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.

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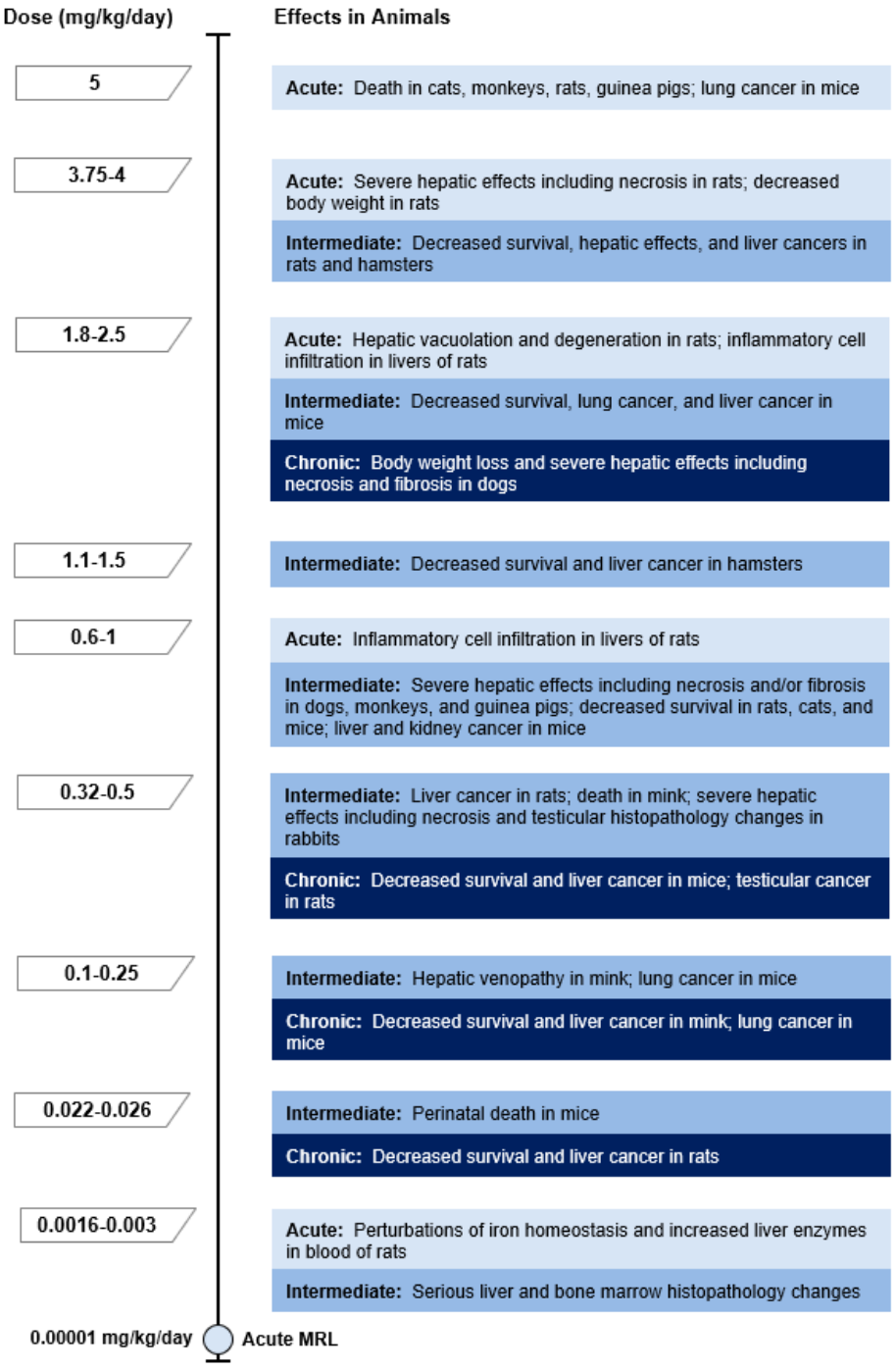
Based on the available information and recognizing the limitations in data on other potential target organs, the most sensitive health endpoints observed after oral exposure of animals to NDMA were cancer, and severe noncancer effects on the liver and developing organism, as shown in Figure 1-1.

