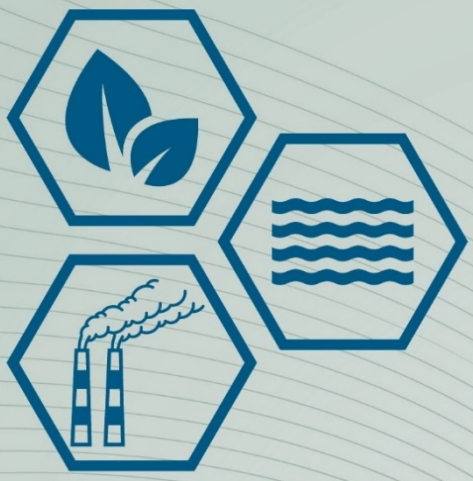

Toxicological Profile for *N*-Nitrosodiphenylamine

November 2017

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

CS274127-A

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.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

*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
December 1988	Final toxicological profile released
April 1993	Updated final toxicological profile released
September 2017	Update of data in Chapters 2, 3, and 7

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Obaid Faroon, DVM, Ph.D.

ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Fernando Llados, Ph.D.
Lisa Ingerman, Ph.D., DABT
Laura McIlroy, B.A

SRC, Inc., North Syracuse, NY

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for N-Nitrosodiphenylamine* was released in 1993. 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 and 3 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects data. However, the focus of the update to this profile is on health effects information.

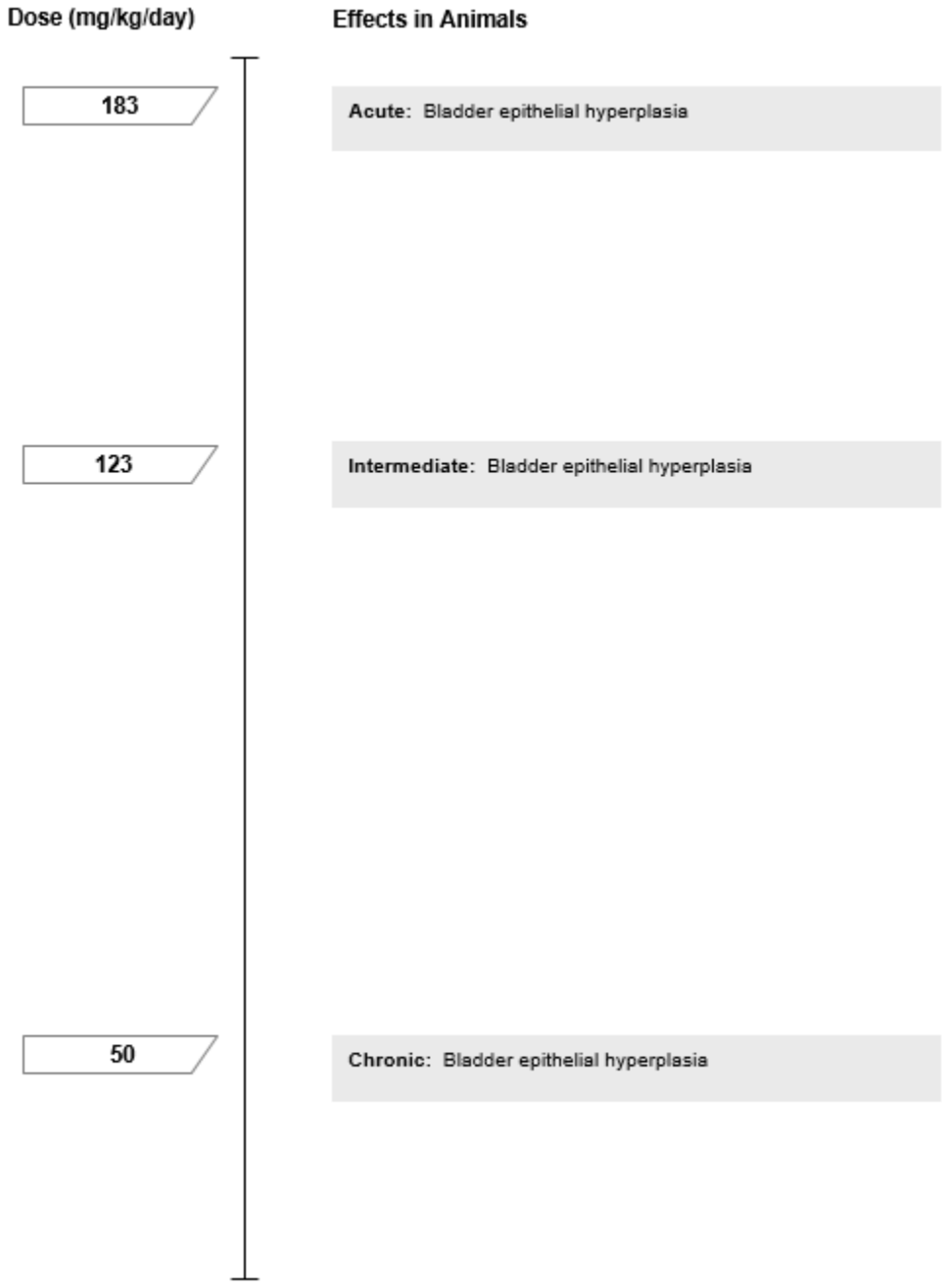
N-Nitrosodiphenylamine ($C_{12}H_{10}N_2O$, CAS No. 86-30-6) belongs to a group of chemicals referred to as nitrosamines, which share a common feature of the N-N=O structure. The general population of the United States does not appear to be exposed to any background levels of *N*-nitrosodiphenylamine. However, no studies investigating the concentrations of *N*-nitrosodiphenylamine in drinking water, foods, or ambient air were located. *N*-Nitrosodiphenylamine is not known to occur naturally in the environment (IARC 1982a). However, there is some evidence that microorganisms can produce *N*-nitrosodiphenyl-amine under laboratory conditions.

