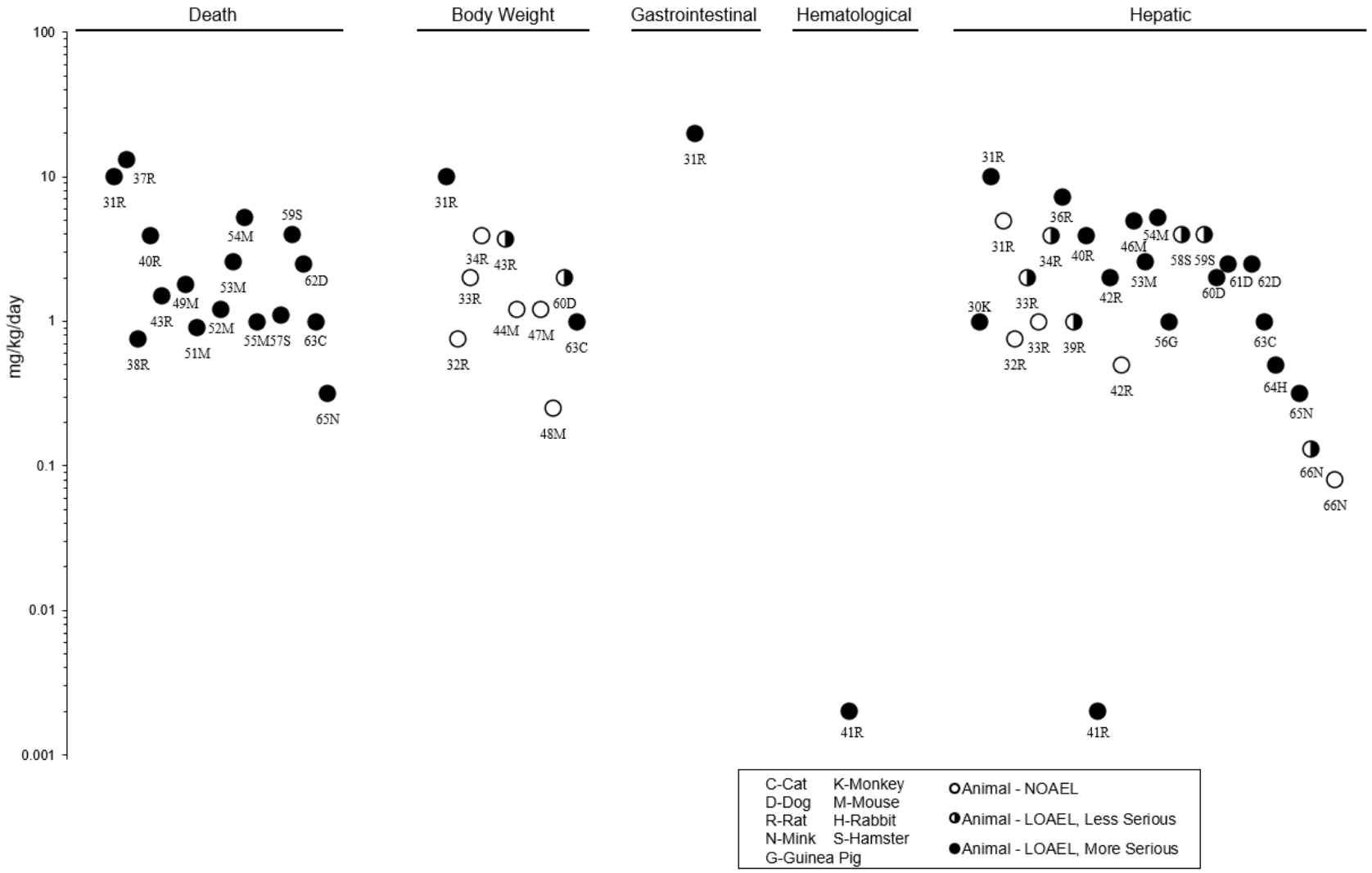


Figure 2-3. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral
Intermediate (15–364 days)

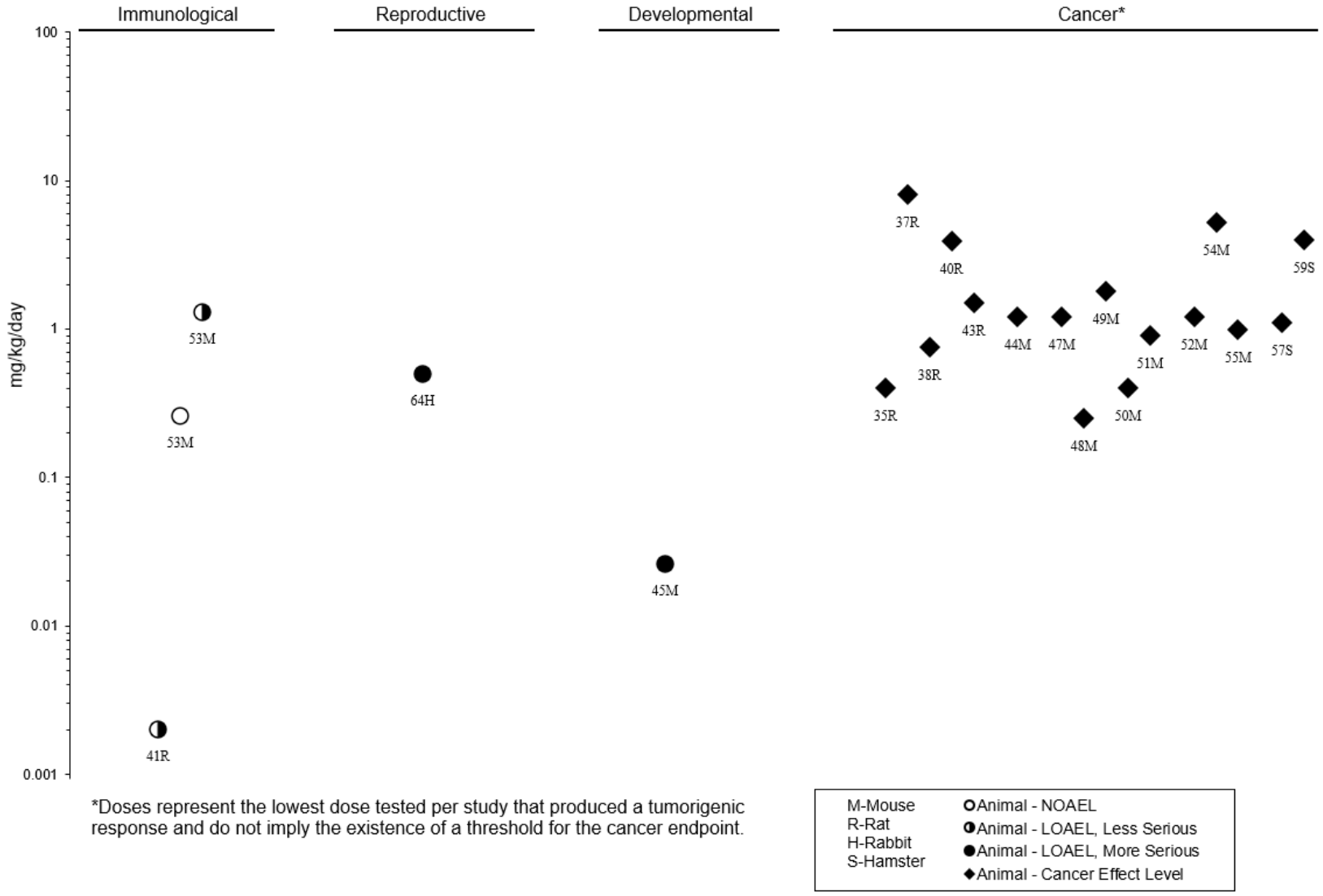
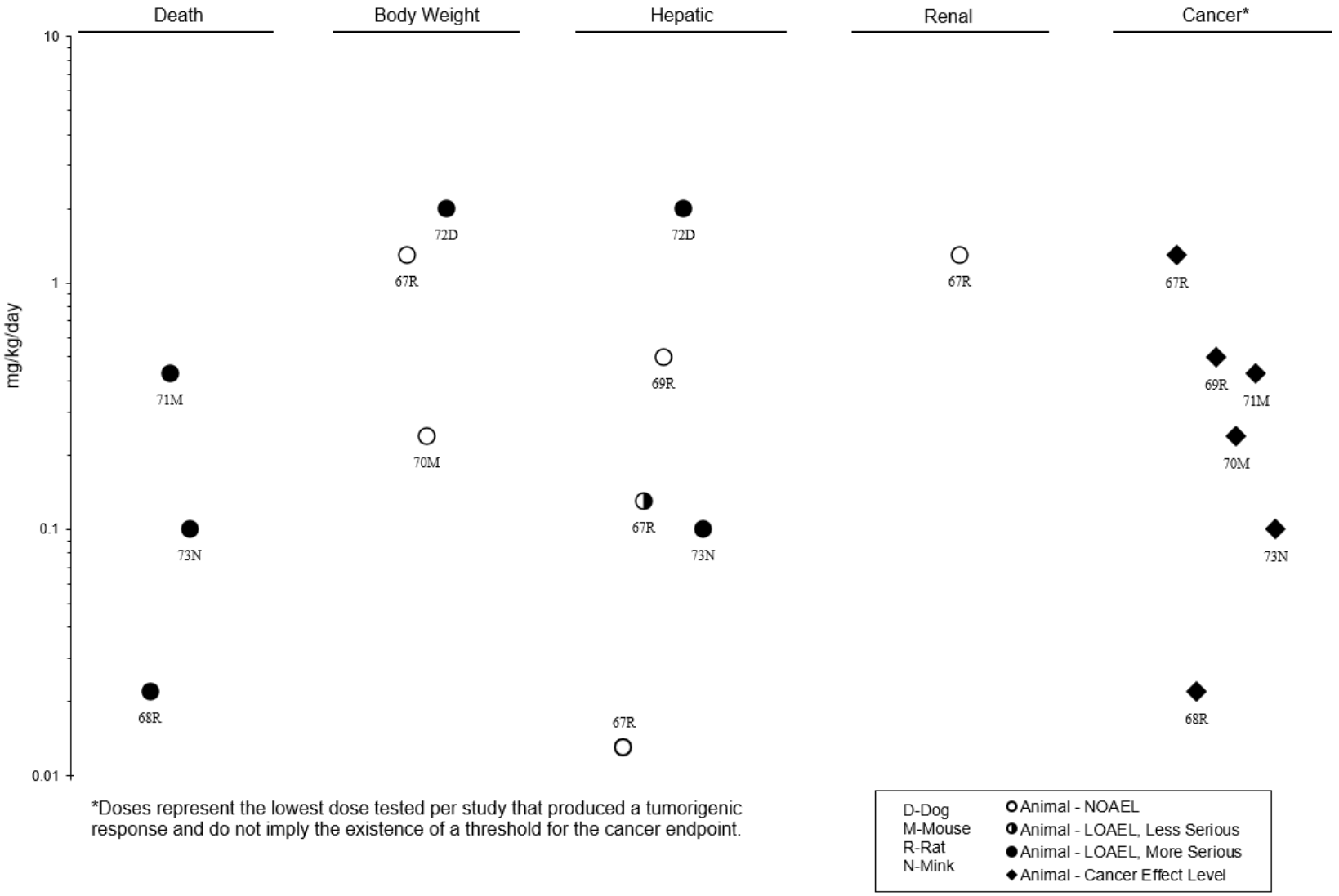


Figure 2-3. Levels of Significant Exposure to N-Nitrosodimethylamine – Oral
Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

2.2 DEATH

At least two human deaths following inhalation of NDMA have been reported in the literature. One was a male chemist who was involved in the production of NDMA and was exposed to an unknown level of fumes for about 2 weeks, and subsequently to an unknown level of fumes during cleanup of a spilled flask (Freund 1937). The subject became ill 6 days later and showed abdominal distention, large amounts of yellow ascitic fluid, and a tender and enlarged liver and enlarged spleen. The subject died 6 weeks after the last exposure. The other death was that of a male worker who was exposed to unknown concentrations of NDMA in an automobile factory. Autopsy of this subject showed a cirrhotic liver with areas of regeneration (Hamilton and Hardy 1974).

At least three human deaths following oral exposure to NDMA have been reported in the literature. One of the fatalities was a woman who was apparently poisoned over a 2-year period by her husband (Fussgaenger and Ditschuneit 1980; Pedal et al. 1982). It was estimated by the authors that she received at least four doses as high as 250–300 mg each, for a total dose of <1.5 g. Both clinical and autopsy findings indicated that she died of liver failure. Two of five people who consumed lemonade tainted with unknown quantities of NDMA (an adult male and a l-year-old boy) died within days, while the other three people (an adult female, adult male, and 2.5-year-old girl) survived (Cooper and Kimbrough 1980; Kimbrough 1982). Based on animal studies, the authors estimated that the adult might have received about 1.3 g and the boy might have received about 300 mg. In both cases, clinical and autopsy findings primarily showed liver failure and cerebral hemorrhage.

The lethality of inhaled NDMA has been evaluated in several acute-duration studies with animals. Single 4-hour exposure LC_{50} values of 78 ppm (95% confidence limits of 68 and 90 ppm) and 57 ppm (95% confidence limits of 51 and 64 ppm) were determined for rats and mice, respectively (Jacobson et al. 1955). The observation time in these assays was 14 days. The cause of death was not specified, but liver damage and hemorrhage in various abdominal tissues were the predominant pathologic findings. Druckrey et al. (1967) reported that the "LD_{50}" for rats exposed to NDMA by inhalation for 1 hour is 37 mg/kg. The air concentration corresponding to this dose was not reported, but a value of 925 ppm can be calculated from information provided in the report; however, confidence in this value is low, because this information is ambiguously reported. Two of three dogs that were exposed to 16 ppm NDMA for 4 hours died or were moribund by the second day (Jacobson et al. 1955). All dogs that were similarly exposed to 43–144 ppm died or were moribund within 3 days.

Acute-duration oral studies of NDMA in animals have shown mortalities at single doses as low as 15 mg/kg and repeated doses as low as 5 mg/kg/day. Single-dose lethality studies have been conducted in which NDMA was administered to rats and cats by gavage. A dose of 10 mg/kg did not produce deaths in rats within 48 hours (Sumi and Miyakawa 1983). Single doses of 15 and 20 mg/kg were not lethal for nonpregnant rats, but mortalities were seen in pregnant rats treated once on gestation day (GD) 18 at these doses (3/32 at 15 mg/kg and 6/17 at 20 mg/kg) (Nishie 1983). The authors estimated an LD_{50} of ~23 mg/kg for pregnant rats based on these findings (Nishie 1983). Jenkins et al. (1985) reported that single 25 mg/kg doses of NDMA resulted in 100% mortality in an unspecified number of rats; it is not clear whether a control group was used in this study. A group of six male F344 rats survived a single dose of 37 mg/kg NDMA, while 48.1 mg/kg was lethal to 4/5 rats and higher doses were lethal to all animals (Frank et al. 1990). Druckrey et al. (1967) determined an LD_{50} of 40 mg/kg for rats using an unspecified graphic technique; confidence limits and specific mortality data were not reported. All 12 rats that were treated with a single dose of 40 mg/kg in a skin grafting (immunology) experiment died by day 21, but the stress of skin graft rejection may have contributed to mortality (Waynforth and Magee 1974). Two of six cats died when treated with 50 mg/kg (Maduagwu and Bassir 1980).

Administration of a daily dose of 4 mg/kg/day in the drinking water of hamsters for 1, 2, 4, 7, or 14 days did not result in mortality (Ungar 1984). Rats, guinea pigs, cats, and monkeys that were treated with NDMA by gavage at a dose of 5 mg/kg/day for 11 days experienced 30–40% mortality, with deaths occurring as early as 5 days (Maduagwu and Bassir 1980). All three mice given 7 mg/kg/day NDMA by gavage daily died within 6 days, while groups dosed at 2 or 4 mg/kg/day survived 2 weeks of treatment (Doolittle et al. 1987). Rats treated by gavage daily with 8 mg/kg/day NDMA for 6 days experienced 10% mortality within 1 month (McGiven and Ireton 1972); a control group was not evaluated in this study. Administration of NDMA in the drinking water at a daily dose of 10 mg/kg/day for 1 week resulted in decreased survival in mice (Terracini et al. 1966).

Deaths in rats and mice resulting from intermediate-duration oral exposure to NDMA were usually attributed to liver toxicity or carcinogenicity. In these studies, NDMA effects on survival were observed at doses as low as 0.32 mg/kg/day. In rats, decreased survival resulted when NDMA was given in the drinking water for 30 weeks at 0.75 mg/kg/day, 5 days/week (Lijinsky and Reuber 1984) or 1.5 mg/kg/day, 7 days/week (Takahashi et al. 2000). Decreased survival was also reported when rats received 6 mg/kg via gavage for 2 days/week for 30 weeks (Lijinsky et al. 1987); in this study, control animals were not included, but there was 100% mortality by 40 weeks after cessation of treatment. Barnes and Magee (1954) administered NDMA in the diet to small numbers of rats (6/group);

2.5 mg/kg/day produced no deaths, 5 mg/kg/day produced 100% mortality after 62–93 days and 10 mg/kg/day produced 100% mortality after 34–37 days. Rats treated with 3.9 mg/kg/day in the diet for 40 weeks also had high mortality (Magee and Barnes 1956). Jenkins et al. (1985) observed mortality in rats that received 2.5 mg doses of NDMA by gavage for 4 days/week for 9 weeks, but it is unclear if this is dose per kg body weight or per rat. Daily exposure to 1 mg/kg/day by gavage for 30 days had no effect on survival of rats (Maduagwu and Bassir 1980).

In intermediate-duration studies with mice, decreased survival resulted from treatment with doses of 1.8 mg/kg/day via drinking water for 49 days (Clapp and Toya 1970), 1.2 mg/kg/day via drinking water for 13 weeks (Den Engelse et al. 1974), 1 mg/kg/day via drinking water for 38 weeks (Terracini et al. 1966), 2.6 mg/kg/day in drinking water for at least 45 days (Desjardins et al. 1992), and 5.26 mg/kg/day via diet for 5 months (Takayama and Oota 1965). Survival was not affected in mice that received 0.4 mg/kg/day in drinking water for 32 weeks (Clapp and Toya 1970) or 1.3 mg/kg/day for 17 weeks (Desjardins et al. 1992).

Survival data for intermediate-duration oral exposure to NDMA are also available for cats, dogs, guinea pigs, monkeys, hamsters, and mink. Daily gavage exposure to 1 mg/kg for 30 days caused decreased survival in cats but not guinea pigs or monkeys (Maduagwu and Bassir 1980). Among nine mongrel dogs exposed for 4 weeks to capsules containing 2.51 mg/kg NDMA twice per week, one dog died of acute liver failure 2 weeks after the end of exposure (Madden et al. 1970); in other studies in mongrel or Beagle dogs, there were no mortalities for 4 (Hashimoto et al. 1989) or 24 weeks (Boothe et al. 1992) at the same dose and regimen. In hamsters, daily administration of 4 mg/kg/day in the drinking water for 8, 12, or 16 weeks resulted in occasional moribundity (Ungar 1986), while no lethality resulted from daily administration of the same dose for 28 days (Ungar 1984). Once weekly gavage treatment with a dose of 10.7 mg/kg for 4 weeks or 5.4 mg/kg for 20 weeks was lethal for hamsters (Lijinsky et al. 1987). Mink that were given doses of 0.32 or 0.63 mg/kg/day in the diet died after 23–34 days of treatment (Carter et al. 1969), but small numbers of animals were tested (three per dose). Mink fed a contaminated diet that provided approximately 0.18 mg/kg/day died within a 2-month period (Martino et al. 1988), but there is uncertainty about the dietary concentration of NDMA used to calculate the dose and the durations of exposure.

In chronic-duration studies of orally exposed rats, mice, and mink, decreases in survival have been reported, often attributable to cancers. Survival was not affected in 15 rats that received 0.5 mg/kg/day of NDMA in the diet for 54 weeks (Terao et al. 1978). However, in a large (60 rats/sex/dose), multi-dose

(15 nonzero dose levels) carcinogenicity bioassay of rats, Peto et al. (1984, 1991a, 1991b) observed dose-related decreases in survival due to liver tumors at doses ≥0.022 mg/kg/day in drinking water. Decreased survival was noted in mice exposed to 0.43 mg/kg/day in the drinking water for life (average 406 days) (Clapp and Toya 1970). In mink, mortality resulted from ingestion of 0.1 mg/kg/day in the diet for 321–670 days (Koppang and Rimeslatten 1976).

2.3 BODY WEIGHT

No data pertaining to NDMA-induced effects on body weights of humans exposed by any route were located, and no studies reporting body weight effects in animals exposed by dermal contact were located. A chronic study of female rats exposed via inhalation to concentrations of 0, 0.04, 0.2, or 1 ppm (4–5 hours/day, 4 days/week for ~72 weeks) reported lower body weight (~10% based on visual examination of data presented graphically) at the highest exposure level (Klein et al. 1989, 1991). At lower exposures, body weight decrements occurred, but did not reach 10% difference from controls until the animals reached advanced age (~3 years), and survivors were few.

In animals exposed orally, body weight effects were generally seen only in the context of severe liver toxicity or tumors. Body weight was not affected in female rats given a single dose of 15 or 20 mg/kg by gavage (Nishie 1983) or mice given a single dose of 1 or 5 mg/kg by gavage (Anderson et al. 1992a). Decreased body weight gain was reported in male rats after 15 days of exposure to NDMA at 2 mg/kg/day, and at 4 mg/kg/day, absolute body weight was also decreased (magnitude of change was not reported); severe liver effects accompanied the body weight changes (Rothfuss et al. 2010). In other experiments in mice exposed via drinking water, body weights were not affected by treatment for 4 or 16 weeks at 1.2 mg/kg/day or for 16–72 weeks at ~0.25 mg/kg/day (Anderson 1988; Anderson et al. 1992a). In rats exposed to NDMA in drinking water for 30 weeks, a 10% decrease in terminal body weight was observed at 3.7 mg/kg/day; however, there were mortalities and liver tumors at doses ≥1.5 mg/kg/day in this study (Takahashi et al. 2000). Khanna and Puri (1966) reported progressive body weight loss in rats given 7.2 mg/kg/day NDMA in drinking water for up to 12 weeks. The magnitude of body weight loss was not reported. These animals also exhibited severe hepatic effects (hemorrhagic necrosis throughout the lobule) (Khanna and Puri 1966). No body weight changes were reported in rats given 3.9 mg/kg/day NDMA in drinking water for 8 weeks (Jang et al. 1990) or up to 0.75 mg/kg/day for 16 weeks (Fukushima et al. 2005). Dogs exhibited body weight losses (up to 18%) when given capsules containing 2 mg/kg NDMA on 2 days/week for 24 or 56 weeks; the animals in these experiments exhibited severe liver effects at this dose (Boothe et al. 1992; Butler-Howe et al. 1993).

2.4 RESPIRATORY

An occupational epidemiology study reported increased odds of self-reported respiratory symptoms, including nose bleeds, burning or dry throat, hoarseness, and severe dry cough among 172 Swedish rubber production workers when compared with 118 unexposed subjects (Jönsson et al. 2009). Median breathing zone NDMA concentrations in the workplaces ranged between 0.24 and 8.2 μg/m^3 (Jönsson et al. 2009). Hidajat et al. (2019a) reported significantly increased subdistribution hazard ratios (SHRs) (based on competing risk survival analysis) for mortality from respiratory diseases with increasing cumulative NDMA exposure in a cohort of 36,442 U.K. rubber workers followed for 49 years. The SHR for the highest quartile of cumulative NDMA exposure was 1.41 (95% confidence interval [CI] 1.30, 1.53). Results were not adjusted for smoking status. The authors noted that confounding by unmeasured smoking status was unlikely (based on sensitivity analyses) but could not be ruled out entirely. In humans who expired from NDMA poisoning, autopsies showed hemorrhages in the bronchi, trachea, and/or lungs (Freund 1937; Kimbrough 1982); further details of the fatalities are reported in Section 2.2.

No studies evaluating respiratory effects in animals following inhalation or dermal exposure to NDMA were located. Macroscopic congestion was noted in the lungs of rats exposed to 3.75 mg/kg/day in the diet for 1–12 weeks (Khanna and Puri 1966). The severity of the congestion cannot be determined because results of lung histological examinations were not reported. No chronic-duration oral studies of respiratory effects in animals were located.

2.5 CARDIOVASCULAR

Higher risks of mortality from circulatory and cerebrovascular diseases and ischemic heart disease (SHRs up to 1.48) were reported in a large cohort of 36,441 male U.K. rubber factory workers followed for 49 years (Hidajat et al. 2020). Confounding by unmeasured smoking status could not be ruled out in this study (Hidajat et al. 2020). In cases of fatal exposure to NDMA, cardiovascular effects seen at autopsy included subpericardial hemorrhage (Freund 1937) and myocardial and endocardial bleeding (Kimbrough 1982). Additional details of these cases are provided in Section 2.2.

No studies were located regarding cardiovascular effects in animals following inhalation exposure to NDMA. Macroscopic congestion was noted in the myocardium of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for 1–12 weeks (Khanna and Puri 1966). The severity of the congestion cannot be determined because results of heart histological examinations were not reported. In rats given 0.2 mg/kg/day (presumably by gavage) daily for 2 weeks, alterations in blood levels of cardiovascular biomarkers were seen: creatine kinase MB activity was increased by 103% compared to controls, while homocysteine levels were decreased by 25% (Sheweita et al. 2014). No other cardiovascular endpoints were evaluated in the study.

2.6 GASTROINTESTINAL

Increased risks of digestive diseases with increasing NDMA exposure were reported among U.K. rubber industry workers in a 49-year follow-up study (Hidajat et al. 2019a). In this study, SHRs across quartiles of cumulative NDMA exposure ranged up to 1.60 (95% CI 1.31, 1.95). In humans who died from NDMA poisoning, autopsy findings included gastrointestinal hemorrhage (Freund 1937; Kimbrough 1982; Pedal et al. 1982); additional details of these cases are reported in Section 2.2. Studies of gastrointestinal effects in animals following inhalation or dermal exposure to NDMA were not located. After intermediate-duration oral exposure of animals, NDMA produced gastrointestinal effects. Barnes and Magee (1954) observed occasional hemorrhage into the gastrointestinal tract in rats that died from treatment with a single 50 mg/kg dose of NDMA by gavage, or with 10 mg/kg/day doses in the diet for 34–37 days. The numbers of animals examined were unspecified (single-dose study) or small (six in the diet study), and the frequency of occurrence was not indicated. Gastrointestinal hemorrhages were also observed in mink that ingested 0.32 or 0.63 mg/kg/day via diet for 23–34 days (Carter et al. 1969). Only three mink per dose were treated, the hemorrhages occurred in a total of three mink, and the dose(s) that the affected mink received was not specified. The cause of the hemorrhages in the mink was attributed to gastric and duodenal erosions.

Rostkowska et al. (1998) observed increases in the specific activities of several lysosomal exoglycosidases (N-acetyl-p-hexosaminidase, β-galactosidase, and α-mannosidase) in the gastrointestinal tracts of rats exposed for 10 or 90 days to NDMA in drinking water (20 μg/L). The study authors suggested that the increased enzyme activities could stem from macrophages recruited by damaged cells in the alimentary canal.

2.7 HEMATOLOGICAL

In five individuals poisoned with unknown amounts of NDMA in lemonade, slight to severe thrombocytopenia was reported (Kimbrough 1982). No other studies were located regarding hematological effects in humans exposed to NDMA or in animals exposed dermally to NDMA. Hematological evaluations were performed in dogs that were exposed to 16–144 ppm NDMA for 4 hours (Jacobson et al. 1955). After exposure at all concentrations, increased coagulation time, prothrombin time, and plasma cholinesterase levels occurred. In addition, leukopenia was observed at all exposure levels. The dogs exhibited severe liver toxicity and mortality (see Section 2.2) at these exposure levels; the hematological effects may have resulted from profound liver toxicity.

Administration of NDMA in drinking water to rats for 10 days resulted in dose-related increases in blood hemoglobin concentration at doses ≥0.0016 mg/kg/day; hematocrit was not affected, and other hematology parameters were not measured. In a corollary study by the same group of investigators (Moniuszko-Jakoniuk et al. 1999), rats exposed via drinking water to 0.002 or 0.003 mg/kg/day for 10 days exhibited no changes in bone marrow histopathology.

When rats were exposed to 4 mg/kg/day NDMA by daily gavage for 15 days, significant decreases in platelet and reticulocyte counts were observed in conjunction with serious liver damage (Rothfuss et al. 2010). After 30 and 90 days of drinking water exposure to NDMA, rats showed increased blood hemoglobin concentrations at 0.0016 mg/kg/day (17–28%); however, hemoglobin concentration was significantly decreased (9%) after 30 days of exposure to 0.0035 mg/kg/day (Roszczenko et al. 1996b). Hematocrit was significantly decreased (10% less than controls) at the high dose in the 30-day experiment (a 90-day experiment at the high dose was not conducted) and no other parameters were measured. Moniuszko-Jakoniuk et al. (1999) reported bone marrow histopathology changes in rats exposed to NDMA in drinking water for 30 or 90 days. After 30 days at 0.003 mg/kg/day and after 90 days at both 0.002 and 0.003 mg/kg/day, bone marrow changes included including focal necrosis of bone marrow, edema, degeneration, decrease in bone marrow megakaryocytes and migration to vascular sinus, and myelosclerosis (Moniuszko-Jakoniuk et al. 1999). Macroscopic congestion was noted in spleens of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for 1–12 weeks (Khanna and Puri 1966). The severity of the congestion cannot be determined because results of spleen histological examinations were not reported.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans or animals following inhalation, oral, or dermal exposure to NDMA.

2.9 HEPATIC

A large cohort mortality study of 36,144 male U.K. rubber factory workers reported an increased risk of mortality from liver disease for workers in the third quartile of cumulative NDMA exposure (SHR 2.22; 95% CI 1.24, 3.99) (Hidajat et al. 2020). In the highest quartile, the SHR was elevated (1.35) but the CI included 1.0. No attempt to adjust for alcohol intake was made.

In a cohort of 2,875 German female rubber workers with occupational exposure to nitrosamines, the rate of mortality from non-alcoholic cirrhosis of the liver was elevated compared with the rate in the general population of German women (Straif et al. 1999). All 10 of the cases of non-alcoholic cirrhosis occurred among women employed in production of technical rubber goods, and the risk of death from this cause increased with earlier year of hire and longer duration of employment in rubber good production (Straif et al. 1999). Straif et al. (1999) reported that the highest documented nitrosamine concentration in the facilities included in their study was NDMA at 170 μg/m^3. The study authors did not report concentrations of other nitrosamines in the women's workplaces; however, the other primary nitrosamine measured in rubber production facilities is N-nitrosomorpholine, which often occurs at exposure levels similar to NDMA (de Vocht et al. 2007; Hidajat et al. 2019b; Jönsson et al. 2009; Straif et al. 2000; Tricker et al. 1989).

Four cases of liver disease in humans resulting from inhalation exposure to NDMA have been described in the literature. Two of the subjects died; these cases are discussed in Section 2.2. Of the subjects who survived, one was a chemist who was exposed to unknown concentrations of fumes and experienced exhaustion, headache, cramps in the abdomen, soreness on the left side, nausea, and vomiting for at least 2 years (Freund 1937). The second case was an automobile factory worker who was exposed to unknown levels of NDMA and became violently ill with jaundice and ascites (Hamilton and Hardy 1974). Five members of a family who consumed unknown quantities of NDMA in lemonade became ill with nausea, vomiting, and serum chemistry changes associated with acute liver disease, as well as generalized bleeding and slight to severe thrombocytopenia (Cooper and Kimbrough 1980; Kimbrough 1982). As indicated in Section 2.2, two of these people died; the other three were released from a hospital 4–21 days

after admission. Another fatality due to ingestion of NDMA was attributed to liver failure (Fussgaenger and Ditschuneit 1980; Pedal et al. 1982). Autopsies of the subjects described above showed that the primary effects were hemorrhagic and cirrhotic changes in the liver and necrosis and hemorrhage in other internal organs. Barnes and Magee (1954) briefly described two cases of liver cirrhosis among three men using NDMA in a research laboratory for about 10 months. In one, cirrhosis was discovered at autopsy after the man died from bronchopneumonia. In the second, cirrhosis was discovered during follow-up for an unrelated operation. The latter patient showed improved liver function after 3 months with no exposure to NDMA (Barnes and Magee 1954).

Hepatotoxicity was reported at lethal concentrations of NDMA in dogs exposed by inhalation. Pathologic examination of dogs following exposure to 16–144 ppm NDMA for 4 hours showed marked necrosis and varying degrees of hemorrhage in the liver (Jacobson et al. 1955). Related effects at all concentrations included increased bilirubin levels and increased sulfobromophthalein retention.

Hepatotoxicity of NDMA has been investigated in numerous oral studies of acute, intermediate, and chronic duration in several animal species. Hepatotoxicity is the most prominent and characteristic systemic effect of NDMA, resulting in centrilobular necrosis, hemorrhage, fibrosis, cirrhosis, and ascites. In acute studies, these characteristic hepatotoxic alterations were seen in rats following single gavage doses as low as 8–20 mg/kg (Asakura et al. 1998; Barnes and Magee 1954; Nishie 1983; Sumi and Miyakawa 1983) and following daily doses of ~4 mg/kg in the diet or via gavage for 1 or 2 weeks (Asakura et al. 1998; Hamada et al. 2015, 2022; Khanna and Puri 1966; Takashima et al. 2015). Jenkins et al. (1985) observed degenerative alterations collapse of reticulum network in the centrilobular areas followed by regeneration in the livers of rats following a single 2.5 mg/kg gavage dose of NDMA; however, a control group was not reported. The alterations were nonnecrotic and did not result in loss of the lobular architecture. After single gavage doses in rats, nonnecrotic histologic alterations (clumping and slight vacuolation of cells in the central vein area) occurred at 1.9 mg/kg and no alterations occurred at 0.7 mg/kg (Korsrud et al. 1973). Hepatocellular hypertrophy was observed in mice administered nitrosamines daily by gavage for 4 days. However, because results were not reported for individual compounds, it was unclear whether NDMA induced hypertrophy in this study (Nishie et al. 1972). After 14 daily gavage doses of NDMA, rats exposed to doses ≥1 mg/kg/day exhibited focal inflammatory cell infiltration in the liver, and at the highest dose of 4 mg/kg/day, effects on the liver included single cell necrosis, anisokaryosis, and increased mitotic figures (Hamada et al. 2015; Takashima et al. 2015). In studies that examined serum chemistry changes, marked increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and/or gamma-glutamyl

transferase (GGT) were observed (Asakura et al. 1998; Doolittle et al. 1987; Garland et al. 1988; Roszczenko et al. 1996a). Daily gavage exposure to 5 mg/kg for 5–11 days produced hemorrhagic necrosis in rats, guinea pigs, cats, and monkeys; this dose was lethal in all species tested (Maduagwu and Bassir 1980). Hamsters that ingested daily doses of 4 mg/kg/day in the drinking water for 1, 2, 4, 7, or 14 days showed portal venopathy (Ungar 1984).

A series of acute- and intermediate-duration studies in rats exposed to low concentrations of NDMA in drinking water was conducted by the same group of investigators (Moniuszko-Jakoniuk et al. 1999; Roszczenko et al. 1996a, 1996b). In these studies, groups of 7–8 male Wistar rats were exposed for 10, 30, or 90 days to concentrations of 10–50 µg/L (0.0007–0.0035 mg/kg/day). Each individual study evaluated limited endpoints, but taken together, the studies demonstrate liver effects at low doses after both acute and intermediate durations. After 10 days of exposure, doses of 0.0016–0.002 mg/kg/day resulted in effects on iron indices (decreased total and latent iron binding capacity) and serum enzymes (≥2-fold increases in AST, ALT, ALP, and GGT) (Roszczenko et al. 1996a, 1996b), but no liver histopathology changes at doses up to 0.003 mg/kg/day (Moniuszko-Jakoniuk et al. 1999). After 30 days of exposure to ≥0.0016 mg/kg/day, similar perturbations of iron indices were observed, and serum enzyme levels remained increased (Roszczenko et al. 1996a, 1996b). In addition, there was evidence for serious liver histopathology changes at 0.002 and 0.003 mg/kg/day, including degeneration, argyrophilic and collagenic fibers, and inflammatory infiltrations near portal biliary tract after 30 days (Moniuszko-Jakoniuk et al. 1999). The effects increased in severity to include steatosis and parenchymatosis after 90 days (Moniuszko-Jakoniuk et al. 1999).

