Toxicological Profile for N-Nitrosodi-n-Propylamine

February 2019

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
February 2019	Update of data in Chapters 2, 3, and 7
July 2010	Addendum to the toxicological profile released
December 1989	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

ATSDR's *Toxicological Profile for N-Nitrosodi-n-Propylamine* was released in 1989. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2, 3, and 7 were revised to reflect the most current health effects and regulations/guidelines data. In some cases, other sections of the profile were updated as needed or for consistency or with the updated health effects data. However, the focus of the update to this profile is on health effects information.

N-Nitrosodi-n-propylamine ($C_6H_{14}N_2O$, CAS No. 621-64-7) belongs to a group of chemicals referred to as nitrosoamines, which share a common feature of the N-N=O structure. The general population can be exposed to N-nitrosodi-n-propylamine, and other nitrosoamines, in sodium nitrite-treated foods and certain alcoholic beverages or from the *in vivo* generation during digestion of nitrite- or secondary amine-containing foods or drugs (Magee et al. 1976; Roenen et al. 1980; Sakai et al. 1984). Tobacco products are also a source of N-nitrosodi-n-propylamine. Small quantities of N-nitrosodi-n-propylamine are produced for laboratory research. Typical N-nitrosodi-n-propylamine exposure levels have not been quantified and biomarkers of exposure have not been identified.

1.2   SUMMARY OF HEALTH EFFECTS

Information on the toxicity of N-nitrosodi-n-propylamine comes primarily from a small number of oral studies in laboratory animals. No epidemiology studies were identified. The 10 oral exposure studies only examined four possible health outcomes: death, liver toxicity, alterations in body weight gain, and carcinogenicity. Knowledge of the toxicity of N-nitrosodi-n-propylamine is supplemented with the results of intratracheal instillation and injection studies, which examined the hepatic, immune, developmental, and cancer endpoints.

The lowest-observed-adverse-effect levels (LOAELs) for liver, body weight, and cancer effect levels (CELs) identified in oral studies are presented in Figure 1-1.

Hepatic Effects. Lethal single oral doses of N-nitrosodi-n-propylamine produced hepatic necrosis and hemorrhagic lesions in the liver (Druckrey et al. 1967). Similar effects were reported by Nishie et al. (1972), who observed that gavage doses of 40 mg/kg/day for 4 consecutive days produced swelling of

hepatocytes and possibly necrosis in the centrilobular area of the liver in mice. Hydropic degeneration, hepatitis, and increases in liver weight were also observed in mice administered intraperitoneal doses of N-nitrosodi-n-propylamine (Kaminiski et al. 1989). Hepatocellular necrosis was observed in rats administered 10 mg/kg/day for 14 days (Terashima et al. 2015). No liver effects were observed in mice administered 9.5 mg/kg/day for 1 week (Tyndall et al. 1978).

Hepatotoxicity and hemorrhagic lesions in the liver and other internal tissues are also the primary acute effects of other dialkylnitrosamine compounds (Magee et al. 1976). Based on data for other dialkylnitrosamines, it can be inferred that systemic effects of intermediate- or chronic-duration exposure to N-nitrosodi-n-propylamine are likely to include acute-type responses and preneoplastic alterations. Additionally, human fatalities due to intentional oral and accidental inhalation exposures to unknown levels of N-nitrosodimethylamine have been described in case reports in which hemorrhagic, necrotic, and cirrhotic alterations in the liver and diffuse internal bleeding were observed (Barnes and Magee 1954; Cooper and Kimbrough 1980; Freund 1937; Fussgaenger and Ditschuneits 1980; Pedal et al. 1982).

Carcinogenic Effects. Information regarding the carcinogenicity of N-nitrosodi-n-propylamine in humans was not located. In animals, carcinogenicity of N-nitrosodi-n-propylamine has been demonstrated in several species in all studies that have been conducted. In rats observed for life, daily or partial weekly (administered 2 or 5 days/week) oral exposure produced tumors primarily in the liver, nasal cavity, and esophagus (Druckrey et al. 1967; Lijinsky and Reuber 1981, 1983; Lijinsky and Taylor 1978, 1979). In mice, increased incidences of forestomach tumors occurred as a result of twice weekly orally treatment for 50 weeks (Griciute et al. 1982). Respiratory tract, esophagus, and/or liver tumors have also been observed in monkeys, rats, mice, and hamster following chronic parenteral administration of N-nitrosodi-n-propylamine (Adamson and Sieber 1979, 1983; Althoff et al. 1973a, 1973b, 1977b; Dickhaus et al. 1977; Pour et al. 1973, 1974; Reznik et al. 1975).

The U.S. Department of Health and Human Services categorized N-nitrosodi-n-propylamine as reasonably anticipated to be a human carcinogen (NTP 2016), the U.S. Environmental Protection Agency (EPA) categorized it as a probable human carcinogen (Group B2) (IRIS 2002), and the International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (group 2B) (IARC 1987).

1. RELEVANCE TO PUBLIC HEALTH

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to N-Nitrosodi-n-Propylamine

Dose (mg/kg/day)   Effects in Animals

40   Acute: Decreased body weight gain

10   Acute: Liver necrosis

0.3   Intermediate: Forestomach and pulmonary tumors
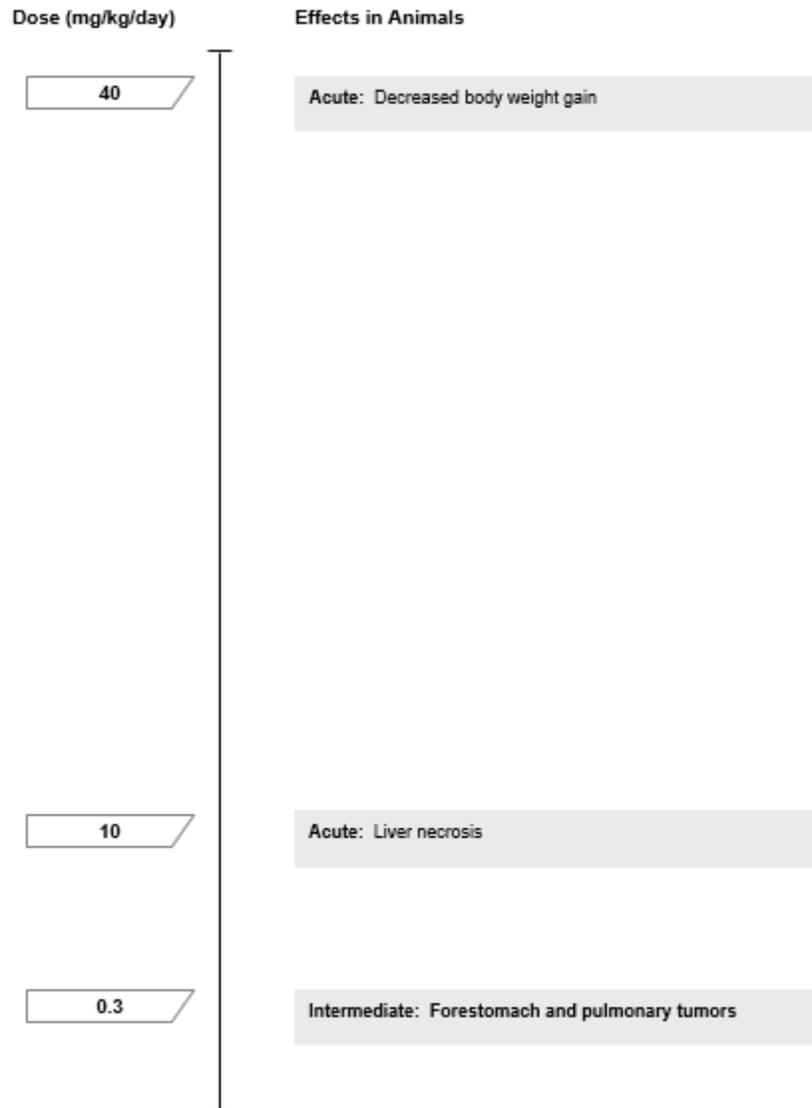
1. RELEVANCE TO PUBLIC HEALTH

1.3   MINIMAL RISK LEVELS (MRLs)

No inhalation studies were identified for N-nitrosodi-n-propylamine, thus precluding derivation of inhalation MRLs. The oral database was not considered adequate for derivation of an acute-duration oral MRL for N-nitrosodi-n-propylamine (Table 1-1). Liver and body weight were the only endpoints examined following acute-duration exposure. Cancer was the only adverse effect observed following intermediate-duration exposure, and no chronic oral studies were identified.

Table 1-1. Minimal Risk Levels (MRLs) for N-Nitrosodi-n-Propylamine[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information

NOAEL = no-observed-adverse-effect level

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 N-nitrosodi-n-propylamine. 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 ($\leq$14 days), intermediate (15–364 days), and chronic ($\geq$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 N-nitrosodi-n-propylamine, but may not be inclusive of the entire body of literature.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. Animal oral studies are presented in Table 2-1 and Figure 2-2; no inhalation or dermal data were identified for N-nitrosodi-n-propylamine. 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 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 N-nitrosodi-n-propylamine are indicated in Table 2-1 and Figure 2-2.

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.

The health effects of N-nitrosodi-n-propylamine have been evaluated in laboratory animal studies. As illustrated in Figure 2-1, all of the health effects data come from oral exposure studies in animals. Animal data are only available for hepatic effects following acute exposure and cancer following intermediate-duration exposure.

The available animal studies suggest the following targets of toxicity:

- **Liver Endpoint:** Evidence of liver damage including increases in pentobarbital sleep time and necrosis have been observed in laboratory animals following acute-duration exposure.

- **Cancer Endpoint:** Forestomach, nasal, lung, and liver tumors have been observed in laboratory animals following intermediate-duration oral exposure.

2. HEALTH EFFECTS

Figure 2-1. Overview of the Number of Studies Examining N-Nitrosodi-n-Propylamine Health Effects*

Studies examined the potential hepatic or cancer effects of N-nitrosodi-n-propylamine
All studies evaluated health effects in animals (counts represent studies examining endpoint)

Body weight — 1
Respiratory —
Cardiovascular —
Gastrointestinal —
Hematological —
Musculoskeletal —
Hepatic — 4
Renal —
Dermal —
Ocular —
Endocrine —
Immunological —
Neurological —
Reproductive —
Developmental —
Other Noncancer —
Cancer — 6

Exposure Route Studied

Oral
100%

Exposure Duration Studied

Intermediate
60%

Acute
40%

*Includes studies discussed in Chapter 2. A total of 10 studies, including those finding no effect, have examined toxicity; some studies examined more than 1 endpoint.