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

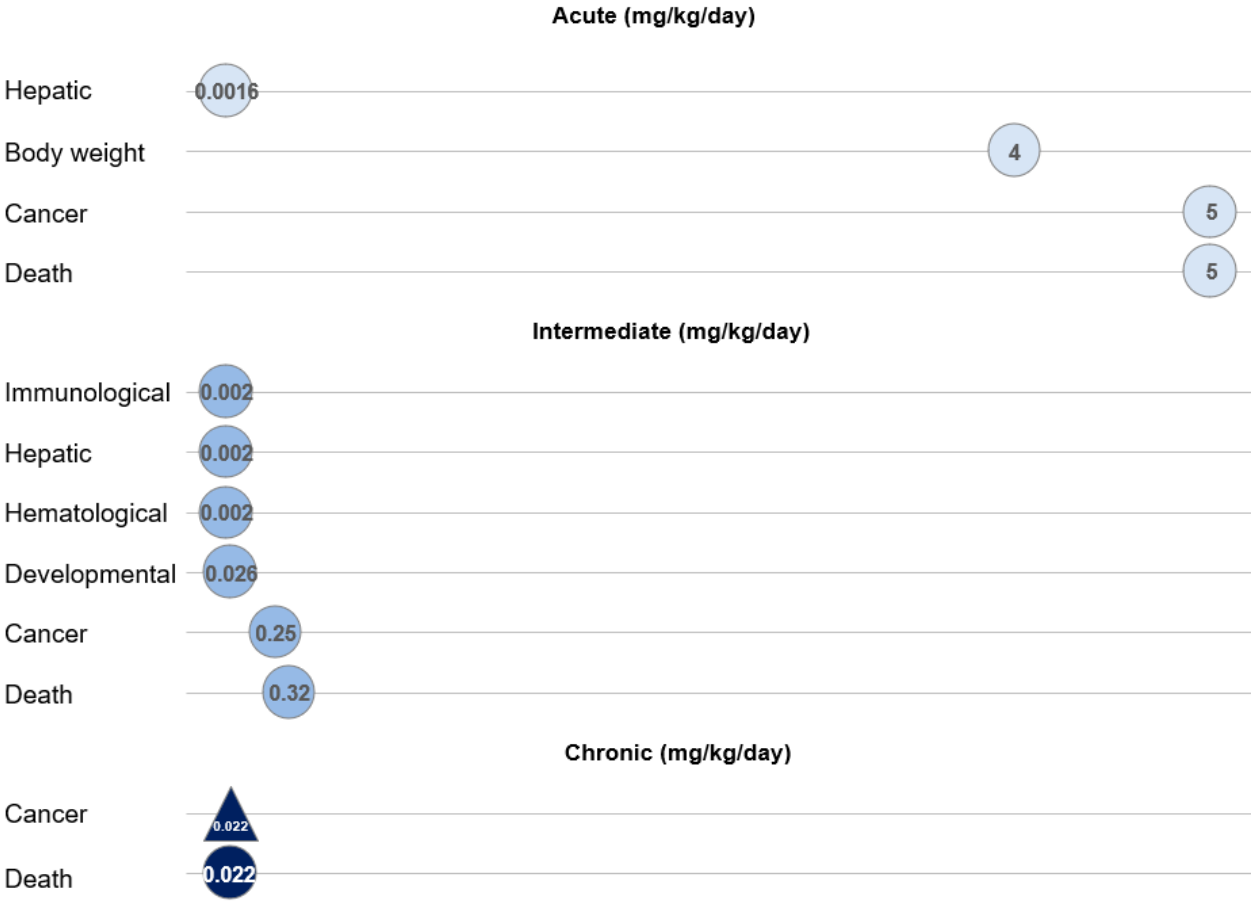


Table 1-1. Minimal Risk Levels (MRLs) for N-Nitrosodimethylamine (NDMA)[a]

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