In other intermediate-duration studies with rats exposed to higher doses, characteristic hepatic effects (as described above) were produced by treatment with NDMA in the diet at doses of ≥2 mg/kg/day for 15 days (Rothfuss et al. 2010), 7.2 mg/kg/day for 4–12 weeks (Khanna and Puri 1966), 10 mg/kg/day for 62–95 days (Barnes and Magee 1954), and 3.9 mg/kg/day for 40 weeks (Magee and Barnes 1956). No liver histopathology changes were observed at 0.5 mg/kg/day for 15 days (Rothfuss et al. 2010). Inflammatory cell infiltration in the liver was observed at low incidence in rats given 28 daily gavage doses of 2 mg/kg/day; no other effects were reported (Hamada et al. 2015; Takashima et al. 2015). Jenkins et al. (1985) observed cirrhosis in rats that received 2.5 mg doses of NDMA by gavage for 4 days/week for 9 weeks, but it is unclear if this is dose per kg body weight or per rat. A dose of 1 mg/kg/day administered by gavage for 30 days produced centrilobular congestion and vacuolation of hepatocytes without necrosis in rats (Maduagwu and Bassir 1980). Hepatic alterations were not observed in rats treated with 5 mg/kg/day in the diet for 110 days (Barnes and Magee 1954). Preneoplastic lesions

(eosinophilic or mixed-cell foci or glutathione-S-transferase placental type positive [GST-P+] foci) in the liver were observed in rats given 3.9 mg/kg/day NDMA in drinking water for 8 weeks (Jang et al. 1990) or 0.075 mg/kg/day in water for 16 weeks (Fukushima et al. 2005). In a drinking water study in rats exposed to a very low dose of NDMA (0.002 mg/kg/day), 2–4-fold increases in ALT, ALP, and/or GGT (compared to controls) were observed after 30 or 90 days; however, liver histopathology was not examined, so the severity of the observed liver toxicity is uncertain (Roszczenko et al. 1996a).

In mice, hemorrhagic necrosis was observed in the livers after doses of 5 mg/kg/day in the drinking water for 1–4 weeks (Anderson et al. 1986) or ≥5.26 mg/kg/day in the diet for at least 5 months (Takayama and Oota 1965). In an immunotoxicity study, Desjardins et al. (1992) observed ascites, presumably resulting from hepatotoxicity, in mice exposed to 2.6 mg/kg/day NDMA in drinking water for 4–17 weeks.

Liver effects resulting from intermediate-duration oral exposure have been observed in species other than rat and mouse. Treatment with 1 mg/kg/day by gavage for 30 days was hepatotoxic for guinea pigs, cats, and monkeys (Maduagwu and Bassir 1980). Dogs given NDMA by capsule at 2–2.5 mg/kg/day on 2 days/week for 4–24 weeks exhibited profound hepatic injury including necrosis, cholestasis, fibrosis, cirrhosis, lobular collapse, and ascites (Boothe et al. 1992; Hashimoto et al. 1989; Madden et al. 1970; Strombeck et al. 1983). Central vein congestion, erythrocyte hemolysis, and vacuolar degeneration were seen in rabbits given 0.5 mg/kg/day NDMA by daily gavage for 12 weeks (Sheweita et al. 2017). Fibrotic and proliferative alterations without necrosis or hemorrhage were observed in rabbits treated with an average NDMA dose of 1.6 mg/kg/day in the diet for 22 weeks; this experiment did not include a control group (Magee and Barnes 1956). Occlusive alterations in the portal veins developed in hamsters that received daily 4 mg/kg doses in the drinking water for 28 days or 8, 12, or 16 weeks (Ungar 1984, 1986). Similar hepatic venopathy occurred in mink exposed to 0.13–0.15 mg/kg/day in the diet for 122 days (Koppang and Rimeslatten 1976). Mink that were given doses of 0.32 or 0.63 mg/kg/day in the diet for 23–34 days had widespread liver necrosis (Carter et al. 1969), but low numbers of animals were tested (three per dose). Liver necrosis was also observed in mink that ingested 0.18 mg/kg/day via diet (Martino et al. 1988); however, interpretation of this study is limited by uncertainty regarding exposure duration and concentration.

The only chronic oral study of NDMA that used more than one dose was Peto et al. (1984, 1991a, 1991b); these authors conducted a large cancer dose-response study in rats and reported limited information on nonneoplastic changes. Groups of 60 rats/sex were exposed to 1 of 15 concentrations of NDMA in drinking water (between 0.033 and 16.896 ppm) for 3.5 years. These water concentrations yielded

estimated doses from 0.001 to 0.697 mg/kg/day (as reported in Peto et al. 1984, 1991b). Controls (240/sex) received untreated water. Groups of six rats/sex/dose were sacrificed after 12 and 18 months, and the remaining animals were observed until natural death, moribund appearance, or appearance of palpable liver abnormalities. Macroscopic examinations were performed on all animals. Histopathology examinations were performed on grossly observed lesions; apart from these, only the liver and esophagus (target for N-nitrosodiethylamine, which was also tested) were routinely examined microscopically. Results for the interim sacrifices were not reported separately. In both male and female rats, NDMA doses ≥0.022 mg/kg/day were associated with decreased survival due to liver tumors. Significant dose-related trends were observed for several nonneoplastic or preneoplastic liver lesions, including hyperplastic nodules, cytomegaly, cysts, hepatocyte shrinkage (males only), and abnormality of glycogen-containing cells (females only). However, statistically significant increases in the incidence of these nonneoplastic changes (either individually or grouped) were seen only at doses ≥0.022 mg/kg/day. Because both increased liver tumor incidence and reduced survival due to tumors were observed at the same doses (≥0.022 mg/kg/day), neither a NOAEL nor a LOAEL for noncancer endpoints can be identified from these data.

In other chronic-duration studies, hepatotoxic effects were not observed in rats that were treated with 0.5 mg/kg/day NDMA in the diet for 54 weeks and then observed untreated for 15 weeks (Terao et al. 1978). At an early interim sacrifice (after 5 weeks of exposure) of only one animal per group, the liver from the exposed animal exhibited proliferation of the smooth endoplasmic reticulum under electron microscopy; at the terminal sacrifice, however, no histopathologic changes were reported in the liver. It is possible that any adverse effects on the liver were partially reversed during the post-exposure recovery period. Necrosis, fibrosis, cirrhosis, and ascites were seen in mongrel dogs given 2 mg/kg NDMA by capsule 2 days/week for 56 weeks (Butler-Howe et al. 1993). Liver injury in mink that ingested 0.1 mg/kg/day doses of NDMA in the diet for 321–670 days consisted of occlusive changes in the hepatic veins with focal necrosis (Koppang and Rimeslatten 1976).

Mechanisms of Hepatotoxicity. NDMA treatment in dogs and rats has been used as a model for human liver fibrosis (and its sequelae of cirrhosis, portal hypertension, and hepatocellular carcinoma) for nearly 40 years. As a result, a great deal of research has been performed to investigate the molecular mechanisms and pathophysiology of NDMA-related hepatic effects. George et al. (2019) published a succinct review of this research, detailing the effects of NDMA and its metabolites on hepatic cell populations. As discussed therein and summarized briefly below, NDMA induces liver effects through inflammation and oxidative stress mediated by metabolites.

As discussed further in Section 3.1.3, NDMA is rapidly metabolized in the liver by microsomal membrane-bound cytochrome P450 (CYP) 2E1 to form hydroxymethylnitrosamine, which then undergoes nonenzymatic degradation to formaldehyde and the reactive methyldiazonium ion. Downstream metabolites of these compounds include methanol and the methyl carbonium ion. Several of these metabolites are known to be potent hepatotoxicants. The methyldiazonium ion is a potent alkylating agent that methylates deoxyribonucleic acid (DNA) and proteins, resulting in damage to hepatic tissues. In addition, formaldehyde is an electrophilic molecule that reacts with a wide range of macromolecules, including proteins. Protein alkylation and cross-linking is a candidate molecular initiating event leading to hepatic fibrosis in NDMA-exposed organisms.

NDMA metabolites induce fibrosis through interactions with hepatocytes, lymphocytes, and sinusoidal endothelial cells (George et al. 2019). Both formaldehyde and methanol induce inflammation in the liver, leading to hemorrhagic necrosis. Generation of reactive oxygen species results, exacerbating the injury to hepatocytes and leading to lymphocyte release of proinflammatory cytokines (e.g., transforming growth factor β1 and nuclear factor-κB) and activation of Kupffer cells. Oxidative stress and lipid peroxidation deplete hepatic antioxidants and antioxidant enzymes including catalase and glutathione peroxidase.

Injury to endothelial cells results in the release of fibrogenic mediators including fibroblast growth factor-1 and connective tissue growth factor as well as induction of hedgehog signaling (promotes hepatic regeneration). In addition, release of Factor VIII (a blood-clotting protein also known as anti-hemophilic factor) from injured endothelial cells may result in aggregation of platelets, which triggers further production of inflammatory (transforming growth factor β1) and fibrogenic (platelet-derived growth factor) mediators. Fibrogenic cytokines are also released from activated Kupffer cells, leading to activation of resting stellate cells. The activated stellate cells produce collagen and other connective tissue proteins in an effort to repair the injured liver. Deposition of collagen fibrils in the extracellular matrix leads to fibrosis, cirrhosis, and portal hypertension. In addition to the DNA damage induced by reactive intermediates of NDMA metabolism, repeated injury and repair induced by these metabolites may also be involved in the mechanism of liver cancer from NDMA exposure (George et al. 2019).

2.10 RENAL

No studies were located regarding renal effects in humans following any exposure to NDMA or in animals exposed by inhalation or dermal application.

Limited information is available regarding renal effects of orally administered NDMA in animals. In a study by Nishie (1983), pregnant and nonpregnant rats were treated with a single NDMA dose of 15 or 20 mg/kg/day by gavage. An unspecified number of deceased animals (dose and pregnancy state not indicated) had distal tubule necrosis two days following treatment, while surviving rats had normal kidneys. Macroscopic congestion was noted in kidneys of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for 1–12 weeks (Khanna and Puri 1966). The severity of the congestion cannot be determined because results of kidney histological examinations were not reported. Moderate tubule congestion and other effects (glomerulus dilatation, slightly thickened Bowman's capsule) were observed in mink that ingested 0.18 mg/kg/day via diet (Martino et al. 1988); limitations of this study include uncertainty regarding exposure duration and dietary concentration.

2.11 DERMAL

No studies were located regarding dermal effects in humans or animals following inhalation or oral exposure to NDMA. Small ulcerations and scarring of the skin were observed in hairless mice that were treated once weekly with topical doses of 33.3 mg/kg for 20 weeks (Iversen 1980).

2.12 OCULAR

In a group of 172 Swedish rubber industry workers exposed to NDMA concentrations up to 8.4 $\mu g/m^3$, odds of self-reported itching, runny, or burning eyes were increased when compared with 118 unexposed subjects (Jönsson et al. 2009). No other studies reporting ocular effects in humans exposed to NDMA were identified in the literature searches. No studies were located regarding ocular effects in animals following oral or dermal exposure.

Little information is available regarding ocular effects of inhaled NDMA. Doolittle et al. (1984) reported reddened eyes in rats exposed to 500 or 1,000 ppm for 4 hours. As noted in Section 2.2, acute exposure to much lower concentrations of NDMA was lethal to rats, mice, and dogs. The lack of mortality in rats at the higher concentrations in the Doolittle et al. (1984) study may be attributable to the fact that the animals were killed immediately following exposure and not observed for subsequent death.

2.13 ENDOCRINE

Adrenal relative weight and mitotic count were increased in rats following a single 20 mg/kg gavage dose of NDMA (Nishie 1983). Histological examinations of the adrenal glands were not described. There was no effect on thyroid weight or histology in the same study.

2.14 IMMUNOLOGICAL

One study of immune system markers in humans exposed to NDMA during work in rubber production (Jönsson et al. 2009) was located; no other immunological studies in humans were identified. In a group of 172 Swedish rubber industry workers exposed to NDMA and several other nitrosamines, blood levels of eosinophils and immunoglobulin G (IgG) were significantly increased (14 and 11%, respectively) when compared with 118 unexposed subjects. There were no significant differences in leukocyte or neutrophil counts or in levels of α1-antitrypsin, C-reactive protein, or IgA, IgM, or IgE. Across the eight facilities where the exposed workers were employed, median detected breathing zone concentrations of NDMA ranged between 0.24 and 8.2 $\mu g/m^3$ (Jönsson et al. 2009). Other nitrosamines, including N-nitrosomorpholine, N-nitrosodiethylamine, N-nitrosodi-n-butylamine, N-nitrosopiperidine, and N-nitrosopyrrolidine, were detected less frequently and at lower concentrations.

No studies of immunological effects in animals following inhalation or dermal exposure to NDMA were located. Information regarding immunological effects of orally administered NDMA in animals is limited but demonstrates splenic histopathology changes and immune suppression after intermediate-duration exposure.

In a single dose study, skin graft survival time and white blood cell count were not reduced in rats after a 40 mg/kg dose of NDMA by gavage. All of the animals died by day 21, possibly due to the stress of skin graft rejection in addition to NDMA toxicity (Waynforth and Magee 1974).

Effects on splenic histology (megakaryocytes in red pulp and enhanced lymphatic "texture") were observed in rats exposed for 90 days to NDMA in drinking water at doses of 0.002 or 0.003 mg/kg/day; there were no changes after 30 days at either dose (Moniuszko-Jakoniuk et al. 1999). Desjardins et al. (1992) investigated humoral and cellular immune responses in mice following exposure to NDMA in the drinking water (0.26–5.3 mg/kg/day) for 30–120 days. Doses ≥2.6 mg/kg/day resulted in deaths and hepatotoxicity as evidenced by peritoneal ascites. Immunoglobulin M (IgM) antibody response to sheep

red blood cells (SRBCs) was significantly reduced at doses ≥1.3 mg/kg/day after 90 days of treatment and at 2.6 mg/kg/day after 120 days of treatment. Cellular immune response, monitored by allogeneic stimulation of cells in mixed lymphocyte reaction (MLR), was also suppressed at doses ≥1.3 mg/kg/day NDMA after 90 days of treatment and at 2.6 mg/kg/day after 120 days of treatment. No changes in immunological parameters were noted at 0.26 mg/kg/day. In other groups exposed for 90 days and then maintained without exposure for 30 days, immune suppression was reversed at 1.3 mg/kg/day, but not at 2.6 mg/kg/day (Desjardins et al. 1992).

2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans exposed to NDMA or in animals exposed via inhalation or dermal contact. Dogs treated with 2.5 mg/kg/day by capsule on 2 consecutive days/week for 3 weeks reportedly experienced marked central nervous system (CNS) depression; however, these effects were not further characterized (Strombeck et al. 1983). As these dogs developed liver necrosis and hepatic insufficiency, it is possible that the CNS depression was secondary to liver damage rather than a direct neurological effect of NDMA.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following inhalation, oral, or dermal exposure to NDMA; studies in animals are limited to two intermediate-duration oral studies.

When male New Zealand rabbits were given daily gavage doses of 0.5 mg/kg/day NDMA for 12 weeks, marked reductions in serum testosterone were noted (81 and 96% less than controls at 8 and 12 weeks, respectively) along with variable increases in plasma estradiol (152 and 27% at 8 and 12 weeks) (Sheweita et al. 2017). At sacrifice at the end of exposure, testicular histopathology changes in treated rabbits included disorganized seminiferous tubules, interstitial edema, degeneration of germinal epithelium in seminiferous tubules and Sertoli cells, exfoliation of cells in lumen of tubules, blood vessel congestion, and proliferation of Leydig cells (incidences not reported, but effects not seen in controls). Biochemical analyses of the testes showed that the pathological changes accompanied a significant increase in oxidative stress (more than doubling of free radical thiobarbituric acid reactive substances [TBARS]), and depletion of antioxidant enzyme activities (glutathione, glutathione S-transferase, superoxide dismutase, and catalase) and 17 β-hydroxysteroid dehydrogenase (steroidogenic enzyme) (Sheweita et al. 2017).

There was no significant increase in time-to-conception in mice that were exposed to 0.026 mg/kg/day via drinking water for 75 days prior to mating (Anderson et al. 1978). Other reproductive indices were not evaluated.

2.17 DEVELOPMENTAL

No data pertaining to developmental effects in humans exposed to NDMA or in animals exposed via inhalation or dermal contact were located.

Acute-duration oral exposure of pregnant rats to NDMA has resulted in fetal mortality. A single 30 mg/kg dose administered by gavage on various GDs between 1 and 15 resulted in fetal mortality (Aleksandrov 1974; Napalkov and Alexandrov 1968). In addition, NDMA reportedly caused fetal deaths in rats when administered in the diet at a dose of 5 mg/kg/day beginning in early pregnancy (specific day and treatment duration not indicated) (Bhattacharyya 1965), by gavage at a dose of 2.9 mg/kg/day during the first or second weeks of gestation (Napalkov and Alexandrov 1968), or by gavage at a dose of 1.4 mg/kg/day throughout gestation until GDs 17–21 (not further specified) (Napalkov and Alexandrov 1968).

Teratogenic effects were not eva1uated in the studies of Nishie (1983) and Bhattacharyya (1965). Although Aleksandrov (1974) and Napalkov and Alexandrov (1968) evaluated these endpoints and observed no effect of NDMA treatment, confidence in the studies is low as these studies provided insufficient information regarding experimental design and results. Deficiencies in these studies include lack of control data, lack of maternal toxicity data, use of pooled data, and/or uncertain treatment schedule.

Fetuses of rats that received single 20 mg/kg doses of NDMA by gavage on GDs 15 or 20 had significantly decreased body weights. However, fetal survival data were not reported, and this dose was toxic to the dams as indicated by reduced body weight, hepatotoxicity, and mortality (Nishie 1983).

Intermediate-duration exposure of mice to NDMA in drinking water (0.026 mg/kg/day) for 75 days prior to mating and then during pregnancy and lactation resulted in a significant increase in neonatal mortalities (20% compared with 10% in controls) (Anderson et al. 1978). The deaths in treated offspring were equally distributed between stillbirths (19/185 versus 5/182 controls) and deaths up to postnatal day

(PND) 2 (19/186 versus 13/182). The incidence of litters with deaths was higher in the treated group (11/20) than in the controls (8/20) but the difference was not statistically significant. In one litter, all of the offspring died; the number of offspring in the litter was not reported.

2.18 OTHER NONCANCER

No other noncancer effects were reported in the NDMA literature.

2.19 CANCER

Overview. Evaluations of the carcinogenicity of NDMA by HHS (NTP 2021), EPA (IRIS 1987), and IARC (1987) have concluded that NDMA is "reasonably anticipated to be" or "probably" a human carcinogen, based primarily on robust evidence in animals. Human epidemiological data on the association between NDMA exposure and cancer, while extensive, are limited by numerous potential confounding factors, including challenges in estimating dietary intake of NDMA and its precursors, variations in endogenous formation of NDMA and uncertainties in the factors influencing such formation, and co-exposures to other carcinogenic agents. In contrast, there are abundant data showing the carcinogenicity of orally administered NDMA in acute-, intermediate-, and chronic-duration studies with rats, mice, hamsters, and mink. In addition, NDMA has been shown to induce mutations via metabolic activation in a multitude of *in vitro* and *in vivo* assays.

Endogenous Production of NDMA. NDMA is produced endogenously in the human body via nitrosation of amine and nitrate precursors in the stomach and other tissues (Hrudey et al. 2013). Estimates of the amount of NDMA produced endogenously in humans vary widely, depending on precursor intake as well as a variety of other factors (see Section 3.1), but available information suggests that for most people, endogenous formation is the largest source of exposure to NDMA (Hrudey et al. 2013). Most of the human studies of NDMA and cancer examined exposure to exogenous sources of NDMA (in food or drugs, or in the workplace) without considering the impact of differences in endogenous formation. Because of the significant contribution of endogenous formation of NDMA to human exposure levels, there is potential for misclassification of exposure in the human epidemiological studies, which would bias the results toward the null (no association).

Some epidemiological studies of NDMA and cancer have included estimates of endogenous N-nitroso compound formation using iron or heme-iron intake as a proxy (Jakszyn et al. 2006; Keszei et al. 2013).

These estimates are based on correlations between iron or heme-iron intake and total fecal excretion of N-nitroso compounds in humans (Jakszyn et al. 2006), so the findings are not specific to NDMA. In a European cohort study, Jakszyn et al. (2006) observed an association between iron intake and non-cardia adenocarcinoma of the stomach among subjects with *Helicobacter pylori* infection or low plasma vitamin C, but not uninfected persons or those with normal vitamin C levels. Keszei et al. (2013) observed a significant association between heme-iron intake and esophageal squamous cell carcinoma incidence among men in a large cohort study in the Netherlands. No association was observed in females, or among males or females in analyses of esophageal or gastric adenocarcinomas.

Epidemiological Studies. Available epidemiological data pertaining to cancers associated with exogenous NDMA exposure include occupational studies, studies of drugs contaminated with NDMA, and studies of dietary exposure to NDMA. Only one occupational epidemiology study (Hidajat et al. 2019a) identified in the literature reported associations between cancer and exposure to NDMA itself.

Hidajat et al. (2019a) followed 36,441 male employees in the United Kingdom rubber industry from 1967 to 2015 (total of 880,794 person-years). For these workers, exposure was likely to have been primarily via inhalation. Job information for each employee was available for 1967, and the authors assumed that the employees stayed in the same department and remained employed until retirement, death, or emigration. Exposure to NDMA was evaluated using a quantitative job-exposure matrix based on historic exposure measurements in the industry. Cases were determined based on underlying cause of death on death certificates. SHRs (comparable to Cox proportional hazard ratios) were estimated using competing risk survival analysis for quartiles of cumulative NDMA exposure, as follows: quartile 1 (Q1): <3.12 year $\mu g/m^3$; Q2: 3.12–5.96 year $\mu g/m^3$; Q3: 5.96–9.67 year $\mu g/m^3$; and Q4: >9.67 year $\mu g/m^3$. A lag time of 15 years was assumed in the models.

Cumulative NDMA exposure was associated with increased risks for several tumor types (Hidajat et al. 2019a). Results showed exposure-related linear trends in SHRs for bladder (up to 2.82 in Q4), stomach (up to 1.72 in Q4), leukemia (up to 3.47 in Q4), multiple myeloma (up to 2.81 in Q4), prostate (up to 5.36 in Q4), and liver (up to 2.86 in Q4). In addition, increased SHRs (without exposure-related trends) were observed in subjects of the fourth cumulative exposure quartile for brain (SHR=2.5), lung (1.7), NHL (2.25), esophagus (3.04), and pancreas (2.6). Cumulative exposures to N-nitrosomorpholine, total nitrosamines, and/or rubber dust and fumes were also associated with mortality from one or more of the cancer types for which an association with NDMA was observed.

This study (Hidajat et al. 2019a) had a number of strengths, including large cohort size with lengthy (49-year) follow-up and quantitative cumulative exposure estimates based on historic exposure measurements. The limitations noted by the study authors were: (1) the subject's individual employment histories prior to 1967 and during follow-up were not available (suggesting the possibility of exposure misclassification), (2) the 15-year lag time assumed in the analysis may not be suitable for blood cancers with shorter lag times; (3) some cancers may have been undercounted due to the use of underlying cause of death on death certificates; (4) information on confounders such as smoking history was not available for the subjects; (5) there was potential for selection bias because only workers who lived to 35 years of age were eligible for inclusion; (6) measurement error in individual exposure assessment was possible due to the use of a job-exposure matrix; and (7) there were correlations between NDMA and other exposures in the industry (other nitrosamines, nitrosomorpholine, rubber dust and fumes), as well as the possibility of cross-contamination across departments. These limitations make it difficult to establish clear associations between NDMA exposure and mortality from specific cancers.

There is a substantial number of studies of cancer in workers in the rubber industry, and these data formed the basis for the IARC classification of rubber industry work as carcinogenic to humans (IARC 1982, 1987). In addition to nitrosamines, rubber industry workers may be exposed to a wide range of other chemicals with known or potential carcinogenicity, including aromatic compounds, chlorinated compounds, metals, and others (IARC 1982). NDMA is known to be one of two primary nitrosamine exposures in this industry, the other being N-nitrosomorpholine (de Vocht et al. 2007; Hidajat et al. 2019b; Jönsson et al. 2009; Straif et al. 2000; Tricker et al. 1989). The large database of cancer studies in rubber industry workers was evaluated in a meta-analysis by Boniol et al. (2017). With the more recent study published by Hidajat et al. (2019a) that assessed NDMA specifically, the meta-analysis provides a synopsis of the relevant data from epidemiology of cancer in rubber industry employees.

Boniol et al. (2017) conducted a comprehensive meta-analysis of cancer associations with employment in rubber manufacturing, using the IARC definition for exposure to rubber manufacturing. These authors reviewed 234 publications and selected 46 cohort and 59 case-control studies for inclusion. Boniol et al. (2017) excluded case-control studies of nitrosamine exposure that were not specific to the rubber industry; thus, nitrosamine exposures in other industries, which may not include exposure to NDMA, were excluded. In addition, Boniol et al. (2017) cross-referenced studies that reported results for the same cohort, ensuring that the studies of a given cancer in the same cohort were not included multiple times in the analysis. Summary relative risk estimates were estimated using a random effects model.

Boniol et al. (2017) evaluated studies of 32 individual cancer sites. Their analysis showed increased summary relative risks for bladder cancer (1.36, 95% CI 1.18, 1.57), leukemia (1.29, 95% CI 1.11, 1.52), cancers of the lymphatic and hematopoietic systems not otherwise specified (1.16, 95% CI 1.02, 1.31), and cancer of the larynx (1.46, 95% CI 1.10, 1.94). A borderline increased summary relative risk was calculated for lung cancer (1.08, 95% CI 0.99, 1.17); risks for other cancer sites were not increased. Significant heterogeneity between studies was observed for all of the above cancer sites except for unspecified cancers of the lymphatic and hematopoietic systems. The increased risks for bladder cancer, lung cancer, and leukemia were not changed when the trim and fill method to correct potential publication bias was applied to the data. Stratification of studies by participants' date of first employment showed that there were no increases in risks for bladder cancer, lung cancer, or leukemia among workers who began work after 1960, although the numbers of studies of recent employment were small.

In July 2018, NDMA contamination was discovered in some batches of the drug, Valsartan (an angiotensin II receptor antagonist used to treat hypertension and heart failure) (see Sections 5.5 and 5.6 for further information on NDMA contamination of medications). Since that time, two large cohort studies (Gomm et al. 2021; Pottegard et al. 2018) investigated whether use of NDMA-contaminated Valsartan was associated with cancer risk. Pottegard et al. (2018) and Gomm et al. (2021) conducted similarly designed cohort studies in which subjects using Valsartan were identified using national health and prescription registries (in Denmark and Germany, respectively). Both studies employed manufacturer and lot number data from the registries to identify subjects exposed to the contaminated batches. The cohort in the study by Pottegard et al. (2018) consisted of 5,150 people followed for a median of 4.6 years. Gomm et al. (2021) followed 409,183 subjects who were exposed to NDMA-contaminated Valsartan and 372,688 subjects who were not for 3.25 years. Neither study observed a significant increase in overall cancer risk or risk of specific cancer types, with the exception of a slight increase in liver cancer risk reported by Gomm et al. (2021) (hazard ratio [HR] 1.16, 95% CI 1.03, 1.31). When Gomm et al. (2021) categorized exposure into dose categories, however, there was no evidence for a dose-response relationship between liver cancer incidence and exposure to NDMA-contaminated Valsartan.

Strengths of both studies include use of nationwide registries of Valsartan prescriptions, limiting potential selection and recall biases. In addition, the large size of the cohort in the study by Gomm et al. (2021) provides substantial statistical power to detect an effect. Both studies controlled for covariates including age, sex, exposures to other medications, and comorbidities, but did not control for smoking or dietary intake of NDMA or its precursors. Importantly, the brief follow-up time (3.25 and 4.6 years in Gomm et

al. [2021] and Pottegard et al. [2018], respectively) is a significant limitation of both studies. This follow-up time is inadequate for most cancer types, which have much longer latency times.

The finding of NDMA contamination in ranitidine and nizatidine (drugs used to block stomach acid) in 2019 also prompted a number of epidemiological studies of cancer. Unlike the contamination of Valsartan, the source of the NDMA in ranitidine and nizatidine was not traced to a specific manufacturer. As a consequence, cohort studies of exposure to NDMA in these drugs have relied on referent groups composed of people prescribed other drugs to block stomach acid (H2 blockers like cimetidine and famotidine or proton pump inhibitors like omeprazole). The use of referent groups with exposure to other types of drugs introduces additional confounding into the analysis, because other drugs may modify the risk of cancer. For example, some epidemiological studies have reported an association between use of proton pump inhibitors (PPIs) and increased risk of stomach cancer (reviewed by Cheung and Leung 2019; Moon et al. 2019).

As shown in Table 2-3, the cohort studies of cancer among users of ranitidine and/or nizatidine (Adami et al. 2021; Iwagami et al. 2021; Kim et al. 2021a, 2021b; Nørgaard et al. 2022; Yoon et al. 2021) generally found no positive association with cancers of the stomach, colorectum, liver, kidney, breast, or pancreas. Adami et al. (2021) reported a significant increase in adenocarcinomas of the esophagus among ranitidine users compared with users of cimetidine, famotidine, or PPIs; in contrast, Kim et al. (2021b) reported a decreased incidence of esophageal cancer in ranitidine users compared with users of omeprazole (PPI) or famotidine.

In cohort studies, an increase in bladder cancer was associated with ranitidine use when the referent group consisted of PPI users (Nørgaard et al. 2022) but not when the referent group was users of other H2 blockers (Nørgaard et al. 2022; Yoon et al. 2021). A case-control study of 3,260 bladder cancer cases in Scotland reported a significant trend for increased odds of higher ranitidine use among cases after adjustment for smoking, age, comorbidities, and other medication use (Cardwell et al. 2021). The trend was seen when exposure categories were based on estimated daily doses or prescription numbers. In analyses of other acid blocking medications (cimetidine, other H2 receptor agonists apart from ranitidine, or PPIs), there was no association with bladder cancer (Cardwell et al. 2021). Unlike the cohort studies, this case-control study was not limited by potential confounding from exposure to other acid-blocking drugs. In addition, while many case-control studies are subject to recall bias (when exposures are assessed by subject questionnaire), Cardwell et al. (2021) used prescriptions in a database of general practice medical records to assess exposure.

Table 2-3. Overview of Epidemiological Studies of Ranitidine Use and Cancers

Reference (location)	Study type and population size	Follow-up time (years)	Case identification	Cancer site	Results[a]
Adami et al. 2021 (Denmark)	Cohort: 103,565 adult new users of ranitidine; compared with 182,497 adults who first used cimetidine or famotidine, and 807,725 first-time users of PPIs	14	Cancer Registry	Stomach	↔
				Esophagus	↑ (adenocarcinoma)
				Liver	↔
				Pancreas	↔
Iwagami et al. 2021 (Japan)	Cohort: 113,745 adult new users of ranitidine or nizatidine compared with 503,982 new users of other H2 blockers	2.4 or 2.3	Administrative insurance claims database	Stomach	↔
				Colorectal	↔
				Breast	↔
Kim et al. 2021a (South Korea)	Cohort: 132,629 adults using ranitidine at least 30 days, compared with 13,629 controls and 13,629 users of other H2 blockers	5	National health claims database	Stomach	↔
Kim et al. 2021b (United States)	Cohort: 582,028 adults prescribed ranitidine compared with 2,179,048 prescribed omeprazole and 909,970 prescribed famotidine	Up to 10	Private electronic medical record database (IBM®Explorys)	Stomach	↓
				Esophagus	↓
				Colorectal	↓
				Liver	↓
				Pancreas	↓
McGwin 2020 (United States)	Cohort: 13,856 ranitidine users compared with 128,107 users of PPIs or other H2 blockers	7	Cancer reports to FDA Adverse Event Reporting System	Stomach	↑
				Esophagus	↑
				Colorectal	↑
				Liver	↑
				Pancreas	↑
				Pharynx	↑
Nørgaard et al. 2022 (Denmark)	Cohort: 31,393 adult first-time users of ranitidine compared with 65,384 first-time users of other H2 blockers and 509,849 first-time users of PPIs	14, 15, and 11	Cancer Registry	Bladder	↑ (compared with PPI users but not users of H2 blockers)
				Kidney	↔

Table 2-3. Overview of Epidemiological Studies of Ranitidine Use and Cancers

Reference (location)	Study type and population size	Follow-up time (years)	Case identification	Cancer site	Results[a]
Yoon et al. 2021 (South Korea)	Cohort: 40,488 adult users of ranitidine compared with 10,122 famotidine users	7	National health claims database	Stomach	↔
				Colorectal	↔
				Liver	↔
				Bladder	↔
				Kidney	↔
				Breast	↔
Cardwell et al. 2021 (Scotland)	Nested case-control: 3,260 cases and 14,037 controls	Not applicable	Prescriptions in medical records	Bladder	↑

[a]↑: significant association (confidence limits for the effect estimate do not include 1.0); ↔: no significant association (confidence limits for the effect estimate include 1.0).

FDA = U.S. Food and Drug Administration; H2 = histamine receptor 2; PPI = proton pump inhibitor

McGwin (2020) evaluated whether there was a higher rate of cancer reports to the FDA's Adverse Event Reporting System (AERS) among adverse events reported for ranitidine compared with adverse events reported for other acid-blocking medications. The study authors reported increases in the reporting of cancers of the stomach, esophagus, colorectum, liver, pancreas, and pharynx among ranitidine adverse events compared with the referent groups. However, it should be noted that this study shows only that there was increased reporting of cancers and does not demonstrate increased incidence of cancers. Reports to the AERS may be submitted by consumers, physicians, lawyers, or others, and media reports on the ranitidine recall could have influenced submissions. For example, McGwin (2020) reported the numbers of adverse events by year from 2012 to 2020 and observed a marked increase (more than double) in adverse events from 2017 to 2018, when NDMA contamination in ranitidine was first discovered. A similar phenomenon was reported by Cohen Sedgh et al. (2021), who observed a marked increase in the reporting of Valsartan-related cancers to the FDA AERS after the recall date and associated media attention.

A total of 18 studies examining associations between NDMA exposure in the diet and cancer were located in the literature searches; Table 2-4 provides an overview of these studies. There is substantial uncertainty in the exposure estimates from dietary intake studies, due to variability in NDMA concentrations in foods, variability in the intake of NDMA precursors, and uncertainty regarding factors influencing endogenous formation of NDMA. With few exceptions (LaVecchia et al. 1995; Michaud et al. 2009; Pobel et al. 1995), these studies controlled for tobacco use, a significant additional source of NDMA exposure and confounding factor for some cancer types. Similarly, potential confounding by alcohol intake was considered in most studies, with the exception of Knekt et al. (1999) and La Vecchia et al. (1995).