2. HEALTH EFFECTS

Table 2-1. Levels of Significant Exposure to N-Nitrosodi-n-Propylamine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (BD) NS	Once (G)	NR	LE, HP	Death			480	LD$_{50}$
					Hepatic			480	Necrosis
Druckery et al. 1967									
2	Mouse (Swiss Webster) 10 M	4 days (GO)	0, 40	FX	Hepatic		40		Hepatocellular swelling and increased pentobarbital sleep time
Nishie et al. 1972									
3	Rat (CD) 5 M	14 days (GW)	0, 10, 20, 40	CS, BW, OW, HP	Bd wt	20	40		13% decrease in body weight gain
					Hepatic		10		Minimal single cell hepatocellular necrosis at 10 mg/kg/day; decreased liver weight, minimal hepatocellular hypertrophy, mild centrilobular hepatocellular necrosis, minimal centrilobular inflammation, diffuse hepatocellular vacuolation at ≥20 mg/kg/day
Terashima et al. 2015									
4	Mouse (BALB/c) 6 F	1 week (F)		BC	Hepatic	9.5			Only assessed serum enzymes
Tyndall et al. 1978									
INTERMEDIATE EXPOSURE									
5	Rat (BD) 14-16NS	Lifetime (F)	0, 4, 8, 15, 30	HP	Cancer			4	Liver carcinoma
Druckery et al. 1967									

2. HEALTH EFFECTS

Table 2-1. Levels of Significant Exposure to N-Nitrosodi-n-Propylamine – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
6	Mouse (C57BL) 38M, 32F	2 days/week 50 weeks (G)	0,1	CS, BW, GN, HP	Cancer			1	Forestomach, pulmonary tumors
Griciute et al. 1982									
7	Rat (Fischer 344) 20 NR	5 days/week 30 weeks (W)	2.6	LE, HP	Death			2.6	8/20 deaths at week 30; 100% mortality 10 weeks post-exposure
					Cancer			2.6	Esophagus, forestomach tumors
Lijinsky and Reuber 1981									
8	Rat (Fischer 344) 12 F	2 days/week 30 weeks (GO)	6.3	LE, HP	Death			6.3	5/12 deaths 20-weeks post-exposure, 100% mortality 40 weeks post-exposure
					Cancer			6.3	Hepatic and nasal carcinomas
Lijinsky and Reuber 1983									
9	Rat (Fischer 344) 20 M	2 days/week 30 weeks (GO)	12.6	LE, HP	Death			12.6	100% mortality 10 weeks post-exposure
					Cancer			12.6	Hepatic, esophageal, lung, and nasal carcinomas
Lijinsky and Reuber 1983									
10	Rat (Sprague-Dawley) 15 M	5 days/week 30 weeks (W)	5.1	LE, HP	Death			5.1	100% mortality 30 weeks-post-exposure
					Cancer			5.1	Hepatic and esophageal carcinomas and nasal adenocarcinomas
Lijinsky and Taylor 1978, 1979									

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

BW = body weight; CS = clinical signs; (F) = exposure in feed; F = female(s); FX = fetal toxicity; (G) = gavage; (GO) = gavage in oil vehicle; GN = gross necropsy; HP = histopathology; LD_{50} = lethal dose, 50% mortality; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NR = not reported; (W) = water

2. HEALTH EFFECTS

Figure 2-2. Levels of Significant Exposure to N-Nitrosodi-n-Propylamine – Oral
Acute (≤ 14 days)

M-Mouse	o Animal - NOAEL
R-Rat	◐ Animal - Less Serious LOAEL
	● Animal - Serious LOAEL
	■ Animal - LD50/LC50

Figure 2-2. Levels of Significant Exposure to N-Nitrosodi-n-Propylamine – Oral
Intermediate (15-364 days)
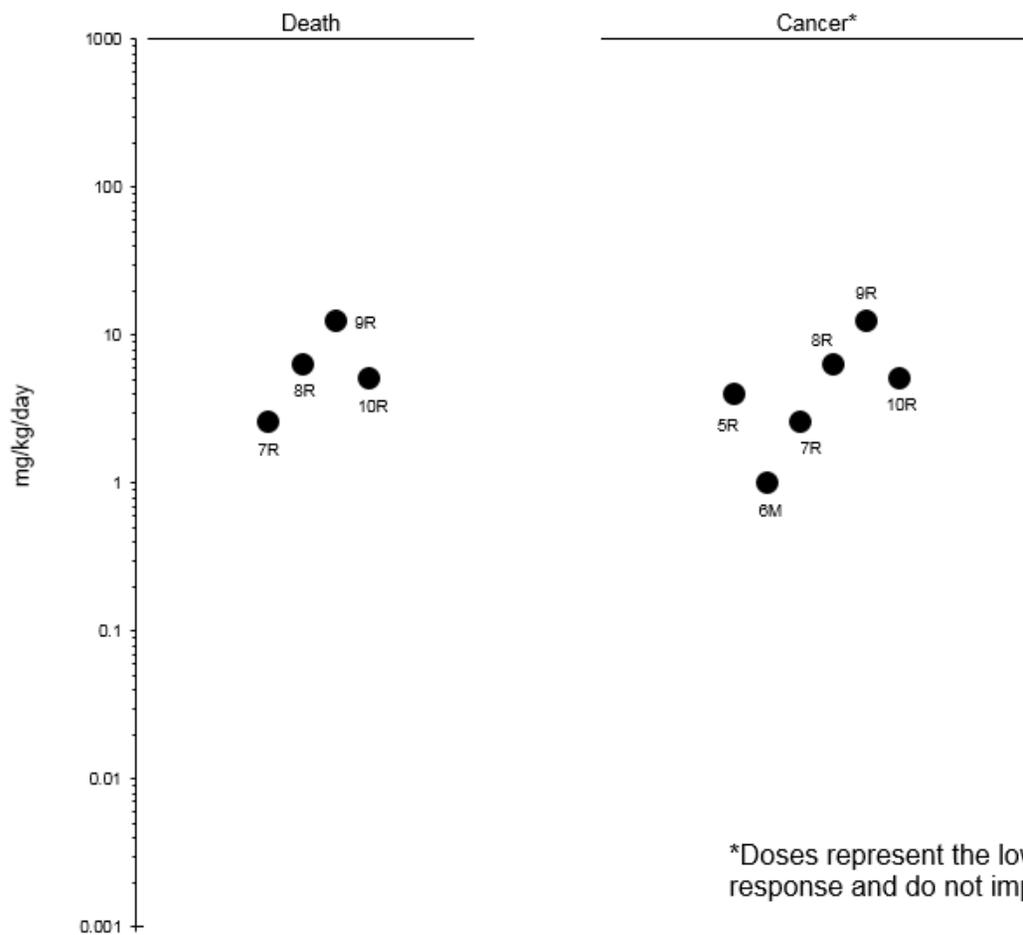
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

M-Mouse   ○ Animal - NOAEL
R-Rat   ● Animal - Serious LOAEL

2.2   DEATH

Druckrey et al. (1967) determined a single dose gavage LD_{50} of 480 mg/kg for N-nitrosodi-n-propylamine in rats. The value was determined using an unspecified graphic technique, but specific mortality data were not reported. Deaths occurred after 3–7 days and appear to have been due primarily to hepatotoxicity. Other acute oral lethality data were not located in the reviewed literature.

Decreased longevity occurred in rats that were treated with N-nitrosodi-n-propylamine at doses of 6.3 mg/kg/day (females) or 12.6 mg/kg/day (males) by gavage for 2 days/week for 30 weeks (Lijinsky and Reuber 1983), or 5.1 mg/kg/day (males) via drinking water for 5 days/week for 30 weeks (Lijinsky and Taylor 1978, 1979). Mortality in the Lijinsky and Reuber (1983) study was 92–100% after 40–60 weeks compared to 5–10% after 100 weeks in controls; comparable data were reported by Lijinsky and Taylor (1978, 1979) for the treated rats, but a control group was not used. The mortality in these studies was due to tumor development (see Section 2.19). No studies were located regarding survival in animals following chronic oral exposure to N-nitrosodi-n-propylamine.

2.3   BODY WEIGHT

Data on the effect of N-nitrosodi-n-propylamine on body weight are limited to an acute-duration oral study, which reported a 13% decrease in body weight gain in rats administered 40 mg/kg/day for 14 days (Terashima et al. 2015).

2.4   RESPIRATORY

No studies were located regarding respiratory effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.5   CARDIOVASCULAR

No studies were located regarding cardiovascular effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.6   GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.7   HEMATOLOGICAL

No studies were located regarding hematological effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.8   MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.9   HEPATIC

Pathologic examinations of rats that received single lethal doses of various nitrosamines, including N-nitrosodi-n-propylamine, showed centrilobular necrosis and fatty degeneration of the liver (Druckrey et al. 1967). Specific doses of N-nitrosodi-n-propylamine that produced these effects were not reported, but the LD_{50} was determined to be 480 mg/kg; this dose is indicated in Table 2-1 and Figure 2-1 as a serious LOAEL for hepatic effects in rats due to acute oral exposure.

Nishie et al. (1972) determined pentobarbital sleeping time (PST) in mice that were treated by gavage with single doses or with four consecutive daily doses of various nitrosamines, including N-nitrosodi-n-propylamine. Doses of N-nitrosodi-n-propylamine were 160 mg/kg/day in the single-dose study and 40 mg/kg/day in the 4-day study. N-Nitrosodi-n-propylamine treatment resulted in significantly prolonged PST in both studies. Liver histology was evaluated in the 4-day study, but results of the histologic examinations were not reported specifically for any of the nitrosamines. Hepatic histological alterations attributed to unspecified nitrosamines included hepatocyte swelling and necrosis in the centrilobular areas; due to the inadequately reported data, it cannot be determined whether N-nitrosodi-n-propylamine was among the nitrosamines that produced these effects. However, considering the aforementioned findings for nitrosamines in general as well as evidence for hepatotoxicity of N-nitrosodi-n-propylamine and other nitrosamines from other studies, the increase in PST provides an indirect indication of adverse liver effects. Therefore, since N-nitrosodi-n-propylamine markedly increased PST in the 4-day study, 40 mg/kg/day can be regarded as a LOAEL for less serious hepatic effects due to acute oral exposure (Table 2-1 and Figure 2-1).

Liver histology and activities of liver-associated serum enzymes (aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, γ-glutamyl transferase) were unaltered in mice exposed to 9.5 mg/kg/day via drinking water for 1 week (Tyndall et al. 1978). In a 14-day gavage study, single cell hepatocellular necrosis was observed in rats administered 10 mg/kg/day (Terashima et al. 2015). Hepatocellular hypertrophy, necrosis, and vacuolation and centrilobular inflammation were observed in rats administered 20 and 40 mg/kg/day. The severity of the hepatocellular necrosis was graded as minimal at 10 mg/kg/day, mild at 20 mg/kg/day, and moderate at 40 mg/kg/day; the other lesions were graded as minimal.

In addition to these oral studies, increases in organ weight and generalized mild hydropic degeneration were observed in the livers of mice administered ≥50 mg/kg/day N-nitrosodi-n-propylamine via intraperitoneal injections for 7 days (Kaminski et al. 1989). Mild chronic hepatitis was also observed at 90 mg/kg/day.

2.10 RENAL

No studies were located regarding renal effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.11 DERMAL

No studies were located regarding dermal effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.12 OCULAR

No studies were located regarding ocular effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine. A 7-day intraperitoneal injection study reported a suppressed antibody response to sheep red blood cells in mice administered ≥50 mg/kg/day; the ED_{50} was 60.8 mg/kg/day (Kaminiski et al. 1989). Decreases in spleen and thymus weights were also observed at ≥50 mg/kg/day.

2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans or animals following inhalation, oral, or dermal exposure to N-nitrosodi-n-propylamine. Limited information regarding developmental effects of N-nitrosodi-n-propylamine is available from subcutaneous injection transplacental carcinogenesis studies with hamsters (Althoff and Grandjean 1979; Althoff et al. 1977a). Injection of a single dose of 100 mg N-nitrosodi-n-propylamine/kg on day 8, 10, 12, or 14 of gestation did not produce gross malformations in the offspring, but the scope of the examination was not specified. However, transplacental carcinogenicity was observed in the offspring of dams treated with N-nitrosodi-n-propylamine. There were no treatment-related effects on litter size, but postnatal mortality in the first 4 weeks was increased (Althoff et al. 1977a). Transplacental transport of N-nitrosodi-n-propylamine by the hamsters was demonstrated by detection of the chemical in the placenta, fetus, and amniotic fluid.

2.18 OTHER NONCANCER

Plasma esterase profiles were examined in mice exposed to various carcinogenic, weakly carcinogenic, and noncarcinogenic chemicals in the drinking water for 1 week (Tyndall et al. 1978). N-Nitrosodi-n-propylamine, administered at a dose of 9.5 mg/kg/day, produced esterase alterations that were similar to

those produced by other N-nitrosodialkylamines. The alterations were not accompanied by weight loss, altered liver-associated serum enzymes, or histologic effects. This study was conducted to determine whether altered esterase patterns in plasma would provide a more sensitive indicator of exposure to a carcinogenic chemical than standard clinical chemistry tests. It was concluded that it is not known if the altered esterase profiles that were observed for N-nitrosodi-n-propylamine, and the other carcinogens are related to carcinogenicity, toxicity, or metabolism. Since the biological significance of the altered esterase profiles is unknown, it cannot be determined if 9.5 mg/kg/day represents a NOAEL or LOAEL for serum chemistry alterations due to acute oral exposure.