Many of the epidemiological studies have focused on cancers of the gastrointestinal tract, and especially gastric cancers. A meta-analysis published in 2015 (Song et al. 2015) showed an increased risk of gastric cancer associated with NDMA exposure. The authors selected eight articles comprising 11 studies: seven were cohort studies (Jakszyn et al. 2006; Keszei et al. 2013; Knekt et al. 1999; Larsson et al. 2006 [four cohorts consisting of men and women with cardia and noncardia adenocarcinomas]) and four were case-control studies (De Stefani et al. 1998; La Vecchia et al. 1995; Palli et al. 2001; Pobel et al. 1995). These studies are summarized in Table 2-4. Song et al. (2015) calculated the relative risk of gastric cancer and NDMA intake (comparing high versus low) by random-effects model to be 1.34 (95% CI 1.02–1.76). Significant heterogeneity was observed in the studies of NDMA. There was no evidence of publication

Table 2-4. Overview of Epidemiological Studies of N-Nitrosodimethylamine Dietary Intake and Cancers

Cancer site	Citation (location)	Study type and population size	Food and beverage intake questionnaire	Case identification	Results[a]
Stomach	Keszei et al. 2013 (Netherlands)	Case-control: 497 cases of gastric noncardia adenocarcinoma and 166 cases of gastric cardia adenocarcinoma, 4,032 control men and women; mean follow-up 14.3 years	150 items; administered at baseline	Cancer registry, pathology confirmed	↑ for noncardia adenocarcinoma in men; ↔ for cardia adenocarcinoma or for either type in women
	Loh et al. 2011[b] (United Kingdom)	Cohort: 23,363 men and women; 64 cases; mean follow-up 11.4 years	131 items; administered at baseline	Cancer registry	↔
	Jakszyn et al. 2006 (Europe)	Cohort: 153,447 men and 368,010 women; 314 cases; mean follow-up 6.6 years	Number of items not reported; administered at baseline	Cancer registries, pathology confirmed	↔
	Larsson et al. 2006 (Sweden)	Cohort: 61,433 women; 156 cases; mean follow-up 18 years	67 or 97 items; administered at baseline	Cancer registries	↑
	Knekt et al. 1999 (Finland)	Cohort: 9,985 men and women; 68 cases; maximum follow-up 24 years	Number of items not reported; administered at baseline	Cancer registry	↔
	Palli et al. 2001 (Italy)	Case-control: 382 cases and 561 population-based controls	181 items	Hospital recruitment, pathology confirmed	↔
	De Stefani et al. 1998 (Uruguay)	Case-control: 340 cases and 698 hospital-based controls	Number of items not reported	Hospital recruitment	↑
	La Vecchia et al. 1995 (Italy)	Case-control: 746 cases and 2,053 hospital-based controls	29 items	Hospital recruitment, pathology confirmed	↑
	Pobel et al. 1995 (France)	Case-control: 92 cases and 128 hospital-based controls	61 items	Hospital recruitment, pathology confirmed	↑

Table 2-4. Overview of Epidemiological Studies of N-Nitrosodimethylamine Dietary Intake and Cancers

Cancer site	Citation (location)	Study type and population size	Food and beverage intake questionnaire	Case identification	Results[a]
Colon/rectum	Loh et al. 2011[b] (United Kingdom)	Cohort: 23,363 men and women; 276 colon and 137 rectal cancer cases; mean follow-up 11.4 years	131 items; administered at baseline	Cancer registry	↑ for rectum; ↔ for colon
	Knekt et al. 1999 (Finland)	Cohort: 9,985 men and women; 73 cases; maximum follow-up 24 years	Number of items not reported; administered at baseline	Cancer registry	↑
	Zhu et al. 2014 (Canada)	Case-control: 1,760 cases and 2,481 population-based controls	170 items	Regional familial cancer registries, pathology confirmed	↑
Esophagus	Keszei et al. 2013 (Netherlands)	Case-control: 151 cases of esophageal squamous cell carcinoma, 151 cases of esophageal adenocarcinoma and 4,032 control men and women; mean follow-up 14.3 years	150 items, administered at baseline	Cancer registry, pathology confirmed	↑ for squamous cell carcinoma, ↔ for adenocarcinoma
	Loh et al. 2011[b] (United Kingdom)	Cohort: 23,363 men and women; 55 cases; mean follow-up 11.4 years	131 items; administered at baseline	Cancer registry	↔
Upper aero-digestive tract	Rogers et al. 1995 (United States/ Washington state)	Case-control: 645 cases and 45 population-based controls	125 items	Cancer Surveillance System	↔
Head and neck	Knekt et al. 1999 (Finland)	Cohort: 9,985 men and women; 48 cases; maximum follow-up 24 years	Number of items not reported; administered at baseline	Cancer registry	↔
Liver	Zheng et al. 2021 (United States/Texas)	Case-control: 827 cases and 1,013 controls	131 items	Hospital recruitment, histologically or radiologically confirmed	↑ for plant sources of NDMA ↔ for animal sources of NDMA or all sources

Table 2-4. Overview of Epidemiological Studies of N-Nitrosodimethylamine Dietary Intake and Cancers

Cancer site	Citation (location)	Study type and population size	Food and beverage intake questionnaire	Case identification	Results[a]
Brain/spinal cord (glioma/ meningioma)	Michaud et al. 2009 (United States)	Cohorts: 49,935 men (HPFS), 92,468 women (NHS I), 95,391 women (NHS II); 133 cases of glioma among men and 202 among women; maximum follow-up 18 years (HPFS), 24 years (NHS I), and 14 years (NHS II)	61 or 130 items; administered at baseline and every 4 years	Self-identification at biennial questionnaire, confirmed by review of medical and pathology records	↔ in individual or pooled cohorts
	Giles et al. 1994 (Australia)	Case-control: 409 glioma cases and 409 population-based controls	59 items	Hospital recruitment	↑ among men
	Boeing et al. 1993 (Germany)	Case-control: 115 glioma and 81 meningioma cases and 418 population-based controls	42 items	Clinic recruitment, pathology confirmed	↑
Bladder	Jakszyn et al. 2011 (Europe)	Cohort: 481,419 men and women; 1,001 cases; mean follow-up 8.7 years	Number of items not reported; administered at baseline	Cancer registries, health insurance records, cancer and pathology hospital registries, and active follow-up	↔
Pancreas	Zheng et al. 2019 (United States/Texas)	Case-control: 1,110 cases and 1,010 controls recruited among friends, spouses, and in-laws of patients with other cancer types	84 or 131 items; administered at baseline	Hospital recruitment, pathology confirmed	↑

Table 2-4. Overview of Epidemiological Studies of N-Nitrosodimethylamine Dietary Intake and Cancers

Cancer site	Citation (location)	Study type and population size	Food and beverage intake questionnaire	Case identification	Results[a]
Lung	Loh et al. 2011[b] (United Kingdom)	Cohort: 23,363 men and women; 235 cases; mean follow-up 11.4 years	131 items; administered at baseline	Cancer registry	↔
	De Stefani et al. 1996 (Uruguay)	Case-control: 320 cases and 320 hospital-based controls	70 items	Hospital recruitment	↑

[a]↑: significant association (confidence limits for the effect estimate do not include 1.0); ↔: no significant association (confidence limits for the effect estimate include 1.0).
[b]Loh et al. (2011) observed no association between N-nitrosodimethylamine intake and breast, prostate, or ovarian cancers.

HPFS = Health Professionals Follow-Up Study; NHS = Nurses' Health Study

bias in the studies used in the NDMA. Geographic area was identified as a primary source of heterogeneity, but this factor was not the only source. In sensitivity analyses, the small case-control study by De Stefani et al. (1998) was shown to influence the association; without this study, the relative risk was 1.18 (95% CI 0.97–1.43).

Studies of dietary intake of NDMA and other cancer types are more limited. As shown in Table 2-4, two cohort studies and one case control study (Knekt et al. 1999; Loh et al. 2011; Zhu et al. 2014) observed positive associations between NDMA exposure and cancers of the colon or rectum. Findings are inconclusive for associations between NDMA and esophagus (Keszei et al. 2013; Loh et al. 2011) and lung cancers (De Stefani et al. 1996; Loh et al. 2011). In a case-control study of hepatocellular carcinomas, an association was observed with NDMA from plant-based sources (primarily grains and rice), but not with animal-based food sources or when both sources were combined (Zheng et al. 2021). Two older case-control studies (Boeing et al. 1993; Giles et al. 1994) reported positive associations between NDMA intake and gliomas and/or meningiomas.

However, analysis of three large cohorts (the Health Professionals Study and Nurses' Health Studies I and II) with follow up of at least 14 years showed no association with glioma, either in individual cohorts or pooled analysis (Michaud et al. 2009). Single studies of dietary NDMA and several other cancer types were evaluated. Positive associations were observed for the upper aerodigestive tract (Rogers et al. 1995) and pancreas (Zheng et al. 2019), but not for cancers of the head and neck (Knekt et al. 1999), bladder (Jakszyn et al. 2011), or breast, prostate, or ovaries (Loh et al. 2011).

Animal Studies. Three animal studies showed some evidence for induction of cancers after inhalation exposure. Klein et al. (1989, 1991) observed increases in the incidences of nasal tumors (aesthioneuroblastomas, mucoepidermoid tumors, squamous cell carcinomas, and neurogenic and osteogenic sarcomas) at all exposure levels (0.04, 0.2, and 1 ppm) in female rats exposed by inhalation to NDMA 4 hours/day, 5 days/week for ~72 weeks and observed until death. The incidences of nasal tumors were not clearly or consistently reported in the two publications but were increased with exposure based on available information indicating that zero or one control developed a nasal tumor. Twice weekly 30-minute exposures to 50 or 100 ppm NDMA vapor for life produced malignant nasal cavity tumors in rats (Druckrey et al. 1967). The incidence of tumors was 67% in each group, and the time to induce tumors in 50% of the rats was 400 days. Group sizes were small (12 and 6 animals at 50 and 100 ppm, respectively), control data were not reported, and additional information regarding longevity was not provided. Rats and mice that were continuously exposed to 0.07 ppm NDMA for 25 and

17 months, respectively, developed significantly increased incidences of lung, liver, and kidney tumors (Moiseev and Benemanski 1975). Tumor types included various adenomas, carcinomas, and sarcomas in the lung, liver and kidneys, and hemangiomas in the liver, but the types were not tabulated according to species or concentration. Induction of nasal tumors was not reported. Exposure to 0.002 ppm NDMA according to the same schedule did not produce significantly increased incidences of tumors in either species.

The carcinogenicity of orally administered NDMA has been demonstrated unequivocally in acute-, intermediate-, and chronic-duration studies with rats, mice, hamsters, and mink. The liver and lungs are the primary targets for NDMA carcinogenesis but tumors of the kidneys and testes can also occur. Incidences of liver and lung tumors are generally very high (often 50–100%), but liver tumors appear to occur most frequently in rats and hamsters and lung tumors appear to occur most frequently in mice. The liver tumors are usually hemangiosarcomas and hepatocellular carcinomas, and lung tumors are usually adenomas and liver tumor metastases.

A single dose of 5 mg/kg NDMA administered by gavage resulted in a significantly increased incidence of lung tumors (15/30 versus 4/30 in controls) in A/JNCr mice when sacrificed 16 weeks after dosing; no significant increase was seen with a single dose of 1 mg/kg (Anderson et al. 1992a). Daily treatment of Swiss mice with 10 mg/kg/day in drinking water for 1 week produced kidney and lung tumors (Terracini et al. 1966). Incidences of kidney and lung adenomas were 6/10 and 10/10 females, respectively. There were no kidney tumors in controls; lung adenoma incidences in controls were 2/17 females and 2/5 females (Terracini et al. 1966). Low incidences of epithelial tumors (8.6%) and mesenchymal tumors (14.5%) developed in the kidneys of rats following treatment with 8 mg/kg/day for 6 days (Ireton et al. 1972; McGiven and Ireton 1972). Evaluation of the results of McGiven and Ireton (1972) and Ireton et al. (1972) is complicated by the lack of a control group.

Aleksandrov (1974) reported possible evidence of transplacental carcinogenesis in rats exposed once to NDMA. A single dose of 30 mg/kg was administered by gavage to pregnant rats on GD 21, and offspring were necropsied at the time of natural death (~274 days after exposure). Histological examination of the offspring showed tumors (sites not reported) in 5 of 20 animals. Confidence in this finding is low, however, as the study did not report control findings or specific tumor types.

Numerous oral carcinogenicity studies of NDMA of intermediate duration (with exposure durations between 20 and 40 weeks) have been conducted in rats, mice, and hamsters. Carcinogenicity (liver, lung,

and/or kidney tumors) was observed in all studies. For example, rats administered NDMA in the drinking water at doses ≥0.3 mg/kg/day for 30 weeks developed malignant liver tumors (Keefer et al. 1973; Lijinsky and Reuber 1984; Takahashi et al. 2000). Lijinsky et al. (1987) observed high incidences of liver, lung, and kidney tumors in rats that were treated by gavage with 6 mg/kg twice weekly for 30 weeks. Untreated or vehicle controls were not used in the latter study, which compared tumorigenicity of different nitrosamines. However, similar findings were observed in a subsequent study with an untreated control (Lijinsky and Kovatch 1989), in which liver and kidney tumors were observed at NDMA doses ≥8.1 mg/kg (by gavage) twice weekly for 20–30 weeks. In a diet study with rats (10/sex exposed), daily treatment with a dose of 3.9 mg/kg for 26–40 weeks resulted in hepatic tumors in 19/20 animals (Magee and Barnes 1956). Neither Lijinsky and Kovatch (1989) nor Magee and Barnes (1956) reported the control incidences of tumors.

NDMA is also a carcinogen in mice. Liver, lung, and/or kidney tumors developed in mice after daily exposure to NDMA via drinking water at doses of ~1 mg/kg/day for 4, 13, 16, or 38 weeks (Anderson 1988; Anderson et al. 1992a; Den Engelse et al. 1974; Terracini et al. 1966), 1.8 mg/kg/day for 7 weeks (Clapp and Toya 1970), 0.91 for 38 weeks (Clapp and Toya 1970), ~0.4 mg/kg/day for 32 or 58 weeks (Clapp and Toya 1970), or 0.25 mg/kg/day for 32–48 weeks (Anderson et al. 1992a). In studies where NDMA was administered via the diet, doses of 13 mg/kg for 16–92 days (Otsuka and Kuwahara 1971), 5.26 mg/kg for 5 months (Takayama and Oota 1965), or 9.04 mg/kg for 10 months (Takayama and Oota 1965) also induced liver, lung, and/or kidney tumors in mice. Confidence in the results from Otsuka and Kuwahara (1971) and the 10-month experiment reported by Takayama and Oota (1965) is low, as both lacked appropriate control groups. In the only intermediate-duration gavage study with mice, twice weekly doses of 1 mg/kg for 50 weeks resulted in high (37–53%) incidences of malignant liver tumors (Griciute et al. 1981).

Intermediate-duration oral studies in hamsters and mink provided supporting evidence for NDMA carcinogenicity but were hampered by the lack of control or other study quality limitations. Daily administration of 4 mg/kg/day in the drinking water to hamsters for 12 or 16 weeks resulted in high incidences of cholangiocellular adenocarcinomas (Ungar 1986). Hamsters that were treated with NDMA by gavage twice weekly with a dose of 5.4 mg/kg for 6.5 weeks, once weekly with a dose of 10.7 mg/kg for 4 weeks, once weekly with a dose of 5.4 mg/kg for 20 weeks, or via drinking water with a dose of 1.1 mg/kg/day for 7 months developed high (60–79%) incidences of liver tumors (Bosan et al. 1987; Lijinsky et al. 1987). However, control groups were not included in the studies by Lijinsky et al. (1987) and Bosan et al. (1987). Hemangiomatous liver tumors occurred in 55% of deceased mink that received

NDMA in the diet at an estimated dose of 0.18 mg/kg/day (Martino et al. 1988); limitations of this study include uncertainty regarding exposure duration and concentration, examination only of animals that died, and use of historical controls.

Chronic oral carcinogenicity studies of NDMA have been conducted with rats, mice, and mink; these studies showed dose-related increases in the incidences of liver and testicular tumors in rats, liver and lung tumors in mice, and liver tumors in mink.

The largest and most comprehensive carcinogenicity study of NDMA was conducted by Peto et al. (1984, 1991a, 1991b). Groups of 60 rats/sex were exposed to 1 of 15 concentrations of NDMA in drinking water (between 0.033 and 16.896 ppm), yielding estimated doses of 0.001–0.697 mg/kg/day (Peto et al. 1991b). Controls received untreated water. Groups of six rats/sex/dose were sacrificed after 12 and 18 months; however, data from the interim sacrifices were not reported separately. The remaining animals were observed until natural death, moribund appearance, or appearance of palpable liver abnormalities (up to 3.5 years). Histopathology examinations were performed on grossly observed lesions; apart from these, "a few" sections of apparently normal liver and esophagus were routinely examined microscopically. In both male and female rats, NDMA doses ≥0.022 mg/kg/day (0.528 ppm) were associated with decreased survival due to liver tumors. The liver tumors included malignant hepatocellular, mesenchymal, and Kupffer cell tumors as well as benign tumors of the bile ducts. The incidences were reported separately for fatal and incidental tumors; most tumors were fatal. The incidences of any liver tumor (summed across cell type and fatal/incidental) were statistically significantly increased at doses ≥0.022 mg/kg/day. In analyses pooled across male and female rats, statistically significant trends for dose-related increases in the incidences of tumors (malignant or benign) at other sites (presumably detected at gross necropsy, as histopathology evaluations were not routinely performed for other organs) were reported for the prostate, seminal vesicles, or Cowper's complex; bronchus or lung; skin; and lymphatic or hematopoietic tissues.

Increased incidences of liver tumors occurred in Wistar rats that received ≥0.14 mg/kg/day doses of NDMA in the diet for 96 weeks; no increase was seen at 0.013 mg/kg/day (Arai et al. 1979; Ito et al. 1982). At the highest dose, female rats also exhibited a significantly increased incidence of leukemia (not further characterized; Arai et al. 1979). In a preliminary report that suffered from limitations in reporting (study design, implementation, and findings), Crampton (1980) administered NDMA to rats in the drinking water at concentrations between 0.033 and 1.69 ppm doses for life and reported increased liver tumor incidences at 0.132 ppm. The study authors estimated a dose range of 0.002–1.5 mg/kg/day;

however, the dose range (750-fold) appears to be inconsistent with the concentration range (51-fold), and efforts to validate the dose estimates using standard methodologies were not successful; thus, reliable dose estimates cannot be determined for this study. Two studies reported increased incidences of testicular tumors in rats exposed to NDMA. Terao et al. (1978) observed an increase in the incidence of testicular Leydig-cell tumors (7/15 versus 0/30 controls) in Wistar rats treated with 0.5 mg/kg/day of NDMA in the diet for 54 weeks. In contrast with other studies of rats exposed to doses in this range (e.g., Arai et al. 1979; Keefer et al. 1973; Lijinsky and Reuber 1984), these authors observed no tumors in the liver or other tissues. Nonsignificant increases in the incidences of testicular tumors were reported in Wistar rats exposed to 0.13 and 1.3 mg/kg/day NDMA in feed (60 and 52.9% compared with 28.6% in controls; Arai et al. 1979)

In A/JNCr mice exposed to NDMA in drinking water at a dose of 0.24 mg/kg/day for 72 weeks, the average number of lung tumors per tumor-bearing mouse was significantly increased (2.4 versus 1.5 in controls) (Anderson et al. 1992a). The incidence of tumors in treated mice did not differ from controls (88 versus 83%); however, this strain of mouse has a high spontaneous incidence of lung tumors. Clapp and Toya (1970) administered NDMA to RF mice via drinking water at daily doses of 0.43 and 0.91 mg/kg/day for life and observed that incidences of lung tumors and liver hemangiosarcomas were significantly increased at both doses; mean survival time at the low and high doses were 12 and 17 months, respectively. Hemangiomatous liver tumors developed in mink exposed to 0.1 mg/kg/day NDMA in the diet for 321–607 days (Koppang and Rimeslatten 1976).

One intermediate-duration study of cancer in animals exposed by dermal application of NDMA was located. A low incidence of lung adenomas (13%), but no skin tumors, developed in hairless mice that were treated once weekly with 33.3 mg/kg topical doses of NDMA for 20 weeks (Iversen 1980). Lung and skin tumors were not observed in historical control groups. Although Iversen (1980) concluded that the lung cancers were related to the topical applications of NDMA, it should be noted that the mice were housed in groups of eight in each cage, so oral exposure via grooming cannot be ruled out. In addition, inhalation exposure was possible as the application site was not occluded.

Mechanisms. The World Health Organization (WHO 2008) reviewed the mechanisms of NDMA carcinogenicity. NDMA is believed to induce cancer via genotoxicity induced by reactive metabolites, especially the methyldiazonium ion (see Section 3.1.3 for further detail). This intermediate is an alkylating agent that methylates DNA, forming several adducts including N^7-methylguanine, O^6-methylguanine, N^3-methyladenin, and O^4-methylthymine. The predominant adducts are

N^7-methylguanine (65% of all adducts) and O^6-methylguanine (7%). Depurination of the N^7-methylguanine adduct results in apurinic sites that can, if unrepaired, result in mutations (G-T transversions). The O^6-methylguanine adduct, while not the predominant adduct seen after NDMA exposure, is persistent and its relationship to mutations (G:C to A:T transitions) leading to carcinogenicity is well-established. These transition mutations have been detected in lung tumors of mice exposed to NDMA and in transgenic mice exposed to NDMA (reviewed by WHO 2008).

Souliotis et al. (1995, 2002) conducted experiments to investigate the relationship between O^6-methylguanine adducts and liver tumors in rats, using drinking water concentrations at which Peto et al. (1984, 1991a, 1991b) observed liver tumors. Souliotis et al. (1995) observed that the kinetics of O^6-methylguanine adduct accumulation did not fully explain the increase in cancer incidence reported by Peto et al. (1984, 1991a, 1991b). Steady-state adduct accumulation exhibited a small decrease in slope at doses >0.056 mg/kg/day, in contrast to the sharp increase in liver tumor incidences above this dose. In a subsequent experiment in rats, Souliotis et al. (2002) demonstrated increased DNA replication in rat hepatocytes after exposure to NDMA at concentrations >1 ppm (~0.044 mg/kg/day in the study by Peto et al. 1984, 1991a, 1991b). The authors suggested that the hepatic carcinogenicity of NDMA in rats was influenced both by DNA damage and increased replication.

The O^6-methylguanine adduct can be repaired by O^6-methylguanine DNA-methyltransferase (MGMT), and indeed reduced expression of this enzyme is seen in many tumor types (Sharma et al. 2009). Nakatsuru et al. (1993) demonstrated that transgenic mice expressing higher levels of MGMT develop fewer tumors after NDMA exposure than those expressing normal levels. Expression and activity of MGMT vary across tissues and by age and species, and polymorphisms of the enzyme have also been identified (Sharma et al. 2009; WHO 2008). These variations may contribute to tissue, species, and population differences in adduct accumulation and tumor susceptibility. In humans, MGMT activity is highest in the liver, followed by lung, kidney, and colon, with lower levels in the pancreas, hematopoietic and lymphoid cells, and brain (Sharma et al. 2009). In patas monkeys exposed once to 0.1 mg/kg NDMA by gavage, the highest levels of O^6-methylguanine adducts were detected in the gastric mucosa and liver; levels in leukocytes, esophagus, ovary, pancreas, urinary bladder, and uterus were about half the levels in gastric mucosa and liver (Anderson et al. 1996). In the same study, MGMT activities were highest in the liver > stomach > pancreas ≈ colon ≈ kidney ≈ small intestine.

There is some evidence that MGMT activity may be higher in humans than in laboratory rodents. Gerson et al. (1986) measured MGMT activity *in vitro* in tissues from humans, rats, and mice. In the liver,

intestine, lungs, brain, lymphocytes, and bone marrow, the MGMT activity in humans was higher than in rats or mice. In contrast, both rats and mice had higher MGMT activity in the kidney than humans. The study authors noted that there was substantial variation in activity levels between individual human donors and between individual animals, suggesting that some individuals may have lower MGMT activity and thus be at higher risk from exposure to alkylating agents such as NDMA (Gerson et al. 1986).

Kay et al. (2021) showed the importance of the mammalian alkyladenine DNA glycosylase (AAG) enzyme, which removes methylated bases and is the first step in base excision repair, in determining the carcinogenic action of NDMA. Using mice with the *Aag* gene knocked out (resulting in increases in replication-blocking 3-methyl adenine adducts) as well as mice overexpressing *Aag* (resulting in increased DNA strand breaks), the study authors showed that the absence of the *Aag* gene increased NDMA-induced cancer incidence relative to wild-type mice (86 versus 67%, with 4.5 tumors/mouse versus 1 tumor/mouse, respectively). In contrast, the overexpression of the *Aag* gene reduced cancer incidence, but resulted in early mortality (13% within 2 weeks of exposure compared with 0.7% of wild-type mice) (Kay et al. 2021).

O^6-methylguanine adducts were detected in fetal tissues of patas monkeys exposed to NDMA during pregnancy (Chhabra et al. 1995). In addition, Anderson et al. (1989) reported significantly increased incidences of hepatocellular carcinomas in offspring of C3H/HeNCr MTV^- mice given 7.4 mg/kg NDMA by i.p. injection on GD 16 or 19. These studies provide support for the findings of Aleksandrov (1974), who reported tumors (sites unspecified) in the offspring of rats exposed orally to NDMA on GD 21.

As discussed in Section 2.20, both *in vitro* and *in vivo* tests for mutagenicity of NDMA have consistently shown positive results both with and without metabolic activation.

HHS concluded that NDMA is "reasonably anticipated to be a human carcinogen," based on sufficient evidence in animals (NTP 2021). EPA (IRIS 1987) classified NDMA in Group B2 (probable human carcinogen) based on sufficient evidence of carcinogenicity in animals. In addition, IARC (1987) assigned NDMA to Group 2A (probably carcinogenic to humans) based on inadequate information in humans and sufficient evidence in experimental animals. EPA's Integrated Risk Information System (IRIS) reports an oral slope factor of 51 per mg/kg/day and an inhalation unit risk of 0.014 per $\mu g/cm^3$ for NDMA. For its Six-Year Review 3 Technical Support Document for Nitrosamines (EPA 2016), EPA's Office of Water derived an oral slope factor of 21 per mg/kg/day for NDMA using the Peto et al. (1991a,

1991b) study, which had not been published at the time when EPA's IRIS review of NDMA was prepared (1987).

2.20 GENOTOXICITY

Methylated DNA adducts (7-methylguanine and O^6-methylguanine) were detected in the liver of a 23-year-old man who died from suspected NDMA poisoning (Herron and Shank 1980). No other studies of genotoxicity in humans exposed to NDMA were located. NDMA has been extensively tested for genotoxicity in both *in vitro* and *in vivo* animal systems, yielding positive results in most assays. As a result, NDMA is routinely used as a positive control in genotoxicity studies.

Table 2-5 provides an overview of the *in vitro* results; the studies presented are representative of the database, but do not reflect every available study. *In vitro* assays have demonstrated increased mutation frequencies in bacteria, yeast, and mammalian cell systems incubated with NDMA with metabolic activation (see Table 2-5). Increases in the frequency of chromosomal aberrations have been observed in several rat cell types, Chinese hamster lung, ovary, and fibroblast cells, and in human fibroblast cells. As with the mutation assays, the positive results were seen in the presence of exogenous metabolic activation or in metabolically competent cell systems. *In vitro* tests for micronuclei have shown mixed results; increases in micronuclei were observed in human lymphoblastoid cells (Crofton-Sleigh et al. 1993) and in human hepatoma (HepG2) cells (Valentin-Severin et al. 2003) tested without metabolic activation, and in Chinese hamster lung cells tested with activation (Matsushima et al. 1999). Assays with other human cell types and with rat and mouse cells yielded negative results (see Table 2-5). In a large number of other *in vitro* tests, NDMA was shown to induce sister chromatid exchanges and DNA damage, repair synthesis, or unscheduled synthesis (see Table 2-5).

Table 2-5. Genotoxicity of N-Nitrosodimethylamine *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium	Gene mutation	+	NT or –	Araki et al. 1984; Bartsch et al. 1980; Bringezu and Simon 2022; De Flora et al. 1984; Ishidate and Yoshikawa 1980; Langenbach et al. 1986; Prival and Mitchell 1981; Surh et al. 1995; Wagner et al. 2014; Wang et al. 2017

Table 2-5. Genotoxicity of N-Nitrosodimethylamine *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Escherichia coli	Gene mutation	+	NT	Araki et al. 1984; Bringezu and Simon 2022; De Flora et al. 1984; Jiao et al. 1993
Saccharomyces cerevisae	Gene mutation	+	NT	Frezza et al. 1983; Jagannath et al. 1981
Human lymphoblastoid (AHH-1, MCL-5, MCL-1) cells	Gene mutation	NA	+	Davies et al. 1989; Dobo et al. 1997, 1998
Chinese hamster V79 and ovary cells	Gene mutation	+	–	Adair and Carver 1983; Bartsch et al. 1980; Carver et al. 1981; Dickins et al. 1985; Hsie et al. 1978; Katoh et al. 1982; Kuroki et al. 1977; Langenbach 1986; Lawson and Kolar 1992; O'Neill et al. 1982; Swedmark et al. 1994
Mouse lymphoma L578Y cells	Gene mutation	+	–	Amacher and Paillet 1983; Clive et al. 1979
Rat hepatocyte (NRL cl-B, NRL cl-C, and ARL) cell lines	Chromosomal aberrations	NT	+	Kulka et al. 1993
Chinese hamster lung, ovary, or V79 fibroblast cells	Chromosomal aberrations	+	NT or –	Bean et al. 1994; Ishidate and Yoshikawa 1980; Johnson et al. 1996; Kulka et al. 1993; Matsuoka et al. 1979, 1986; Matsushima et al. 1999
Human fibroblast (L136) cells	Chromosomal aberrations	+	NT	Bean et al. 1994
Rat ascites hepatoma (AH66B) and rat esophageal (R1, R3) tumor cells	Chromosomal aberrations	NT	+	Ikeuchi and Sasaki 1981
Human lymphoblastoid (MCL5) cells	Micronuclei	NT	+	Crofton-Sleigh et al. 1993
Human peripheral blood lymphocytes	Micronuclei	–	NT	Katic et al. 2010
Human lymphoblasts (TK6) and peripheral blood lymphocytes	Micronuclei	NT	–	Liviac et al. 2011
Human hepatoma (HepG2) cells	Micronuclei	NT	+	Valentin-Severin et al. 2003
Rat hepatoma (H4IIEC3) cells	Micronuclei	NT	–	Roscher and Wiebel 1989
Mouse embryo fibroblast (NIH3T3) cells	Micronuclei	NA	–	Wang et al. 2017
Chinese hamster lung cells	Micronuclei	+	NT	Matsushima et al. 1999

Table 2-5. Genotoxicity of N-Nitrosodimethylamine *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Primary rat hepatocytes	Sister chromatid exchange	NT	+	Eckl et al. 1987
Rat hepatocyte (NRL cl-B, NRL cl-C, and ARL) cell lines	Sister chromatid exchange	NT	+	Kulka et al. 1993
Rat esophageal tumor, ascites hepatoma	Sister chromatid exchanges	NT	+	Abe and Sasaki 1982; Ikeuchi and Sasaki 1981
Human lymphocytes	Sister chromatid exchange	+	–	Inoue et al. 1983; Madle et al. 1987
Human fibroblasts	Sister chromatid exchange	+	NT	Tomkins et at. 1982
Chinese hamster ovary cells	Sister chromatid exchange	+	NT	Blazak et al. 1985; Johnson et al. 1996; Okinaka et al. 1981; Tomkins et al. 1982
Chinese hamster V79 fibroblast cells	Sister chromatid exchange	+	–	Blazak et al. 1985; Kulka et al. 1993; Madle et al. 1987; Sirianni and Huang 1987
Chinese hamster primary lung cells	Sister chromatid exchange	+	–	Shimizu et al. 1984
Rat hepatocytes	DNA damage	NT	+	Bermudez et al. 1982; Bradley et al. 1982; Martelli et al. 1988; Pool et al. 1988; Singh and Roscher 1991
Rat hepatoma (H4IIEC3) cells	DNA damage	NT	+	Singh and Roscher 1991
Human hepatocytes	DNA damage	NT	+	Martelli et al. 1985, 1988
Human hepatoma (HepG2, HepaRG) cells	DNA damage	NT	+	Erkekoglu and Baydar 2010; Le Hegarat et al. 2010; Uhl et al. 1999; Valentin-Severin et al. 2003
Human lung or kidney cells	DNA damage	NT	+	Robbiano et al. 2006
Rat lung or kidney cells	DNA damage	NT	+	Robbiano et al. 2006
Rat kidney cells	DNA damage	NT	–	Brendler et al. 1992
Human lymphoblasts (TK6)	DNA damage	–	+	Liviac et al. 2011
Human hepatoma (HepG2) cells	DNA damage	NT	+	Valentin-Severin et al. 2003
Chinese hamster ovary cells	DNA damage	+	–	Wagner et al. 2014
Mouse splenocytes	DNA damage	+	–	Kim et al. 1989
Mouse embryo fibroblast (NIH3T3) cells	DNA damage	NA	–	Wang et al. 2017

Table 2-5. Genotoxicity of N-Nitrosodimethylamine *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Rat hepatocytes	DNA methylation/ adducts	NT	+	Lachapelle et al. 1994; Lachapelle et al. 1992
S. cerevisae	DNA repair	NT	+	He et al. 2021
Rat hepatocytes	DNA repair synthesis	NT	+	Andrae and Schwarz 1981; Rossberger et al. 1987
Rat hepatoma (H4IIEC3) cells	DNA repair synthesis	NT	+	Rossberger et al. 1987
Human hepatocytes	DNA repair synthesis	NT	+	Martelli et al. 1988
Rat hepatocytes	Unscheduled DNA synthesis	NT	+	Martelli et al. 1988; Shaddock et al. 1993
Human lymphoblasts	Unscheduled DNA synthesis	+	NT	Andrae et al. 1979
Mouse hepatocytes	Unscheduled DNA synthesis	NT	+	McQueen et al. 1983
Hamster hepatocytes	Unscheduled DNA synthesis	NT	+	McQueen et al. 1983
Rat pancreatic cells	Unscheduled DNA synthesis	NT	–	Steinmetz and Mirsalis 1984

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

Table 2-6 provides an overview of the *in vivo* results; the studies presented are representative of the database, but do not reflect every available study. NDMA has been tested extensively for mutagenicity in transgenic rodent models including the Big Blue® and Big Blue® cII rat and Big Blue®, Big Blue® cII, and Muta™ mouse (reviewed by Lambert et al. 2005; see also Table 2-6). In these studies, NDMA was administered orally (diet or gavage) or via i.p. injection for one or more days at doses between 1.8 and 54 mg/kg/day. Tissues, including liver, lung, kidney, bone marrow, spleen, bladder, and forestomach were sampled for mutations from 1 to 183 days after exposure. In these experiments, NDMA has consistently yielded increased mutations in the liver regardless of species, exposure route, duration, sampling time, and transgene (*lacI, cII, lacZ*). In mice, increased mutation frequencies were also observed in the lung and kidney (reviewed by Lambert et al. 2005).

Table 2-6. Genotoxicity of N-Nitrosodimethylamine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Rat kidney	Mutations	+	Horesovsky et al. 1995
Rat (transgenic Big Blue® and Big Blue® cII) liver	Mutations	+	Gollapudi et al. 1998
Mouse (transgenic Big Blue®) liver, lung, kidney	Mutations	+	Ashby et al. 1994; Butterworth et al. 1998; Cunningham et al. 1996; Davies et al. 2000; Delker et al. 2008; Hayward et al. 1995; Lefevre et al. 1994; Mirsalis et al. 1993; Shane et al. 1999, 2000a, 2000b; Shephard et al. 1995; Suzuki et al. 1996; Tinwell et al. 1994a, 1995
Mouse (transgenic Big Blue® cII) liver	Mutations	+	Shane et al. 2000b
Mouse (Muta™ mouse transgenic) liver, lung, spleen		+	Fletcher et al. 1998; Jiao et al. 1997; Lefevre et al. 1994; Souliotis et al. 1998; Suzuki et al. 1998; Tinwell et al. 1994b, 1995, 1998
Mouse (transgenic Big Blue®) testes, bone marrow, bladder, forestomach	Mutations	–	Ashby et al. 1994; Shephard et al. 1995; Suzuki et al. 1996
Mouse (Muta™ mouse transgenic) bone marrow, kidney	Mutations	–	Jiao et al. 1997; Souliotis et al. 1998; Suzuki et al. 1998
Mouse intestine	Mutations	+	Winton et al. 1990
Mouse lymphocytes	Mutations	–	Dass et al. 1998
Mouse lung tumors	Mutations	+	Chen et al. 1994; Devereux et al. 1991; Ramakrishna et al. 2000
Drosophila melanogaster	Mutations	+	Blount et al. 1985; Brodberg et al. 1987; Goto et al. 1999; Koike et al. 2018; Lee et al. 1983; Negishi et al. 1991, 2020; Nivard et al. 1996; Vogel et al. 1990
Fish liver	Mutations	+	Hobbie et al. 2012
Rat liver	Aneuploidy	+	Clawson et al. 1992
Drosophila melanogaster	Aneuploidy	+	Woodruff and Seeger 1991
Hamster embryonic fibroblasts (transplacental)	Chromosome aberrations	+	Inui et al. 1979
Rat liver	Chromosome aberrations	+	Asakura et al. 1998; Sawada et al. 1991
Rat and mouse liver	Micronuclei	+	Braithwaite and Ashby 1988; Cliet et al. 1989; Hamada et al. 2015; Mehta et al. 1987; Sawada et al. 1991; Suzuki et al. 2005, 2009; Takashima et al. 2015; Tates et al. 1980
Rat kidney	Micronuclei	+	Robbiano et al. 1997
Rat bone marrow and spleen	Micronuclei	+	Krishna and Theiss 1995
Rat bone marrow	Micronuclei	+/–	Trzos et al. 1978

Table 2-6. Genotoxicity of N-Nitrosodimethylamine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Rat bone marrow	Micronuclei	–	Hamada et al. 2015; Takashima et al. 2015
Mouse bone marrow and/or spleen	Micronuclei	+	Bauknecht et al. 1977; Fritzenschaf et al. 1993; Krishna et al. 1990; Morrison and Ashby 1994; Odagiri et al. 1986; Sato et al. 1992; Wild 1978
Mouse bone marrow	Micronuclei	–	Cliet et al. 1989, 1993
Rat peripheral blood	Micronuclei	–	Rothfuss et al. 2010
Mouse peripheral blood	Micronuclei	+	Sasaki 1991; Sato et al. 1992
Rat and mouse peripheral blood	Micronuclei	–	Suzuki et al. 1996, 2005
Rat stomach and colon	Micronuclei	–	Hamada et al. 2015; Takashima et al. 2015
Hamster embryonic fibroblasts (transplacental)	Micronuclei	+	Inui et al. 1979
Mouse spermatid	Micronuclei	+	Cliet et al. 1993
Hen egg	Micronuclei	+	Wolf et al. 2003
Rat liver	Sister chromatid exchanges	+	Sawada et al. 1991
Hamster bone marrow	Sister chromatid exchanges	+/–	Neal and Probst 1983
Mouse bone marrow	Sister chromatid exchanges	+	Bauknecht et al. 1977; Sharma et al. 1983
Drosophila melanogaster	Miotic recombination	+	Rodriguez-Arnaiz et al. 1996
Human liver	DNA methylation/ adducts	+	Herron and Shank 1980
Rat, mouse, hamster and/or gerbil liver	DNA methylation/ adducts	+	Bamborschke et al. 1983; Bianchini and Wild 1994; Camus et al. 1990; Chin et al. 1993; Dai et al. 1991; Fadlallah et al. 1994; Fan et al. 1989; Klaude et al. 1989; Kroeger-Koepke et al. 1992; Ma et al. 2015; O'Connor et al. 1982; Pegg and Hui 1978; Pegg et al. 1981; Scherer et al. 1989; Souliotis et al. 1995; Stumpf et al. 1979; Takahashi et al. 1996
Rat kidney, mammary glands, and leukocytes	DNA methylation/ adducts	+	Bianchini and Wild 1994; Chhabra et al. 2000; Fadlallah et al. 1994; Fan et al. 1989; Souliotis et al. 1995
Rat fetal liver, lung, and/or kidney	DNA methylation/ adducts	+	Chhabra et al. 2000
Rat esophagus	DNA methylation/ adducts	–	Scherer et al. 1989
Human placenta	DNA methylation/ adducts	–	Annola et al. 2009

Table 2-6. Genotoxicity of N-Nitrosodimethylamine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Rat liver, lung, kidney, nasal cavity, and/or peripheral blood lymphocytes	DNA damage	+	Abanobi et al. 1979; Bermudez et al. 1982; Brambilla et al. 1981, 1987, 1992; Dahlhaus and Appel 1993; McNamee and Bellier 2015; Petzold and Swenberg 1978; Pool et al. 1990; Pool-Zobel et al. 1992; Rothfuss et al. 2010; Webster et al. 1996
Rat liver and kidney	DNA damage	+	Barbin et al. 1983
Rat kidney	DNA damage (double-strand breaks)	–	McLaren et al. 1994
Rat lung	DNA damage	–	Barbin et al. 1983
Mouse liver, kidney, bladder	DNA damage	+	Cesarone et al. 1982; Tsuda et al. 2001
Hamster liver	DNA damage	+	Barbin et al. 1983
Hamster lung	DNA damage	–	Barbin et al. 1983
Rat stomach	DNA damage	–	McNamee and Bellier 2015; Ohsawa et al. 1993; Okabe et al. 2019
Mouse colon	DNA damage	–	Tsuda et al. 2001
Fetal mouse liver and lung	DNA damage	+	Bolognesi et al. 1988
Drosophila melanogaster	DNA damage	+	Negishi et al. 1991
Rat liver	Unscheduled DNA synthesis	+	Asakura et al. 1994; Bakke and Mirsalis 1984; Doolittle et al. 1984, 1987; Kornbrust and Dietz 1985; Mirsalis and Butterworth 1980; Mirsalis et al. 1989; Sawada et al. 1989, 1995
Mouse liver	Unscheduled DNA synthesis	+	Mirsalis et al. 1989
Rat upper respiratory tract	Unscheduled DNA synthesis	+	Doolittle et al. 1984
Rat stomach	Unscheduled DNA synthesis	–	Ohsawa et al. 1993
Rat spermatocytes	Unscheduled DNA synthesis	–	Doolittle et al. 1984
Mouse testes	Unscheduled DNA synthesis	+	Cesarone et al. 1979
Rat embryo	Unscheduled DNA synthesis	+	Huang and Catalano 1994
Rat liver	Replicative DNA synthesis	+	Asakura et al. 1998
Mouse testes	Inhibition of DNA synthesis	+	Friedman and Staub 1976

– = negative result; + = positive result; +/– = equivocal results; DNA = deoxyribonucleic acid

Studies that examined the spectrum of mutations induced by NDMA have shown that the most common mutations in the Muta™ (*lacZ*) and Big Blue® (*lacI*) mouse are GC→AT transitions, primarily at non-CpG sites (Delker et al. 2008; reviewed by Lambert et al. 2005). GC→AT transitions can be produced if O^6-methylguanine adducts are not repaired, and this particular type of mutation in non-CpG sites is associated with an increased risk of cancer. Other mutations shown in these analyses included A:T→T:A transversions as well as single and multiple base pair deletions and frameshift mutations (Delker et al. 2008; reviewed by Lambert et al. 2005).

There is some evidence that younger animals may be more susceptible to NDMA mutagenicity. In one study, NDMA administration increased the mutation frequency in the livers of Big Blue (lacI) mice when administered as five daily doses of 2 mg/kg/day beginning at 3 weeks of age, but not when administered under the same conditions beginning at 6 weeks of age (reviewed by Lambert et al. 2005). The authors suggested that the difference in response could stem from age-related differences in metabolic activation, DNA adduct removal rates, or rates of mutation fixation. Delker et al. (2008) treated this same strain with three daily doses of 7 mg/kg/day beginning at 12 weeks of age and observed a significant increase in mutation frequency in the liver.

Along with the results in transgenic rodents, other *in vivo* studies have provided additional evidence for the genotoxicity of NDMA. As shown in Table 2-6, exposure to NDMA has resulted in mutations in rat kidney, mouse intestine and lymphocytes, *Drosophila melanogaster*, and fish liver; chromosomal aberrations or aneuploidy in rat liver, hamster fibroblasts, and *Drosophila*; and micronuclei in several species and tissues. In addition, NDMA has induced DNA methylation and adducts, DNA damage, and unscheduled DNA synthesis, especially in the liver, in a number of species (see Table 2-6).

Further discussion of the genotoxic mechanisms of cancers induced by NDMA, including specific DNA adducts, DNA repair enzymes, and tissue distribution of adducts and repair enzymes is presented in Section 2.19 (Cancer) under *Mechanisms*.

Taken together, the *in vitro* and *in vivo* genotoxicity data demonstrate unequivocally that one or more metabolites of NDMA is genotoxic to the liver in a wide range of species. In accordance with this finding, the liver is the primary target of NDMA carcinogenesis, suggesting that genotoxicity plays a role in the mechanism by which NDMA induces cancer.

NDMA has not shown genotoxic activity in germ cells *in vivo* or *in vitro*. No increase in unscheduled DNA synthesis was seen in spermatocytes of rats exposed to NDMA by inhalation (Doolittle et al. 1984). In addition, NDMA was negative for dominant lethal mutations in ICR/Ha Swiss mice exposed by i.p. injection (Epstein et al. 1972). In CF-1 mice exposed by i.p., intravenous (i.v.), or oral administration, ^{14}C NDMA did not alkylate sperm heads at doses from 4 to 14 mg/kg (Stott and Watanabe 1980). These study authors suggested that the lack of binding might stem from relatively low levels of the active NDMA metabolites in the testes resulting from low enzyme activity and short half-life of the metabolites. Despite the lack of germ cell genotoxicity in these studies, NDMA did induce O^6-methylguanine adducts in patas monkey fetuses (Chhabra et al. 1995), chromosomal aberrations and micronuclei in the embryos of treated pregnant hamsters (Inui et al. 1979), and transplacental carcinogenesis in mice exposed by i.p. injection (Anderson et al. 1989).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Available toxicokinetic data pertaining to NDMA primarily consist of studies in animals exposed orally and via i.v. injection. No studies examining the absorption, distribution, metabolism, or excretion of NDMA after inhalation or dermal exposure in humans or animals were located. Quantitative data on NDMA kinetics are available from studies in rats, mice, patas monkeys, swine, beagles, hamsters, and ferrets.

- Absorption
  - Absorption of orally administered NDMA occurs primarily in the small intestine.
  - Oral absorption is rapid and complete in all species tested.
  - The oral bioavailability (the fraction of an oral dose that passes through the liver unchanged and enters systemic circulation) of NDMA may vary across species, with estimates ranging from about 10% in hamsters and rats to >90% in beagles at comparable administered doses (1–3 mg/kg). Oral bioavailability may also vary with dose.
  - Absorption of inhaled NDMA is inferred from human fatalities after inhalation and limited animal data.

- Distribution
  - In rats, hamsters, and pigs, unmetabolized NDMA passes freely between blood and tissues, with little to no accumulation in any given tissue.
  - *In vitro* studies using plasma from several species showed that NDMA does not bind plasma proteins.

- Metabolism
  - NDMA is metabolized by microsomal membrane-bound CYP2E1, to hydroxymethyl-nitrosamine. The latter is nonenzymatically converted to formaldehyde and the reactive methyldiazonium ion; additional metabolic products include methanol and a reactive methyl carbonium ion. Denitrosation of NDMA, yielding formaldehyde and monomethylamine, has also been demonstrated.
  - Metabolism of NDMA is saturable. In both swine and beagles, metabolism is saturated at an oral dose of 5 mg/kg.
  - Clearance of NDMA from blood is primarily via metabolism.

- Excretion
  - Very little unchanged NDMA is excreted in urine after oral exposure.
  - Methylamine is the primary urinary metabolite in rats exposed to NDMA orally.
  - Enterohepatic circulation of NDMA has been shown in pigs.
  - Enterosalivary circulation of NDMA has been demonstrated in beagles.

As discussed further in Section 5.6, NDMA is produced endogenously through both acid-catalyzed nitrosation of amine precursors (primarily in the stomach) and through biologically catalyzed nitrosation

in other tissues including the oral cavity, intestine, liver, blood, and bladder (Hrudey et al. 2013). Estimates of the amount of NDMA produced endogenously vary widely. Using three different methods and available literature on measured human NDMA blood levels, O^6-methylguanine DNA adducts, and urinary excretion levels, Hrudey et al. (2013) estimated the rate of endogenous production to be approximately 1 mg/day (equivalent to 0.014 mg/kg/day for a 70-kg adult). In a study of volunteers in which urinary NDMA was measured before and after consuming fish meals rich in amines along with the acceptable daily intake of nitrate, Vermeer et al. (1998) estimated endogenous production of NDMA to be 174 µg/day (about 0.0029 mg/kg/day). Krul et al. (2004) employed an *in vitro* model of the human gastrointestinal tract to estimate NDMA formation occurring with gradual intake of nitrate at a range of doses from 0.1 to 10 times the acceptable daily intake. The study authors estimated cumulative NDMA amounts of 1.3–422 µg when a rapid decrease in gastric pH was simulated and 1.8–42.7 µg when gastric pH was modeled at slow decrease.

3.1.1 Absorption

No studies were located regarding the rate and extent of absorption of NDMA following inhalation exposure of humans or animals to NDMA. However, it can be inferred that NDMA is absorbed from the air since it can be detected in the urine of rats (Klein and Schmezer 1984) and dogs (CARB 1986) after inhalation exposure. Absorption is also indicated by reports of human deaths following inhalation of NDMA (Freund 1937; Hamilton and Hardy 1974).

No studies were located regarding the absorption of NDMA following oral exposure of humans. The absorption of NDMA from the gastrointestinal tract of animals is rapid and essentially complete. In studies of beagles, swine, patas monkeys, rats, and ferrets exposed to oral doses between 0.15 and 5 mg/kg, the maximum concentration of NDMA in blood was reached within 30 minutes (Anderson et al. 1992b; Gombar et al. 1987, 1988, 1990; Streeter et al. 1990a, 1990b; see Table 3-1). Less than 2% of the labelled compound could be recovered from the gastrointestinal tract 15 minutes after oral administration of ^{14}C-NDMA to rats (Gomez et al. 1977).

Table 3-1. Maximum Blood Concentration and Time to Maximum in Animals Exposed to N-Nitrosodimethylamine (NDMA) by Oral Administration

			Unchanged NDMA	
Reference(s)	Species	Oral dose (mg/kg)	Cmax (ng/mL)	Tmax (minutes)
Mico et al. 1985	Rat	0.15	NR	~15[a]
Hinuma et al. 1990	Rat	0.20	174	5
Anderson et al. 1992b; Gombar et al. 1990	Patas monkey	1.0	205–210	25–30
Wishnok et al. 1987	Ferret	1.0	NR	30
Hino et al. 2000	Beagle	2.0	~800 [a]	~30 [a]
Gombar et al. 1987	Beagle	1.0	424	20
		5.0	2,677	25
Gombar et al. 1988	Swine	1.0	144	23
		5.0	2,217	23

[a]Approximate values were estimated by visual inspection of data presented graphically.

NR = not reported

In the rat, NDMA is absorbed much faster from the small intestine than from the stomach, in both isolated preparations (Heading et al. 1974) and *in vivo* (Hinuma et al. 1990; Pegg and Perry 1981). Ishiwata et al. (1978) reported that in guinea pigs exposed to NDMA directly to the ligated stomach or small intestine, NDMA was absorbed more rapidly (measured as disappearance from excised tissues) from the small intestine. The rate of disappearance from both tissues in the 20 minutes after exposure followed first-order kinetics (Ishiwata et al. 1978).

Oral bioavailability estimates for unchanged NDMA, obtained by comparing the area under the blood concentration-time curves (AUCs) after oral and i.v. administration, varied by species in studies using oral doses of 0.15–3 mg/kg. Relatively low fractional bioavailability (8–31%) was observed for rats and hamsters (Mico et al. 1985; Streeter et al. 1990a, 1990b); bioavailability in patas monkeys and swine was higher (49–67%; Gombar et al. 1988, 1990), and the highest values were obtained with beagles (93%; Gombar et al. 1987). Because NDMA is essentially completely absorbed from the gastrointestinal tract and does not bind plasma proteins (Gombar et al. 1987, 1988; Streeter et al. 1990a, 1990b) or associate with erythrocytes, the reasons for the wide variation in bioavailability are not fully understood. Little to no unchanged NDMA is excreted in urine or expired air (Anderson et al. 1992b; Magee 1956; Swann et al. 1984). The higher bioavailability in larger species has been suggested to result from significant extrahepatic metabolism (Gombar et al. 1990). This hypothesis is supported by observations of constant systemic clearance rates (normalized to body weight) despite large differences in hepatic extraction ratios

(Gombar et al. 1990). Both kidneys and lungs have been shown to exhibit NDMA demethylase activity and may contribute to extrahepatic metabolism; however, there are no estimates of the extent or rate of renal or pulmonary NDMA metabolism in larger mammals

There are few data with which to evaluate the dose-dependence of NDMA oral bioavailability. Mico et al. (1985) reported an oral bioavailability estimate of 21% in male rats given deuterated NDMA at a dose of 0.15 mg/kg; this estimate is comparable to the bioavailability estimate of 31% obtained in male rats given 1 mg/kg deuterated NDMA (Streeter et al. 1990a). In contrast, Harrington et al. (1990) observed dose-dependent hepatic extraction of NDMA in swine, with little unmetabolized NDMA reaching the bloodstream after oral doses of 0.1 mg/kg, while larger fractions escaped the liver unchanged at doses of 1 and 10 mg/kg.

No studies were located regarding the absorption of NDMA following dermal exposure of humans or animals. Indirect evidence indicating that NDMA may be absorbed through the skin of mice was found in a study published by Iversen (1980) in which topical application of NDMA induced lung adenomas in mice. The results from Iversen, however, should be interpreted with caution since the mice were housed eight animals to a cage and could have licked the NDMA from each other or inhaled this volatile compound. In an *in vitro* assay using excised human skin obtained at autopsy, Brain et al. (1995) reported a percutaneous flux of 11.32 μg/cm^2 and absorbed fraction of 2.57% over 48 hours after application of an infinite dose of NDMA in isopropyl myristate.

3.1.2 Distribution

In mice, hamsters, and pigs, unmetabolized NDMA was widely distributed throughout the body after i.v. injection, passing freely between blood and tissues (Gombar et al. 1988, 1990; Streeter et al. 1990b). In these species, the steady-state volume of distribution (V_{ss}) was approximately equal to total body water, suggesting little to no accumulation in tissues. In beagles, however, the V_{ss} (1.7–2.1 L/kg; Gombar et al. 1987; Hino et al. 2000) exceeded total body water (0.693 L/kg; Davies and Morris 1993), suggesting significant tissue accumulation. Table 3-2 shows V_{ss} values for several species. Gombar et al. (1990) used these data to derive an allometric equation for body weight scaling of V_{ss} and estimated a NDMA V_{ss} of 64,800 mL (~926 mL/kg) for a 70-kg human.

Table 3-2. Species Differences in Steady-State Volume of Distribution for Unmetabolized N-Nitrosodimethylamine (NDMA) (V_{ss}) after Intravenous Exposure

Reference(s)	Species	Intravenous dose(s) (mg/kg)	V_{ss} (mL/kg)
Gombar et al. 1990[a]	Mouse	1.0–2.0	769–796
Mico et al. 1985	Rat	0.10	297
Streeter et al. 1990b	Hamster	0.31	582
Hino et al. 2000; Gombar et al. 1987	Beagle	1–2	1,700–2,100
Gombar et al. 1988	Swine	0.1–1.0	1,000–1,900
Anderson et al. 1992b; Gombar et al. 1990[a]	Patas monkey	0.5–5.0	1,027–1,417

[a]Vd values from Gombar et al. (1990) were converted from mL to mL/kg using animal body weights reported by the study authors.

NDMA = N-nitrosodimethylamine; V_{ss} = steady-state volume of distribution

Unmetabolized NDMA was also observed to be evenly distributed among the main organs of mice and rats shortly after i.v. injection to animals in which the metabolism of NDMA had been inhibited (Johansson and Tjalve 1978; Magee 1956). Wishnok et al. (1978) reported a similar finding in rats following i.p. injections.

In rats that were administered 0.2 mg/kg NDMA by i.v. injection, concentrations of unmetabolized NDMA in liver, spleen, kidney, lung, and brain were approximately 70% of the arterial blood concentrations and declined in parallel with blood concentrations to nondetectable levels within 4 hours after exposure, suggesting that these tissues do not accumulate NDMA in the rat. One hour after a dose of 6 mg ^{14}C-NDMA/kg was administered by i.p. injection to mice, the liver contained 2 times as much radioactivity as the kidney, spleen, and thymus (Johnson et al. 1987).

In vitro experiments (using equilibrium dialysis or a micropartitioning system) to evaluate whether ^{14}C-NDMA binds plasma proteins have shown no evidence for binding in plasma from rats (Streeter et al. 1990a), hamsters (Streeter et al. 1990b), swine (Gombar et al. 1988), and beagles (Gombar et al. 1987) at concentrations between 1 and 1,000 ng/mL.

No studies were located regarding the distribution of NDMA following inhalation exposure of humans or animals.

No studies were located regarding the distribution of NDMA following oral exposure of humans. Few studies have measured tissue levels of unmetabolized NDMA or NDMA-derived radioactivity in animals. Anderson et al. (1986) measured NDMA in tissues of A/J or A/JCr mice exposed to 50 ppm NDMA in drinking water for 1–4 weeks. Concentrations of unchanged NDMA in kidney, lung, and brain were similar to those in the blood, while liver concentrations were lower. For example, after 4 weeks of exposure, concentrations in blood, kidney, lung, and brain were 65, 51, 38, and 32 ppb (respectively), while a concentration of 6 ppb was measured in the liver (Anderson et al. 1986). Coadministration of ethanol, a competitive inhibitor of CYP2E1, increased the concentrations of NDMA in blood and all tissues; in the group receiving 50 ppm NDMA with ethanol for 4 weeks, concentrations were 218, 64, 444, 182, and 72 ppb in blood, kidney, lung, brain, and liver, respectively.

Daugherty and Clapp (1976) reported that 15 minutes after oral administration of ^{14}C-NDMA to mice, the relative amounts of radioactivity in the homogenates of heart, forestomach, esophagus, liver, and lung were 1, 2, 3, 10, and 70, respectively. The differences in tissue levels reported in this study are likely due to the study authors' measurement of radioactivity (including metabolites); studies that measured unchanged NDMA (e.g., Anderson et al. 1986) showed little variation in tissue concentrations. Measurable amounts of NDMA were reported in blood, liver, kidney, lungs, and brain of mice exposed to 5 mg/kg/day in drinking water for up to 4 weeks (Anderson et al. 1986). NDMA has been detected in maternal blood, placenta, fetus, and amniotic fluid of pregnant Syrian hamsters for up to 2 hours after a single subcutaneous (s.c.) dose of 12.5 mg/kg of the chemical (Althoff et al. 1977). NDMA and/or its metabolites is also distributed to breast milk; when nursing rats were given NDMA by gavage, O^6-methylguanine adducts or NDMA-derived radiolabel were detected in DNA from pup kidney and liver (Chhabra et al. 2000; Diaz Gomez et al. 1986).

No studies were located regarding the distribution of NDMA following dermal exposure of humans. The study by Iversen (1980), in which lung adenomas were noticed in mice after skin application of NDMA, indicates that this chemical (or a metabolite) was distributed to the lungs.

Maternal-fetal Transfer. NDMA can cross the placenta, leading to fetal exposure. After pregnant patas monkeys were exposed to 1.0 mg/kg NDMA, O^6-methylguanine adducts were detected in both placental DNA and DNA in the fetal liver (Chhabra et al. 1995). Using a dual recirculating human placental perfusion model, Annola et al. (2009) detected radioactivity in the fetal circulation after ^{14}C-NDMA exposure to the maternal circulation, indicating transplacental transfer. The study authors noted that transportation across the placenta likely occurred by passive diffusion, as the rate of transfer was similar

to that of antipyrine and the radioactivity levels in maternal and fetal circulations equilibrated within 3 hours (Annola et al. 2009). Co-treatment of perfused human placentas with ethanol and NDMA did not alter the placental transfer of NDMA (Veid et al. 2011).

3.1.3 Metabolism

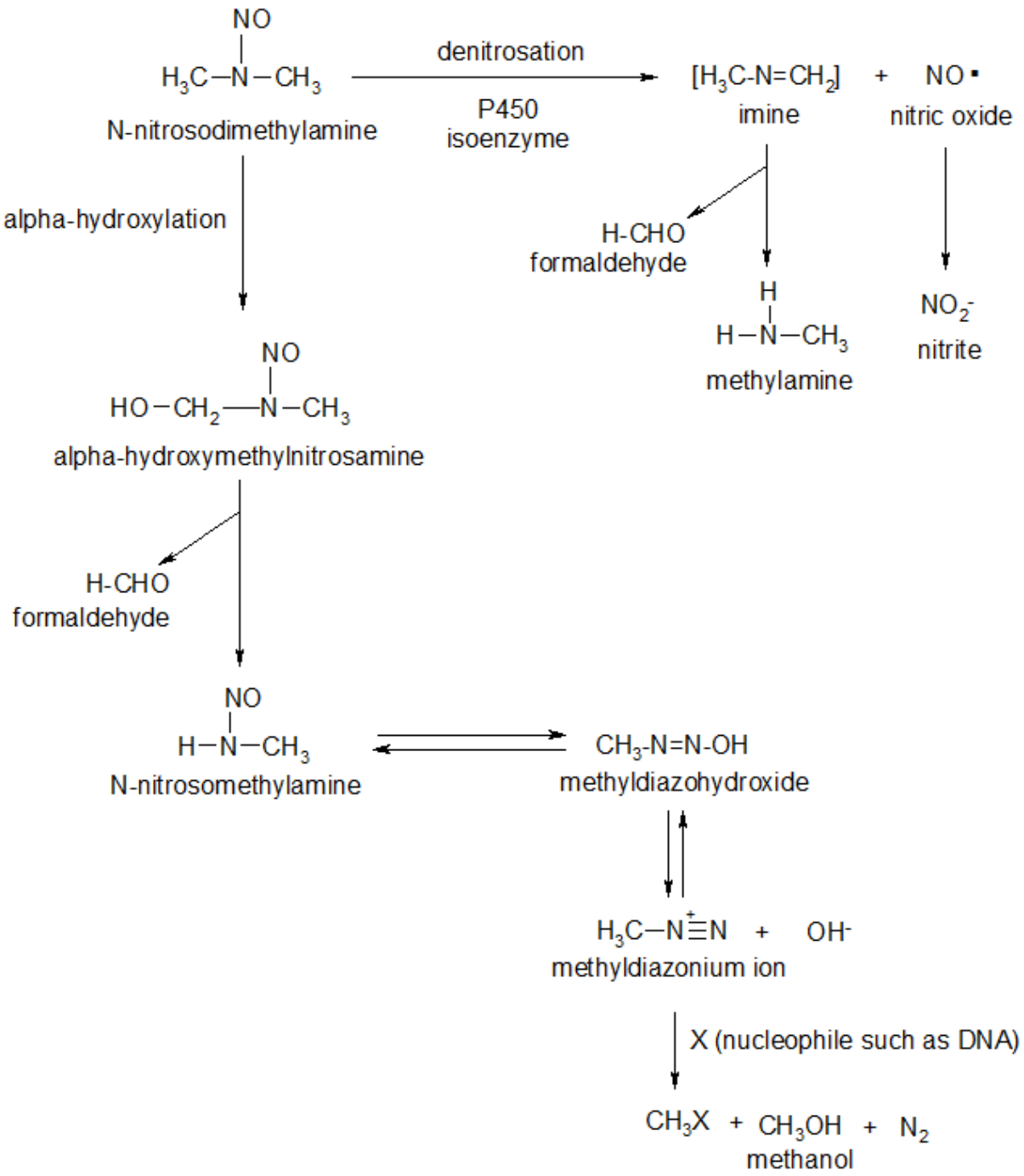
Metabolism of NDMA involves two pathways: α-hydroxylation or denitrosation. It is primarily the hydroxylation pathway that is believed to yield toxic metabolites responsible for liver toxicity and carcinogenicity (George et al. 2019; WHO 2008). Denitrosation of NDMA, yielding formaldehyde (an alkylating agent) and monomethylamine, has also been demonstrated. In rats exposed to doses of ~1 mg/kg NDMA orally, measurement of monomethylamine in blood showed that denitrosation accounted for approximately 21% of total NDMA elimination (Streeter et al. 1990a). Urinary excretion of labelled methylamine was also observed after i.v. administration of ^{14}C-NDMA to rats (Keefer et al. 1987), and methylamine was detected in human liver microsomes exposed to NDMA (Yoo et al. 1988).

α-Hydroxylation of NDMA is catalyzed by cytochrome p450 isozymes, forming α-hydroxymethyl-nitrosamine, which decomposes to monomethylnitrosamine and formaldehyde (George et al. 2019; WHO 2008). Monomethylnitrosamine is unstable and is non-enzymatically converted to formaldehyde and the reactive methyldiazonium ion. Formaldehyde is subsequently oxidized to carbon dioxide or reduced to form methanol. The methyldiazonium ion is an alkylating agent that methylates macromolecules including nucleic acids and proteins (Magee and Hultin 1962).

As discussed in Section 2.9, both formaldehyde and methanol are toxic to the liver and are believed to play a role in the hepatic effects of NDMA. However, the most toxic metabolite is believed to be the methyldiazonium ion. For example, *in vitro* experiments in rat hepatocytes exposed to metabolites of NDMA showed that monomethylamine, formaldehyde, and methanol did not produce cytotoxicity comparable to the parent compound, while a precursor of the methanediazonium ion produced cytotoxicity equivalent to that induced by NDMA (Lee et al. 1996).

The metabolism of NDMA is summarized in Figure 3-1.

Figure 3-1. Metabolism of N-Nitrosodimethylamine



Sources: George et al. 2019; Haggerty and Holsapple 1990; Keefer et al. 1987; Lee et al. 1996; Streeter et al. 1990a; Yoo et al. 1988

In vitro assays have shown that several CYP isozymes are involved in the α-hydroxylation of NDMA, but the enzyme that most efficiently catalyzes this reaction is CYP2E1 (Yang et al. 1985, 1990; Yoo et al. 1988, 1990; Sulc et al. 2004). Sulc et al. (2010) compared the kinetics of NDMA hydroxylation by purified CYP2B4, CYP3A6, and CYP2E1 isolated from rabbit liver after pretreatment with specific enzyme inducers. The lowest Km (Michales-Menten constant, 7.5 µmol/L) and highest Vmax (maximal reaction velocity, 3.8 nmol formaldehyde/minute/nmol CYP) were observed for CYP2E1, but both CYP2B4 (Km of 180 µmol/L; Vmax of 1.8 nmol formaldehyde/minute/nmol CYP) and CYP3A6 (Km of 30 µmol/L; Vmax of 1.3 nmol formaldehyde/minute/nmol CYP) were also active in hydroxylating NDMA (Sulc et al. 2010). Similar results were seen in liver microsomes from rabbits pretreated with ethanol or phenobarbital; microsomes pretreated with ethanol (increasing primarily CYP2E1 activity) exhibited the lower Km and higher Vmax compared with those pretreated with phenobarbital (increasing primarily CYP2B4 activity) (Sulc et al. 2004). Using pretreatments to inhibit enzymes of the CYP2A family, Pelkonen et al. (1994) observed only weak inhibition of NDMA metabolism in liver microsomes isolated from the pretreated hamsters, suggesting little to no role for these enzymes in its metabolism in hamsters.

Human liver microsomes have been shown to demethylate NDMA, with substantial interindividual variation in the extent of metabolism (Bellec et al. 1996; Camus et al. 1993). In genetically modified human cells stably expressing specific human P450s, CYP2E1 was also shown to be the primary isozyme involved in demethylation of NDMA (measured as production of formaldehyde) (Bellec et al. 1996). In this study, CYPs 1A2, 2A6, 2C8, 2C9, 2D6, and 3A4 were also shown to produce measurable formaldehyde, while CYPs 1A1 and 2C19 did not (Bellec et al. 1996).

Fujita and Kamataki (2001) tested the mutagenicity of NDMA in Ames tests using genetically modified *Salmonella typhimurium* strains expressing 11 different CYP enzymes. The investigators confirmed that metabolism by CYP2E1 yielded a mutagenic response to NDMA; none of the other enzymes did.

In vivo studies have indicated that metabolism of NDMA is saturable in swine and beagles. After oral exposure in both species, measurements of the area under the blood NDMA concentration:time curve were not proportional to dose suggesting saturation of metabolism at doses of about 5 mg/kg (Gombar et al. 1987, 1988). This finding is supported by evidence for competitive inhibition of NDMA metabolism by ethanol. When mice and patas monkeys were co-exposed to ethanol and NDMA by oral administration, greater quantities of NDMA escaped first-pass metabolism, presumably due to ethanol's competitive inhibition of CYP2E1 (Anderson et al. 1986, 1992b). Metabolic saturation is also supported

by evidence that different forms of enzymes appear to be responsible for NDMA metabolism at differing doses (Kroeger-Koepke and Michejda 1979; Lotlikar et al. 1978).

Studies of NDMA toxicokinetics in multiple species (rats, mice, hamsters, dogs, swine, and patas monkeys) exposed orally have shown that clearance of NDMA from blood is primarily via metabolism (Anderson et al. 1992b; Gombar et al. 1987, 1988, 1990; Hino et al. 2000; Streeter et al. 1990a, 1990b).

No studies were located regarding the metabolism of NDMA following inhalation exposure of humans or animals.

No studies were located regarding the metabolism of NDMA following oral exposure of humans.

Hepatic extraction of NDMA was dose-dependent in pigs. After pigs were given NDMA orally at doses of 0.1, 1, or 10 mg/kg, the concentrations of unchanged NDMA were measured in hepatic portal blood (entering the liver from the gastrointestinal tract) and hepatic blood (exiting the liver) at various time points up to 10 hours after dosing (Harrington et al. 1987, 1990). At the highest dose, the maximum concentration of NDMA in hepatic blood was approximately half that of the concentration in portal blood. At lower doses, greater proportions of NDMA were metabolized, leading to smaller ratios of hepatic:portal blood concentration (about 1:4 at 1 mg/kg, and approaching 1:10 at 0.1 mg/kg, based on visual inspection of data presented graphically). Hepatic extraction was nearly complete at the lowest dose. These data suggest that the level of unchanged NDMA reaching the bloodstream is dependent on dose in pigs, and that at low doses (0.1 mg/kg), most NDMA is metabolized in the liver.

No studies were located regarding the metabolism of NDMA following dermal exposure of humans or animals.

3.1.4 Excretion

NDMA was not detected (detection limit of 10 ng/L) in the urine of 59 nonsmokers who consumed drinking water containing 2 mg nitrate/L (geometric mean) (Levallois et al. 2000). Only one of the eight nitrosamines analyzed in the urine samples was detected: N-nitrosopiperidine (Levallois et al. 2000). Labelled CO_2 can be detected in the exhaled air 1 hour after i.p. administration of 5 mg/kg ^{14}C-NDMA to rats (Phillips et al. 1975). Hemminki (1982) administered labelled NDMA by i.p. injection to rats and was able to detect three main radioactive fractions in the urine over a period of 5 days. Fraction I was

composed of radioactive amino acids, fraction II was composed of allantoin and a metabolite of thiazolidine-4-carboxylic acid, and fraction III was composed of 7-methylguanine.

Klein and Schmezer (1984) reported that 10–30% of NDMA is excreted by exhalation after exposing rats to the chemical during 10 minutes by endotracheal intubation. In beagle dogs, 23% of the administered radioactive label is exhaled in 30 minutes after a 3-hour inhalation exposure (CARB 1986).

Very little human data are available on the excretion of NDMA after oral exposure. Spiegelhalder et al. (1982) reported that in a 24-hour period, volunteers excreted in the urine between 0.5 and 2.4% of an ingested dose of 12–30 pg of NDMA added to drinking fluids containing ethanol.

Only small amounts of unchanged NDMA were recovered in the urine of rats up to 24 hours after a single oral dose of 50 mg or i.v. dose of 500 mg/kg; the cumulative amounts excreted represented about 1.7% of the oral dose and 4.7–11% of the i.v. dose (Magee 1956). No NDMA was detected in feces samples over the same time frame (Magee 1956). Swann et al. (1984) did not detect labelled NDMA in the urine of rats after oral administration of 30 µg/kg of ^{14}C-NDMA in water. After i.v. administration of 1 mg/kg NDMA, rats excreted 0.11% of the dose as unchanged NDMA in urine (Streeter et al. 1990a). No unchanged NDMA was detected in urine of beagles in the 24 hours after i.v. dose of 1 mg/kg (Gombar et al. 1987) or in the urine of hamsters in 72 hours after an i.v. dose of 0.31 mg/kg (Streeter et al. 1990b). In patas monkeys given 1 mg/kg NDMA (Anderson et al. 1992b) and pigs given 10 mg/kg (Harrington et al. 1987, 1990) by i.v. administration, trace amounts of unchanged NDMA were detected in urine.

Phillips et al. (1975) determined that after administration of a single oral dose of 5 mg of ^{14}C-NDMA to female rats, the maximum rate of $^{14}CO_2$ production was 12.4% of the dose/hour, and that 48% of the dose could be recovered as $^{14}CO_2$ in the exhaled air in 7 hours and 5.7% as ^{14}C (total label) in a 24-hour urine sample. Excretion of monomethylamine resulting from NDMA denitrosation was demonstrated in rats given ^{14}C-NDMA intravenously (1 mg/kg). During the 72 hours after injection, 5.63% of the administered dose was excreted as monomethylamine (Streeter et al. 1990a). The authors estimated that monomethylamine accounted for as much as 21% of total NDMA elimination in rats.