2.19 CANCER

No studies involving exposure to airborne N-nitrosodi-n-propylamine were located. In an intratracheal instillation study (1.5 mg instilled once a week for 15 weeks), tracheal tumors were observed in 72% of hamsters (Ishinishi et al. 1988); no liver tumors were observed.

The carcinogenicity of N-nitrosodi-n-propylamine has been demonstrated in oral studies. High incidences of liver carcinomas, nasal cavity carcinomas, esophageal carcinomas and papillomas, forestomach tumors, or tongue tumors occurred in rats that were exposed to N-nitrosodi-n-propylamine by gavage at doses of 6.3 or 12.6 mg/kg/day for 2 days/week for 30 weeks (Lijinsky and Reuber 1983), via drinking water at a dose of 2.6 mg/kg/day for 5 days/week for 30 weeks (Lijinsky and Reuber 1981), via drinking water at a dose of 5.1 mg/kg/day for 5 days/week for 30 weeks (Lijinsky and Reuber 1981; Lijinsky and Taylor 1978, 1979), and via diet daily at reported doses of 4–30 mg/kg/day for life (survival duration not specified) (Druckrey et al. 1967). Tumor incidences in the liver, nasal cavity, esophagus, and forestomach were generally in the range of 60–100%, and tongue tumor incidences ranged from 30 to 40%. The Lijinsky and Reuber (1983) study was the only study that used control groups; no tumors occurred in the control rats at any of the sites in which tumors developed in the treated rats. The lack of controls in the other studies is not considered to be a serious deficiency due to the high tumor incidences. As indicated in Section 2.2, tumor development in all of the rat studies was life-shortening.

In an oral carcinogenicity study conducted with mice, the animals received an estimated N-nitrosodi-n-propylamine dose of 1 mg/kg by gavage, twice a week for 50 weeks (Griciute et al. 1982). Incidences of forestomach papillomas, forestomach carcinomas, and pulmonary adenomas were significantly higher than in mice that were similarly treated with 40% ethanol; a vehicle (water) control was not used.

Additional support for the carcinogenicity of N-nitrosodi-n-propylamine comes from several parenteral administration studies. Weekly subcutaneous injections of N-nitrosodi-n-propylamine to rats (Althoff et al. 1973b, Reznik et al. 1975), mice (Dickhaus et al. 1977), and hamsters (Althoff et al. 1973a, 1977b; Pour et al. 1973, 1974) for life produced high incidences of tumors, primarily in the nasal cavity and other parts of the respiratory system, but also in the liver and esophagus. Subcutaneous injection of single 100 mg/kg doses of N-nitrosodi-n-propylamine into hamsters during gestation induced tumors, primarily in the respiratory and digestive tracts, in the dams and offspring (Althoff and Grandjean 1979; Althoff et al. 1977a). Weekly intraperitoneal injections of 40 mg N-nitrosodi-n-propylamine produced death due to hepatocellular carcinomas in monkeys after an average duration of 28 months (Adamson and Sieber 1979, 1983).

The U.S. Department of Health and Human Services categorized N-nitrosodi-n-propylamine as reasonably anticipated to be a human carcinogen (NTP 2016), EPA categorized it as a probable human carcinogen (Group B2) (IRIS 2002), and the International Agency for Research on Cancer categorized it as possibly carcinogenic to humans (group 2B) (IARC 1987).

2.20 GENOTOXICITY

Genotoxicity of N-nitrosodi-n-propylamine has been demonstrated consistently in numerous *in vitro* studies summarized in Table 2-2. The *in vitro* assays generally required addition of an exogenous metabolic activation system for expression of effects. As indicated in Table 2-2, N-nitrosodi-n-propylamine was mutagenic in several studies using *Salmonella typhimurium* (Araki et al. 1984; Bartsch et al. 1976, 1980; Dahl 1985; Guttenplan and Hu 1984; Guttenplan 1987; Kirkland et al. 2005; McMahon et al. 1979; Mersch-Sundermann et al. 1994; Moore et al. 1985; Okochi et al. 1997; Phillipson and Ioannides 1985; Probst et al. 1981; Rao et al. 1979, 1982; Yahagi et al. 1977), *Escherichia coli (*Araki et al. 1984; McMahon et al. 1979; Mersch-Sundermann et al. 1994; Nakajima et al. 1974; Rao et al. 1981, 1982), mouse lymphoma cells (Amacher and Paillet 1982, 1983; Amacher et al. 1979), and Chinese hamster V79 cells (Bartsch et al. 1980; Jones and Huberman 1980; Kuroki et al. 1977; Langenbach 1986).

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Table 2-2. Genotoxicity of N-Nitrosodi-n-Propylamine *In Vitro*

Species (test system)	Endpoint	Results Activation With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	+	–	Araki et al. 1984
S. typhimurium	Gene mutation	+	–	Bartsch et al. 1976, 1980
S. typhimurium	Gene mutation	+	–	Dahl 1985
S. typhimurium	Gene mutation	+	–	Guttenplan and Hu 1984
S. typhimurium	Gene mutation	+	–	Guttenplan 1987
S. typhimurium	Gene mutation	+	NA	Kirkland et al. 2005
S. typhimurium	Gene mutation	+	–	McMahon et al. 1979
S. typhimurium (strain TA1330)	Gene mutation	+	NA	Mersch-Sundermann et al. 1994
S. typhimurium	Gene mutation	+	–	Moore et al. 1985
S. typhimurium (strain 1535)	Gene mutation	+	NA	Okochi et al. 1997
S. typhimurium	Gene mutation	+	–	Phillipson and Ioannides 1985
S. typhimurium	Gene mutation	+	–	Probst et al. 1981
S. typhimurium	Gene mutation	+	–	Rao et al. 1979
S. typhimurium	Gene mutation	+	–	Rao et al. 1982
S. typhimurium	Gene mutation	+	–	Yahagi et al. 1977
Escherichia coli	Gene mutation	+	–	Araki et al. 1984
E. coli	Gene mutation	+	–	McMahon et al. 1979
E. coli (strain PQ37)	Gene mutation (SOS chromotest)	+	NA	Mersch-Sundermann et al. 1994
E. coli	Gene mutation	+	–	Nakajima et al. 1974
E. coli	Gene mutation	+	–	Rao et al. 1981, 1982
Eukaryotic organisms				
Mouse lymphoma L5178Y cells	Gene mutation	+	–	Amacher et al. 1979
Mouse lymphoma L5178Y cells	Gene mutation	+	–	Amacher and Paillet 1982, 1983
Chinese hamster V9 cells	Gene mutation	+	–	Bartsch et al. 1980
Chinese hamster V9 cells	Gene mutation	+	–	Jones and Huberman 1980
Chinese hamster V9 cells	Gene mutation	+	–	Kuroki et al. 1977
Chinese hamster V9 cells	Gene mutation	+	–	Langenbach 1986
Human hepatocytes	DNA fragmentation	+	NA	Brambilla et al. 1987b
Human hepatocytes	DNA fragmentation	+	NA	Knasmüller et al. 1998
Human hepatocytes	DNA fragmentation	+	NA	Martelli et al. 1988

2. HEALTH EFFECTS

Table 2-2. Genotoxicity of N-Nitrosodi-n-Propylamine *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Human kidney cells	DNA fragmentation	+	NA	Robbiano et al. 1996
Rat hepatocytes	DNA fragmentation	+	NA	Bradley and Dysart 1981a, 1981b
Rat hepatocytes	DNA fragmentation	+	NA	Bradly et al. 1982
Rat hepatocytes	DNA fragmentation	+	NA	Parodi et al. 1982
Rat hepatocytes	DNA fragmentation	+	NA	Martelli et al. 1988
Rat kidney cells	DNA fragmentation	+	NA	Robbiano et al. 1996
Rat hepatocytes	DNA Repair	+	NA	Yamazaki et al. 1985
Human hepatocytes	Unscheduled DNA synthesis	+	NA	Martelli et al. 1988
Rat hepatocytes	Unscheduled DNA synthesis	+	NA	Martelli et al. 1988
Rat hepatocytes	Unscheduled DNA synthesis	+	NA	Probst et al. 1981
Rat hepatocytes	Unscheduled DNA synthesis	+	NA	Shu and Hollenberg 1996
Mouse HeLa cells	Unscheduled DNA synthesis	+	–	Martin et al. 1978
Chinese hamster fibroblasts	Chromosome aberrations	+	–	Kaneko et el. 1978
Chinese hamster lung cells	Chromosome aberrations	(+)	–	Matsuoka et al. 1979

+ = positive results; (+) = weakly positive results; – = negative results; DNA = deoxyribonucleic acid; NA = not applicable

Deoxyribonucleic acid (DNA) damage (fragmentation) was observed in human hepatocytes and kidney cells (Brambilla et al. 1987b; Knasmüller et al. 1998; Martelli et al. 1988; Robbiano et al. 1996) and in rat hepatocytes and kidney cells (Bradley and Dysart 1981a, 1981b; Bradly et al. 1982; Parodi et al. 1982; Martelli et al. 1988; Robbiano et al. 1996; Yamazaki et al. 1985) in the presence of metabolic activation. Studies evaluating unscheduled DNA synthesis also produced positive results in human hepatocytes (Martelli et al. 1988), rat hepatocytes (Martelli et al. 1988; Probst et al. 1981; Shu and Hollenberg 1996), and mouse HeLa cells (Martin et al. 1978). In the study by Shu and Hollenberg (1996), the extent of DNA damage was significantly increased in hepatocytes of rats pre-treated with phenobarbital and pyridine, demonstrating a correlation between cytochrome P450 activity and genotoxic potency. N-Nitrosodi-n-propylamine also induced chromosome aberrations in Chinese hamster fibroblasts and lung cells (Kaneko et al. 1978; Matsuoka et al. 1979) in the presence of metabolic activation.

As indicated in Table 2-3, N-nitrosodi-n-propylamine produced positive results in several *in vivo* studies in experimental animals. Single doses of 0.31–25 mg/kg N-nitrosodi-n-propylamine produced dose-

related DNA fragmentation in rats treated orally (Brambilla et al. 1981, 1987a), sister chromatid exchanges in mice administered 172 mg/kg via intraperitoneal injection (Parodi et al. 1983), and DNA synthesis suppression in the tubular and renal epithelia of mice treated by intraperitoneal injection (Amlacher and Rudolph 1981). In addition, intraperitoneal injection of 133 mg/kg of N-nitrosodi-n-propylamine to rats resulted in propylation of DNA and ribonucleic acid (RNA), an event regarded as critical in the initiation of carcinogenesis by this and related alkylating agents (Park et al. 1980). In a repeated exposure study, gavage administration of N-nitrosodi-n-propylamine for 14 days resulted in increases the number of micronucleated hepatocytes in rats, but did not alter the number of micronucleated immature erythrocytes (Terashima et al. 2015).