Harrington et al. (1987, 1990) demonstrated that NDMA is secreted into the bile of pigs after intraarterial injection of a 10 mg/kg dose. Concentrations in bile reached blood levels within an hour after injection and peaked about 2 hours after injection. Biliary levels of NDMA declined at approximately the same rate as blood levels (Harrington et al. 1987, 1990). In rats exposed to NDMA by i.p. injection

(20 mg/kg), biliary excretion of NDMA accounted for 2.74–4.38% of the administered dose (Alaneme and Maduagwu 2004). Biliary excretion was lowest in rats given a very low protein diet (3.4%) and highest in those given a high protein diet (64%) (Alaneme and Maduagwu 2004).

Enterosalivary circulation of NDMA was observed in a study of beagle dogs (Hino et al. 2000). NDMA was detected in the dogs' saliva 15 minutes after oral or i.v. doses of 2 mg/kg NDMA, and salivary concentrations were comparable to or higher than plasma concentrations (Hino et al. 2000). After i.v. exposure, the concentration in salivary showed monoexponential decline similar to that seen in plasma. However, after oral exposure, plasma and saliva concentrations both remained relatively constant during the 2 hours following exposure when measurements were made, suggesting reabsorption from swallowed saliva. The study authors estimated that salivary excretion accounted for only about 2.4% of total body clearance of NDMA (Hino et al. 2000).

No studies were located regarding the excretion of NDMA following dermal exposure of humans or animals.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

PBPK modeling studies for NDMA were not located in the literature reviewed.

3.1.6 Animal-to-Human Extrapolations

There are large interspecies differences in the systemic availability of unmetabolized NDMA, ranging from 8% in rats to 93% in beagles (based on AUC for unchanged NDMA in blood after oral and i.v. dosing; Gombar et al. 1987, 1988, 1990; Streeter et al. 1990a, 1990b). In patas monkeys, the only

nonhuman primate tested, systemic availability was 49%. Based on the systemic availability estimates, it has been suggested that in larger species, a significant portion of the NDMA dose escapes first-pass metabolism and is metabolized elsewhere (based on observation that systemic clearance rates normalized to body weight are similar across species despite differing hepatic extraction ratios) (Gombar et al. 1990). Because toxicity is induced by a metabolite, there may be other target organ(s) in larger species depending on where metabolism occurs. No data on other potential target organs in larger species are available, and epidemiological studies are not adequate to identify a target organ for oral exposure to NDMA in humans because they have focused on associations with cancer.

The primary CYP involved in demethylation of NDMA is CYP2E1 in both laboratory animals and in human liver extracts (see Section 3.1.3), demonstrating that humans are capable of NDMA bioactivation.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to NDMA are discussed in Section 5.7, Populations with Potentially High Exposures.

Data on NDMA levels measured in human infant blood or tissues have not been reported. Infants may be exposed to NDMA in infant formula, drinking water, food, and air (particularly in indoor environments with ambient tobacco smoke). Infants may also be exposed to very low levels of leaching from rubber baby bottle nipples or pacifiers; Sections 5.5 and 5.6 provide further information on these potential exposures. Two older studies (Lakritz and Pensabene 1984; Uibu et al. 1996) reported detections of

NDMA in human breast milk, but more recent data are not available. Studies of animals exposed during pregnancy demonstrate that NDMA crosses the placenta (Althoff et al. 1977; Chhabra et al. 1995) and can be excreted in breast milk (Chhabra et al. 2000; Diaz Gomez et al. 1986).

The susceptibility of infants and children to NDMA toxicity is complex, with some factors suggesting decreased susceptibility (e.g., reduced metabolic activation) and others suggesting increased susceptibility (e.g., reduced ability to repair DNA adducts).

Age-Related Pharmacokinetic Differences. Bioactivation of NDMA results from its oxidative metabolism, primarily via CYP2E1. The expression and activity of CYP2E1 varies by age, with lowest levels seen in infants. Vieira et al. (1996) evaluated CYP2E1 protein and ribonucleic acid (RNA) levels in hepatic microsomes from humans of various ages. The study authors observed no detectable CYP2E1 protein, and very little messenger RNA (mRNA), in hepatic microsomes from human fetuses. Within the first 24 hours after birth, CYP2E1 levels reached approximately 20% of adult activity; levels increased steadily over the first year of life, reaching about 80% of adult levels by 1 year of age (Vieira et al. 1996). Few differences in CYP2E1 activity are seen among children and adults. In a study of older children and adults, Blanco et al. (2000) observed no significant difference in CYP2E1 activity toward ethoxycoumarin in livers from humans <10, 10–60, or >60 years old.

Age-related differences in NDMA metabolic capacity have been seen in animals. No CYP2E1 protein was detected in livers from rat fetuses obtained at GD 10 or 20, but CYP2E1 was detectable in neonatal (4-day-old) rat liver (Borlakoglu et al. 1993). CYP2E1 mRNA levels did not differ with age. NDMA-demethylase activity was not detectable in fetal rat liver microsomes but increased more than 3-fold between PND 4 and 60 (Borlakoglu et al. 1993). In mice, hepatic NDMA-demethylase activity was present as early as GD 16 (3% of adult levels) and increased steadily after birth, reaching adult levels by PND 7 (Anderson et al. 2000; Jannetti and Anderson 1981). Yoo et al. (1987) observed increased NDMA-demethylase activity (and mutagenicity) in liver microsomes from weanling rats compared with adult rats; no age differences were seen in hamster liver microsomes.

Consumption of alcohol during pregnancy may increase the bioactivation of NDMA in infants. When pregnant rats were exposed to ethanol, hepatic CYP2E1 content was significantly increased in both maternal and fetal liver; the increase in the fetal liver was more than 2-fold compared with fetuses of rats that did not receive ethanol (Carpenter et al. 1997). Fetal liver microsomes from dams exposed to ethanol

also showed increased N-nitrosodimethylamine demethylase activity (1.5-fold higher compared with controls) (Carpenter et al. 1997)

Age-Related Differences in Susceptibility. Factors that may increase the susceptibility of infants and children (relative to adults) to the toxic effects of NDMA include increased cell proliferation associated with growth and lower capacity to repair DNA adducts, both of which may lead to greater mutation frequency in developing organisms. Coccia et al. (1988) observed markedly higher (>4-fold) levels of O^6-methylguanine adducts in newborn mice compared with adult mice after i.p. administration of the same dose of NDMA. These authors also measured the activity of O^6-methylguanine DNA methyltransferase (an enzyme that repairs DNA adducts induced by alkylating agents) and reported levels almost 4 times higher in adult mice compared with newborn mice, consistent with the differences in adduct levels (Coccia et al. 1988).

There is some evidence that younger animals may be more susceptible to NDMA mutagenicity. In one study, NDMA administration increased the mutation frequency in the livers of Big Blue (lacI) mice when administered as five daily doses of 2 mg/kg/day beginning at 3 weeks of age, but not when administered under the same conditions beginning at 6 weeks of age (reviewed by Lambert et al. 2005). The authors suggested that the difference in response could stem from age-related differences in metabolic activation, DNA adduct removal rates, or rates of mutation fixation. No difference in the fold-change in mutation frequency was observed in lac I transgenic mice exposed to a single oral dose of 10 mg/kg NDMA at 8–12 or 72 weeks of age (Tinwell et al. 1994a).

Transgenerational Effects. Available studies have not shown evidence for NDMA-induced germ cell mutagenicity or dominant lethal mutations (Doolittle et al. 1984; Epstein et al. 1972; Stott and Watanabe 1980); however, two studies suggested that NDMA may induce transplacental carcinogenesis after oral administration in rats (Aleksandrov 1974) or i.p. administration in mice (Anderson et al. 1989). Aleksandrov (1974) did not report data in control animals or specific tumor types, limiting the utility of this study. When pregnant C3H/HeNCr MTV- mice were treated by i.p. administration on GD 16 or 19, NDMA induced significant increases in hepatocellular carcinomas in male and female offspring and a significant increase in sarcomas in male offspring (Anderson et al. 1989). In contrast, Beebe et al. (1993) did not observe increases in lung or liver tumors in offspring of pregnant Swiss mice exposed by the same route at a higher dose on GD 19. Beebe et al. (1993) sacrificed the offspring at 1 year of age, while Anderson et al. (1989) did not sacrifice animals until they were moribund (average age 17–21 months), which may explain the disparate findings.

Other Factors Influencing Susceptibility. Because the liver is the primary target of NDMA toxicity, individuals with liver disease may be at increased risk from NDMA exposure. In addition, a recent study showed that infection of hamsters with cagA+ *H. pylori* or *Opisthorchis viverrine* (human liver fluke) prior to NDMA exposure resulted in increased cholangitis, hepatic lymphoid follicles, cholangiofibrosis, and cholangiocarcinoma incidence relative to NDMA alone (Dangtakot et al. 2021). Effects seen in the group infected with liver fluke were more severe than those seen in the group infected with *H. pylori.* While liver fluke infection is not common in the United States, *H. pylori* (all strains) infection is; Hooi et al. (2017) estimated the prevalence of infection in the United States to be 35.6%.

Interindividual variability in the expression and/or activity of CYP2E1 and other enzymes that bioactivate NDMA may lead to variable susceptibility to NDMA effects; however, there are no *in vivo* data in humans investigating this potential. Increased CYP2E1 activity has been demonstrated in obese individuals (Emery et al. 2003) and moderate to heavy consumers of alcohol (Liangpunsakul et al. 2005), suggesting a potential for greater bioactivation of NDMA in these individuals. Individuals consuming alcohol may be at greater risk of extrahepatic effects from NDMA exposure, based on studies of animals co-exposed to ethanol and NDMA via oral administration; these studies are discussed in Section 3.4. In animals, ethanol competitively inhibits the metabolic activation of NDMA in the liver, leading to greater systemic availability of unchanged NDMA and enhanced metabolic activation of NDMA in other tissues. Similar results may occur with other drugs that are metabolized by CYP2E1.

Polymorphisms in MGMT, the enzyme that repairs O^6-methylguanine adducts that are associated with cancer, may also alter the susceptibility of individuals to NDMA carcinogenicity. The importance of this enzyme in protecting against NDMA-induced cancers was shown in animals: MGMT knock-out mice exhibited higher incidences of lung and liver tumors compared with wild-type mice after i.p. exposure to NDMA (Iwakuma et al. 1997). Similarly, a recent study (Kay et al. 2021) showing that both the absence and the overexpression of *Aag* gene (encoding the alkyladenine DNA glycosylase) increase NDMA-induced effects (cancers and lethality, respectively) suggests that polymorphisms in the *Aag* gene may profoundly impact individual susceptibility to both cancer and other toxic effects of NDMA.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to NDMA are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for NDMA from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by NDMA are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Biomarkers of internal exposure to NDMA include urinary methylmercapturic acid and methylated DNA adducts. It should be noted that neither of these biomarkers distinguishes between exogenous and endogenously formed NDMA, and neither is specific to NDMA (other methylating agents will yield methylmercapturic acid and methylated DNA adducts).

As discussed in Section 3.1.2, metabolism of NDMA yields the alkylating methyldiazonium ion, which may be conjugated with glutathione and excreted as methylmercapturic acid. Recent advances in analytical techniques have enabled the detection of low levels of methylmercapturic acid. Scherer et al. (2010) developed a method using liquid chromatography (LC)-tandem mass spectrometry (MS/MS) analysis with positive electrospray ionization to measure methylmercapturic acid in urine along with other mercapturic acid products of tobacco-derived alkylating agents. Methylmercapturic acid was measured as a marker of exposure to all methylating agents, including NDMA as well as methyl halides and NNK (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone). The method was tested on urine from a group of 100 adult smokers of conventional cigarettes. In a clinic setting, these adults either continued smoking conventional cigarettes or were switched to an electronic cigarette or stopped smoking for 8 days and changes in the urinary levels of alkylated mercapturic acids were measured. While the levels of other tobacco-derived mercapturic acids (2-cyanoethylmercapturic acid and 2-hydroxyethylmercapturic acid) were substantially reduced in groups switching to electronic cigarettes or discontinuing smoking, urinary levels of methylmercapturic acid were not affected. The authors concluded that methylmercapturic acid was not a suitable biomarker for exposure to tobacco-derived methylating agents, speculating that endogenously produced methylating agents (such as NDMA and other endogenously produced nitrosamines) accounted for most of the methylmercapturic acid, masking the smaller contribution of tobacco-derived exposures (Scherer et al. 2010).

The methyldiazonium ion metabolite of NDMA also reacts with DNA to form methylated DNA adducts. Methylated DNA adducts are not specific to NDMA, as they may also occur as a result of exposure to other alkylating agents, including other nitrosamines that are endogenously produced (e.g., N-methyl-N-nitrosourea) or commonly encountered (N-nitroso-N-dimethylamine), as well as chemotherapeutic agents such as temozolomide and procarbazine. The primary methylated DNA adducts resulting from exposure to nitrosamines such as NDMA are, in order of declining prevalence, N^7-methylguanine, O^6-methylguanine, N^3-methyladenine, and O^4-methylthymine (Gallo et al. 2008). The O^6-methylguanine adduct is postulated to derive primarily from endogenous production of NDMA, and measurements in

humans have been used as one method to estimate endogenous production (Georgiadis et al. 2000; Hrudey et al. 2013). In a review examining the use of these adducts as biomarkers of nitrosamine exposure, Gallo et al. (2008) concluded that measurement of N^7- and O^6-methylguanine adducts in lymphocytes could be used as biomarkers for exogenous and endogenous nitrosamine exposure for the purpose of epidemiology studies. Immunoassay methods are recommended due to increased sensitivity and high throughput potential (Gallo et al. 2008; Georgiadis et al. 2010). It was noted, however, that these adducts are short-lived and may not represent long-term exposure (Gallo et al. 2008). Animal studies have demonstrated the presence of O^6-methylguanine adducts in liver (Souliotis et al. 1995, 2002), blood leukocytes (Kyrtopoulos 1998; Souliotis et al. 1995, 2002), and fetal tissues following oral exposure to NDMA (Chhabra et al. 1995). A discussion of the relevance of these DNA adducts to carcinogenesis is provided above in *Mechanisms* under Section 2.19 (Cancer).

3.3.2 Biomarkers of Effect

Methylated DNA adducts (described further as biomarkers of exposure in Section 3.3.1) may be considered biomarkers of preneoplastic changes induced by NDMA or other methylating agents. In particular, the O^6-methylguanine adduct induced by NDMA exposure is persistent and is known to induce mutations leading to tumors. Mutations (consisting of G:C to A:T transitions) derived from these adducts have been detected in lung tumors of mice exposed to NDMA and in transgenic mice exposed to NDMA (reviewed by WHO 2008).

NDMA has been used as a model for liver fibrosis and cancer in studies searching for biomarkers for these endpoints. Saha et al. (2007) evaluated the utility of several biomarkers for liver fibrosis in rats treated with NDMA by i.p. injection. These investigators observed significant correlations between the severity of liver histopathology and declining plasma protein C (an anti-inflammatory protein produced in the liver), C-reactive protein, haptoglobulin, albumin, and total protein. In addition, fibrosis severity was correlated with higher plasma levels of cytokines and chemokines including monocyte chemoattractant proteins 1 and 3 (MCP-1 and MCP-3) and macrophage-colony-stimulating-factor (M-CSF); increased circulating neutrophils; and elevated serum hyaluronic acid levels (Saha et al. 2007). George and Stern (2004) identified serum hyaluronan and hyaluronidase as early biomarkers of NDMA-induced hepatotoxicity. Both markers were markedly increased in the first 2 days of a 7-day exposure regimen; 2-fold increases in AST and ALT were first seen on day 3 (George and Stern 2004).

Kma and Sharan (2014) suggested that poly-ADP ribosylation (PAR, a post-translational modification of chromosomal proteins) of blood lymphocyte histones may represent a sensitive biomarker for cancer detection after observing time-dependent decline in PAR of specific histones in mice during exposure to carcinogenic doses of NDMA. The decline in PAR histones was correlated with changes in the superstructure (relaxation) of genomic DNA, making it more susceptible to degradation and, presumably, carcinogenicity. However, there is no indication that histone PAR levels are specific to NDMA.

3.4 INTERACTIONS WITH OTHER CHEMICALS

NDMA can be formed endogenously via acid-catalyzed nitrosation of amine precursors in the gastrointestinal tract, especially the stomach (Mirvish 1975). NDMA formation in the stomach has also been demonstrated in rats and guinea pigs treated with dimethylamino-containing drugs and sodium nitrite (Omori et al. 1979). Rao and co-authors (1982) detected small amounts of NDMA in human saliva incubated for 1 hour with aminopyrene or oxytetracycline at pH 3 or 4; concentrations ranged from 5 to 10 μg/mL (Rao et al. 1982). Addition of food constituents to the saliva generally inhibited the formation of NDMA. NDMA formation in the saliva was increased by chemicals such as chlorogenic acid, which is found in coffee, and decreased by caffeic acid, tannic acid, and ascorbic acid, which are found in coffee, tea, and citrus fruits, respectively.

Nutritional factors can influence NDMA-induced liver effects. Rats exposed to NDMA (in water) along with diets rich in proteins, cysteine, or choline exhibited less hepatic toxicity and greater regenerative activity compared to rats exposed to NDMA with a standard diet (Khanna and Puri 1966). In rats given NDMA with diets deficient in proteins, cysteine, or choline, hepatotoxicity was prolonged: there was minimal regenerative activity after 12 weeks, while the group receiving NDMA with the standard diet showed marked regenerative activity and pseudolobule formation at this time. Some of the liver effects were attributable to the nutritional deficiencies. Animals fed diets low in protein or cysteine without NDMA developed vascular congestion and necrosis after 12 weeks, and those on choline-deficient feed developed fatty metamorphosis and central vein congestion after 4 weeks (Khanna and Puri 1966).

Alcohol has been shown to competitively inhibit NDMA metabolic activation via CYP2E1, leading to mitigation of liver effects but potentiation of extrahepatic tumorigenicity in animals exposed to NDMA orally. In mice co-exposed to 50 ppm NDMA and 10–30% ethanol in drinking water, blood and tissue levels of NDMA were higher (≥10-fold in some cases) than in mice exposed only to NDMA, reflecting decreased metabolism (Anderson et al. 1986). Liver hemorrhage and necrosis were less severe in mice

co-treated with 10% ethanol compared with 50 ppm NDMA alone (Anderson et al. 1986). In contrast, when NDMA was administered by i.p. injection in rats pretreated or co-treated with alcohol (ethanol or isopropanol), the effects on the liver were more severe with the alcohol than without it (Lorr et al. 1984; Ma et al. 1991; Maling et al. 1975), presumably due to induction of CYP2E1 and enhanced metabolic activation of NDMA. In humans, moderate to heavy consumption of alcohol increases hepatic CYP2E1 activity (Liangpunsakul et al. 2005), which may increase the bioactivation of NDMA and its toxicity in these individuals.

Ethanol enhanced the tumorigenic effect of NDMA in the lungs and kidneys when both were administered orally in mice, either as a single dose or for 16–72 weeks via drinking water (Anderson 1988; Anderson et al. 1992a). When NDMA was administered by other routes (intravenous, intraperitoneal, or subcutaneous injection), ethanol did not influence tumor incidence or counts; thus, the increase in tumorigenesis was attributable to inhibition of first-pass clearance in the liver, enabling greater quantities of NDMA to circulate to other organs and tissues. Toxicokinetic studies in patas monkeys demonstrated a similar effect of ethanol. In this species, oral administration of NDMA and ethanol resulted in 10–50-fold increases in the area under the blood concentration:time curve and 4–13-fold increases in mean residence time compared with oral administration of NDMA alone (Anderson et al. 1992b). In rats, oral intake of alcohol and NDMA during lactation increased the formation of O^6-methylguanine adducts in offspring kidney and lung, while decreasing adducts in offspring liver (Chhabra et al. 2000). These studies demonstrate that in both laboratory rodents and primates, ethanol increases the systemic availability of orally-administered NDMA and the potential for extrahepatic toxicity, mutagenicity, or carcinogenicity. It is likely that other drugs or chemical that are metabolized by CYP2E1 may have similar effects.

Interactions between NDMA and heavy metals may vary depending on the valence state, compound, dose, route and timing of administration, and potentially the health effect of interest, as heavy metals can both induce and deplete levels of various antioxidants. Hexavalent chromium coexposure resulted in the increased formation of O^6-methylguanine DNA adducts in the livers of rats exposed to NDMA in drinking water (compared with NDMA alone) and decreased hepatic GSH levels (Ma et al. 2015). Pretreatment of rats with cadmium or zinc to induce metallothionein (a scavenger of reactive oxygen species [ROS]) before NDMA exposure resulted in increased levels of GSH and reductions in markers of toxicity including methemoglobin and nitric oxides (Rana and Kumar 2000, 2001). Consistent with a protective effect of zinc, NDMA induced higher incidences of stomach cancer in rats fed diets low in zinc than in those fed normal diets (Ng et al. 1984). However, Wade et al. (1987) observed synergistic effects

of cadmium and NDMA on kidney tumor incidence in rats when cadmium was administered after NDMA. Selenium pretreatment before NDMA exposure increased plasma AST levels without affecting the severity of hepatic necrosis, while decreasing plasma and liver concentrations of vitamin E (Skaare and Nafstad 1978). Rats fed diets low in copper developed more kidney tumors from NDMA than rats fed normal diets (Carlton and Price 1973). In contrast, rats given NDMA and cupric acetate had fewer tumors than rats given NDMA (Yamane et al. 1984).

Subcutaneous administration of aminoacetonitrile (200 mg/kg) to female Wistar rats treated at the same time with 30 mg/kg NDMA (i.p.) decreased the metabolism of NDMA (as measured by clearance from the blood) as well as its methylation of nucleic acids in the liver and kidney (Fiume et al. 1970).

Klein et al. (1989) examined the influence of SO_2 and NO_X on NDMA-induced carcinogenicity in a long-term study of rats exposed by inhalation. The authors characterized their publication as an interim report, but a final report was not located in the published literature. Comparisons between groups treated with NDMA alone (0.2 ppm) or co-treated with 6 ppm of SO_2 or NO_X did not show any significant differences in body weight (data not reported) or incidences of nasal tumors after 20 months of exposure (Klein et al. 1989). Mortality was slightly higher in the group co-treated with NO_X and NDMA compared with NDMA alone (9/36 versus 4/36) but the difference was not statistically significant.

A number of studies have shown that liver fibrosis and cirrhosis induced by NDMA can alter the pharmacokinetics of drugs in laboratory animals. A review of such interactions by Lee and Oh (2015) reported effects of NDMA-induced cirrhosis in rats on plasma protein binding and clearance of drugs with a wide range of hepatic extraction ratios, including oltipraz (used to treat schistosomiasis), chlorzoxazone (a muscle relaxant), sildenafil (used to treat erectile dysfunction), omeprazole (a proton pump inhibitor used for gastric reflux), and DL-Praeruptorin A (a calcium influx blocker). In general, cirrhotic rats exhibited lower protein-binding and lower non-renal clearance rates for these medications. The alterations in non-renal clearance observed in the NDMA-treated rats were attributed to changes in hepatic intrinsic clearance due to changes in CYP expression in the liver, the fraction of free (unbound) drug in plasma, and hepatic blood flow. In cirrhotic rats, for example, expression of CYP2B1/2, CYP2C11, CYP2E1, and the CYP1A, CYP2D, and CYP3A subfamilies were significantly decreased compared with controls (Lee and Oh 2015). Effects on drug clearance were also noted in dogs with liver injury induced by oral administration of NDMA: clearance of antipyrine (a non-narcotic analgesic) and caffeine decreased with progressive liver disease (Boothe et al. 1994).

Numerous studies have been conducted to identify drugs, nutrients, and/or supplements that could be used to treat human liver fibrosis or cirrhosis using NDMA administration in rats as an animal model. In these studies, NDMA was administered by i.p. injection; thus, their relevance to human exposure to NDMA is limited. Many of these studies showed that coadministration of antioxidants can mitigate the hepatotoxicity of NDMA, which is consistent with oxidative stress as one mechanism by which NDMA induces liver injury (see Section 2.9). Some example antioxidants shown to modulate NDMA liver toxicity include resveratrol (Abdu and Al-Bogami 2019; Hong et al. 2010), gallic acid (Chen et al. 2018), silymarin and curcumin (George et al. 2006), hesperidin (Elshazly and Mahmoud 2014), and vitamin E (Skaare and Nafstad 1978). Other compounds that may mitigate liver effects of NDMA include those that decrease the activity of enzymes that metabolically activate NDMA. Examples include the adrenergic antagonist dibenamine (Stripp et al. 1974), aminoacetonitrile (Fiume et al. 1970), and dimethylformamide (Heath 1962).

Little information is available to evaluate potential synergistic or antagonistic effects of NDMA and other chemicals on noncarcinogenic effects on organs other than the liver. Administration of four daily oral doses of 3.75 mg/kg/day NDMA increased the sedative effects of pentobarbital; sleeping time increased 39% over that of control mice (Nishie et al. 1972).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of NDMA are listed in Table 4-1.

Table 4-1. Chemical Identity of N-Nitrosodimethylamine

Characteristic	Information	Reference
Chemical name	Methanamine, N-methyl-N-nitroso	O'Neil 2013
Synonym(s) and registered trade name(s)	N-Nitrosodimethylamine; dimethylnitrosamine; DMNA; DMN; NDMA	O'Neil 2013
Chemical formula	$C_2H_6N_2O$	O'Neil 2013
Chemical structure	$(CH_3)_2N–N=O$	O'Neil 2013
CAS Registry Number	62-75-9	O'Neil 2013

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of NDMA are presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of N-Nitrosodimethylamine

Property	Information	Reference
Molecular weight	74.08	Weast 1983
Color	Yellow	IARC 1978
Physical state	Liquid	IARC 1978
Melting point	-25°C	Lyman 1985
Boiling point	154°C	Weast 1983
Density at 20°C	1.0059 (specific gravity, 20/4°C)	EPA 2014a
Odor	No distinct odor	Frank and Berry 1981
Odor threshold:		
Water	Not available	
Air	Not available	
Solubility:		
Water at 20°C	Miscible	Mirvish et al. 1976
Organic solvents	Soluble in alcohol, ether, other organic solvents	IARC 1978; Weast 1983

Table 4-2. Physical and Chemical Properties of N-Nitrosodimethylamine

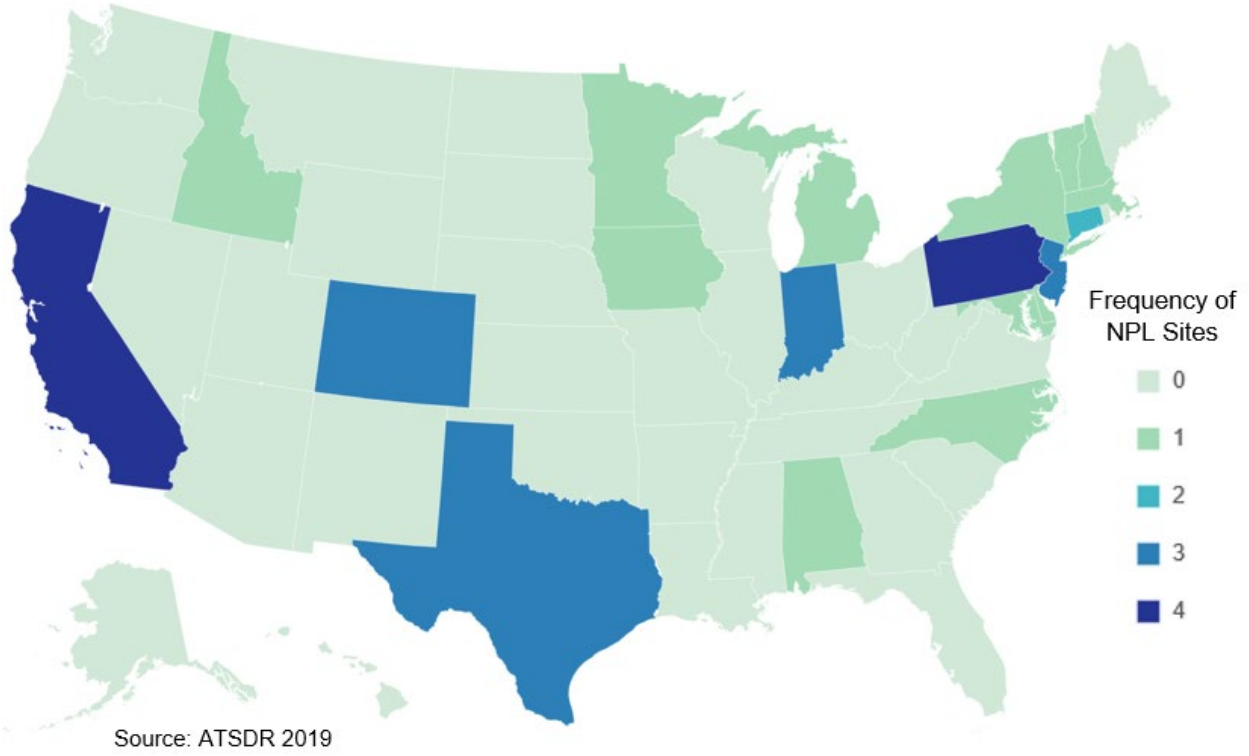
Partition coefficients:		
Log K_{ow}	-0.57	Hansch et al. 1995
Log K_{oc}	1.07 (estimated using Equation 4-8)	Lyman 1982
Vapor pressure at 20°C	2.7 mmHg	Klein 1982
Henry's law constant	$1.99x10^{-6}$ atm-m^3/mol at 37°C; $2.63x10^{-7}$ atm-m^3/mol at 20°C (estimated using vapor pressure and water solubility data); $2.24x10^{-6}$ atm-m^3/mol at 25°C	Haruta et al. 2011; Mirvish et al. 1976
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	ppm (v/v)x3.08=mg/m^3 mg/m^3x0.325=ppm (v/v)	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

NDMA has been identified in at least 34 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which NDMA has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with NDMA Contamination



- NDMA is naturally formed in the body from precursors that normally exist in the body and in foods. The general population may also be exposed to trace amounts of NDMA through ingesting foods containing nitrosamines such as cured or smoked meats and fish; ingesting foods containing alkylamines, which can form NDMA in the stomach; ingesting drinking water or malt beverages containing NDMA; and inhalation of tobacco smoke.

- NDMA has been detected in some prescription and over-the-counter pharmaceutical products (for example, valsartan, ranitidine, and metformin). Many of these substances have been recalled by the U.S. Food and Drug Administration (FDA) or the manufacturers, but exposure could have occurred prior to the recall or through continued use of purchased products.

- Potential occupational exposure to NDMA may occur in leather tanneries; rubber and tire industries; dye manufacturers; soap, detergent, and surfactant industries; foundries; fish-

processing industries; pesticide manufacturers; warehouse and sales rooms (especially for rubber products); and research laboratories where NDMA is synthesized/studied.

- Very low levels of NDMA may form as an unintentional byproduct of the chlorination of drinking water at treatment plants that use chloramines and chlorine for disinfection. NDMA may also be formed in wastewater, but human exposure to wastewater is expected to be very limited.

- NDMA degrades rapidly by direct photolysis. In the absence of sunlight, NDMA will likely undergo biodegradation. NDMA is expected to have high mobility in soil and is unlikely to bioconcentrate in aquatic organisms.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

NDMA is not produced for commercial use in the United States (EPA 2014a) but can be prepared by reaction of nitrous acid with dimethylamine or by addition of acetic acid and sodium.

NDMA and other N-nitrosamines form as unintentional byproducts in water treatment plants using chloramines during the disinfection process. It has also been shown to form during chlorination and ozonation of treated drinking water if certain precursors are present (EPA 2016). NDMA in drinking water has become more prevalent because potable water utilities switched from predominantly free chlorine to chloramines for disinfection purposes in the early 2000s in response to EPA Maximum Contaminant Levels (MCLs) for regulated disinfection byproducts. The goal was to reduce the levels of four halomethanes (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) as well as five haloacetic acids (mono-, di-, and trichloroacetic acid, bromoacetic acid, and dibromoacetic acid), which can form by reaction of chlorine or bromine with natural organic matter. Consequently, NDMA is observed as a disinfection byproduct in chloraminated drinking water systems more than free chlorine-based systems. The formation of NDMA from precursors and strategies for its removal are discussed in multiple reviews (Krasner et al. 2013, 2018; Sgroi et al. 2018; Tan et al. 2019). Leavey-Roback et al. (2016) studied the formation of NDMA at 20 water treatment facilities in Canada and the United States using chloramine disinfection and correlated water quality measurements and other treatment practices (e.g., pre-chlorination time, use of biofilters, etc.) to the level of NDMA that was formed during the treatment process. NDMA and other nitrosamines also occur unintentionally in certain foods, beverages, herbicides, and pharmaceutical products.

Table 5-1 lists the facilities in each state that manufacture or process NDMA, the intended use, and the range of maximum amounts of nitrobenzene that are stored on site. The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2005).

Table 5-1. Facilities that Produce, Process, or Use N-Nitrosodimethylamine

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AR	1	10,000	99,999	9, 12
IL	1	1,000	9,999	7, 12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI21 2022 (Data are from 2021)

5.2.2 Import/Export

Data pertaining to the import of NDMA into the United States were not located in the available literature. It is unlikely that there are significant quantities of NDMA directly imported or exported to or from the United States.

5.2.3 Use

NDMA has been prepared in laboratory-scale quantities solely for use as a research chemical (EPA 2014a). NDMA was formerly used (prior to April 1, 1976) as an intermediate in the production of 1,1-dimethylhydrazine, a storable liquid rocket fuel, which was believed to have contained up to 0.1% NDMA as an impurity (IARC 1978). NDMA had also been used or proposed for use as an antioxidant,

an additive for lubricants, and a softener for copolymers (Windholz 1983). NDMA had also been used as a solvent and rubber accelerator (Hawley 1981).

5.2.4 Disposal

Current information on recommended disposal method(s) for NDMA was not located. Combustion in an incinerator equipped with an afterburner and NOx scrubber is the recommended method for disposing NDMA (Castegnaro et al. 1982). Liquid wastes should be neutralized, if necessary, filtered to remove solids, and then put into closed polyethylene containers for transport. All equipment should be thoroughly rinsed with solvent, which should be added to the liquid waste for incineration. Great care should be practiced to ensure that there is no contamination on the outside of the solvent container. If possible, solid waste should also be incinerated. If this is not possible, the nitrosamine should be extracted from the waste and the extract should be handled as a liquid waste. Any rags, papers, or other materials that are contaminated during the disposal process should be incinerated. Contaminated solid materials should be enclosed in sealed plastic bags that are labeled to indicate the presence of a carcinogen, with the name and amount of carcinogen. Bags should be stored in well-ventilated areas until they are incinerated (Castegnaro et al. 1982). Nitrosamine residues generated in laboratory research or accidental spills in research laboratories should be diluted to a concentration of <10 µg/L and then reduced to innocuous amines, ammonia, or alcohols by aluminum-nickel alloy powder and aqueous alkali (Castegnaro et al. 1982). This method of disposal is applicable to a variety of media (water, mineral oil, olive oil, dimethylsulfoxide, solutions of agar gel), but is not recommended for use in solutions of acetone or dichloromethane because reactions are slow and incomplete. After the reduced reaction mixture is filtered, the liquid can be disposed of by pouring it over a sufficient amount of absorbent material to convert it to a solid waste for incineration. The filtercake is discarded with non-burnable solid wastes (Castegnaro et al. 1982). Other methods of destruction of NDMA in laboratory wastes (e.g., using hydrobromic acid or potassium permanganate/sulfuric acid) are described by Castegnaro et al. (1982).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of

generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

NDMA can be unintentionally produced and then subsequently released from a number of industrial sources by chemical reactions involving alkylamines with nitrogen oxides, nitrous acid or nitrite salts (EPA 2014a). Some possible industrial sources are tanneries, pesticide manufacturing facilities, rubber and tire producers, alkylamine manufacture and use sites, fish processing facilities, foundries, and dye manufacturers (Tricker et al. 1989). NDMA is inadvertently formed in drinking water supplies during water disinfection (EPA 2016). Further, NDMA was found in municipal sewage sludge in the 1980s (Brewer et al. 1980; Mumma et al. 1984) and may thus be released from sewage treatment plants or the application of sludge for biosolids. Tobacco smoke has also been shown to be a source of NDMA release into the air (WHO 2008). NDMA may be released to the air during the grilling of meats such as beef, pork, and duck (Kim et al. 2019).