Table 2-3. Genotoxicity of N-Nitrosodi-n-Propylamine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster	Host-mediated DNA-repair assay	+	Knasmüller et al. 1990
Rat (liver)	DNA alkylation	+	Park et al. 1980
Rat (hepatocytes)	DNA fragmentation	+	Brambilla et al. 1981, 1987a
Mouse (liver and renal epithelial cells)	Suppressed DNA synthesis	+	Amlacher and Rudolph 1981
Mouse (bone marrow)	Sister chromatid exchange	+	Parodi et al. 1983
Rat (hepatocytes)	Micronucleus assay	–	Hamada et al. 2015
Rat (bone marrow/peripheral blood)	Micronucleus assay	–	Hamada et al. 2015
Rat (hepatocytes)	Micronucleus assay	+	Terashima et al. 2015
Rat (bone marrow)	Micronucleus assay	–	Terashima et al. 2015
Mouse (bone marrow)	Micronucleus assay	–	Morita et al. 1997
Mouse (peripheral blood)	Micronucleus assay	–	Suzuki et al. 1999

+ = positive results;– = negative results; DNA = deoxyribonucleic acid

In contrast to much of the data, micronucleus assays in rats and mice produced mixed results. Hamada et al. (2015) reported positive results for induction of micronuclei in hepatocytes, but negative results in bone marrow of rats administered 10–40 mg/kg N-nitrosodi-n-propylamine via gavage for 14 days. Similarly, Morita et al. (1997) reported negative results for induction of micronuclei in bone marrow of mice interperitoneally injected with 50–400 mg/kg N-nitrosodi-n-propylamine. Negative results were also reported for induction of micronuclei in peripheral blood of mice interperitoneally injected with 250 mg/kg, although increases in *LacZ* mutation frequency in the liver, lung, and kidney (target organs for carcinogenesis) were observed (Suzuki et al. 1999).

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A single host-mediated DNA repair assay was available (Knasmüller et al. 1990). *Drosophila Melanogaster* were simultaneously injected with a mixture of two *E. coli* strains (*uvrB/recA* and *uvr+/rec+*) and 0.5–10.5 mmol/L solutions of N-nitrosodi-n-propylamine. DNA damage was reported within 3 hours after injection and there was a dose-dependent differential killing effect.

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

3.1 TOXICOKINETICS

There are limited data regarding N-nitrosodi-n-propylamine toxicokinetics in humans and laboratory animals; these data are summarized below.

- N-Nitrosodi-n-propylamine is absorbed following oral and dermal exposure, and presumably following inhalation exposure; however, no data are available on the rate or extent of absorption.

- There are limited data on the distribution of N-nitrosodi-n-propylamine. Studies of related nitrosoamines suggest that it would be widely distributed.

- The primary pathway of metabolism of N-nitrosodi-n-propylamine is hydroxylation at the α-carbon. This pathway ultimately results in the formation of propionaldehyde, 1-propanol, and 2-propanol metabolites.

- N-Nitrosodi-n-propylamine is primarily excreted in the urine as metabolites.

3.1.1 Absorption

No studies were located regarding absorption in humans or animals following inhalation exposure to N-nitrosodi-n-propylamine. However, structurally similar compounds, such as N-nitrosodimethylamine and N-nitrosodiethanolamine, are readily absorbed (70–90% of the dose) following inhalation exposure in experimental animals (Klein and Schmezer 1984; Preussmann et al. 1981). Absorption was inferred by monitoring urinary excretion of the unchanged compounds.

No studies were located regarding absorption in humans following oral exposure to N-nitrosodi-n-propylamine. Specific information regarding absorption in animals following oral exposure to N-nitrosodi-n-propylamine was not located. Gastrointestinal absorption of N-nitrosodi-n-propylamine by rodents is indicated by the occurrence of metabolites in the urine following oral treatment (Section 3.4.1) and effects in oral carcinogenicity and toxicity studies (Chapter 2). Other nitrosamines are rapidly absorbed from the gastrointestinal tract after oral exposure. Diaz Gomez et al. (1977) found that <2% of radiolabelled dimethylnitrosamine could be recovered from the stomach and intestine of rats 15 minutes after administration. Also in rats, Lijinsky et al. (1981) and Preussmann et al. (1978) estimated absorption extents of 25 and 70% of the dose for N-nitrosodiethanolamine, respectively (estimates are from urinary excretion).

Absorption of N-nitrosodi-n-propylamine through human skin *in vivo* (Edwards et al. 1979) and *in vitro* (Bronaugh et al. 1979, 1981) has been demonstrated. Diffusion of N-nitrosodi-n-propylamine through rat skin *in vitro* has been demonstrated (Wishnok et al. 1982). Information regarding dermal absorption of N-nitrosodi-n-propylamine by animals *in vivo* was not located in the reviewed literature. Dermal absorption of N-nitrosodiethanolamine has been determined in pigs (Marzulli et al. 1981), monkeys (Marzulli et al. 1981), and rats (Airoldi et al. 1984; Lijinsky et al. 1981). The degree of absorption varied greatly (4–78%); differences in the test animal species, site of the application, and the vehicle used preclude direct comparisons across the studies. Based on the data for N-nitrosodimethylamine and N-nitrosodiethanolamine, it is likely that N-nitrosodi-n-propylamine will be absorbed following dermal exposure.

3.1.2   Distribution

Route-specific distribution data for N-nitrosodi-n-propylamine in humans were not located in the reviewed literature. Quantitative analyses of six volatile nitrosamines in postmortem organs (brain, liver, kidneys, pancreas) from four human subjects were conducted (Cooper et al. 1987). N-Nitrosodi-n-propylamine was detected only in the liver of one of the subjects (female, age 84 years) at a concentration of 19.30 ng/50 g of tissue. The ages of the other subjects (two males, one female) ranged from 47 to 80 years. N-Nitrosodi-n-propylamine was not detected in the other examined tissues (brain, kidney, and pancreas) from the four subjects. Unusual sources of nitrosamine exposure or causes of death were not indicated.

Transplacental transport of N-nitrosodi-n-propylamine was shown in pregnant hamsters (Althoff and Grandjean 1979; Althoff et al. 1977a). After a single 100 mg/kg subcutaneous injection, N-nitrosodi-n-propylamine was detected in the maternal blood, placenta, fetus, and amniotic fluid. The concentration of the chemical in maternal blood reached a maximum 45 and 90 minutes after the injection, whereas a single peak at 90 minutes was observed in the fetus. Analysis for metabolites was not conducted, but 1.6 and 1.3% of the unchanged compound was found in the placenta and in the fetus, respectively, at day 14 of gestation. Detection of 0^6-methylguanine in human placental DNA by immunoassay indicate that nitrosamines, as a group, can reach the placenta in humans (Foiles et al. 1988).

The limited data available regarding the distribution of related nitrosamines suggest that they are widely distributed in the body. Daugherty and Klapp (1976) reported that after oral administration of ^{14}C-N-nitrosodimethylamine to mice, radioactivity could be detected in the homogenates of heart,

forestomach, esophagus, liver, and lungs. Radioactivity was detected in all organs and tissues of rats after oral doses of ^{14}C-N-nitrosodiethanolamine (Lethco et al. 1982). After intravenous injection of ^{14}C-N-nitrosodi-n-butylamine to rats, the highest concentrations of radiolabel occurred in the nasal mucosa, liver, and preputial gland (Brittebo and Tjalve 1982).

3.1.3 Metabolism

No studies were located regarding metabolism in humans following exposure to N-nitrosodi-n-propylamine. *In vitro* and *in vivo* studies with rodents have been conducted that provide evidence that N-nitrosodi-n-propylamine can be metabolized via oxidation at the alpha, beta, and gamma carbon positions (Figure 3-1). Alpha carbon oxidation (hydroxylation) is regarded as the primary pathway, resulting in formation of propionaldehyde and 1-propanol and 2-propanol as metabolites (Farrelly et al. 1984; Park and Archer 1978; Park et al. 1977). 1-Propanol and 2-propanol are formed via propyldiazohydroxide and a propyl cation (carbonium ion). It is generally believed that the carbonium ions can also react with nucleic acids to form propylated adducts, but Park et al. (1980) have suggested that propylation takes place via a bimolecular reaction. However, reaction of DNA with propylnitrosourea (a direct acting equivalent of N-nitrosodi-n-propylamine) results in formation of n-propyl and isopropyl DNA adducts, suggesting that carbonium ions are involved. Alkylation of nucleic acids and proteins by metabolites of nitrosamines has been suggested as the mechanism responsible for the toxic and carcinogenic properties of these substances.

Beta-carbon hydroxylation yields N-nitroso-2-hydroxy-propylpropylamine, which is excreted as the glucuronide or further oxidized to a small extent to N-nitroso-2-oxopropylpropylamine (Bauman et al. 1985; Leung and Archer 1981; Park and Archer 1978; Suzuki and Okada 1981). Methylated hepatic nucleic acids have been recovered from rats and hamsters treated with N-nitrosodi-n-propylamine (Althoff et al. 1977b; Kruger 1971, 1973; Kruger and Bertram 1973; Leung and Archer 1984). Putative methylating intermediates, formed from N-nitroso-2-oxo-n-propylamine, are N-nitrosomethyl-propylamine and diazomethane.

Gamma-carbon hydroxylation yields N-nitroso-3-hydroxy-propylpropylamine and its oxidation product, N-propyl-N-(2-carboxyethyl)nitrosamine (Baumann et al. 1985; Blattmann and Preussman 1973; Suzuki and Okada 1981). Urinary N-propyl-N-(2-carboxyethyl)nitrosamine amounted to approximately 5% of a 300 mg/kg oral dose of N-nitrosodi-n-propylamine in rats (Suzuki and Okada 1981).

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

Figure 3-1. Metabolism of N-Nitrosodi-n-Propylamine

N-nitrosodi-n-propylamine

alpha-hydroxylation

beta-hydroxylation

gamma-hydroxylation

N-nitroso-2-hydroxypropylpropylamine

N-nitroso-3-hydroxypropylpropylamine

propionaldehyde + propyldiazohydroxide

N-nitroso-2-oxopropylpropylamine

glucuronide

N-propyl-N-(2-carboxyethyl)nitrosamine

carbonium ion

carbonium ion

2-propanol

1-propanol
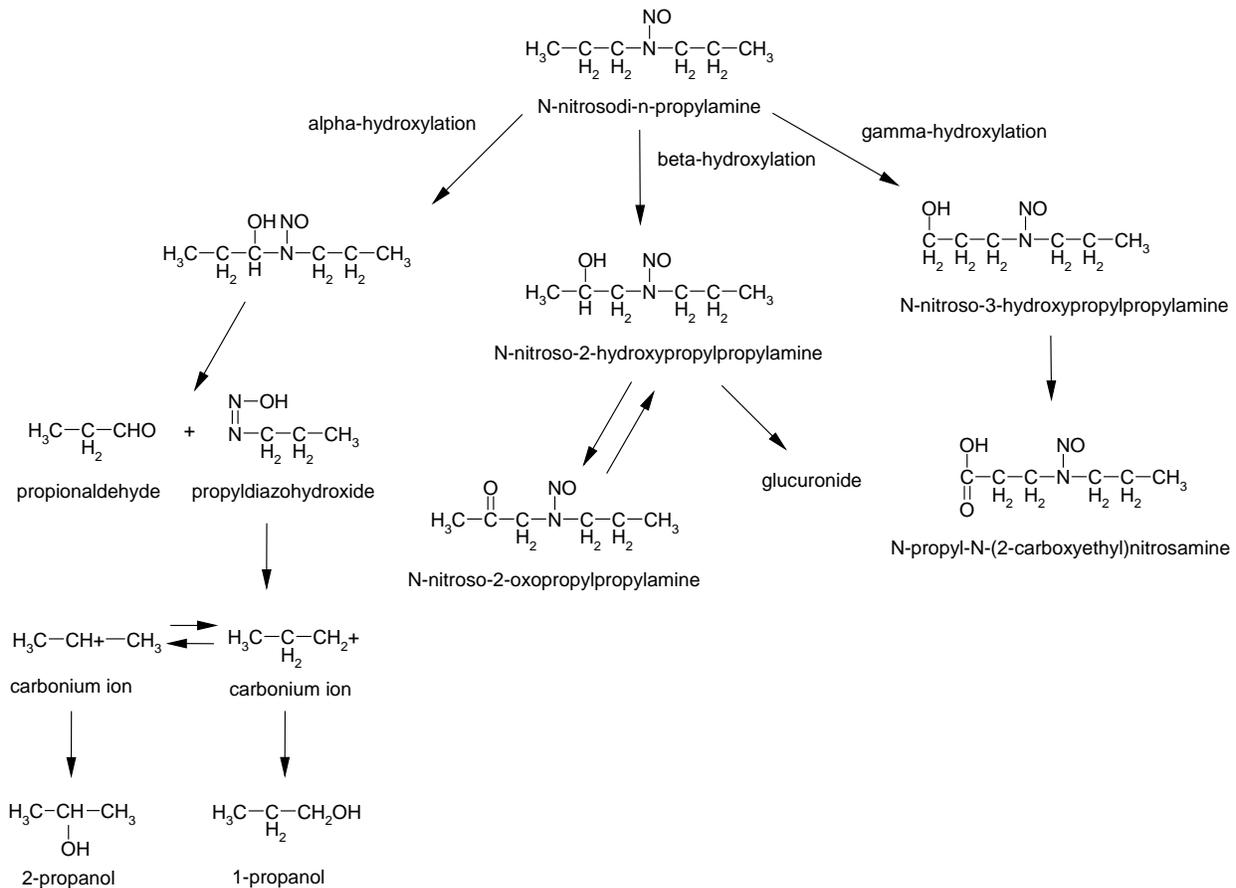
Several studies have examined the cytochrome P450 isoforms involved in N-nitrosodi-n-propylamine metabolism. Induction of cytochrome P450 2B1 resulted in increases in dealkylation specific for α-carbons (Shu and Hollenberg 1996). Cytochrome P450 2E1 is the predominant isoform responsible for N-nitrosodi-n-propylamine α-hydroxylation (Shu and Hollenberg 1996; Teiber and Hollenberg 2000; Teiber et al. 2001), whereas cytochrome P450 isoforms 1A1/1A2 and 4A1/4A2 do not appear to be involved in N-nitrosodi-n-propylamine metabolism (Shu and Hollenberg 1996). Cytochrome P450 2E1 and 2B1 isoforms also mediate the oxidation of the metabolite, N-nitroso-2-hydroxypropylpropylamine, to N-nitroso-2-oxopropylpropylamine (Teiber et al. 2001).