5.3.1 Air

Estimated releases of <1 pound of NDMA to the atmosphere from two domestic manufacturing and processing facilities in 2021, accounted for 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use N-Nitrosodimethylamine[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AR	1	0.2	0	0	0	0	0.2	0	0.2
IL	1	0	0	0	0	0	0.2	0	0

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use N-Nitrosodimethylamine[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
Total	2	0.2	0	0	0	0	0	0	0.2

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

The use of amine-containing solvents in post-combustion CO_2 capture plants to reduce greenhouse emissions from anthropogenic point sources such as fossil fuel fired power plants can result in atmospheric emissions of NDMA and other nitrosamines (SEPA 2015; Sørensen et al. 2015).

The EPA National Emissions Inventory is a comprehensive and detailed estimate of air emissions of criteria pollutants, criteria precursors, and hazardous air pollutants from air emissions and includes point and nonpoint sources, on- and off-road sources, and other events such as wildfires. Data from 2014 and 2017 for NDMA are shown in Table 5-3.

Table 5-3. Emissions of N-Nitrosodimethylamine (NDMA) to Air Reported to the National Emissions Inventory

Sector	2014 Emissions (pounds)[a]	2017 Emissions (pounds)[b]
Fuel combustion, electric generation, coal	54.41	622.10
Industrial processes, ferrous metals	35.60	57.60
Industrial processes, chemical manufacturing	0.00	32.25

Table 5-3. Emissions of N-Nitrosodimethylamine (NDMA) to Air Reported to the National Emissions Inventory

Sector	2014 Emissions (pounds)[a]	2017 Emissions (pounds)[b]
Waste disposal	16.78	26.38
Fuel combustion, electric generation, oil	155.48	24.48
Industrial processes, petroleum refineries	17.00	15.38
Fuel combustion, industrial boilers, internal combustion engines, other	2.40	3.40
Fuel combustion, electric generation, natural gas	0.45	0.41
Industrial processes, not elsewhere classified	0.02	0.04
Solvent, degreasing	0.00	0.003
Solvent, industrial surface coating and solvent use	0.00	0.0001

[a]EPA 2014b.
[b]EPA 2017.

5.3.2 Water

There were no releases of NDMA to water from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022).

5.3.3 Soil

There were no releases of NDMA to soil from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022).

5.4 ENVIRONMENTAL FATE

NDMA is not released into environmental matrices via the same pathways by which industrial compounds or pesticides may be emitted; rather, it is unintentionally produced and released from industrial sources as a result of chemical reactions involving alkylamines with nitrogen oxides, nitrous acid, or nitrite salts (EPA 2014a). Based on its physical-chemical properties, NDMA is expected to volatilize from soil or water surfaces into the air where it is susceptible to photolysis. Environmental fate of NDMA produced in water treatment facilities would be subject to biodegradation and photolysis.

5.4.1 Transport and Partitioning

Air. Organic compounds in the atmosphere having vapor pressures >10^{-4} mm Hg are expected to exist almost entirely in the vapor phase (Eisenreich et al. 1981). The estimated vapor pressure of NDMA at 20°C [2.7 mm Hg (see Table 4-2)] indicates that this compound should not partition from the vapor phase to particulates in the atmosphere.

Water. Using linear regression equations based on log K_{ow} data (log K_{ow} of -0.57 [see Table 4-2]), a bioconcentration factor of 0.2, and a soil adsorption coefficient (K_{oc}) of 12 have been estimated for NDMA (Bysshe 1982; Hansch et al. 1995; Lyman 1982). These values, as well as the complete water solubility of NDMA, indicate that bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments in water would not be important environmental fate processes. The low Henry's Law constant for NDMA ($2.63x10^{-7}$ atm-m^3/mol at 20°C [see Table 4-2]) suggests that volatilization is expected to occur slowly in water (Thomas 1982).

Sediment and Soil. NDMA is expected to be highly mobile in soil and it has the potential to leach into groundwater supplies (Dean-Raymond and Alexander 1976; Greene et al. 1981; Swann et al. 1983). If NDMA were released to soil surfaces, as might be the case during application of contaminated pesticides, a substantial proportion of the nitrosamine would volatilize. The volatilization half-life from soil surfaces under field conditions is estimated to be on the order of 1–2 hours (Oliver 1979). If NDMA were incorporated into subsurface soil, far less of the nitrosamine would enter the atmosphere by volatilization and the rate of volatilization would be greatly reduced. Under these circumstances, volatilization would be of minor importance (Oliver 1979).

5.4.2 Transformation and Degradation

Air. In the atmosphere, NDMA vapor would rapidly degrade by direct photolysis to form dimethylnitramine. Based on experimental data, the photolytic half-life of NDMA vapor exposed to sunlight has been determined to be about 5–30 minutes (Hanst et al. 1977; Tuazon et al. 1984). Reaction of NDMA with photochemically-generated hydroxyl radicals or ozone molecules in the atmosphere would be too slow to be environmentally significant (Atkinson and Carter 1984; Tuazon et al. 1984).

Water. Data suggest that NDMA would be subject to photolysis in natural waters exposed to sunlight (Abusallout and Hua 2016; EPA 1979; Lee et al. 2005; Polo and Chow 1976). In unlit waters, it appears

that NDMA would be rather persistent, eventually degrading as the result of microbial transformation (Kaplan and Kaplan 1985; Kobayashi and Tchan 1978; Tate and Alexander 1975). There is evidence that suggests that formaldehyde and methylamine may form as biodegradation products of NDMA (Kaplan and Kaplan 1985). NDMA is not expected to undergo hydrolysis under the conditions found in natural waters (EPA 1979; Oliver et al. 1979). Because NDMA has strong absorbance at approximately 227 and 254 nm wavelengths and a large quantum yield at these absorption frequencies, photolysis by ultraviolet (UV) irradiation at water reuse and drinking water facilities, is a treatment technique to reduce NDMA levels (Szczuka et al. 2020; Sharpless and Linden 2003). UV-based advanced oxidation processes utilize irradiation of aqueous solution in conjunction with hydrogen peroxide or photocatalysts such as titanium dioxide, which produce powerful oxidizing agents (hydroxyl radicals), to assist in the degradation of NDMA at water treatment facilities (Fujioka et al. 2017; Szczuka et al. 2020). A field study conducted using a drinking water treatment plant in China suggested that photolysis and biodegradation are the primary removal mechanisms for NDMA in conventional drinking water treatment plants with less significant loss by off-gassing (Qiu et al. 2019). Sakai et al. (2012) studied the effects of UV wavelength on the degradation kinetics of NDMA in water. Three different light sources were studied: a 222-nm Kr Cl excimer UV lamp, a 254-nm mercury UV lamp, and a 230–270-nm filtered medium pressure (FMP) mercury UV lamp. It was concluded that a higher degradation efficiency of irradiated NDMA solutions was observed using the 222-nm lamp and FMP lamp as opposed to the 254-nm lamp but water quality parameters such as the amount of naturally occurring organic matter could affect the degradation efficiency. Nitrosamines such as NDMA have been shown to undergo direct photolysis under environmental conditions with the half-life on the order of several minutes (Sørensen et al. 2015). Direct photolysis of NDMA under simulated environmental conditions (wavelengths >290 nm) was investigated by Plumlee and Reinhard (2007). Using a light source that simulated Southern California midsummer, midday sun (intensity 765 W/m^2), the direct photolysis half-life of NDMA was determined to be 16 minutes; however, increasing amounts of dissolved organic matter decreased the degradation rate of NDMA since these substances also absorb photons in the environmental UV spectrum. The direct photolysis half-life of NDMA in infiltration basins (advanced purified, recycled water) at initial levels up to 9.0 ng/L prior to sunrise declined to below the detection limit (<1.5 ng/L) by 10:00 A.M. due to natural photolysis, and the half-life ranged from 33 to 86 minutes depending upon the intensity of solar irradiation (Reny et al. 2021). Chen et al. (2010) used experimental photolysis data to derive a quantitative structure-activity relationship (QSAR) for the rate of photolysis of NDMA and several other disinfection byproducts produced in water treatment facilities.

Sediment and Soil. It appears that microbial degradation would be an important removal process for NDMA in subsurface soil. Oliver et al. (1979) amended Metapeake loam with 10 ppm NDMA at 23°C and observed a half-life of 50 days (Oliver et al. 1979). Loss of NDMA was attributed to volatilization and biodegradation. Tate and Alexander (1975) amended silt loam with 22.5 ppm NDMA at 30°C and observed a lag of approximately 30 days before slow disappearance from soil commenced; 50% loss occurred after about 55 days incubation and 60% loss occurred after about 70 days incubation. As part of the same study, 40% loss was observed in 2 days in soil amended with 50 ppm NDMA and 44% loss was observed in 5 days in soil amended with 250 ppm NDMA. These initial losses were followed by very little or no loss over the next 3 weeks. Initial, rapid loss of NDMA was attributed to volatilization and slow, gradual loss of NDMA was attributed to biodegradation. Mallik and Tesfai (1981) incubated NDMA at 4, 25, and 37°C and found that at all three temperatures, about 20–30% of added NDMA disappeared in the first 20 days of incubation, but little loss was noted thereafter; even after 30 days of incubation, over 50% of the NDMA was retained. The rate of disappearance of NDMA was found to be slightly higher in sandy loam soil than in either clay or silt loam soil. The rate of loss was also found to be slightly higher in aerobic soil at field capacity compared to super saturated (anaerobic) soil. After a 30-day incubation period, 60% of added NDMA remained in soil at field capacity and 70% of added NDMA remained in super saturated soil. Available data on the degradation of NDMA in water and air indicate that photolysis may be an important removal process on soil surfaces as well.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to NDMA depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of NDMA in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on NDMA levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.5 parts per trillion[b]	Sawicki et al. 1977
Drinking water	0.28 ng/L	EPA 2004 (Method 521)
Surface water and groundwater	0.15 µg/L	EPA 1996 (Method 8070)
Soil	5.7 ng/g[c]	Venkatesan et al. 2014
Sediment	5.7 ng/g[c]	Venkatesan et al. 2014
Whole blood	0.1 µg/L	Lakritz et al. 1980

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Detection limits in air are dependent upon the sampling time/volume; this value is for 150 L volume of air collected.
[c]Measured in biosolids.

Detections of NDMA in air, water, and soil at NPL sites are summarized in Table 5-5.

Table 5-5. N-Nitrosodimethylamine (NDMA) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	29.5	366	607	4	4
Soil (ppb)			No data		
Air (ppbv)			No data		

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Limited data on levels of NDMA in ambient air are available, and much of the available data was obtained many years ago in the vicinity of industrial sources. Because commercial uses of NDMA have been discontinued, and environmental control technologies have been instituted to reduce inadvertent NDMA formation and release, current levels in ambient air are expected to be lower. When it was used as a rocket fuel intermediate, NDMA was identified in ambient air on-site and in the vicinity of factories that were manufacturing rocket fuel (EPA 1978; Fine et al. 1977a). At a plant in Baltimore, Maryland, which was manufacturing unsymmetrical dimethylhydrazine rocket fuel, the average concentration on-site was 11.6 µg/m^3, and in neighboring residential communities, it was 1.07 µg/m^3, with levels ranging between 30 and 100 ng/m^3 in the downtown area (Fine et al. 1977a). As a result of these findings, the use

of NDMA was discontinued at this plant (Shapley 1976). During December 1975, NDMA was found in air samples collected in Belle, West Virginia near a factory that was manufacturing dimethylamine. The highest level found (0.980 μg/m^3) was collected during a temporary weather inversion (Fine et al. 1976). NDMA was measured in ambient air in urban areas with no known point sources of nitrosamines: Baltimore, Maryland several miles upwind of the rocket fuel plant (0.02–0.1 μg/m^3); the Cross Bronx Expressway in New York City (0.8 μg/m^3); and Philadelphia, Pennsylvania (0.025 ppb) (Fine et al. 1976; Shapley 1976). NDMA has been found in fogs and clouds at concentrations ranging from 7.5 to 397 ng/L (Hutchings et al. 2010; SEPA 2015).

Mean NDMA concentrations in fine particulate matter ($PM_{2.5}$) collected from ambient air in central London were 0.00136 and 0.0049 μg/m^3 in winter and summer, respectively (Farren et al. 2015). In the 1990s, NDMA was found to be above the detection limits of 0.0029–0.0048 μg/m^3 in 20 out of 41 samples obtained from a chemical production facility in Ontario, Canada (WHO 2008). The maximum level of NDMA in air samples within the perimeter of the production facility was reported as 0.230 μg/m^3, while the maximum level collected in air samples nearby the facility was 0.079 μg/m^3 (WHO 2008).

Occurrence of volatile nitrosamines in air has been associated with tire and rubber products, leather tanneries, and automotive upholstery, and, as a result, measurable levels of the nitrosamines have, in the past, been found in certain confined areas (e.g., automobile interiors). In studies conducted in the 1980s, levels of NDMA in interior air of new cars were found to range from <0.02 to 0.83 μg/m^3 (EPA 1985; Rounbehler et al. 1980). Newer information was not located. As materials used in automobile interiors have changed since the 1980s, the relevance of these measurements to potential current exposures is unknown.

Tobacco smoke is an established source of airborne NDMA. The maximum NDMA level in indoor air for a residence with smokers was reported as 0.24 μg/m^3 and the level in the air of a residence for a nonsmoker was below the detection level of 0.003 μg/m^3 (WHO 2008). In their review of the chemical composition of tobacco smoke, IARC (2004) noted that NDMA concentrations in indoor spaces where people were smoking (restaurants, bars, conference rooms) ranged between <0.01 and 0.24 μg/m^3.

5.5.2 Water

NDMA is formed as an unintentional byproduct of the chlorination of wastewater and drinking water at treatment plants, especially where chloramines are used for disinfection (EPA 2016). Monitoring for NDMA was conducted under the Unregulated Contaminant Monitoring Rule (UCMR) Cycle 2 (EPA 2016). The EPA employs the UCMR program to obtain data for contaminants in PWSs that do not have health-based standards set under the Safe Drinking Water Act. In monitoring data collected from 2008 through 2010, 18,040 samples from 1,198 PWSs were analyzed for NDMA (EPA 2016). NDMA was detected in samples from 324 PWSs and at levels above the minimum reporting level of 0.002 µg/L in 1,841 samples (EPA 2016). The median and mean NDMA concentrations across all samples with detections were 0.0041 and 0.008 µg/L, respectively, well below the EPA's drinking water health advisory level of 0.07 µg/L. EPA (2016) estimated the size of the population served by PWSs with NDMA detections to be ~65 million people. As discussed in Section 5.6, exposures to NDMA in drinking water are very low compared to endogenous production and other exogenous sources.

Detections of NDMA in drinking water samples were most common from facilities using chloramines (34%) compared with chlorine or other disinfectants (4%) or no disinfection (1.8%) (EPA 2016). The maximum concentration detected in the positive samples from facilities using chloramines was 0.630 µg/L; in positive samples from facilities using chlorine or other disinfectants, the maximum was 0.0846 µg/L (EPA 2016). Other factors affecting the NDMA concentration included the source water type and the sample type. Systems using surface or mixed water sources had higher detection rates than systems using groundwater sources. In addition, samples collected at "maximum residence time locations" were higher than those collected at distribution entry points, suggesting ongoing formation of NDMA in the distribution system (EPA 2016).

In a review of published literature on NDMA exposure sources (publications dated between 2004 and 2011), Gushgari and Halden (2018) reported that the average NDMA concentration in U.S. potable waters was 0.0177 µg/L, and that its concentration was higher than those of other nitrosamines. It has been estimated that NDMA accounts for between 5 and 13% of total N-nitrosamines in potable waters (Dai and Mitch 2013; Gushgari and Halden 2018). NDMA formation can be enhanced depending upon algae concentrations during the disinfection process. Du et al. (2022) studied the effects of chlorination on nitrosamines formation from two algae (*Microcystis aeruginosa* and *Cyclotella meneghiniana*) and observed that NDMA was the dominant nitrosamine produced.

NDMA was detected in treated water within the distribution system from 20 chloramine treatment plants located in Canada and the United States at maximum, mean, and median levels of 0.0586, 0.0094, and 0.0043 µg/L, respectively (Leavey-Roback et al. 2016). Repeated samples were collected over a 2-year period, but the specific dates were not provided. Liew et al. (2015) collected a total of 211 samples from 38 drinking water treatment plants across five states and one territory in Australia from 2007 to 2013. Nine out of 38 facilities reported NDMA levels above 0.005 µg/L. The highest concentration of NDMA was 0.074 µg/L and was obtained from a facility using chloramine for disinfection.

The formation of NDMA in potable water supplies has been attributed to precursors contained in natural organic matter, tertiary and quaternary amines, anion exchange resins and cationic coagulant polymers (such as polydiallyldimethylammonium chloride), and/or in source waters impacted by wastewater contamination (which may include tertiary amine-based drugs, cosmetics, or toiletries) (Atkinson et al. 2020; Dai and Mitch 2013; EPA 2016; Tan et al. 2019; Zeng et al. 2016). It has been shown that the pharmaceutical agent, methadone, which is often used to treat heroin withdrawal symptoms, has a high potential to form NDMA in water treatment facilities (Hanigan et al. 2015; Hsieh et al. 2020). A review by Krasner et al. (2013) discusses the formation of NDMA and other nitrosamines from various precursors in water treatment facilities and the different methods to limit the formation of NDMA, such as physical removal of precursors by biologically activated carbon and granular activated carbon or the degradation of such compounds by ozonation or increased pre-chlorination time. The most important precursors are amine-containing coagulation polymers and effluent-impacted source waters (Krasner et al. 2013). In a separate study of 21 full-scale drinking water plants, ozonation of raw or settled water was shown to be an effective method of degrading NDMA precursors and increasing the free pre-chlorination time from <3 minutes of treatment to over 1 hour potential from 21 to 90% (Krasner et al. 2018). Hanigan et al. (2012) studied the ability of activated carbon to adsorb precursors and reduce the NDMA formation potential from river water and effluent from a wastewater treatment plant and found that the NDMA formation potential was in the range of 37–91%, depending upon the concentration of the activated charcoal used. While ozonation can facilitate the degradation of NDMA-forming precursors, it may also result in the formation of NDMA in the treatment of wastewater or highly contaminated surface water (Gao et al. 2022; Sgroi et al. 2014, 2016, 2018; Vaidya et al. 2021). Gao et al. (2022) demonstrated formation of NDMA from ozonation treatment of 3-(dimethylamino)-1-propylamine (DMAPA) with higher levels of NDMA formation observed with increasing pH (from 5 to 9) and ozone dosages. NDMA formation upon ozone treatment of the anti-yellowing agent, 4,4'-hexamethylenebis

(1,1-dimethylsemicarbazide) (HDMS), has also been demonstrated with higher yields under slightly alkaline (pH 8) conditions (Shen et al. 2019).

EPA (2016) reported that several studies have demonstrated the presence of NDMA precursors in wastewaters. NDMA itself was detected in effluents from four wastewater plants in Connecticut at levels ranging between 0.0076 and 0.4 μg/L (Schreiber and Mitch 2006). Concentrations of NDMA in the receiving waterways were generally below the detection limit except in the river downstream of the Wallingford, Connecticut treatment plant, where concentrations of ~0.015 and 0.05 μg/L were detected (Schreiber and Mitch 2006). Sack et al. (2021) measured NDMA levels in the range of 20.7–56.7 ng/L in wastewaters from five large hospitals in Israel. Samples from 101 wastewater treatment plants (WWTPs) in Ontario, Canada were analyzed for the presence of NDMA from 1990 to 1998 (WHO 2002, 2008). NDMA was detected in raw surface water samples from 37 of the plants, with a maximum concentration of 0.008 μg/L. Wastewaters used for landscape irrigation may contain elevated concentrations of NDMA, but a field study (Gan et al. 2006) showed very little NDMA in leachate (detectable at 2 ng/L in only 9 of 400 samples) from turfgrass after 4 months of application of wastewater containing an average of 930 ng/L NDMA.

NDMA is infrequently found in groundwater samples, except in the vicinity of industrial activities such as rubber manufacturing and rocket engine testing (Gushgari and Halden 2018). However, it was the finding of very high NDMA concentrations in groundwater downgradient from rocket engine testing facilities in California that lead to the discovery of NDMA associated with chlorinamine/chlorine disinfection (Mitch et al. 2003). Groundwater monitoring wells showed NDMA concentrations as high as 400 μg/L on site and as high as 20 μg/L in drinking water wells downgradient of the sites (Mitch et al. 2003). These findings led the California Department of Health Services to conduct a survey (in 2002) of NDMA in drinking waters in the state, which revealed the occurrence of NDMA in drinking waters influenced by chlorine-disinfected wastewaters, and in drinking water supplies where chloroamine and chlorine disinfection were used (Mitch et al. 2003). NDMA was monitored for, and detected in, both groundwater and river water in Tokyo, Japan (Van Huy et al. 2011). Levels were <0.5–5.2 ng/L (median: 0.9 ng/L) in groundwater and <0.5–3.4 ng/L (median: 2.2 ng/L) in river water.

NDMA has been detected in pool water. Analysis of water in 23 indoor pools in South Carolina, Georgia, and North Carolina revealed that NDMA levels ranged from 2 to 83 ng/L (0.002–0.083 μg/L), with an average concentration of 26.5 ng/L (0.0265 μg/L) (Kanan 2010). UV treatment is often used as a disinfection technique in large pool maintenance. However, Soltermann et al. (2013) reported that UV

treatment (at wavelengths of 254 nm) of swimming pool water containing chlorinated dimethylamine and monochloramine resulted in slightly increased NDMA formation instead of the expected decreases.

5.5.3 Sediment and Soil

Few data on NDMA in soil or sediment were located. Only one study of NDMA in soil was identified, and it was published in 1977. In that study, NDMA was found in soil at l–8 µg/kg (dry basis) in Belle and Charleston, West Virginia, New Jersey, and New York City (Fine et al. 1977b). NDMA in soil may arise from absorption of NDMA in air, from absorption of dimethylamine from air and its subsequent N-nitrosation, or from pesticide application. NDMA was not detected in any sediment or soil samples from 2020 to 2022 in a search of the EPA Water Quality Portal (WQP 2022). Gushgari et al. (2017) analyzed 40 freshwater sediments in the vicinity of 13 WWTPs in the United States. Three nitrosamines (N-nitrosodibutylamine, N-nitrosodiphenylamine, and N-nitrosopyrrolidine) were detected in some of the sediment cores; however, NDMA was not detected (10.2 ng/g detection limit) in any of the sediments tested.

5.5.4 Other Media

NDMA has been detected in a variety of other media including foods and beverages, pharmaceutical products, toiletries and cosmetics, tobacco products, rubber products, pesticides, and sewage sludge. For media other than beverages and pharmaceutical products, however, the majority of published literature on NDMA levels in these media dates from before 1990, and more recent data were not located. In general, after NDMA was initially detected in foods, beverages, and rubber products (more than 40 years ago), producers and manufacturers modified their processes and techniques to reduce nitrosamine formation. However, due the ubiquitous nature of NDMA precursors and its facile formation, complete elimination of NDMA from these products has proved to be challenging. The discovery of NDMA contamination in prescription and over-the-counter drugs is a relatively recent phenomenon (2019 to present), and the FDA continues to update its information on affected medications (see https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications).

Foods and Beverages. Current food exposures to NDMA are uncertain because of changes in food processing techniques (Lee 2019). Food processing methods that foster the formation of NDMA or other nitrosamines include pickling, storage in humid conditions, smoking with saturated nitrogen, high temperature drying, and curing with nitrate or nitrite (Stuff et al. 2009). The use of nitrite and nitrate

preservatives was thought to be a significant contributor to elevated NDMA levels in processed meats, and these uses have declined in the years since much of the data were collected (Lee 2019). However, Stuff et al. (2009) noted that many foods contain naturally occurring precursors that can yield NDMA or other nitrosamines under some conditions.

Based on food concentrations of N-nitrosamines in literature published between 1979 and 2015, Gushgari and Halden (2018) estimated the average concentration of NDMA across all food types to be 2.2 μg/kg; average concentrations for other N-nitrosamines ranged between 0.02 and 1.5 μg/kg (for N-nitrosodi-n-propylamine and N-nitrosodi-n-butylamine, respectively). In a study in Turkey, NDMA was detected in all samples (n=20) of salami tested, with levels ranging from 0.09 to 3.56 μg/kg (Özbay and Sireli 2021). Lee (2019) reviewed the available literature (publications dated 1985–2018) on N-nitrosamine levels in meats and poultry, identifying data from 14 countries. Table 5-6 shows the ranges of concentrations reported in the literature reviewed by Lee (2019). Weighting the published values by number of samples analyzed, Lee (2019) estimated the mean levels of N-nitrosamines in 40 different processed meats and poultry products. The estimated mean NDMA concentration ranged between 0.3 and 5.7 μg/kg; the highest means were estimated for fried-out bacon fat (5.7 μg/kg), fried pork fat, (4.1 μg/kg), ham and turkey (3.8 μg/kg), and blood sausage (3.5 μg/kg) (Lee 2019). For most other meats and poultry, estimated mean concentrations were ≤1 μg/kg. In foods other than meat and poultry, similar concentrations have been measured; however, these data are also older. In a review of literature published between 1988 and 2006, Stuff et al. (2009) reported NDMA concentrations for several other food types (see Table 5-6), with the highest concentrations (in foods other than meats and poultry) found in oysters (>11 μg/kg), sauerkraut (6.6 μg/kg), and fried fish (1.7 μg/kg). It is important to note that not all samples of a particular type of food contained detectable levels of NDMA; only the measurements above the detection limit are reported in the table.

Table 5-6. Detection of N-Nitrosodimethylamine in Foods and Beverages

Food item	Concentration
Foods other than meat and poultry[a] (μg/kg)	
Dairy (milk, butter, cottage cheese)	0.14–0.76
French fries	0.24
Margarine	0.26
Refried beans	0.33
Breads (rolls, bagels, muffins)	0.5
Fried fish	1.69
Sauerkraut	6.60

Table 5-6. Detection of N-Nitrosodimethylamine in Foods and Beverages

Food item	Concentration
Oysters	11.39
Meat and poultry products[b] (µg/kg)	
Lamb products	1.0
Sausage products	0.1–3.6
Hot dogs	0.2–2.2
Ham products	0.1–4.9
Poultry products	0.5–5.0
Pork products	0.1–4.9
Bacon products	0.3–20.2
Chorizo	ND–109.4
Alcoholic beverages (µg/L)	
Alcoholic beverages (beer, wine)[a]	0.25–2.02
U.S. beer[c]	0.145
Beers produced other countries[c]	0.118–0.225
Lager[d]	0.105
Ale[d]	0.108
Dark beer[d]	0.055
Light beer[d]	0.05

[a]As reported in literature review published by Stuff et al. (2009) based on publications dated between 1988 and 2006; country of origin not limited.
[b]As reported in literature review published by Lee (2019) based on publications dated between 1986 and 2018 that reported levels in foods in the United States or in other countries with predominantly Western diets.
[c]Fan and Lin (2018).
[d]Baxter et al. (2007).

Malt beverages, including domestic and foreign beers and whiskeys, may contain NDMA. In the 1970s, research suggested that NDMA in these beverages may result from formation during direct-fired kiln-drying of malt (from amines in the cereals and nitrogen oxides in the drying air), so malting processes were modified to reduce nitrosamine formation, leading to a sharp reduction in NDMA levels by the 1980s (Baxter et al. 2007). The FDA established an action level of 5 ppb (5 µg/L) for NDMA in malt beverages sold in the United States (FDA 2005a), and there are few publications reporting levels of NDMA in beverages produced since that time. NDMA concentrations ranging between 0.118 and 0.225 µg/L were measured in 10 beer samples from six different countries (dates of sample collection were not reported but assumed to be within a few years of publication); as shown in Table 5-6, the concentration in the one U.S. sample was 0.145 µg/L (Fan and Lin 2018). Baxter et al. (2007) analyzed 138 different beers from 42 different countries (obtained in 2003) for the presence of NDMA. A total of 21% of the beers sampled had detectable levels of NDMA (detection limit 0.1 µg/L) and three samples showed concentrations >0.5 µg/L. NDMA content in beer was not correlated with alcohol level, type, or

geographical origin. Baxter et al. (2007) traced the source of elevated NDMA (1.9 µg/L) in one lager sample to an ion exchange resin used to treat water used in the brewery.

NDMA may occur in human breast milk; however, available data are limited to two studies published in 1996 and 1984. Uibu et al. (1996) reported NDMA levels ranging from <0.5 to 1.2 µg/L in milk from 10 of 54 nursing women (NDMA was not detectable in milk from the remaining women). In a 1984 study, 51 samples of breast milk were collected from 13 nursing women. NDMA concentrations >0.2 µg/L were found in 23.5% of the samples, and the maximum concentration detected was 1.1 µg/L (Lakritz and Pensabene 1984). While no measurements of NDMA in infant formula were located in the literature reviewed, Hrudey et al. (2013) calculated estimated NDMA levels in the range of 0.002–0.06 ng/g for prepared formula (made from cow's milk) using concentrations measured in milk proteins or nonfat dry milk. NDMA was detected in 100% of milk powder samples (n=64) at an average concentration of 2.6 µg/kg (Genualdi et al 2020).

Pharmaceuticals. In recent years, the FDA has detected NDMA (and other nitrosamines) in some prescription and over-the-counter medications, including angiotensin II receptor blockers (valsartan, losartan, irbesartan) (FDA 2019a); metformin extended-release (used to treat Type II diabetes) (FDA 2020a); and drugs used to block stomach acid such as ranitidine (also known by its brand name, Zantac) and nizatidine (FDA 2019b). NDMA was detected in about one-third of tested samples of metformin extended-release, one-half of the tested samples of valsartan, and in all samples of ranitidine and nizatidine tested. FDA testing showed that the amounts of NDMA in each tablet or other oral dose of drug were 0.33–20.19 µg in valsartan samples, 0.004–0.86 µg in ranitidine samples, 0.01–0.03 µg in nizatidine samples, and 0.005–0.19 µg in metformin extended-release samples (FDA 2019a, 2019b, 2020a). A number of these products have been the subject of voluntary or mandatory recalls (beginning in 2018 for valsartan products, 2019 for ranitidine and nizatidine products, and 2020 for metformin extended-release). In 2019, FDA established an interim limit of 96 ng/day (0.000096 mg/day) for NDMA intake from the use of angiotensin II receptor blockers such as valsartan; the limit is based on cancer risk. It is not clear whether the limit would also apply to other affected medications such as ranitidine. The FDA's investigation into nitrosamine impurities in medications is ongoing, and the reader is referred to the FDA website on this topic (https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications) for up-to-date information pertaining to medications containing NDMA and recall of specific products. Other governments have also assessed levels of NDMA in pharmaceutical products. For example, the Ministry of Food and Drug Safety in South Korea suspended the manufacture and sale of 269 ranitidine products following a study that found levels as high

as 53.50 ppm in some products; this is several hundred times greater than the provisional limit of 0.16 ppm set by the government (Kim et al. 2021a).

Recent *in vitro* studies using ranitidine tablets in simulated gastric fluid showed that NDMA was formed, but only at levels atypical of physiologic conditions (Gao et al. 2021). The authors of this study determined that the conversion of ranitidine to NDMA only began to occur under acidic conditions characteristic of human physiology when gastric nitrite concentrations were approximately 50 times greater than normal levels. Braunstein et al. (2021) also noted an increase in NDMA levels when ranitidine was in simulated gastric fluid at a constant pH of 2.5, but also at very high sodium nitrite levels (>2.5 mmol/L). A randomized study was conducted to assess the 24-hour urinary excretion levels of NDMA in a group of participants receiving oral ranitidine (300 mg) compared with a group given placebo. Each group was evaluated when the subjects were following a diet using noncured meats, and also when following a diet with cured meats containing high levels of nitrites (Florian et al. 2021). The study found that the group receiving ranitidine did not have a significantly increased 24-hour urinary excretion of NDMA as compared to the control group not receiving ranitidine. The study authors concluded that orally ingested ranitidine is not likely to be converted to NDMA in normal healthy human populations.

Accurate analytical testing methodologies are crucial for determining the concentrations of NDMA in pharmaceutical products. A comprehensive review of important analytical methods that may be used for the quantification NDMA in various active pharmaceutical ingredients has been published (Parr and Joseph 2019). A recent study by Yang et al. (2020) discussed the findings of NDMA levels in 38 metformin drug products. A private testing laboratory found that 16 of 38 of the metformin drug products they tested had NDMA levels greater than the allowable intake of 96 ng/day. However, FDA testing using orthogonal methods on the same set of 38 samples determined only 8 of the 38 products had levels over the allowable limit and generally observed much lower values than reported by the private testing firm. For example, a 500 mg tablet of metformin had a reported NDMA level of 0.364 ng/mg when analyzed by a private laboratory; however, a duplicate analysis using an FDA method found the level to be 0.021 ng/mg (Yang et al. 2020). Further investigation revealed that the cause of these discrepancies was a lack of specificity, because N,N-dimethylformamide (DMF) caused interference with NDMA measurements. Fritzsche et al. (2022) presented a review of analytical methodologies for measuring NDMA in metformin products (two metformin immediate release formulations and one extended-release formulation), in which they compared measurements of NDMA levels obtained from four laboratories using orthogonal mass spectrometric methods. They observed artefactual formation of

NDMA when the solvent dichloromethane was used during the extraction step leading to inaccurate results that overestimate NDMA levels; however, artefactual NDMA was not formed *in-situ* when a mixture of water, methanol and acetonitrile were used in the extraction process.

A comprehensive review of NDMA levels in metformin for both the active pharmaceutical ingredient (API) and the finished dosage forms (FDF) was recently published (Keire et al. 2022). The results strongly suggest that NDMA is formed during the manufacture of the final product and that the active ingredient typically does not contain NDMA. These researchers tested 1,090 samples (875 FDF and 215 API samples) and found 213 out of 215 API lots tested had no measurable level of NDMA. For FDF samples tested, 156 out of 875 had levels above the acceptable intake (AI) of 96 ng per day. Other research seems to support these conclusions. Analyses of 105 samples of metformin tablets from 13 different manufacturers found that NDMA was not detected in the API; however, NDMA was detected in 64 (85.3%) and 22 (91.7%) of the finished product and prolonged finished product samples, respectively (Zmysłowski et al. 2020). Additional research showed that NDMA formation during the metformin manufacturing process can be reduced by limiting residual dimethylamine (DMA) and inorganic nitrites and nitrates of inactive ingredients used to create the marketed tablets (Schlingemann et al. 2022). They noted that NDMA content increased during wet granulation process and coating, which introduces heat and polyvinylpyrrolidone binder as a significant source of nitrite. Jireš et al. (2021) detected an increase in NDMA in coated metformin tablets following production and after 7 days of storage. They observed that samples of film-coated tablets produced from metformin containing high DMA content and polyvinylpyrrolidone with high peroxide content contained a significantly higher amount of NDMA than other batches. Nasr et al. (2021) also investigated the cause of NDMA formation in metformin pharmaceutical products and identified water, heat, and excipients with high nitrite content as key factors affecting NDMA formation. Their findings indicated that the polyvinylpyrrolidone (PVP K30) tested had lower nitrite and nitrate levels than other excipients such as sodium carboxymethyl cellulose and optimization of the granulation process and low nitrite/nitrate containing excipients can lead to the manufacture of NDMA-free product. Golob et al. (2022) detected NDMA in FDF of high blood pressure tablets, but not in the bulk drug product. They identified nitrocellulose primer in a lidding foil as the likely source of NDMA formation during blistering operations at elevated temperatures and recommended using nitrocellulose-free blister material as a replacement.

Tsutsumi et al. (2019) investigated methods for analyzing NDMA levels in valsartan with GC-MS/MS using selected ion monitoring (SIM) mode. They tested commercially available products in Japan which originated from a company in whose products NDMA had previously been detected; however, they

observed that there were no NDMA levels in these samples above the detection limits of the analytical method they used to test the samples. Khorol'skii et al. (2019) also discussed analytical methods for accurately determining levels of NDMA in valsartan by using direct-introduction or vapor-phase analysis employing GC-MS/MS in SIM and multiple reaction monitoring (MRM). They determined direct-introduction SIM and MRM methods were comparable to SIM and MRM methods using vapor-phase analysis with similar detection and quantification limits.