Documented and postulated metabolites of N-nitrosodi-n-propylamine have been shown to be carcinogenic in hamsters and rats (IARC 1978). These include N-nitroso-bis-(2-hydroxy-n-propyl)amine, N-nitroso-2-oxo-n propylpropylamine, N-nitroso-bis(2-oxo-n-propyl)amine, and N-nitroso-bis(2acetoxy-n-propyl)amine. Main tumor sites of many of these metabolites include those associated with N-nitrosodi-n-propylamine treatment (Section 2.19).

3.1.4 Excretion

Rats excreted metabolites but not unchanged N-nitrosodi-n-propylamine in the urine following oral dosing with N-nitrosodi-n-propylamine (Blattmann and Preussmann 1973; Suzuki and Okada 1981). The principal metabolite in the Suzuki and Okada (1981) study, N-propyl-N-(2-carboxyethyl)nitrosamine, amounted to approximately 5% of the administered dose. Additional information regarding the extent or rate of excretion in either of the studies was not reported.

Excretion of unchanged N-nitrosodiethanolamine in the urine of rats has been reported in several studies after cutaneous application of N-nitrosodiethylamine (Airoldi et al. 1984; Lijinsky et al. 1981; Preussmann et al. 1981).

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.

No PBPK models were identified for N-nitrosodi-n-propylamine.

3.1.6 Animal-to-Human Extrapolations

No studies were identified that provide evidence to suggest differences in the toxicity or toxicokinetics of N-nitrosodi-n-propylamine. Most of the available toxicity/carcinogenicity studies have been conducted in rats, which does not allow for a comparison across species. Studies in rats and hamsters have demonstrated the N-nitrosodi-n-propylamine metabolites in both species (IARC 1978).

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 N-nitrosodi-n-propylamine are discussed in Section 5.7, Populations with Potentially High Exposures.

No studies have evaluated the toxicity of N-nitrosodi-n-propylamine in children; the toxicity is assumed to be similar to that in adults. Although the developmental toxicity has not been evaluated following inhalation, oral, or dermal exposure; a parenteral exposure study demonstrated the transplacental carcinogenicity of N-nitrosodi-n-propylamine (Althoff and Grandjean 1979; Althoff et al. 1977a).

No populations with unusual susceptibility to health effects of N-nitrosodi-n-propylamine have been identified. However, heavy consumers of alcoholic beverages might be considered to be a susceptible population based on a single report in which ethanol was shown to potentiate the carcinogenicity of N-nitrosodi-n-propylamine in mice (Griciute et al. 1982). Co-exposure to other compounds that induce CYP2E1 may result in increased metabolism of N-nitrosodi-n-propylamine, which could result in increased toxicity and/or carcinogenicity.

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

No biomarkers of exposure have been identified for N-nitrosodi-n-propylamine.

3.3.2   Biomarkers of Effect

No biomarkers of effect have been identified for N-nitrosodi-n-propylamine.

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.4   INTERACTIONS WITH OTHER CHEMICALS

Ethanol was found to enhance the carcinogenicity of N-nitrosodi-n-propylamine. Mice that were treated with estimated 1 mg/kg doses of N-nitrosodi-n-propylamine dissolved in 40% ethanol by gavage, twice a week for 50 weeks, developed higher incidences of tumors than mice that were similarly treated with the same dose of compound in water (Griciute et al. 1982). The most pronounced tumor enhancement was in the forestomach (51% carcinomas versus 10% in N-nitrosodi-n-propylamine/water group), but increases in pulmonary adenomas and lymphomas also occurred.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1   CHEMICAL IDENTITY

Data pertaining to the chemical identity of N-nitrosodi-n-propylamine are listed in Table 4-1.

Table 4-1. Chemical Identity of Nitrosodi-n-Propylamine

Characteristic	Information	Reference
Chemical name	1-Propanamine, N-nitroso-N-propyl	CAS 1988
Synonym(s) and registered trade name(s)	N-nitrosodipropylamine; N,N-dipropylnitrosamine; N-Nitroso-N-di-n-propylamine; NDPA; DPNA; DPN	HSDB 1988; SANSS 1988
Chemical formula	$C_6H_{14}N_2O$	CAS 1988
Chemical structure		SANSS 1988
CAS Registry	621-64-7	CAS 1988

CAS = Chemical Abstracts Services

4.2   PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of N-nitrosodi-n-propylamine are presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of N-Nitrosodi-n-Propylamine

Property	Information	Reference
Molecular weight	130.19	Weast 1983
Color	Yellow	IARC 1978
Physical state	Liquid	IARC 1978
Melting point	6.6°C (estimated)	Lyman 1985
	-12°C (estimated)	EPA 1986a
Boiling point	206°C	Weast 1983
Density at 20°C	0.9163	Weast 1983
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of N-Nitrosodi-n-Propylamine

Solubility:		
Water at 23–25°C	9,894 mg/L	Mirvish et al. 1976
Organic solvents	Soluble in alcohol, ether, other organic solvents	IARC 1978; Weast 1983
Partition coefficients:		
Log K_{ow}	1.36	Hansch and Leo 1985
Log K_{oc}	2.11 (estimated)	Hansch and Leo 1985
Vapor pressure at 20°C	0.086 mm Hg (estimated)	Klein 1982
Henry's law constant at 20°C	1.47×10^{-6} atm-m^3/mole (estimated from vapor pressure and water solubility data)	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits in air	No data[a]	
Conversion factors ppm (v/v) to mg/m^3 in air (20°C) mg/m^3 to ppm (v/v) in air (20°C)	ppm (v/v)x5.41=mg/m^3 mg/m^{3}x0.185=ppm (v/v)	
Explosive limits		

[a]Vapor probably does not form an explosive mixture with air at ordinary temperatures (OHM-TADS 1988).

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

N-Nitrosodi-n-propylamine has been identified in at least 71 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which N-nitrosodi-n-propylamine 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 N-Nitrosodi-n-Propylamine Contamination

Source: ATSDR 2017

Frequency of NPL Sites: 1, 2, 3, 4, 6, 8
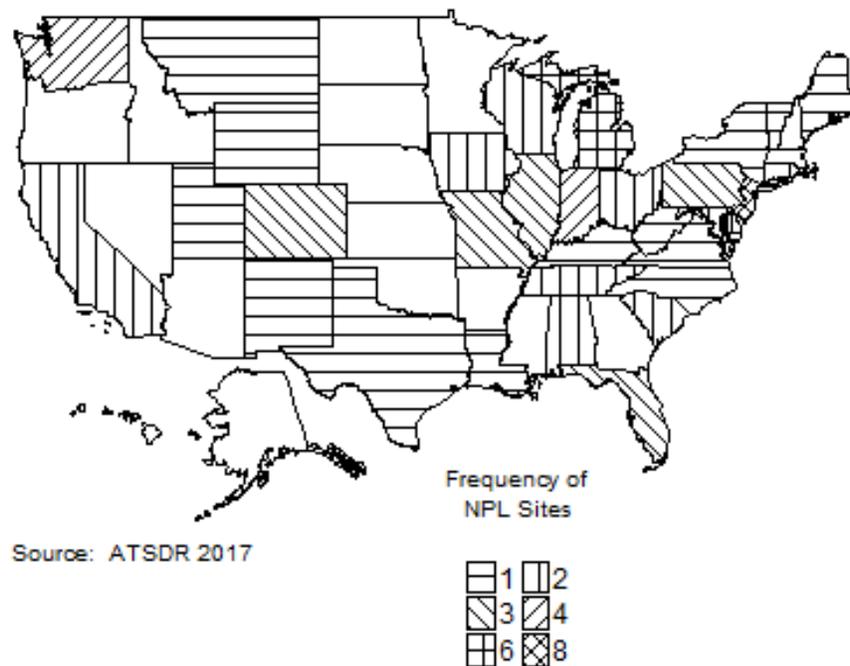
- N-nitrosodi-n-propylamine is produced in small, laboratory-scale quantities for research purposes. It is also produced inadvertently during certain manufacturing processes, occurring as an impurity in some dinitroaniline pesticides and during manufacture of some extruded rubber products.

- Limited data are available concerning exposure of the general population to N-nitrosodi-n-propylamine. It appears that exposure possibly results from formation in the upper gastrointestinal tract during digestion of certain foods or drugs that contain secondary amines, ingestion of some foods containing N-nitrosodi-n-propylamine (e.g., certain cheeses, cured meats and fishes, and alcoholic beverages), and inhalation of cigarette smoke.

- Low levels of N-nitrosodi-n- propylamine may be released to the environment from contaminated products and industrial sites of inadvertent production or disposal of wastes. It may also be released from waste disposal sites where the precursor secondary amines have been discharged.

- N-Nitrosodi-n-propylamine is not expected to be a persistent environmental contaminant. In air and soil surfaces, it is likely degraded by photolysis and volatilization. In water and subsurface soil, N-nitrosodi-n-propylamine would be susceptible to biodegradation under both aerobic and anaerobic conditions.

5.2   PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1   Production

N-Nitrosodi-n-propylamine is not produced for commercial use in the United States (HSDB 1988). Table 5-1 contains a list the number of facilities per state that produced, processed, or used N-nitrosodi-n-propylamine in 2016, as well as information on the amount of N-nitrosodi-n-propylamine on site and related activities and uses (TRI16 2017). Manufacturers are required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements. The TRI data should be used with caution since only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use N-Nitrosodi-n-Propylamine

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
IN	1	100	999	12
OH	1	100	999	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: TRI16 2017 (Data are from 2016)

5.2.2   Import/Export

No U.S. import data were found for N-nitrosodi-n-propylamine.

5.2.3   Use

N-Nitrosodi-n-propylamine is prepared in laboratory-scale quantities solely for use as a research chemical (HSDB 1988).

5.2.4   Disposal

Landfill disposal procedures should be confirmed by responsible environmental engineers and regulatory officials (OHM-TADS 1988). N-Nitrosodi-n-propylamine may be destroyed by high-temperature incineration in an incinerator equipped with a NOx scrubber (OHM-TADS 1988). Chemical treatment methods may also be used to destroy N-nitrosodi-n-propylamine. These methods involve: (a) denitrosation by reaction with 3% hydrobromic acid in glacial acetic acid; (b) oxidation by reaction with potassium permanganate-sulfuric acid; or (c) extraction of the nitrosamine from the waste using dichloromethane and subsequent reaction with triethyloxonium tetrafluoroborate (TOEF) (Castegnaro et al. 1982).

5.3   RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data, presented in Table 5-2, 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).

5. POTENTIAL FOR HUMAN EXPOSURE

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

State[c]	RF[d]	Reported amounts released in pounds per year[b]					Total release		
		Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
IN	1	1	0	0	0	No data	1	0	1
OH	1	No data	No data	No data	No data	No data	No data	No data	No data
Total	2	1	0	0	0	0	1	0	1

[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, waste water 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: TRI16 2017 (Data are from 2016)

5.3.1 Air

Estimated releases of 1 pound (~0.00045 metric tons) of N-nitrosodi-n-propylamine to the atmosphere from 4 domestic manufacturing and processing facilities in 2016, accounted for about 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

Occurrence of part per million levels of N-nitrosodi-n-propylamine in various dinitroaniline herbicides may result in release of small amounts of the nitrosamine into the atmosphere during and after application (Cohen et al. 1978; Crosby 1979; Oliver 1981). The occurrence of N-nitrosodi-n-propylamine in air in the production area of a rubber products plant where common nitrosating agents (e.g., oxides of nitrogen) were used in conjunction with rubber formulations containing secondary amine-based compounds suggests that plants using this type of production process are a potential source of N-nitrosodi-n-propylamine emissions (NIOSH 1982).

5.3.2   Water

No releases of N-nitrosodi-n-propylamine to surface water or publicly owned treatment works (POTWs) were reported from facilities required to report to the TRI (TRI16 2017).

N-Nitrosamines may be formed inadvertently in situations in which amines come in contact with nitrogen oxides, nitrous acid, nitrite salts, nitro compounds, or nitroso compounds (Fajen et al. 1980). This suggests that under appropriate industrial conditions where di-n-propylamine is present, N-nitrosodi-n-propylamine could be formed inadvertently and released to the environment via effluent discharges. Limited monitoring data that support this supposition indicate that N-nitrosodi-n-propylamine has been released in waste water from some textile plants and manufacturers and/or users of amines. Small amounts of N-nitrosodi-n-propylamine may also be released to surface waters either directly or indirectly (e.g., in runoff) as a result of using dinitroaniline herbicides containing the nitrosamine as an impurity.

5.3.3   Soil

No releases of N-nitrosodi-n-propylamine to soils from were reported by facilities required to report to the TRI, and no N-nitrosodi-n-propylamine was released via underground injection (TRI16 2017).

Small amounts of N-nitrosodi-n-propylamine may be released to soil during the application of some dinitroaniline herbicides. For example, a typical 1 kg/hectare application of trifluralin containing 1 ppm N-nitrosodi-n-propylamine would result in application of 0.01 ng nitrosamine/cm^2 (Oliver 1979). Federal regulations require trifluralin formulations to contain <1 ppm N-nitrosodi-n-propylamine (EPA 1979). Data pertaining specifically to the formation of N-nitrosodi-n- propylamine in soil were not found in the literature; however, formation of N-nitrosodimethylamine (NDMA) in soil containing dimethylamine and nitrate or nitrite suggests that a similar mechanism may exist for N-nitrosodi-n-propylamine (Mills and Alexander 1976; Oliver 1981; Pancholy 1976).

5.4   ENVIRONMENTAL FATE

5.4.1   Transport and Partitioning

Air.   Organics having a vapor pressure of $>10^{-4}$ mm Hg should exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). The estimated vapor pressure of N-nitrosodi-n-propylamine

(0.086 mm Hg at 25°C; 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}=1.36; see Table 4-2), a bioconcentration factor of 6 and an adsorption coefficient (K_{oc}) of 129 have been estimated for N-nitrosodi-n-propylamine (Bysshe 1982; Hansch and Leo 1985; Lyman 1982). These values indicate that bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments in water would not be important fate processes. The low Henry's Law constant for N-nitrosodi-n-propylamine (1.47×10^{-6} atm-m^3/mol; see Table 4-2) suggests that volatilization would be a relatively insignificant fate process in water.

Sediment and Soil.   If an herbicide containing N-nitrosodi-n-propylamine were applied to warm, moist soil surfaces, most of the nitrosamine would be expected to volatilize. The volatilization half-life from soil surfaces under field conditions is estimated to be on the order of 2–6 hours (Berard and Rainey 1979; Oliver 1979). If an herbicide containing N-nitrosodi-n- propylamine were incorporated into soil (below the soil surface), volatilization would be of minor importance (Oliver 1979). When incorporated into soil, N-nitrosodi-n-propylamine is expected to be highly mobile and it has the potential to leach into shallow groundwater supplies (Saunders et al. 1979; Swann et al. 1983).

5.4.2   Transformation and Degradation

Air.   In the atmosphere, N-nitrosodi-n-propylamine vapor would be rapidly degraded by direct photolysis and/or reaction with photochemically-generated hydroxyl radicals. Crosby et al. (1980) determined a pseudo-first order half-life of 5–7 hours for photolysis of N-nitrosodi-n-propylamine vapor in air exposed to sunlight. Although experimental conditions did not closely simulate environmental conditions (the concentration of N-nitrosodi-n-propylamine was relatively high), results of this study did indicate that N-nitrosodi-n-propylamine is susceptible to rapid photolysis. The half-life for the reaction of N-nitrosodi-n-propylamine vapor with photochemically-generated hydroxyl radicals has been estimated to be about 16 hours in typical ambient air. This value is based on a reaction rate constant of 2.42×10^{-11} cm^3/molecules-see at 25°C, which was estimated using the method of Atkinson (1987).

Water.   N-Nitrosodi-n-propylamine is not expected to undergo abiotic degradation under the conditions found in natural waters (Callahan et al. 1979; Oliver et al. 1979; Saunders and Mosier 1980). The dominant removal process for N-nitrosodi-n-propylamine in surface water is probably photolysis. A

study of low levels (0.65 ppm) of N-nitrosodi-n-propylamine in lake water resulted in a photolytic half-life of about 2.5 hours. The major photoproduct was found to be n-propylamine, but the formation of di-n-propylamine was also observed (Saunders and Mosier 1980). Beyond the reach of sunlight, it appears that N-nitrosodi-n-propylamine would be subject to slow microbial degradation in aerobic waters (Tabak et al. 1981; Tate and Alexander 1975). Insufficient data are available to predict the rate at which this would occur.

Sediment and Soil.   It appears that microbial degradation would be the dominant removal process for the nitrosamine in subsurface soil under aerobic conditions. Half-lives ranging from 14 to 40 days have been observed in aerobic subsurface soil and from 47 to 80 days in anaerobic subsurface soil (Oliver et al. 1979; Saunders et al. 1979; Tate and Alexander 1975). Initial losses were due primarily to volatilization; however, biodegradation was the dominant fate process. Available data on the degradation of the nitrosamine in water and air indicate that photolysis may be an important removal process on soil surfaces.

5.5   LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to N-nitrosodi-n-propylamine depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of N-nitrosodi-n-propylamine 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 N-nitrosodi-n-propylamine 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 5-3 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	<0.04 µg/m^3	Cooper 1987
Drinking water	0.05 µg/L (for 100 mL sample)	Drescher and Frank 1978
Groundwater	10 µg/L	EPA 1986b, 1987; Fisk 1986
Soil	0.025 µg/g	Pancholy 1976
Sediment	330 µg/kg	EPA 1987; Fisk 1986

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Whole blood	0.6 ng/kg	Maki 1980
Urine	0.05 µg/L (for 100 mL sample)	Drescher and Frank 1978

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Detections of N-nitrosodi-n-propylamine in air, water, and soil at NPL sites are summarized in Table 5-4.

Table 5-4. N-Nitrosodi-n-Propylamine Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of concentrations	NPL sites
Water (ppb)	21	11.4	6,420	8	8
Soil (ppb)	1,900	1,470	3,970	11	10
Air (ppbv)	No data	No data	No data	No data	No data

[a]Concentrations found in ATSDR site documents from 1981 to 2015 for 1,854 NPL sites (ATSDR 2017). 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

There is no indication in the available literature that N-nitrosodi-n- propylamine has been detected in ambient air in the United States. Air samples collected above agricultural fields before, during, and after application of the pesticide trifluralin contained no detectable levels of N-nitrosodi-n-propylamine (detection limit 50 ng/m^3) (Day et al. 1982, West and Day 1979).

5.5.2   Water

No data were available regarding the monitoring and detection of N-nitrosodi-n-propylamine in ambient surface water, groundwater, or drinking water in the United States except at EPA NPL hazardous waste sites. There were only a couple of monitoring studies available pertaining to the occurrence N-nitrosodi-n-propylamine in treated waste water. In a survey of 32 U.S. textile plants, N-nitrosodi-n-propylamine was detected at concentrations of 2–20 µg/L in 2 out of 32 samples of secondary effluent, while no detectable levels were found in samples of raw waste water from these same plants (Rawlings and

Samfield 1979). This suggests that N-nitrosodi-n-propylamine was formed during the treatment process.
N-Nitrosodi-n-propylamine has also been detected at a maximum concentration of 1.2 µg/L in the final
effluent from a German chemical manufacturing plant involved in the manufacture and/or use of amines
(Hartmetz and Slemrova 1980). A survey of stormwater runoff samples collected from 15 cities
geographically located across the United States revealed that N-nitrosodi-n-propylamine is not a typical
contaminant of stormwater runoff (Cole et al. 1984). Water samples collected from agricultural fields
immediately following application of the pesticide trifluralin contained no detectable levels of
N-nitrosodi-n-propylamine (detection limit 0.01–0.02 µg/L) (Ross et al. 1978; West and Day 1979).

5.5.3   Sediment and Soil

Soil samples collected from agricultural fields immediately following application of the pesticide
trifluralin contained no detectable levels of N-nitrosodi-n-propylamine (detection limit 0.2–1 ng/g) (Ross
et al. 1978; West and Day 1979).

5.5.4   Other Media

A number of studies have focused on the monitoring of volatile N-nitrosamines in various foodstuffs,
including cheese, cured meats, cooked fish, and alcoholic beverages; however, N-nitrosodi-n-propylamine
has rarely been detected (Alliston et al. 1972; Gavinelli et al. 1988; Goff and Fine 1979; Gross and
Newberne 1977; Huang et al. 1981; Sen et al. 1987). The nitrosamines appear to have formed in these
foods as the result of the reaction of secondary amines with the preservative sodium nitrite (Gray and
Dugan 1974). N-Nitrosodi-n-propylamine has been monitored in food at the following levels: salt-
preserved fish (steamed), 0.050 µg/kg; salt-preserved fish (fried), 0.030 µg/kg; salt-preserved fish (raw),
not detected; cheese, 5–30 µg /kg; apple brandy, up to 3.6 µg/kg; and cognac, rum, and whiskey, up to
0.2 µg/kg (Cerutti et al. 1975; Gross and Newberne 1977; Huang et al. 1981; IARC 1978). A study of
cigarette smoke condensate from European cigarettes showed that N-nitrosodi-n-propylamine was found
at a level equivalent to 1 ng per cigarette in smoke condensate from 1 out of 11 types of cigarettes, while
condensate from 10 out of 11 cigarettes had levels below the detection level of 0.5 ng per cigarette
(McCormick et al. 1973). Although a number of volatile N-nitrosamines have been identified in
children's pacifiers and baby-bottle nipples, N-nitrosodi-n-propylamine was not among them (Billedeau et
al. 1986; Gavinelli et al. 1988; Westin et al. 1987). Crops and plants harvested from fields treated with
the pesticides trifluralin, benefin, or oryzalin contained no detectable levels of N-nitrosodi-n-propylamine
(detection limit 0.2 ng/g) (Ross et al. 1978, West and Day 1979).