The sources and levels of NDMA in pharmaceutical products are evolving areas of research. The reader is referred to the FDA website (https://www.fda.gov) for up-to-date information.

Tobacco Products. N-Nitrosamines, including NDMA, may be found in commercially available tobacco products in the United States, but little information on levels of NDMA in these products was identified in available literature. The literature on N-nitrosamine levels in tobacco products is largely focused on compounds other than NDMA (specifically, N-nitrosonornicotine [NNN], 4-[N-nitrosomethylamino]-1-[3-pyridyl]-1-butanone [NNK] N-nitrosoanatabine, and N-nitrosoanabasine) (Gushgari and Halden 2018). In a review of international literature, Smith et al. (2000) reported NDMA concentrations up to 7.6 ng/cigarette in mainstream smoke. In an older study, Brunnemann et al. (1983) reported NDMA in mainstream cigarette smoke (4.2–15 ng/cigarette) and sidestream (secondhand or environmental) cigarette smoke (460–1,880 ng/cigarette). A study from 1973 reported a measurement of 160 ng NDMA in smoke condensate from a cigar (McCormick et al. 1973). In electronic cigarette fluid and nicotine cessation products, concentrations of N-nitrosamines are more than 97% lower than in traditional cigarettes (Gushgari and Halden 2018); however, data on concentrations of NDMA in such products were not located.

Toiletry and Cosmetic Products. N-Nitrosamines have been found to occur in a variety of toiletry and cosmetic products, including shampoos, hair conditioners, color toners, shower gels, bath cremes and oils, children's shampoos, children's bath and health care products, and face tonics, cleansers, and masks. Data on NDMA levels in these products were not located, but according to Hrudey et al. (2013), the levels and associated potential exposure are negligible. Consistent with this characterization, Gushgari and Halden (2018) reported that NDMA represents only a small fraction (0.01%) of the N-nitrosamine content in cosmetic products, which is dominated by N-nitrosodiethanolamine resulting from nitrosation of di- and tri-ethanolamine components.

Rubber Products. Rubber products may contain N-nitrsoamines (including NDMA); these are postulated to derive from additives used in rubber vulcanization (Park et al. 2018). In 1985, the FDA established an action level of 10 ppb (μg/kg) for individual N-nitrosamines in rubber nipples (FDA 2005b). Data on NDMA levels in rubber nipples produced in the United States after the action level was established were not located. Using 30 samples from Korea, Park et al. (2018) reported a range of 1.02–3.67 μg/kg NDMA (presumably reported as μg NDMA per kg rubber sample) when artificial saliva was exposed to silicone and natural rubber nipples for 24 hours. These authors also measured NDMA migrating from other rubber baby products (1.07–1.72 μg/kg in 5 samples) and rubber bakeware (1.38–1.67 μg/kg in 3 samples); NDMA migration was not detected in 16 samples of artificial saliva exposed to rubber cooking utensils (Park et al. 2018). Using a similar technique with a 1-hour exposure duration, RIVM measured the migration of NDMA from rubber balloons; as reported by the Scientific Committee on Consumer Products (SCCP 2007), the maximum estimate of NDMA release was 2.82 mg/kg rubber/hour. SCCP (2007) noted that between samples collected in 2002 and 2004, there was evidence for a reduction in nitrosamine release from balloon samples. Rubber gaskets may also be a source of NDMA in drinking water distribution systems (EPA 2016).

Pesticides. In studies conducted in the 1970s, NDMA was found to occur in various technical and commercial pesticides used in agriculture, hospitals, and homes (Bontoyan et al. 1979; Cohen and Zweig 1978; Hindle et al. 1987; Ross et al. 1977). WHO (2008) reported that concentrations of NDMA in pesticides are decreasing over time, but recent data in the United States were not located. Dimethyl-amine-based pesticides (e.g., bromacil, benzolin, 2,4-D, dicamba, 2-methyl-4-chlorophenoxyacetic acid, and mecoprop) may be contaminated with NDMA. In its Six-Year Review of nitrosamines, the EPA (2016) reported that NDMA was detected in 49 of 100 Canadian samples (collected since 1990) of dimethylamine phenoxy acid herbicides at an average level of 0.44 μg/g (ppm) and a maximum concentration of 2.32 μg/g (ppm).

Municipal Sewage Sludge. Data from the 1980s showed that NDMA was a common constituent of municipal sewage sludge (Brewer et al. 1980; Mumma et al. 1984). In the 1980s, NDMA was detected at levels ranging from 0.6 to 45 ppb in dried sludges from 14 out of 15 cities geographically located throughout the United States (Mumma et al. 1984). Occurrence of NDMA in sewage sludge was attributed to biological and chemical transformation of alkylamines in the presence of nitrite (Ayanaba and Alexander 1974; Mills and Alexander 1976; Pancholy 1978). Biosolids that are often applied to agricultural lands to supply nutrient-rich organic materials to the soils have been shown to contain nitrosamines, including NDMA (Venkatesan et al. 2014). Biosolid materials obtained from 74 WWTPs

in the contiguous United States contained NDMA at a detection frequency of approximately 3% and at an average concentration of 504±417 µg/kg dry weight of biosolid.

5.6 GENERAL POPULATION EXPOSURE

For the general population, the primary route of exposure to NDMA is through endogenous production. Exogenous sources of NDMA to which the general population may be exposed include foods and malt beverages, water, cigarette smoke, and to a lesser extent rubber products, toiletry and cosmetic products, and pesticides. Exposure to NDMA and other nitrosamines from water can arise from direct ingestion of drinking water; through inhalation and dermal contact when showering or bathing; or from inhalation, dermal contact, and incidental ingestion while swimming in a chlorinated pool (Chowdhury 2014; Mustapha et al. 2021). Some people may have had exposures to NDMA through the use of contaminated medications prior to their recall.

Hrudey et al. (2013) prepared a detailed analysis of the endogenous production of NDMA, including estimates of the daily rate of production. NDMA is produced endogenously through acid-catalyzed nitrosation of amine precursors (primarily in the stomach) and through biologically catalyzed nitrosation in other tissues including the oral cavity, intestine, liver, blood, and bladder. The rate of acid-nitrosation is influenced by the pKa of amine precursors in the stomach, while biologically catalyzed nitrosation is influenced by levels of amino acids that compete for nitrite (Hrudey et al. 2013). It is believed that systemic (biologically catalyzed) nitrosation is the primary contributor to endogenous NDMA production (higher than acid-catalyzed) except when there are very high dietary intakes of amine and nitrate precursors (Hrudey et al. 2013). Using different methods based on measured human NDMA blood levels, O^6-methylguanine DNA adducts, and urinary excretion levels, Hrudey et al. (2013) estimated the rate of endogenous production to be approximately 1 mg/day (equivalent to 0.014 mg/kg/day for a 70-kg adult). A study examined the mean urinary excretion of NDMA using 25 subjects who consumed a diet that was initially low in nitrate for 7 consecutive days followed by a diet that was high in nitrate levels in the second week. Mean urinary NDMA levels in the control week were 287 ng per 24-hour period but increased to 871 ng per 24-hour period in the second week when the subjects were consuming a diet high in nitrate concentration (Vermeer et al. 1998). Subjects consuming either a diet of processed red meat or unprocessed white meat (3.75 g/kg body weight) for 2 weeks showed significantly greater urinary excretion of apparent total N-nitroso compounds in the second week when they used drinking water high in nitrate levels as opposed to the first week when nitrate levels in drinking water were kept low (van Breda et al. 2019).

Estimates of exogenous NDMA exposure (primarily food, beverages, and drinking water) among consumers of Western diets have been reported by a few investigators. The most recent estimates, which made use of the extensive drinking water data collected for the UCMR2, were published by Hrudey et al. (2013) and are shown in Table 5-7. White (2020) reported a comparable estimate of adult NDMA intake from food and water (110 ng/day or ~1.6 ng/kg/day for a 70-kg adult).

Table 5-7. Estimates of Daily Intake of N-Nitrosodimethylamine (NDMA) from Endogenous and Exogenous Sources for Selected Age Groups (ng/kg Body Weight/Day)

	Mean			95th Percentile		
Source	0–0.5 years	6–12 years	20–49 years	0–0.5 years	6–12 years	20–49 years
Endogenous production	–[a]	–	1.4–35	–	–	4.1–62
Food[b]						
Without beer included	0.011	1.6–1.8	0.7–0.8	8.9	2.8	1.6
With beer included	NA	NA	1	NA	NA	2.1
Drinking water	0.05–0.37	0.008–0.07	0.007–0.06	0.12–1.6	0.02–0.26	0.02–0.23

[a]No data.
[b]Based on a published study of NDMA concentrations in foods measured between 1987 and 1992 in France.

NA = not applicable

Source: Hrudey et al. 2013.

Hrudey et al. (2013) estimated the mean intake of NDMA in infants exclusively fed powdered infant formula to be 6.9 ng/kg/day (without the contribution of added water), but this estimate is uncertain, as the authors did not identify any measurements of NDMA in formula, but instead used concentrations in milk proteins and nonfat dry milk to calculate intake. Similarly, these authors estimated that exclusively breast-fed infants may take in 15 ng NDMA/kg/day on average, but this estimate is based on NDMA concentrations in breast milk from two older studies (Lakritz and Pensabene 1984; Uibu et al. 1996).

WHO (2002) estimated that "reasonable worst case" exposures to NDMA in ambient air ranged up to 11 ng/kg/day. These estimates were based on measurements of NDMA in short-term samples of ambient air near point sources (rubber production facilities) in Ontario in 1992. As a result, these estimates are of uncertain relevance to long-term exposures under current conditions and at locations further from point sources.

NDMA has been detected in several prescription and over-the-counter medications, including angiotensin II receptor blockers like valsartan, heartburn medications like ranitidine and nizatidine, and the diabetes medication, metformin extended-release (FDA 2019a, 2019b, 2020a). Pottegard et al. (2018) estimated daily NDMA exposures of 0.14–0.31 μg/kg/day from valsartan use based on measured concentrations of NDMA in valsartan tablets. Several of these substances have been recalled by the manufacturers or by the FDA; however, they were commonly used as prescription and over-the-counter treatments prior to this.

No estimates of plausible current general population exposure to NDMA from other sources (tobacco use; migration from rubber products such as bottle nipples, pacifiers, or cooking implements; handling or application of toiletries and cosmetics; or pesticide use) were located. As noted earlier, FDA (2005b) established an action level of 10 ppb (μg/kg) for NDMA in rubber baby bottle nipples in the United States more than 30 years ago, so it is expected that current NDMA levels are lower than 10 μg/kg.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational settings in which there is potential for exposure to NDMA include, but are not limited to, leather tanneries; rubber and tire industries; rocket fuel industries; dye manufacturers; soap, detergent and surfactant industries; foundries (core-making); fish-processing industries (fish-meal production); pesticide manufacturers; warehouse and sale rooms (especially for rubber products); and laboratories using NDMA for experiments (Ducos et al. 1988; de Vocht et al. 2007; Oury et al. 1997; Reh and Fajen 1996; Rounbehler et al. 1979; Spiegelhalder and Preussman 1983; Tricker et al. 1989). Nitrosamines such as NDMA may form in the air of occupational settings when nitrogen oxides, which are ubiquitous in air, react with amines and moisture. Exposure may result from inhalation or dermal contact. N-nitrosamines, including NDMA, were monitored in the breathing zone of 96 workers employed at eight different companies in the rubber industry in Sweden (Jönsson et al. 2009). Total nitrosamine levels ranged from below the detection limits to 36 μg/m^3. For NDMA, the median levels ranged from below the detection limit of 0.19 μg/m^3 (3-hour sampling time) to 8.2 μg/m^3. A comprehensive study that examined levels of nitrosamines in air samples in the British rubber industry using the EU-EXASRUB database over the period of 1977–2002 reported that the arithmetic mean of measured NDMA levels over all job descriptions was 0.32 μg/m^3 (N=2,023), while the reported geometric mean was 0.16 μg/m^3; 88.7% of the samples were below the detection limits (Hidajat et al. 2019a).

It appears that those segments of the general population with potentially high exposure to NDMA from exogenous sources would include tobacco smokers and nonsmokers who come in contact with tobacco smoke for extended periods of time (reviewed by Smith et al. 2000), people who consume large quantities of foods or beverages containing NDMA or its precursors (e.g., nitrites) (Baxter et al. 2007; Fan and Lin 2018; Lee 2019; Stuff et al. 2009), and individuals who have taken medications containing NDMA or its precursors (FDA 2019a, 2019b, 2020a) for prolonged periods of time.

In addition to dietary intake of precursors, other factors can affect the rate of endogenous NDMA production. One of the most important and well-studied appears to be inflammation, which increases endogenous NO production (Hrudey et al. 2013). A number of conditions associated with inflammation have been shown to increase NO synthesis and NDMA formation in animal studies; in humans, bladder infections, schistosomiasis, and liver fluke infections have been demonstrated to result in higher levels of endogenous NDMA (reviewed by Hrudey et al. 2013).

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.

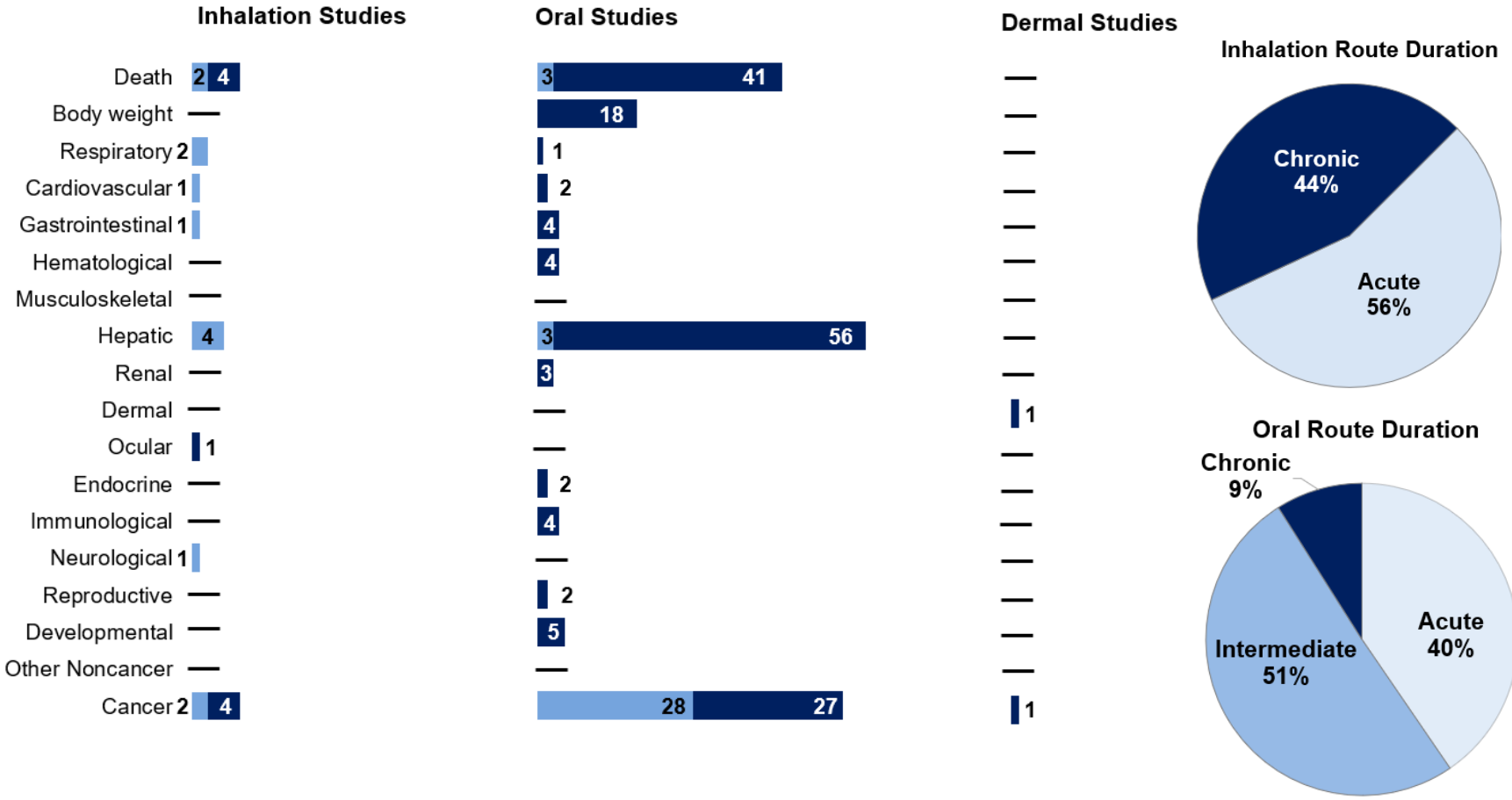
6.1 INFORMATION ON HEALTH EFFECTS

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.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding NDMA in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for NDMA.

Table 7-1. Regulations and Guidelines Applicable to N-Nitrosodimethylamine (NDMA)

Agency	Description	Information	Reference
	Air		
EPA	RfC	Not evaluated	IRIS 1987
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	No data	
	10-Day health advisory (10-kg child)	No data	
	DWEL	No data	
	Lifetime health advisory	No data	
	10^{-4} Cancer risk	0.00007 mg/L	
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	Not evaluated	IRIS 1987
	Provisional peer-reviewed toxicity values		EPA 2007
	Provisional RfD, subchronic and chronic	$8x10^{-6}$ mg/kg/day	
WHO	Drinking water quality guidelines		WHO 2022
	Guideline value	0.0001 mg/L	
FDA	Substances Added to Food[a]	Not listed	FDA 2020b
	Action level for malt beverages	5 ppb (0.005 mg/L)	FDA 2005a
	Action level for rubber baby bottle nipples	10 ppb (µg/kg)	FDA 2005b
	Acceptable intake limit in drug products	96 ng/day[b]	FDA 2021
	Cancer		
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2021

Table 7-1. Regulations and Guidelines Applicable to N-Nitrosodimethylamine (NDMA)

Agency	Description	Information	Reference
EPA	Carcinogenicity classification	B2[c]	IRIS 1987
	Inhalation unit risk	1.4×10^{-2} per µg/m^3	
	Cancer slope factor	51 per mg/kg/day	
	Cancer slope factor	21 per mg/kg/day	EPA 2016
IARC	Carcinogenicity classification	Group 2A[d]	IARC 1987
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction	No data	OSHA 2021a, 2021b, 2021c
	Worker exposure to be controlled through the required use of engineering controls, work practices, and personal protective equipment, including respirators		OSHA 2021d
NIOSH	REL (up to 10-hour TWA)	No data[e]	NIOSH 2019
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[f]	0.082 mg/m^3	
	PAC-2[f]	0.9 mg/m^3	
	PAC-3[f]	10 mg/m^3	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Limit if NDMA is the only nitrosamine. If the total quantity of nitrosamine impurities exceeds 26.5 ng/day, the manufacturer should contact the FDA for evaluation.
[c]B2: probable human carcinogen.
[d]Group 2A: probably carcinogenic to humans.
[e]Potential occupational carcinogen.
[f]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: The acute-duration inhalation data were not considered adequate for derivation of an acute-duration inhalation MRL for NDMA.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. Available animal data consist of acute lethality studies in rats, mice, and dogs exposed once for 4 hours (all reported by Jacobson et al. 1955). These authors reported LC_{50} values of 57 ppm in mice and 78 ppm in rats; in dogs, the lowest concentration tested (16 ppm) was lethal to two of three exposed animals. These data are not adequate for derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: The intermediate-duration inhalation data were not considered adequate for derivation of an intermediate-duration inhalation MRL for NDMA.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. No intermediate-duration inhalation data were located for experimental animals.

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: The chronic-duration inhalation data were not considered adequate for derivation of a chronic-duration inhalation MRL for NDMA.

Rationale for Not Deriving an MRL: No exposure concentration-response data are available for humans. Three chronic inhalation cancer bioassays in rats (Druckrey et al. 1967; Klein et al. 1989, 1991; Moiseev and Benemanski 1975) and one in mice (Moiseev and Benemanski 1975) are available, but the only nonneoplastic endpoints evaluated (by Klein et al. [1989, 1991] only) were survival and body weight, so these data were not adequate for MRL derivation.

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Acute
MRL: 0.00001 ($1x10^{-5}$) mg/kg/day (0.01 µg/kg/day)
Critical Effect: Liver effect causing decreased total blood iron binding capacity
References: Moniuszko-Jakoniuk et al. 1999; Roszczenko et al. 1996a, 1996b
Point of Departure: $BMDL_{1SD}$ of 0.0014 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 18
Species: Rat

MRL Summary: An oral MRL of 0.00001 ($1x10^{-5}$) mg/kg/day (0.01 µg/kg/day) was derived based on the 95% lower confidence limit of a benchmark dose ($BMDL_{1SD}$) of 0.0014 mg/kg/day for a liver effect resulting in decreased total blood iron binding capacity in rats exposed to NDMA in drinking water for 10 days. An uncertainty factor (UF) of 100 (10 for animal to human and 10 for human variability) was applied to the BMDL to derive the acute-duration oral MRL.

Selection of the Critical Effect: No dose-response data are available for humans. Abundant data indicate that the liver is the most sensitive endpoint for toxic effects following oral exposure to NDMA after all durations. In every species tested (including rats, mice, hamsters, monkeys, dogs, cats, guinea pigs, and mink), oral exposure to NDMA induced severe damage to the liver (see, for example, Anderson et al. 1992a; Carter et al. 1969; Khanna and Puri 1966; Maduagwu and Bassir 1980; Nishie 1983; Ungar 1984). The liver effects, mediated by reactive metabolites of NDMA, are typically characterized by hemorrhagic necrosis, followed (if the animal survives) by fibrosis, cirrhosis, and portal hypertension. These effects have been seen after acute-, intermediate-, and chronic-duration exposures. Many of the studies of animals exposed orally to NDMA identified serious LOAELs for hepatic effects without NOAELs.

Table A-1 shows the studies reporting effects at the lowest oral doses in acute-duration studies. Effects observed at the lowest dose (0.0016–0.002 mg/kg/day) included altered iron parameters (Roszczenko et al. 1996b) and increased serum AST, ALT, ALP, and GGT (Roszczenko et al. 1996a). Thus, these studies indicate effects on the circulation of iron in the blood and concurrently on the liver. The liver plays an important role in maintaining iron levels (production of proteins that regulate iron; storage of excess iron; and mobilization of iron to systemic circulation as needed), and perturbations of iron circulation, with concomitant hematological abnormalities, frequently accompany liver disease (reviewed by Anderson and Shah 2013 and Gkamprela et al. 2017). NDMA treatment in dogs and rats has been used as a model for human liver fibrosis (and its sequelae of cirrhosis, portal hypertension, and hepatocellular carcinoma) for nearly 40 years. Hepatic effects have been observed in animals and humans after NDMA exposure. Therefore, it is possible that the decrements in iron binding parameters at the low doses used by Roszczenko et al. (1996b) are related to the early liver effects (increases in serum hepatic enzyme levels) observed at comparable doses in the study by Roszczenko et al. (1996a). Although data demonstrating a clear mechanistic linkage between the iron binding and hepatic changes are not available, it is clear that the decreases in iron circulation parameters are adverse: inadequate circulating iron in humans leads to symptoms of anemia including fatigue, weakness, and difficulty concentrating, as well as effects on growth and development in infants and children. Furthermore, the identification of a LOAEL at this dose (0.0016 mg/kg/day; Roszczenko et al. 1996b) is supported by the LOAEL for adverse hepatic effects at a comparable dose (0.002 mg/kg/day) (Roszczenko et al. 1996a).

Table A-1. Summary of Acute-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤5 mg/kg/day)

Species (Strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar, male)	10 days, 7 days/week (W)	0.0007	0.0016	Decreased serum total and latent iron binding capacity	Roszczenko et al. 1996b
Rat (Wistar, male)	10 days, 7 days/week (W)	ND	0.002	Increased serum AST, ALT, ALP, and GGT (no other endpoints evaluated)	Roszczenko et al. 1996a
Rat (Wistar, male)	10 days, 7 days/week (W)	0.003	ND	No changes in liver histopathology	Moniuszko-Jakoniuk et al. 1999
Rat (Crl:CD[SD], male)	14 days, 7 days/week (GW)	ND	1	Inflammatory cell infiltration	Hamada et al. 2015; Takashima et al. 2015
Rat (strain NS)	Once (G)	0.7	1.9	Vacuolation	Korsrud et al. 1973
Mouse (Swiss-Webster)	4 days (G)	ND	3.75	Hepatocellular hypertrophy	Nishie et al. 1972
Rat (strain NS)	7–14 days (F)	ND	3.75 (serious LOAEL)	Necrosis	Khanna and Puri 1966
Mouse (CD-1)	14 days, 7 days/week (G)	ND	4	Increased serum ALT and AST	Doolittle et al. 1987
Hamster (Golden)	1–14 days, 7 days/week (W)	ND	4	Increased serum ALT and AST	Ungar 1984
Rat (F344)	14 days, 7 days/week (G)	ND	4 (serious LOAEL)	Necrosis	Asakura et al. 1998
Other (death, cancer)					
Mouse (A/JNCR)	Once (G)	ND	5 (CEL)	Lung tumors at sacrifice 16 weeks after dosing	Anderson et al. 1992a
Cat (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	LD_{50}	Maduagwu and Bassir 1980
Monkey (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	LD_{50}	Maduagwu and Bassir 1980
Rat (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	LD_{50}	Maduagwu and Bassir 1980

Table A-1. Summary of Acute-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤5 mg/kg/day)

Species (Strain)	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Guinea pig (strain NS)	5–11 days (G)	NA	5 (serious LOAEL)	Death	Maduagwu and Bassir 1980

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEL = cancer effect level; (F) = feed; (G) = gavage; GGT= gamma-glutamyl transferase; (GW) = gavage in water; LD_{50} = medial lethal dose; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; (W) = water

As Table A-1 shows, effect levels for the studies by Roszczenko et al. (1996 a, 1996b) and Moniuszko-Jakoniuk et al. (1999) were substantially lower than the remaining effect levels (≥1.9 mg/kg/day) (Korsrud et al. 1973); thus, these studies were considered for use in deriving the MRL.

Selection of the Principal Study: The lowest LOAEL was 0.0016 mg/kg/day for altered iron indices in the 10-day study by Roszczenko et al. (1996b); a NOAEL of 0.0007 mg/kg/day was identified for this study. A comparable LOAEL of 0.002 mg/kg/day was identified for increased serum AST, ALT, ALP, and GGT in a parallel single dose study by Roszczenko et al. (1996a). Moniuszko-Jakoniuk et al. (1999) was a multi-dose study for which a NOAEL of 0.003 mg/kg/day was identified for liver histology.

Both of the studies by Roszczenko et al. (1996a, 1996b) examined limited endpoints (serum enzyme and iron indices), and neither included organ weight or histopathology evaluation of the liver. The lack of histopathology data in these studies raises the question of whether the dose of 0.0016 mg/kg/day could be considered a serious LOAEL. However, this same group of investigators conducted a third study (Moniuszko-Jakoniuk et al. 1999) of comparable design in which histopathology was examined in the liver, spleen, and bone marrow. All three studies were conducted in male Wistar rats of approximately the same initial body weight (190–220 g), and in all studies, the rats were administered NDMA in drinking water at concentrations of 0.01–0.05 mg/L for 10 days. In the study by Moniuszko-Jakoniuk et al. (1999), a NOAEL of 0.003 mg/kg/day was identified, based on a lack of histopathology changes in the liver, bone marrow, and spleen after 10 days of exposure. The results of this study provide support for the conclusion that the LOAEL identified for Roszczenko et al. (1996b) is not a serious LOAEL.

Considering the data for the three studies together, Roszczenko et al. (1996b) was chosen as the principal study for the derivation of the acute-duration oral MRL. The study identified the lowest LOAEL, with a corresponding NOAEL. Support for the LOAEL and NOAEL determination for Roszczenko et al. (1996b) is provided by the other studies conducted by the same group of investigators (Moniuszko-Jakoniuk et al. 1999; Roszczenko et al. 1996a).

Summary of the Principal and Supporting Studies:

Roszczenko A, Jabloński J, Moniuszko-Jakoniuk J, et al. 1996b. The influence of low doses of N-nitrosodimethylamine on the chosen parameters of iron balance in rat. Polish J Environ Studies 5(5):37-40.

Roszczenko et al. (1996b) administered NDMA in drinking water to groups of seven male Wistar rats for 10 days at concentrations of 10, 20, and 50 µg/L (0.01, 0.02, or 0.05 mg/L) in a study evaluating iron indices. Exposure concentrations were estimated by the study authors to result in doses of 0.0007, 0.0016, or 0.0035 mg/kg/day, respectively. The animals were sacrificed at the end of the 10-day

exposure. Blood was collected for analysis of hematocrit and hemoglobin concentration. In addition, iron, latent iron binding capacity (portion of the plasma transferrin molecule that is not bound to iron), total iron binding capacity (maximum concentration of iron that can be bound to transferrin), and the percentage transferrin saturation were measured in serum. Iron concentrations in the liver and spleen were analyzed. At the lowest dose, no statistically significant effect on any measured parameter was observed. Significant increases in hemoglobin concentration were seen at doses ≥0.0016 mg/kg/day (8 and 15% at 0.0016 and 0.0035 mg/kg/day, respectively). Hematocrit was not significantly increased at any dose. Serum iron concentration was significantly decreased by 36% at the high dose. Significant decreases in total iron binding capacity[1] were observed at doses ≥0.0016 mg/kg/day (18 and 30% at 0.0016 and 0.0035 mg/kg/day, respectively). Latent (unsaturated) iron binding capacity was significantly decreased by 42% at 0.0016 mg/kg/day, but there was no significant difference at 0.0035 mg/kg/day. There was no significant change in the percent transferrin saturation, despite values that decreased with dose (7% decrease at 0.0016 mg/kg/day and 14% decrease at 0.0035 mg/kg/day). After 10 days of exposure, there were no significant differences in the iron content of the liver or spleen. A NOAEL of 0.0007 mg/kg/day and a LOAEL of 0.0016 mg/kg/day were identified for this study based on the decreases in total and latent (unsaturated) iron binding capacity.

Roszczenko A, Jablonski J, Moniuszko-Jakoniuk J. 1996a. [Effect of n-nitrosodimethylamine (NDMA) on activity of selected enzymes in blood serum of the rat (translation and original document)]. Med Pr 47(1):49-53 (Polish).

Roszczenko et al. (1996a) administered NDMA in drinking water at a concentration of 20 µg/L (0.02 mg/L) to groups of seven male Wistar rats for 10 days, yielding a dose estimated by the authors to be 0.002 mg/kg/day. The only endpoints measured were serum enzymes (AST, ALT, ALP, and GGT) assessed at the end of exposure. Statistically significant increases of ≥2-fold (compared with controls) in all four enzymes were observed: serum AST, ALT, and ALP were doubled, and a 6-fold increase in GGT was measured.

Moniuszko-Jakoniuk J, Roszczenko A, Dzieciol J. 1999. Influence of low concentrations of N-nitrosodimethylamine on the iron level and histopathological picture of rats liver, spleen, and bone marrow. Acta Poloniae Toxicologica 7(2):179-186.

In the study by Moniuszko-Jakoniuk et al. (1999) groups of eight male Wistar rats were exposed to NDMA concentrations of 30 or 45 µg/L (0.03 or 0.045 mg/L) in drinking water for 10 days. The study authors did not estimate doses; based on the ratio of dose to concentration (0.0035 mg/kg/day for 0.05 mg/L) reported by Roszczenko et al. (1996b), the concentrations in the Moniuszko-Jakoniuk et al. (1999) study (0.03 and 0.045 mg/L) were estimated to result in doses of approximately 0.002 and 0.003 mg/kg/day, respectively. The control group (n=24) received drinking water without added NDMA. When sacrificed at the end of the exposure period, iron content of the liver and spleen was measured, and histopathology was evaluated in the liver, bone marrow, and spleen. There was no effect on the iron content of the liver or spleen, and there were no histopathological changes observed in the liver, bone marrow, or spleen in either dose group after 10 days of exposure.

Selection of the Point of Departure for the MRL: BMD modeling was performed for each of the iron indices evaluated by Roszczenko et al. (1996b), as shown in Table A-2.

[1]Total iron binding capacity refers to the sum of serum iron and serum unsaturated (latent) iron-binding capacity. Percentage transferrin saturation is calculated by dividing the serum iron concentration by the total iron binding capacity and multiplying by 100.

Table A-2. Changes in Iron Indices in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days

	Exposure dose (mg/kg/day)			
	0	0.0007	0.0016	0.0035
Number of animals	7	7	7	7
Total iron binding capacity (µmol/L)	**138.94±22.74**	**120.13±10.04 (-14%)**	**114.12±13.97[b] (-18%)**	**96.94±4.93[c] (-30%)**
Hematocrit (%)	26.27±1.65[a]	26.1±1.21 (-1%)	27.31±1.58 (4%)	27.3±2.34 (4%)
Hemoglobin (g/L)	11.91±0.73	13.01±1.02 (9%)	12.88±0.74[b] (8%)	13.69±1.27[b] (15%)
Latent iron binding capacity (µmol/L)	100.62±17.56	101.26±10.02 (1%)	57.93±7.28[b] (-42%)	87.14±6.86 (-13%)
Percent transferrin saturation (%)	47.34±6.05	51.16±7.62 (8%)	43.83±6.94 (-7%)	40.52±5.90 (-14%)
Serum iron (µmol/L)	65.88±10.05	66.78±8.09 (1%)	59.21±6.59 (-10%)	41.95±2.41[b] (-36%)

[a]Mean±standard deviation.
[b]Statistically significantly ($p<0.05$) different from controls.
[c]Statistically significantly ($p<0.001$) different from controls.

Source: Roszczenko et al. 1996b

The data for iron indices shown in Table A-2 were fit to continuous models in EPA's Benchmark Dose Software (BMDS; version 3.1.2) using a benchmark response (BMR) of 1 standard deviation. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMDL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the point of departure (POD) when the difference between the BMDLs estimated from these models was ≥3 fold; otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) was chosen. All continuous models were applied to the data and considered for the derivation of a POD except for the Hill model; the continuous Hill model has five parameters and requires a dataset with a minimum of six datapoints (including control).

For latent iron binding capacity (µmol/L), none of the models provided an adequate fit to the variance data with or without the variance model applied.

For total iron binding capacity, constant variance models did not provide adequate fit to the variance data. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means for total iron binding capacity. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Polynomial models and Power model converged on the form of the linear model. The Linear model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.0021 and 0.0014 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-3.

Table A-3. Model Predictions (Non-Constant Variance) for Total Iron Binding Capacity (µmol/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	Scaled residuals[c]		
				AIC	Dose near BMD	Dose near control
Exponential (model 2)[d]	0.0014	0.0010	0.14	223.62	-0.23	0.69
Exponential (model 3)[d]	0.0014	0.0010	0.14	223.62	-0.23	0.69
Exponential (model 4)[d]	0.0010	0.0006	0.10	224.73	-0.90	0.18
Exponential (model 5)[d]	0.0010	0.0006	0.10	224.74	-0.88	0.24
Polynomial (3-degree)[e]	0.0021	0.0014	0.21	223.28	-0.31	1.03
Polynomial (2-degree)[e]	0.0021	0.0014	0.21	223.28	-0.31	1.03
Power[d]	0.0021	0.0014	0.21	223.28	-0.31	1.03
Linear[e,f]	**0.0021**	**0.0014**	**0.21**	**223.28**	**-0.31**	**1.03**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. Constant variance models did not provide adequate fit to the variance data. With non-constant variance model applied, all models provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with a one standard deviation change in outcome from control mean)

For hematocrit, constant variance models provided adequate fit to the variance data; however, the upper bound on the benchmark dose (BMDU) was infinite (unbounded) for all models. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means. The BMDUs for the Exponential 2, Exponential 3, Exponential 4, and Power models could not be determined (infinity); therefore, these models were not considered. The BMD computation failed for the Exponential 5 model; therefore, the BMD and BMDL could not be estimated. Visual inspection of the remaining dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the remaining models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The BMD of the selected model was slightly higher (0.0036 mg/kg/day) than the maximum dose tested (0.0035 mg/kg/day). The Linear model estimated a BMD_{1SD} and $BMDL_{1SD}$ of 0.0036 and 0.0015 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-4.