In the mid-to-late 1970s, N-nitrosodi-n-propylamine was detected in the herbicides trifluralin, oryzalin, and isopropalin at levels as high as 154, <1, and 39–87 mg/L, respectively (Cohen et al. 1978; Ross et al. 1977). Subsequent to these findings, the production process for trifluralin was modified; current levels of the nitrosamine in technical trifluralin are <1 mg/L (EPA 1979; Maybury and Grant 1983; Wotherspoon and Hindle 1988).

5.6 GENERAL POPULATION EXPOSURE

The potential for inhalation of N-nitrosodi-n-propylamine during application and soil incorporation of trifluralin containing N-nitrosodi-n-propylamine is extremely low; N-nitrosodi-n-propylamine levels in breathing zone air of field workers should be on the order of several parts per trillion or less (Day et al. 1982). During 1982, the National Institute for Occupational Safety and Health (NIOSH) carried out a monitoring study at a plant where workers were involved in the production of extruded rubber parts for automobile part interiors. Samples of personal breathing-zone air were found to contain N-nitrosodi-n-propylamine at concentrations ranging from 1.3 to 3.3 $\mu g/m^3$ (241–611 ppt), with a mean concentration of 2.3 $\mu g/m^3$ (430 ppt). Airborne nitrosamine levels at this plant were consistent with those found by NIOSH in other rubber industries where the same type of extruding process was used. Volatile nitrosamines, such as N-nitrosodi-n-propylamine, are emitted from heated rubber after formation by the reaction of common nitrosating agents (e.g., oxides of nitrogen) with secondary amine-based compounds frequently used in rubber formulations (NIOSH 1982). Workers at hazardous waste sites could potentially be exposed to this compound by inhalation and dermal contact. It is not certain whether direct skin contact with N-nitrosodi-n-propylamine would allow the chemical to enter the body.

Based on limited data, it appears that the general population may be exposed to part per trillion levels of N-nitrosodi-n-propylamine in some sodium nitrite-treated foods and certain alcoholic beverages. The general population may be exposed to N-nitrosodi-n-propylamine as a result of its *in vivo* formation during digestion in the upper gastrointestinal tract of nitrite-containing and secondary amine-containing foods or drugs, especially those containing di-n-propylamine (Groenen et al. 1980; Magee et al. 1976; Sakai et al. 1984). One study pertaining to exposure to N-nitrosodi-n-propylamine through inhalation of cigarette smoke suggests that there is a possibility that low levels of this compound (on the order of 1 ng per cigarette) may occur in cigarette smoke. There is no evidence of general population exposure to N-nitrosodi-n-propylamine through ingestion of contaminated drinking water or through dermal contact.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Data are not available for determining those segments of the general population with potentially high exposure.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of N-nitrosodi-n-propylamine is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of N-nitrosodi-n-propylamine.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1   Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to N-nitrosodi-n-propylamine that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of N-nitrosodi-n-propylamine. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

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

6.2   Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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Figure 6-1. Summary of Existing Health Effects Studies on N-Nitrosodi-n-Propylamine By Route and Endpoint*

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

Oral Studies

Endpoint	Count
Body weight	1
Respiratory	—
Cardiovascular	—
Gastrointestinal	—
Hematological	—
Musculoskeletal	—
Hepatic	4
Renal	—
Dermal	—
Ocular	—
Endocrine	—
Immunological	—
Neurological	—
Reproductive	—
Developmental	—
Other Non Cancer	—
Cancer	6
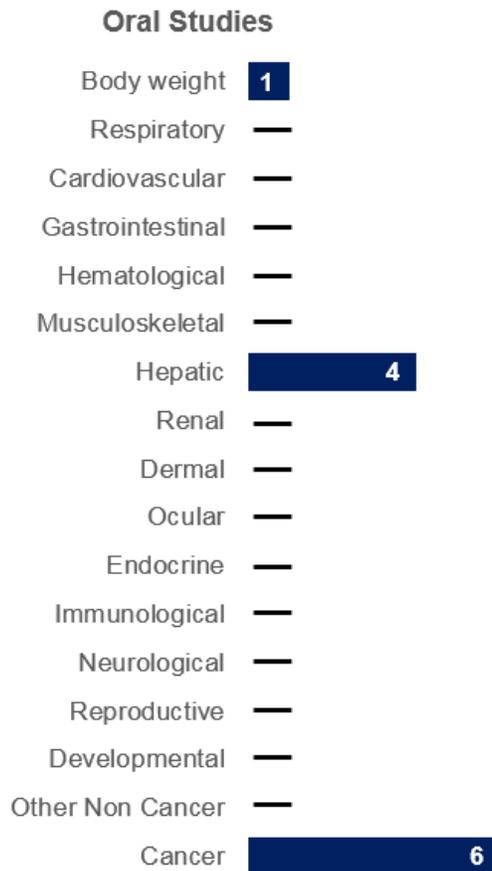
*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Some studies examined more than 1 endpoint. No inhalation or dermal studies in humans or animals were located. Data are also available for other nonrelevant routes of exposure.

6. ADEQUACY OF THE DATABASE

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

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

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

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

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

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

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

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

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

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

Children's Susceptibility. No studies have evaluated the toxicity of N-nitrosodi-n-propylamine in children or young animals. Studies in young animals would be useful to address potential concerns that children may be more susceptible to the toxicity of N-nitrosodi-n-propylamine than adults.

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

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

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

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

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

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

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

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

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

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

6.3   Ongoing Studies

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

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding N-nitrosodi-n-propylamine 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. No MRLs were derived for N-nitrosodi-n-propylamine; see Appendix A for detailed information.

Table 7-1. Regulations and Guidelines Applicable to n-Nitrosodi-n-Propylamine

Agency	Description	Information	Reference
Air			
EPA	RfC	No data	IRIS 2002
WHO	Air quality guidelines	No data	WHO 2010
Water & Food			
EPA	Drinking water standards and health advisories	No data	EPA 2012
	National primary drinking water regulations	No data	EPA 2009
	RfD	No data	IRIS 2002
WHO	Drinking water quality guidelines	No data	WHO 2017
FDA	EAFUS	No data[a]	FDA 2013
Cancer			
ACGIH	Carcinogenicity classification	No data	ACGIH 2016
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[b]	NTP 2016
EPA	Carcinogenicity classification	B2[c,d]	IRIS 2002
	Oral slope factor	7.0E+0 $(mg/kg/day)^{-1}$	
IARC	Carcinogenicity classification	Group 2B[e]	IARC 1987
Occupational			
ACGIH	TLV	No data	ACGIH 2016
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2016

7. REGULATIONS AND GUIDELINES

Table 7-1. Regulations and Guidelines Applicable to n-Nitrosodi-n-Propylamine

Agency	Description	Information	Reference
Emergency Criteria			
EPA	AEGLs-air	No data	EPA 2016
AIHA	ERPGs	No data	AIHA 2015
DOE	PACs-air		DOE 2016a
	PAC-1[f]	5.6 mg/m^3	
	PAC-2[f]	62 mg/m^3	
	PAC-3[f]	95 mg/m^3	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]Based on sufficient evidence of carcinogenicity in experimental animals.
[c]Group B2: probable human carcinogen.
[d]Based on increased tumor incidence at multiple sites in two rodent species and in monkeys administered the compound by various routes.
[e]Group 2B: possibly carcinogenic to humans.
[f]Definitions of PAC terminology are available from DOE (2016b).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; 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; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

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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.

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Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, 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 Division of Toxicology and Human Health Sciences, 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-Nitrosodi-n-propylamine
CAS Numbers: 621-64-7
Date: December 1989
                                    March 2017 – Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: No acute-duration inhalation studies were identified.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

*Chemical Name***:**   N-Nitrosodi-n-propylamine
CAS Numbers: 621-64-7
Date: December 1989
                           March 2017 – Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL.

Rationale for Not Deriving an MRL: No intermediate-duration inhalation studies were identified.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: N-Nitrosodi-n-propylamine
CAS Numbers: 621-64-7
Date: December 1989
                March 2017 – Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: No chronic-duration inhalation studies were identified.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: N-Nitrosodi-n-propylamine
CAS Numbers: 621-64-7
Date: February 2019
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: The acute-duration oral database was not considered suitable for identifying the most sensitive target of toxicity.

There are limited data on the acute toxicity of N-nitrosodi-n-propylamine. In an acute lethality study, hepatic centrilobular necrosis and fatty degeneration were observed (Druckery et al. 1967); although the doses tested were not reported, the LD_{50} was 480 mg/kg/day. Hepatocellular necrosis was observed in rats administered via gavage 10 mg/kg/day for 14 days (Terashima et al. 2015). At 20 and 40 mg/kg/day, hepatocellular necrosis, hypertrophy, and vacuolation and centrilobular inflammation were observed. A 4-day gavage administration of 40 mg/kg/day N-nitrosodi-n-propylamine resulted in hepatocellular swelling and increases in pentobarbital sleep time in mice (Nishie et al. 1972). No alterations in serum aspartate aminotransferase, lactate dehydrogenase, or γ-glutamyl transferase were observed in mice administered 9.5 mg/kg/day via drinking water for 1 week (Tyndall et al. 1978); this study did not include a histological examination. The database was not considered adequate for deriving an MRL because the available acute duration studies only examined the liver and body weight endpoints; and there is uncertainty as to whether the liver would be the most sensitive target of toxicity.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: N-Nitrosodi-n-propylamine
CAS Numbers: 621-64-7
Date: December 1989
                                 March 2017 – Updated literature search
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies examining noncancer endpoints were identified.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: N-Nitrosodi-n-propylamine
CAS Numbers: 621-64-7
Date: December 1989
                                March 2017 – Updated literature search
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: No chronic-duration oral studies were identified.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR N-NITROSODI-n-PROPYLAMINE

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 N-nitrosodi-n-propylamine.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions data for N-nitrosodi-n-propylamine. 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 N-nitrosodi-n-propylamine 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 N-nitrosodi-n-propylamine 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

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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

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for N-nitrosodi-n-propylamine (ATSDR 1989), thus, the literature search was restricted to studies published between January 1987 to March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for N-nitrosodi-n-propylamine. 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 N-nitrosodi-N-propylamine 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	
03/2017	((621-64-7[rn] OR 2920IH58NC[rn] OR "N-nitroso(di-n-propyl)amine"[supplementary

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	concept] OR "N-nitroso(di-n-propyl)amine"[nm]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[mhda])) OR (("N-Nitroso(di-n-propyl)amine"[tw] OR "Di-n-propylnitrosamine"[tw] OR "Di-n-propylnitrosoamine"[tw] OR "N-nitroso-Dipropylamine"[tw] OR "Dipropylnitrosamine"[tw] OR "N, N-Di-n-propylnitrosamine"[tw] OR "N, N-Dipropylnitrosamine"[tw] OR "N-Nitroso-N-propyl-1-propanamine"[tw] OR "N-Nitrosodi-n-propylamine"[tw] OR "N-Nitrosodipropylamine"[tw] OR "Nitrosodipropylamine"[tw] OR "N-nitroso-N-propyl-Propanamine"[tw] OR "N-nitroso-N-di-Propylamine"[tw]) AND (1987/01/01 : 3000[dp] OR 1987/01/01 : 3000[crdat] OR 1987/01/01 : 3000[edat]))
Toxline 03/2017	("n-nitroso (di-n-propyl) amine" OR "di-n-propylnitrosamine" OR "di-n-propylnitrosoamine" OR "n-nitroso-dipropylamine" OR "dipropylnitrosamine" OR "n n-di-n-propylnitrosamine" OR "n n-dipropylnitrosamine" OR "n-nitroso-n-propyl-1-propanamine" OR "n-nitrosodi-n-propylamine" OR "n-nitrosodipropylamine" OR "nitrosodipropylamine" OR "n-nitroso-n-propyl-propanamine" OR "n-nitroso-n-di-propylamine" OR 621-64-7 [rn]) AND 1987:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Toxcenter 03/2017	FILE 'TOXCENTER' ENTERED AT 12:44:25 ON 17 MAR 2017 CHARGED TO COST=EH011.13.01.01
	L1 930 SEA 621-64-7
	L2 915 SEA L1 NOT TSCATS/FS
	L3 901 SEA L2 NOT PATENT/DT
	L4 451 SEA L3 AND PY>=1987
	          ACTIVATE 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?)
	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?)

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	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
	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 338 SEA L4 AND L37
	L39 19 SEA L38 AND MEDLINE/FS
	L40 25 SEA L38 AND BIOSIS/FS
	L41 267 SEA L38 AND CAPLUS/FS
	L42 27 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L43 295 DUP REM L39 L40 L42 L41 (43 DUPLICATES REMOVED)
	L*** DEL 19 S L38 AND MEDLINE/FS
	L*** DEL 19 S L38 AND MEDLINE/FS

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
	L44 19 SEA L43
	L*** DEL 25 S L38 AND BIOSIS/FS
	L*** DEL 25 S L38 AND BIOSIS/FS
	L45 23 SEA L43
	L*** DEL 267 S L38 AND CAPLUS/FS
	L*** DEL 267 S L38 AND CAPLUS/FS
	L46 235 SEA L43
	L*** DEL 27 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L*** DEL 27 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L47 18 SEA L43
	L48 276 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS
	SAVE TEMP L48 NITROSO/A
	D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 621-64-7
NTP	
03/2017	621-64-7 N-Nitroso(di-n-propyl)amine Di-n-propylnitrosamine Di-n-propylnitrosoamine N-nitroso-Dipropylamine Dipropylnitrosamine N,N-Di-n-propylnitrosamine N,N-Dipropylnitrosamine N-Nitroso-N-propyl-1-propanamine N-Nitrosodi-n-propylamine N-Nitrosodipropylamine Nitrosodipropylamine N-nitroso-N-propyl-Propanamine N-nitroso-N-di-Propylamine
NIH RePORTER	
05/2017	Active projects "N-Nitroso(di-n-propyl)amine" OR "Di-n-propylnitrosamine" OR "Di-n-propylnitrosoamine" OR "N-nitroso-Dipropylamine" OR "Dipropylnitrosamine" OR "N,N-Di-n-propylnitrosamine" OR "N,N-Dipropylnitrosamine" OR "N-Nitroso-N-propyl-1-propanamine" OR "N-Nitrosodi-n-propylamine" OR "N-Nitrosodipropylamine" OR "Nitrosodipropylamine" OR "N-nitroso-N-propyl-Propanamine" OR "N-nitroso-N-di-Propylamine"

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Other	Identified throughout the assessment process

aSeveral versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:
- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 453
- Number of records identified from other strategies: 24
- Total number of records to undergo literature screening: 477

B.1.2 Literature Screening

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

- 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: 477
- Number of studies considered relevant and moved to the next step: 44

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: 44
- Number of studies cited in the health effects sections of the existing toxicological profile (December, 1989): 91
- Total number of studies cited in the health effects sections of the updated profile: 113

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

**Figure B-1. March 2017 Literature Search Results and Screen for
N-Nitrosodi-n-Propylamine**
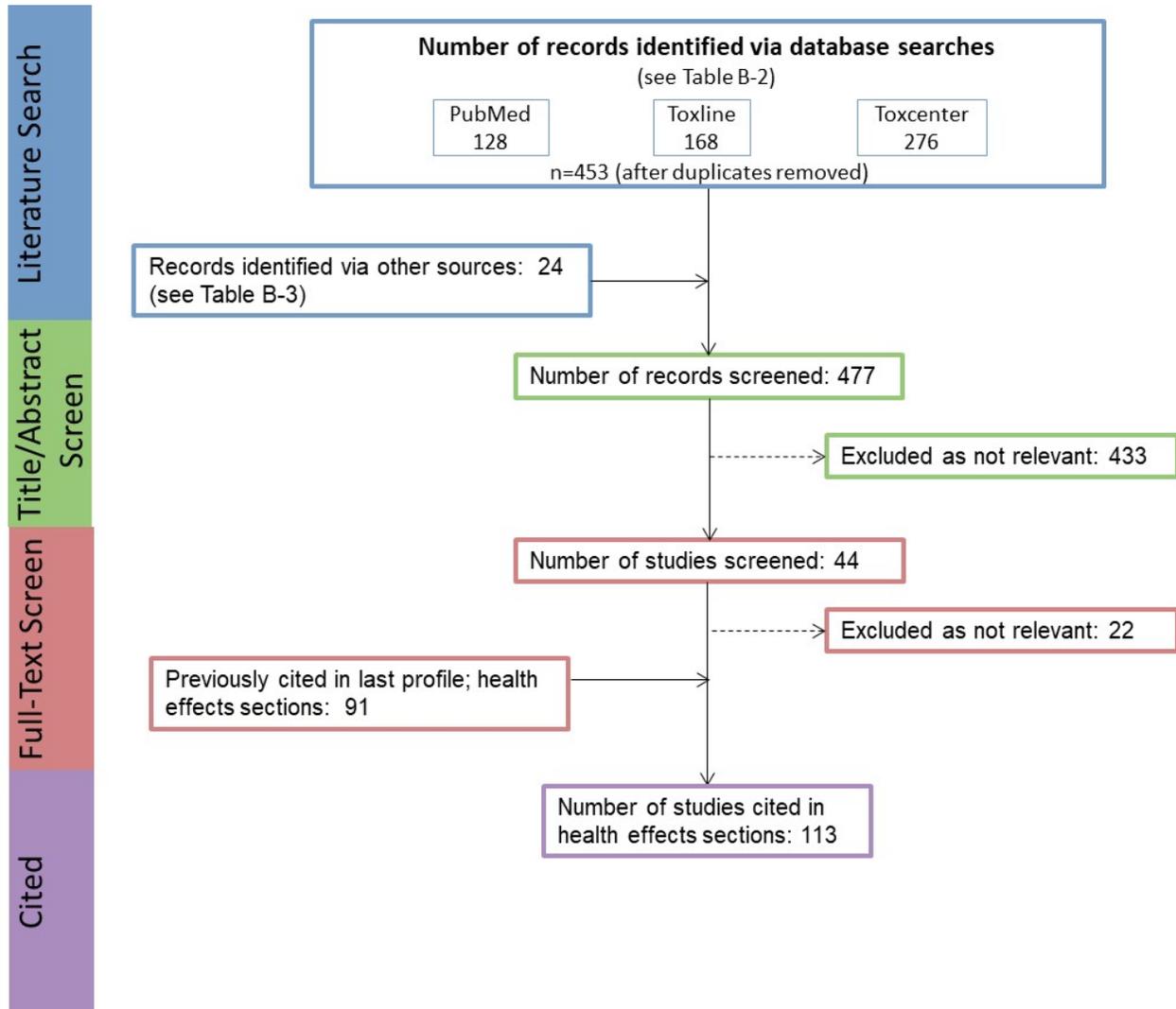
APPENDIX C. USER'S GUIDE

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), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), 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.

(13)   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.

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

(15)   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.

(16)   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).

(17)   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.

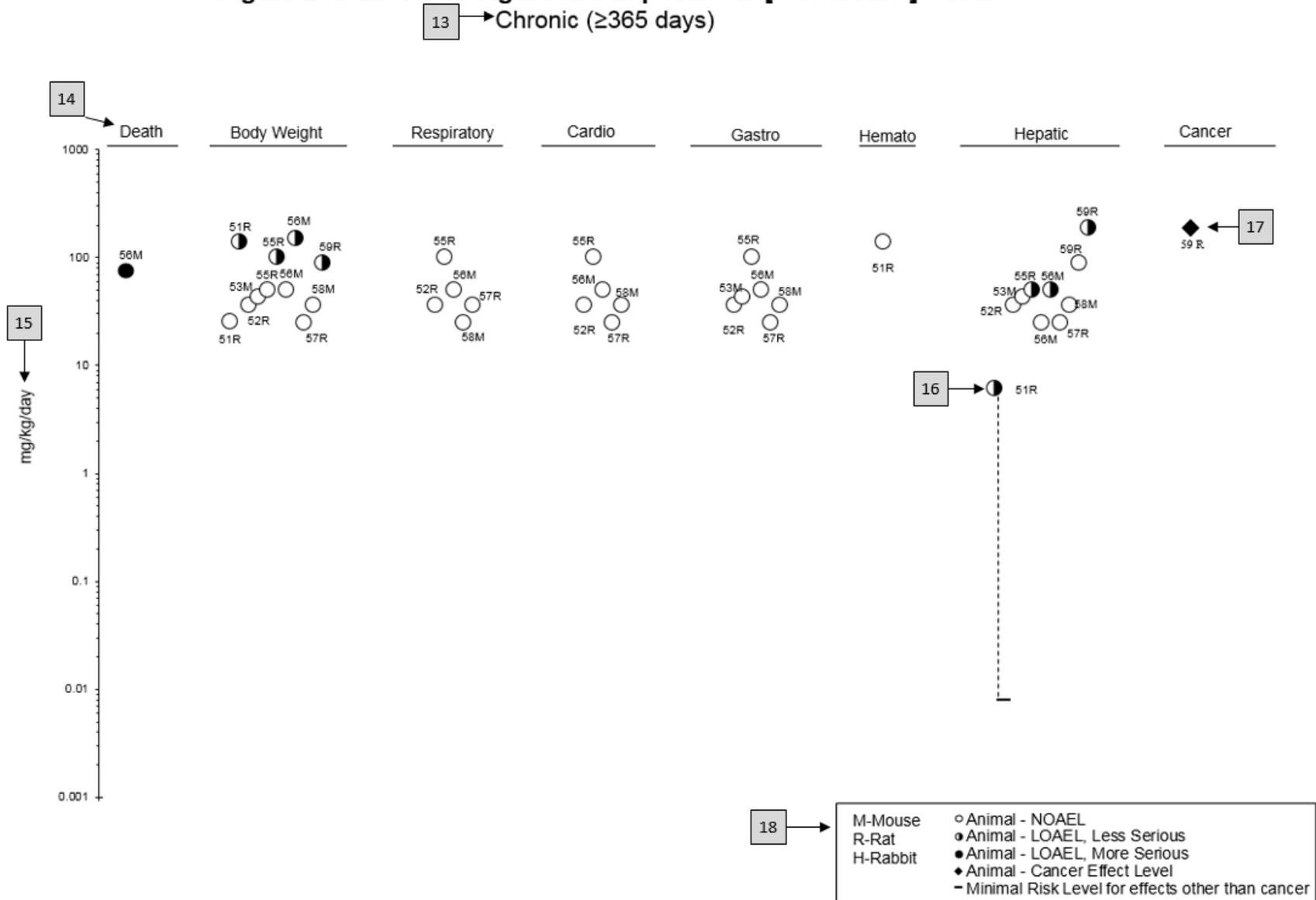(18)   Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
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									
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.

[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).

Callout labels on diagram: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11

Column annotations: 4 Species (strain) No./group; 5 Exposure parameters / Doses; 6 Parameters monitored; 7 Endpoint; 8 NOAEL; 9 Less serious LOAEL / Serious LOAEL

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

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume 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.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

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

APPENDIX D

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.

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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.

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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.

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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.

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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.

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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
DHHS	Department of Health and Human Services
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

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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

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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
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PEHSU	Pediatric Environmental Health Specialty Unit
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 level/limit
REL-C	recommended exposure level-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
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

APPENDIX F

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