Table A-4. Model Predictions (Non-Constant Variance) for Hematocrit (%) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]			0.50	112.44	-0.46	0.20
Exponential (model 3)[d]			0.50	112.44	-0.46	0.20
Exponential (model 4)[d]			0.32	114.38	-0.38	0.31
Exponential (model 5)[d]			0.26	115.35	-9999	0.23
Polynomial (3-degree)[e]	0.0035	0.0015	0.22	115.62	-0.33	0.09
Polynomial (2-degree)[e]	0.0036	0.0015	0.22	115.62	-0.29	0.05
Power[d]			0.23	115.56	-0.33	0.01
Linear[e,f]	**0.0036**	**0.0015**	**0.46**	**113.63**	**-0.28**	**0.12**

[a]BMD and BMDL values for models that do not provide adequate fit, for models that failed to calculate BMDLs, and for models with infinite BMDUs are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data; however, the BMDU was infinity for all models. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means. The BMD computation failed for the Exponential 5 model; therefore, the BMD and BMDL could not be estimated. The BMDUs for the Exponential 2, Exponential 3, Exponential 4, and Power models could not be determined (infinity); therefore, these models were not selected. BMDLs for the remaining models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with a one standard deviation change in outcome from control mean); BMDU = upper bound on the BMD

For hemoglobin, all applicable constant variance models provided adequate fit to the variance data. The BMDU for the Exponential 4 and 5 models could not be determined (infinity) so these models were not selected. Visual inspection of the remaining dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the remaining models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Polynomial 2-degree, polynomial 3-degree and power models converged on the form of the linear model. The Linear model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 0.0022 and 0.0014 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-5.

Table A-5. Model Predictions (Constant Variance) for Hemoglobin Concentration (g/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	0.0023	0.0015	0.24	82.08	-0.12	-0.99
Exponential (model 3)[d]	0.0023	0.0015	0.24	82.08	-0.12	-0.99
Exponential (model 4)[d]			0.18	83.04	0.87	-0.26
Exponential (model 5)[d]			0.18	83.04	0.87	-0.26
Polynomial (3-degree)[e]	0.0022	0.0014	0.25	81.99	-0.16	-0.95
Polynomial (2-degree)[e]	0.0022	0.0014	0.25	81.99	-0.16	-0.95
Power[d]	0.0022	0.0014	0.25	81.99	-0.16	-0.95
Linear[e,f]	**0.0022**	**0.0014**	**0.25**	**81.99**	**-0.16**	**-0.95**

[a]BMD and BMDL values for models that do not provide adequate fit and for models with infinite BMDUs are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model. Constant variance models provided adequate fit to the variance data. The 95% upper bounds for the Exponential 4 and 5 models were infinity. BMDLs for the remaining models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Polynomial 2-degree, polynomial 3-degree and power models converged on the form of the linear model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC is selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with a one standard deviation change in outcome from control mean); BMDU = upper bound on the BMD

For percent transferrin saturation, all applicable constant variance models provided adequate fit to the variance data. Only the Exponential 2 and Linear models provided adequate fit to the means. Visual inspection of the dose-response curves for these models suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear). The Linear model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 0.0026 and 0.0016 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-6.

Table A-6. Model Predictions (Constant Variance) for Percent Transferrin Saturation in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	0.0025	0.0014	0.19	190.72	-0.56	-0.85
Exponential (model 3)[d]			0.09	192.32	0.16	-0.62
Exponential (model 4)[d]			0.07	192.72	-0.56	-0.85
Exponential (model 5)[d]			NA	192.67	0.00	-0.80
Polynomial (3-degree)[e]			0.08	192.52	0.13	-0.61
Polynomial (2-degree)[e]			0.08	192.52	0.13	-0.61
Power[d]			0.08	192.37	0.15	-0.61
Linear[e,f]	**0.0026**	**0.0016**	**0.19**	**190.66**	**-0.01**	**-0.82**

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be negative.
[f]Selected model. Constant variance models provided adequate fit to the variance data. Only the Exponential 2 and Linear models provided an adequate fit to the means. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Linear).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with a one standard deviation change in outcome from control mean)

For serum iron concentration (μmol/L), constant variance models did not provide adequate fit to the variance data. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means, except for the Exponential 4 and 3-degree polynomial models. Visual inspection of the dose-response curves suggested adequate fit, BMDLs were not 10 times lower than the lowest non-zero dose, and scaled residuals did not exceed ±2 units at the data point closest to the predefined BMR. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 3). The Exponential 3 model estimated a BMD_{1SD} and a $BMDL_{1SD}$ of 0.0017 and 0.0011 mg/kg/day, respectively. The results of the BMD modeling are summarized in Table A-7.

Table A-7. Model Predictions (Non-Constant Variance) for Serum Iron Concentration (µmol/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)

Model	BMD_{1SD}[a] (mg/kg/day)	$BMDL_{1SD}$[a] (mg/kg/day)	Test 4 p-Value[b]	AIC	Scaled residuals[c] Dose near BMD	Scaled residuals[c] Dose near control
Exponential (model 2)[d]	0.0011	0.0008	0.18	186.63	0.54	-1.58
Exponential (model 3)[d,e]	**0.0017**	**0.0011**	**0.85**	**184.13**	**-0.16**	**-0.44**
Exponential (model 4)[d]			0.09	188.63	0.53	-1.60
Exponential (model 5)[d]	0.0017	0.0011	0.72	185.92	-0.01	-0.24
Polynomial (3-degree)[f]			NA	188.36	-0.25	-0.50
Polynomial (2-degree)[f]	0.0018	0.0011	0.54	186.17	-0.24	-0.40
Power[d]	0.0018	0.0011	0.61	186.04	-0.18	-0.39
Linear[f]	0.0013	0.0009	0.31	186.15	0.69	-1.25

[a]BMD and BMDL values for models that do not provide adequate fit are not included in the table.
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at concentrations immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance models did not provide adequate fit to the variance data. With the non-constant variance applied, all applicable models provided adequate fit to both the variance and the means, except for the Exponential 4 and 3-degree polynomial models. BMDLs for the adequately fit models were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 3).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{1SD}$ = exposure concentration associated with a one standard deviation change in outcome from control mean)

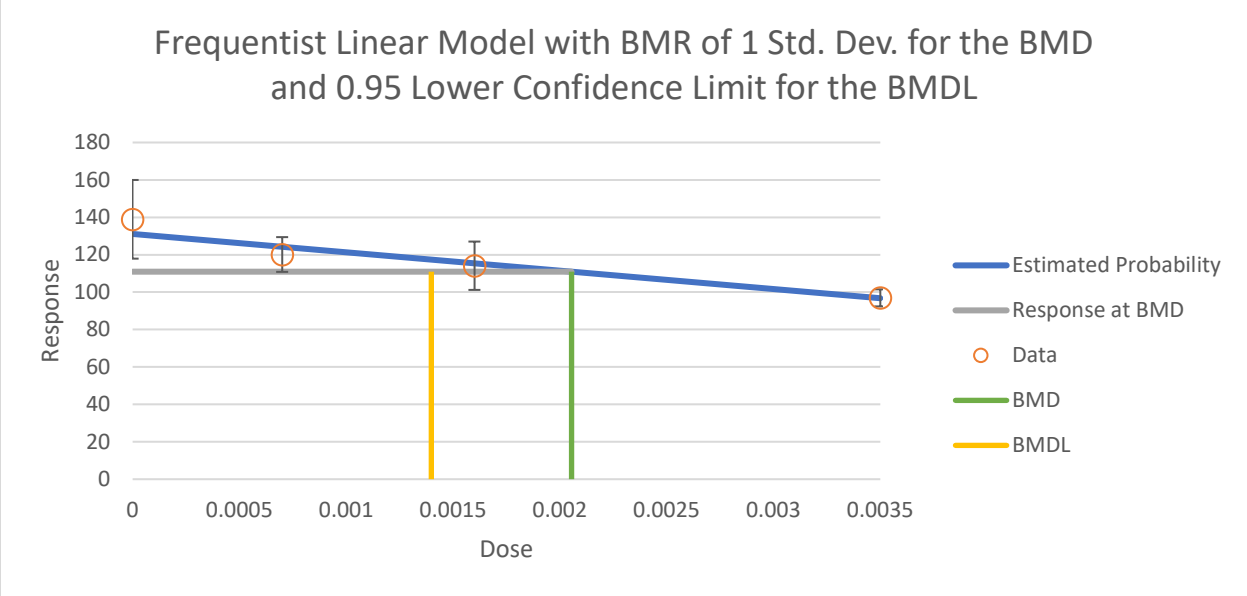
Table A-8 summarizes the potential candidate PODs for the acute-duration oral MRL for NDMA. The BMDL values were similar among the candidate endpoints (0.0011–0.0016 mg/kg/day). The $BMDL_{1SD}$ value of 0.0014 mg/kg/day for decreased total iron binding capacity was selected as the critical effect following acute-duration oral exposure to NDMA, as it is the most sensitive effect showing a monotonic change (Table A-2). Modeling results for the other candidate endpoints provide strong support for the selected POD. The Linear model fit to the total iron binding capacity data is presented in Figure A-1.

Table A-8. Candidate Points of Departure for the Acute-Duration Oral MRL

Endpoint	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ mg/kg/day)
Total iron binding capacity			**0.0021**	**0.0014**
Percent hematocrit			0.0036	0.0015
Hemoglobin			0.0022	0.0014
Latent iron binding capacity	0.0007	0.0016	No model fit	
Percent transferrin saturation			0.0026	0.0016
Serum iron			0.0017	0.0011

BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; SD = standard deviation

Figure A-1. Fit of Linear Model (Non-constant Variance) to Total Iron Binding Capacity (µmol/L) in Male Wistar Rats Following Exposure to N-Nitrosodimethylamine in Drinking Water for 10 Days (Roszczenko et al. 1996b)



Uncertainty Factor: The $BMDL_{1SD}$ was divided by a total uncertainty factor (UF) of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = $BMDL_{1SD}$ ÷ (UF)
0.0014 mg/kg/day ÷ (10 x 10) ≈ 0.00001 mg/kg/day ($1x10^{-5}$ mg/kg/day)

Other Additional Studies or Pertinent Information that Lend Support to this: As discussed above, the studies by Roszczenko et al. (1996a) and Moniuszko-Jakoniuk et al. (1999) provide support for the effect level determinations by Roszczenko et al. (1996b). Examples of other studies that demonstrate liver

toxicity, often severe, after oral exposure to higher doses of NDMA in rats, mice, hamsters, monkeys, dogs, cats, guinea pigs, and mink include: Anderson et al. (1992a); Carter et al. (1969); Hamada et al. 2015; Khanna and Puri (1966); Maduagwu and Bassir (1980); Nishie (1983); Takashima et al. 2015; and Ungar (1984).

Agency Contacts (Chemical Managers): Custodio Muianga, PhD, MPH, CHMM

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: The intermediate-duration oral data were not considered adequate for derivation of an intermediate-duration oral MRL for NDMA.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-9 summarizes results from candidate intermediate-duration oral studies in laboratory animals.

Table A-9. Summary of Intermediate-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤1.5 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.0016 (severity unknown)	Altered iron indices after 30 days	Roszczenko et al. 1996b
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.002 (severity unknown)	Increased serum AST, ALT, ALP, and GGT after 30 days	Roszczenko et al. 1996a
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.002 (serious LOAEL)	Degeneration, argyrophilic and collagenic fibers, and inflammatory infiltrations near portal biliary tract after 30 days; steatosis and parenchymatosis after 90 days	Moniuszko-Jakoniuk et al. 1999
Mink	122 days, 7 days/week (F)	0.08	0.13	Venopathy	Koppang and Rimeslatten 1976
Rabbit (New Zealand)	12 weeks, 7 days/week (GW)	ND	0.5 (serious LOAEL)	Necrosis; vascular degeneration; central vein congestion	Sheweita et al. 2017
Dog (Beagles)	24 weeks, 2 days/week at 2 mg/kg (C)	ND	0.6 (serious LOAEL)	Severe hepatic effects including histopathology; elevated serum enzyme levels; and ascites	Boothe et al. 1992
Dog (Mongrel)	4 weeks, 2 days/week at 2.51 mg/kg (C)	ND	0.72 (serious LOAEL)	Necrosis; fibrosis; increased serum AST and ALT	Hashimoto et al. 1989

Table A-9. Summary of Intermediate-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤1.5 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Dog (Mongrel)	4 weeks, 2 days/week at 2.51 mg/kg (C)	ND	0.72 (serious LOAEL)	Necrosis; fibrosis; increased serum AST, ALT, ALP, and bilirubin; ascites	Madden et al. 1970
Rat (strain NS)	30 days, 1 time/day (G)	ND	1	Vacuolation and congestion	Maduagwu and Bassir 1980
Monkeys and guinea pigs (species NS)	30 days, 1 time/day (G)	ND	1 (serious LOAEL)	Necrosis	Maduagwu and Bassir 1980
Rat (Crl:CD[SD], male)	28 days, 7 days/week (G)	1	2	Inflammatory cell infiltration	Hamada et al. 2015; Takashima et al. 2015
Rat (Sprague-Dawley)	15 days, 1 time/day (GW)	0.5	2 (serious LOAEL)	Hepatocyte degeneration and fibrosis	Rothfuss et al. 2010
Hematology effects					
Rat (Wistar, male)	30 or 90 days, 7 days/week (W)	ND	0.002 (serious LOAEL)	Bone marrow histopathology changes after 90 days: focal necrosis; edema, degeneration; decrease in megakaryocytes and migration to vascular sinus; myelosclerosis	Moniuszko-Jakoniuk et al. 1999
Developmental effects					
Mouse (CD-1)	75 days prior to mating and through pregnancy until weaning (W)	ND	0.026 (serious LOAEL)	Perinatal death (stillborn and within 2 days of birth)	Anderson et al. 1978
Reproductive effects					
Rabbit (New Zealand)	12 weeks, 7 days/week (GW)	ND	0.5 (serious LOAEL)	Histopathology changes in testes	Sheweita et al. 2017
Immune system effects					
Mouse (C57BL/6)	13 weeks, 7 days/week (W)	0.26	1.3	Immunosuppression	Desjardins et al. 1992
Other (death, cancer)					
Mouse (A/JNCr)	16–48 weeks, 7 days/week (W)	ND	0.25 (CEL)	Lung tumors	Anderson et al. 1992a
Mink	23–34 days, 7 days/week (F)	ND	0.32 (serious LOAEL)	Death	Carter et al. 1969
Rat (MRC)	30 weeks, 5 days/week (W)	ND	0.4 (CEL)	Liver tumors	Keefer et al. 1973

Table A-9. Summary of Intermediate-Duration Oral Studies of N-Nitrosodimethylamine in Animals (Doses ≤1.5 mg/kg/day)

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Mouse (RF)	32 weeks, 7 days/week (W)	ND	0.4 (CEL)	Lung tumors	Clapp and Toya 1970
Rat (F344)	30 weeks, (5 days/week) (W)	ND	0.75 (serious LOAEL, CEL)	Decreased survival and liver tumors	Lijinsky and Reuber 1984
Cats (strain NS)	30 days, 1 time/day (G)	ND	1 (serious LOAEL)	Death	Maduagwu and Bassir 1980
Mouse (Swiss)	38 weeks, 7 days/week (W)	ND	1 (serious LOAEL, CEL)	Decreased survival and liver, lung, and kidney tumors	Terracini et al. 1966
Hamster (Syrian Golden)	Up to 7 months, 7 days/week (W)	ND	1.1 (serious LOAEL)	Decreased survival and liver tumors	Bosan et al. 1987
Mouse (C3Hf)	13 weeks, 7 days/week (W)	ND	1.2 (serious LOAEL, CEL)	Decreased survival; liver and lung tumors	Den Engelse et al. 1974
Rat (Wistar)	30 weeks, 7 days/week (W)	ND	1.5 (serious LOAEL, CEL)	Decreased survival and liver tumors	Takahashi et al. 2000

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; (C) = capsule; CEL = cancer effect level; (F) = feed; (G) = gavage; GGT= gamma-glutamyl transferase; (GW) = gavage in water; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; (W) = water

Roszczenko et al. (1996b) identified effects at the lowest dose (0.0016 mg/kg/day) tested in any intermediate-duration study. In this study, groups of seven male Wistar rats were exposed to NDMA in drinking water for 30 or 90 days in a study evaluating iron indices. Exposure concentrations of 10 or 20 μg/L (0.01 and 0.02 mg/L) were estimated by the study authors to yield doses of 0.0007 and 0.0016 mg/kg/day, respectively. At sacrifice at the end of exposure, blood was collected for analysis of hematocrit and hemoglobin concentration. Iron, total and latent iron binding capacity, and percentage transferrin saturation in serum were measured. Iron concentration in the liver and spleen were analyzed. At 0.0007 mg/kg/day, no statistically significant effect on any measured parameter was observed. At 0.0016 mg/kg/day, there was a significant 28% increase in hemoglobin concentration, but no effect on hematocrit. Serum iron concentration was not significantly affected by treatment. Latent iron binding capacity was significantly decreased by 51%, and there was a significant, 22% increase in percent transferrin saturation. Total iron binding capacity was lower than controls at 0.0016 mg/kg/day, but the difference (16%) was not statistically significant. Iron content of the liver did not differ significantly from controls in treated animals, but there was a significant and marked 87% increase in iron content of the spleen.

In the related study by Roszczenko et al. (1996a), NDMA was administered in drinking water at a concentration of 20 μg/L (0.02 mg/L) to groups of seven male Wistar rats for 30 or 90 days, yielding a dose of approximately 0.002 mg/kg/day. The only endpoints measured in this study were serum enzymes (AST, ALT, ALP, and GGT). Statistically significant increases in enzymes were observed at all time

points. After 30 days, serum AST was increased by 10% compared to controls; ALT and ALP concentrations were doubled; and a 4-fold increase in GGT was measured. Results at 90 days were similar to those after 30 days.

Neither of the studies by Roszczenko et al. (1996a, 1996b) evaluated organ weights or liver or other organ histopathology; thus, the severity of the effect levels in the intermediate-duration experiments conducted by these authors is uncertain. In a third study by these investigators (Moniuszko-Jakoniuk et al. 1999), groups of eight male Wistar rats were exposed to NDMA in drinking water (0.03 and 0.045 mg/L) at estimated doses of 0.002 and 0.003 mg/kg/day for 30 or 90 days; iron content of the liver and spleen and histopathology of the liver, bone marrow, and spleen were assessed. After 30 days, liver histopathology changes including degeneration, argyrophilic and collagenic fibers, and inflammatory infiltrations near the portal biliary tract were observed at both doses, and at 0.003 mg/kg/day, there were bone marrow changes including focal necrosis, edema, and degeneration. After 90 days, the liver effects at both doses were more severe, including steatosis and parenchymatosis, and there were histopathology changes at both doses in the spleen and bone marrow. The authors did not report incidences or severity scores for any of the histopathology changes.

The study by Moniuszko-Jakoniuk et al. (1999) demonstrated exposure duration- and dose-related increases in the severity of liver histopathology changes in rats exposed to doses as low as 0.002 mg/kg/day (0.03 mg/L in water) NDMA. Because there are no histopathology data for lower doses/concentrations (0.01 and 0.02 mg/L or 0.0007 and 0.0016–0.002 mg/kg/day) in the 30- and 90-day experiments by Roszczenko et al. (1996a, 1996b), a clear NOAEL cannot be determined, and the LOAELs are of uncertain severity. Therefore, the data for the intermediate duration are insufficient for derivation of a MRL.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** N-Nitrosodimethylamine
CAS Numbers: 62-75-9
Date: April 2023
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The chronic-duration oral data were not considered adequate for derivation of a chronic-duration oral MRL for NDMA.

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-10 summarizes results from candidate chronic-duration oral studies in laboratory animals.

Table A-10. Summary of Chronic-Duration Oral Studies of N-Nitrosodimethylamine in Animals

Species	Exposure scenario	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Other (death, cancer)					
Rat (Wistar)	3.5 years, 7 days/week (W)	ND	0.022 (serious LOAEL, CEL)	Decreased survival due to liver tumors	Peto et al. 1984, 1991a, 1991b
Mink (NS)	1–2 years, 7 days/week (F)	ND	0.1 (serious LOAEL, CEL)	Decreased survival, liver tumors	Koppang and Rimeslatten 1976
Rat (Wistar)	96 weeks, 7 days/week (F)	ND	0.13 (CEL)	Liver tumors	Arai et al. 1979; Ito et al. 1982
Mouse (A/JNCr)	72 weeks, 7 days/week (W)	ND	0.24 (CEL)	Lung tumors	Anderson et al. 1992a
Rat (Wistar)	54 weeks, 7 days/week (F)	ND	0.5 (CEL)	Testicular tumors	Terao et al. 1978
Mouse (RF)	Lifetime (mean 406 days), 7 days/week (W)	ND	0.43 (serious LOAEL, CEL)	Decreased survival and liver and lung tumors	Clapp and Toya 1970
Hepatic effects					
Dog (Beagle)	56 weeks, 2 days/week at 2 mg/kg (C)	ND	0.6[a] (serious LOAEL)	Fibrosis, cirrhosis, necrosis	Butler-Howe et al. 1993

[a]Adjusted for discontinuous exposure (2 mg/kg x 2/7 days/week).

(C) = capsule; CEL = cancer effect level; (F) = feed; LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; NS = not specified; (W) = water

Peto et al. (1984, 1991a, 1991b) conducted a large cancer dose-response study of NDMA in rats. Groups of 60 rats/sex were exposed to 1 of 15 concentrations of NDMA in drinking water (between 0.033 and 16.896 ppm) for 3.5 years. The authors noted that the longer duration was intended to enable effects to be

detected at very low doses. These water concentrations yielded estimated doses of 0.001–0.697 mg/kg/day (Peto et al. 1984, 1991b). Controls received untreated water. Groups of six rats/sex/dose were sacrificed after 12 and 18 months, and the remaining animals were observed until natural death, moribund appearance, or appearance of palpable liver abnormalities. Macroscopic necropsies were performed on all animals. Histopathology examinations were performed on grossly observed lesions; apart from these, only the liver and esophagus were routinely examined microscopically. Results for the interim sacrifices were not reported separately. In both male and female rats, NDMA doses ≥0.022 mg/kg/day were associated with decreased survival due to liver tumors. Significant dose-related trends were observed for several liver lesions, including hyperplastic nodules, cytomegaly, cysts, hepatocyte shrinkage (males only), and abnormality of glycogen-containing cells (females only). The incidences of these lesions were not significantly different from controls at doses <0.022 mg/kg/day in pairwise statistical tests (Fisher's exact test). However, these lesions may reflect preneoplastic changes, and the incidences may have been influenced by progression to tumors (liver neoplasms were observed at all doses); thus, neither NOAEL nor LOAEL values can be identified from these data.

As Table A-5 shows, the remaining chronic studies used single exposure levels much higher than the serious LOAEL of 0.022 mg/kg/day from Peto et al. (1984, 1991a, 1991b) and identified serious LOAELs for decreased survival and/or CELs. Therefore, the available data do not provide an adequate basis for derivation of a chronic-duration oral MRL.

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APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR NDMA

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to NDMA.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for NDMA. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of NDMA have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of NDMA are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the Draft Toxicological Profile for NDMA released for public comment in 2022; thus, the literature search was restricted to studies published between June 2019 and June 2022. The following main databases were searched in June 2022:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for NDMA. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to NDMA were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
06/2022	("Dimethylnitrosamine"[mh] OR 62-75-9[rn] OR "dimethyl-nitrosamine"[tw] OR "Dimethylamine, N-nitroso-"[tw] OR "Dimethylnitrosamine"[tw] OR "Dimethylnitrosoamine"[tw] OR "Methanamine, N-methyl-N-nitroso-"[tw] OR "N,N-Dimethylnitrosamine"[tw] OR "N,N-dimethylnitrous amide"[tw] OR "N-Dimethyl-nitrosamine"[tw] OR "N-Methyl-N-nitrosomethanamine"[tw] OR "N-Nitroaodimethylamine"[tw] OR "N-Nitroso-N,N-dimethylamine"[tw] OR "n-Nitrosodimethylamine"[tw] OR "Nitrosamine, dimethyl-"[tw] OR "Nitrosodimethylamine"[tw] OR "P082"[tw] OR (("DMNA"[tw] OR "NDMA"[tw]) AND ("Nitrosamines"[mh] OR carcinogen*[tw] OR mutagen*[tw] OR disinfect*[tw] OR drinking[tw])) OR (("DMNA"[tw] OR "NDMA"[tw]) NOT medline[sb])) AND (2019/06/01:3000[mhda] OR 2019/06/01:3000[crdat] OR 2019/06/01:3000[edat] OR 2019:3000[dp])
NTRL	
06/2022	Date Published 2018 to 2022 "dimethyl-nitrosamine" OR "Dimethylamine, N-nitroso-" OR "Dimethylnitrosamine" OR "Dimethylnitrosoamine" OR "Methanamine, N-methyl-N-nitroso-" OR "N,N-Dimethylnitrosamine" OR "N,N-dimethylnitrous amide" OR "N-Dimethyl-nitrosamine" OR "N-Methyl-N-nitrosomethanamine" OR "N-Nitroaodimethylamine" OR "N-Nitroso-N,N-dimethylamine" OR "n-Nitrosodimethylamine" OR "Nitrosamine, dimethyl-" OR "Nitrosodimethylamine" OR "DMNA" OR "NDMA"
Toxcenter	
6/2022	FILE 'TOXCENTER' ENTERED AT 15:12:07 ON 09 JUN 2022 CHARGED TO COST=EH038.12.05.LB.04 L1 13422 SEA FILE=TOXCENTER 62-75-9 L2 13208 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 13184 SEA FILE=TOXCENTER L2 NOT TSCATS/FS L4 486 SEA FILE=TOXCENTER L3 AND ED>=20190701 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)

Table B-2. Database Query Strings

Database search date	Query string
	L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN

Table B-2. Database Query Strings

Database search date	Query string
	L35 QUE L33 OR L34 L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 369 SEA FILE=TOXCENTER L4 AND L37 DIS COST FULL L39 96 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L41 273 SEA FILE=TOXCENTER L38 NOT MEDLINE/FS L42 308 DUP REM L39 L41 (61 DUPLICATES REMOVED) L*** DEL 96 S L38 AND MEDLINE/FS L*** DEL 96 S L38 AND MEDLINE/FS L43 96 SEA FILE=TOXCENTER L42 L*** DEL 273 S L38 NOT MEDLINE/FS L*** DEL 273 S L38 NOT MEDLINE/FS L44 212 SEA FILE=TOXCENTER L42 L45 212 SEA FILE=TOXCENTER (L43 OR L44) NOT MEDLINE/FS D SCAN L45

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via Chemview	
06/2022	Compounds searched: 62-75-9
NTP	
06/2022	Years: 2020-2022, 2010-2019 "62-75-9" "Dimethylnitrosamine" "Dimethylnitrosoamine" "Nitrosodimethylamine" Obtained duplicates of above: "dimethyl-nitrosamine" "N-Methyl-N-nitrosomethanamine" "DMNA" "NDMA" "Dimethylamine, N-nitroso-" "Methanamine, N-methyl-N-nitroso" "N,N-dimethylnitrous amide" "N-Dimethyl-nitrosamine" "N-Nitroaodimethylamine" "N-Nitroso-N,N-dimethylamine" "Nitrosamine, dimethyl-" Redundant, search results not considered: "N,N-Dimethylnitrosamine" "n-Nitrosodimethylamine"
Regulations.gov	
06/2022	Limited to: postedDateFrom=2018-01-01&postedDateTo=2022-06-10; dockets and EPA notices. "62-75-9" "Dimethylnitrosamine" "Dimethylnitrosoamine"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Nitrosodimethylamine" "dimethyl-nitrosamine" "N-Methyl-N-nitrosomethanamine" "DMNA" "NDMA
NIH RePORTER	
08/2022	Text Search: "dimethyl-nitrosamine" OR "Dimethylamine, N-nitroso-" OR "Dimethylnitrosamine" OR "Dimethylnitrosoamine" OR "Methanamine, N-methyl-N-nitroso-" OR "N,N-Dimethylnitrosamine" OR "N,N-dimethylnitrous amide" OR "N-Dimethyl-nitrosamine" OR "N-Methyl-N-nitrosomethanamine" OR "N-Nitroaodimethylamine" OR "N-Nitroso-N,N-dimethylamine" OR "n-Nitrosodimethylamine" OR "Nitrosamine, dimethyl-" OR "Nitrosodimethylamine" Fiscal Year: Active Projects (and) Limit to: Project Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed and TOXCENTER (after duplicate removal): 482
- Number of records identified from other strategies: 78
- Total number of records to undergo literature screening: 560

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on NDMA:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

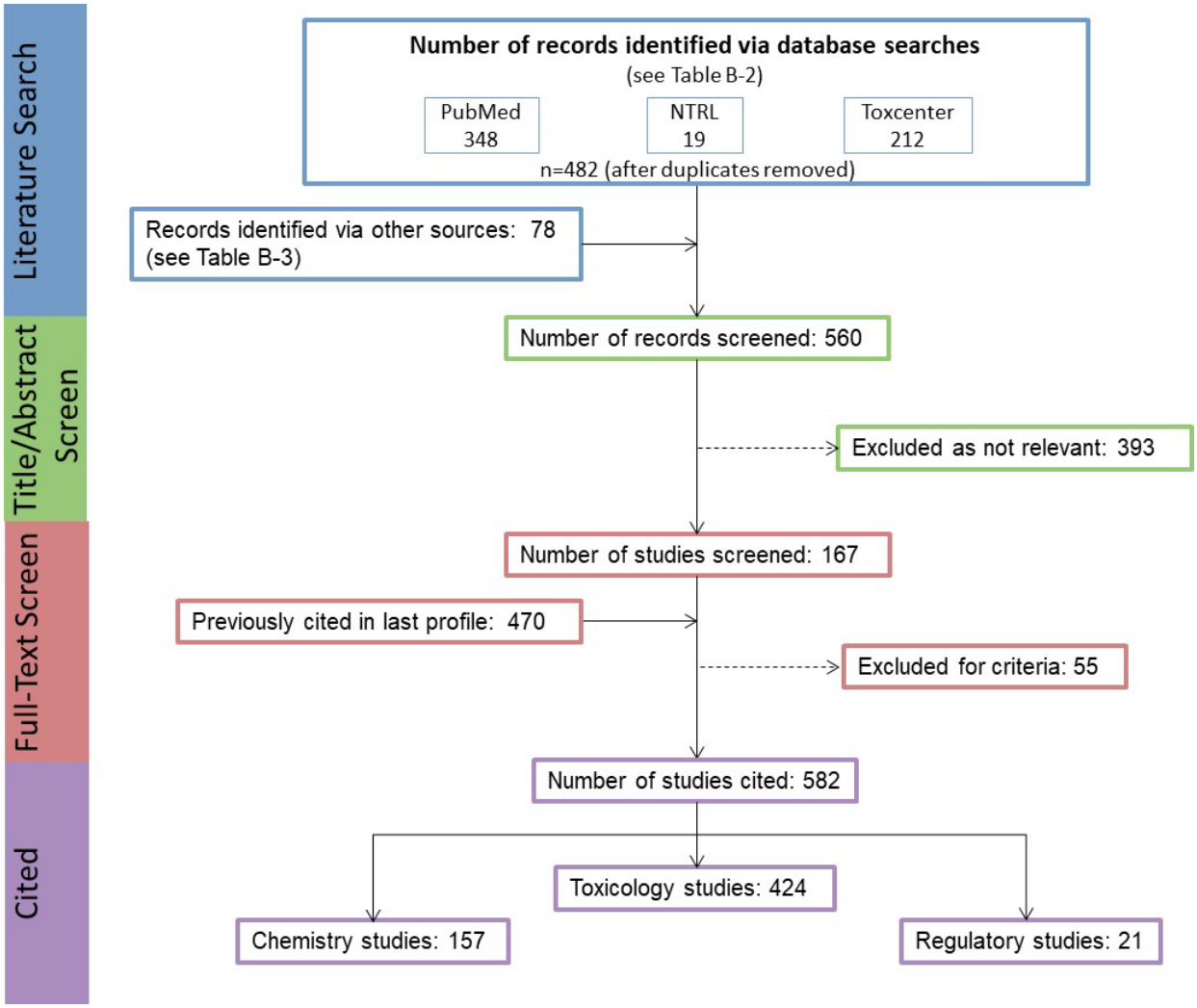
- Number of titles and abstracts screened: 560
- Number of studies considered relevant and moved to the next step: 167

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 167
- Number of studies cited in the pre-public draft of the toxicological profile: 470
- Total number of studies cited in the profile: 582

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. June 2022 Literature Search Results and Screen for NDMA



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

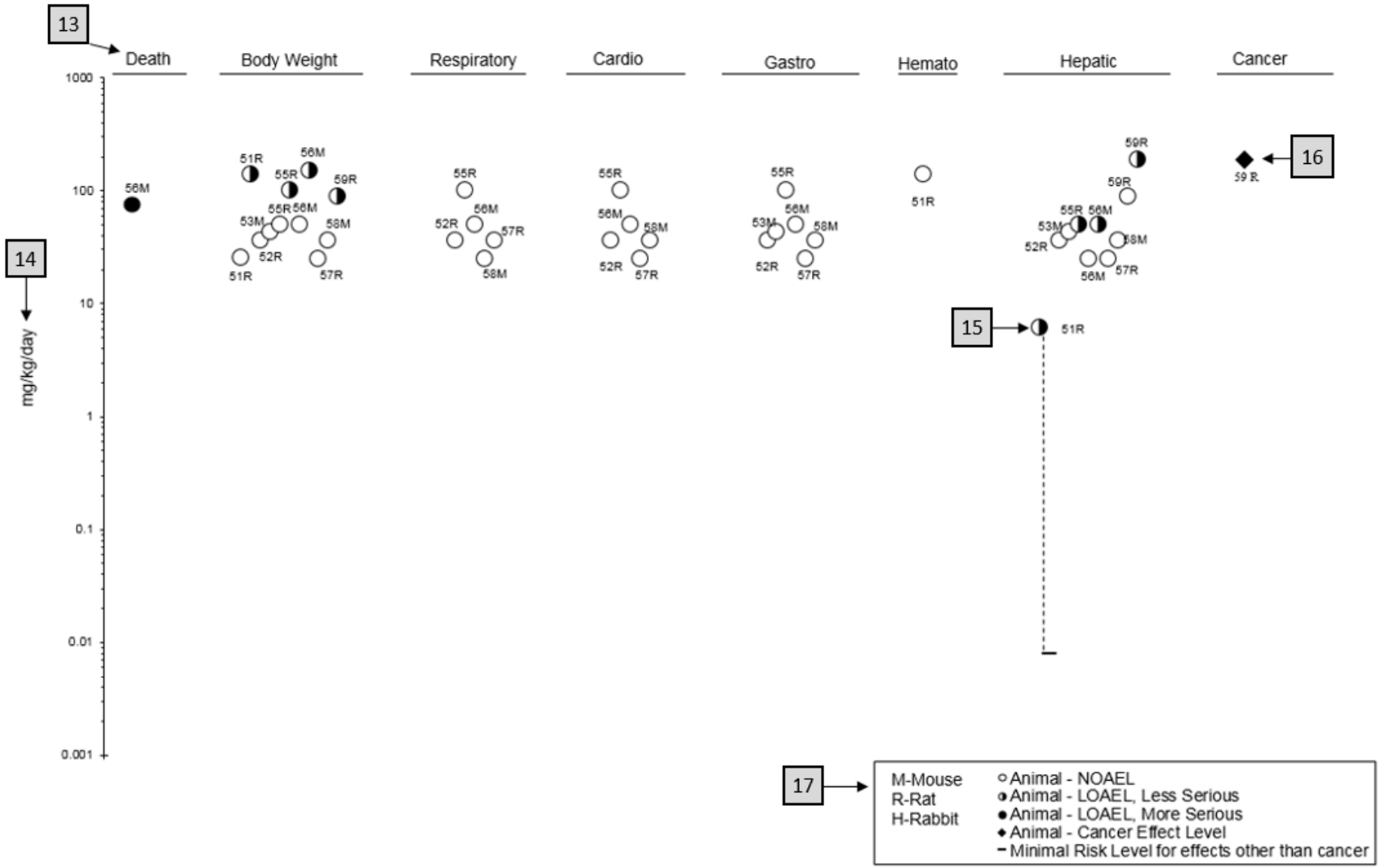
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result