1.2 SUMMARY OF HEALTH EFFECTS

There is virtually no information regarding health effects in humans due to exposure to *N*-nitroso-diphenylamine. There is only limited information regarding effects in animals and it is almost exclusively from oral studies. Only one reliable chronic-duration oral study examined multiple organs and tissues of rats and mice and, other than the urinary bladder, no other organ or tissue showed compound-related gross or microscopic alterations. No studies were located regarding immunological, neurological, reproductive, or developmental effects of *N*-nitrosodiphenylamine in animals. There are multiple studies that examined the genotoxic effects of *N*-nitrosodiphenylamine using a variety of tests; the results have been mixed.

As illustrated in Figure 1-1, the most sensitive effect was urinary bladder lesions in rats, which developed into carcinoma as dose and exposure duration increased.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to *N*-Nitrosodiphenylamine



Cancer. The only neoplastic lesion shown to be significantly correlated with exposure to *N*-nitroso-diphenylamine was an increased incidence of bladder transitional cell carcinoma in rats exposed to 200 mg/kg/day *N*-nitrosodiphenylamine for 100 weeks; no significant increase occurred at 50 mg/kg/day (Cardy et al. 1979; NCI 1979). In a more recent shorter-duration oral study in male rats, preneoplastic urinary bladder lesions (transitional epithelium hyperplasia) were already observed in rats exposed to 183 mg/kg/day *N*-nitrosodiphenylamine for 2 weeks and in rats exposed to 123 mg/kg/day for 4 weeks (Dodd et al. 2013) indicating a concentration and exposure duration relationship of this effect. Other studies reported neoplastic lesions, including cancers of the integumentary system and liver in orally exposed rats and mice (Cardy et al. 1979; Innes et al. 1969; NCI 1968, 1979), but the increased incidences were not statistically significant. Some early studies reported no treatment-related tumors in orally exposed rats (Argus and Hoch-Ligeti 1961; Druckecy et al. 1967); however, the bladder was not routinely examined in these studies. The U.S. Environmental Protection Agency (EPA) classified *N*-nitrosodiphenylamine as a probable human carcinogen (Group B2) (IRIS 2002). The International Agency for Research on Cancer (IARC) determined that *N*-nitrosodiphenylamine is not classifiable as to its carcinogenicity to humans (Group 3) (IARC 2017). The Department of Health and Human Services (HHS) has not classified *N*-nitrosodiphenylamine as to its carcinogenicity (NTP 2016). A study of German workers exposed for years to various nitrosamines, including *N*-nitrosodiphenylamine, in the rubber industry found increases in mortality due to cancers of the prostate and oral cavity and pharynx, but there was no evidence of increased bladder cancer (Straif et al. 2000). Because there was exposure to multiple nitrosamines, the role of *N*-nitrosodiphenylamine in the cancers observed, if any, cannot be determined. The available evidence indicates that Fisher-344 rats, the strain used in studies by Cardy et al. (1979), NCI (1979), and Dodd et al. (2013), are susceptible to *N*-nitrosodiphenylamine-induced urinary bladder cancer, but the relevance of this outcome to human health is unknown.

1.3 MINIMAL RISK LEVELS (MRLs)

No inhalation MRLs were derived for *N*-nitrosodiphenylamine due to lack of adequate studies. In the single inhalation study available (from the Russian literature), rats exposed to 350–400 mg/m^3 *N*-nitrosodiphenylamine dusts for 2 hours/day for 20 days showed catarrhal bronchitis, reduced phagocytic activity of leukocytes, and decreased nerve excitability (Zhilova et al. 1966). This information is insufficient for MRL derivation.

No oral MRLs were derived for *N*-nitrosodiphenylamine due to lack of human studies and the fact that the effects observed at the lowest doses tested in an acute-duration study, an intermediate-duration study, and

a chronic-duration study in rats were considered precancerous lesions (epithelial hyperplasia and squamous metaplasia of the urinary bladder) (Dodd et al. 2013; NCI 1979). Only the urinary bladder was examined in the acute- and intermediate-duration studies (Dodd et al. 2013). In the chronic-duration study (NCI 1979), transitional cell carcinoma of the urinary bladder developed in male and female rats dosed with 200 mg/kg/day *N*-nitrosodiphenylamine (highest dose tested).

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*-nitrosodiphenylamine. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to *N*-nitrosodiphenylamine, 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 relevant inhalation or dermal data were identified for *N*-nitrosodiphenylamine.

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*-nitrosodiphenylamine 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.

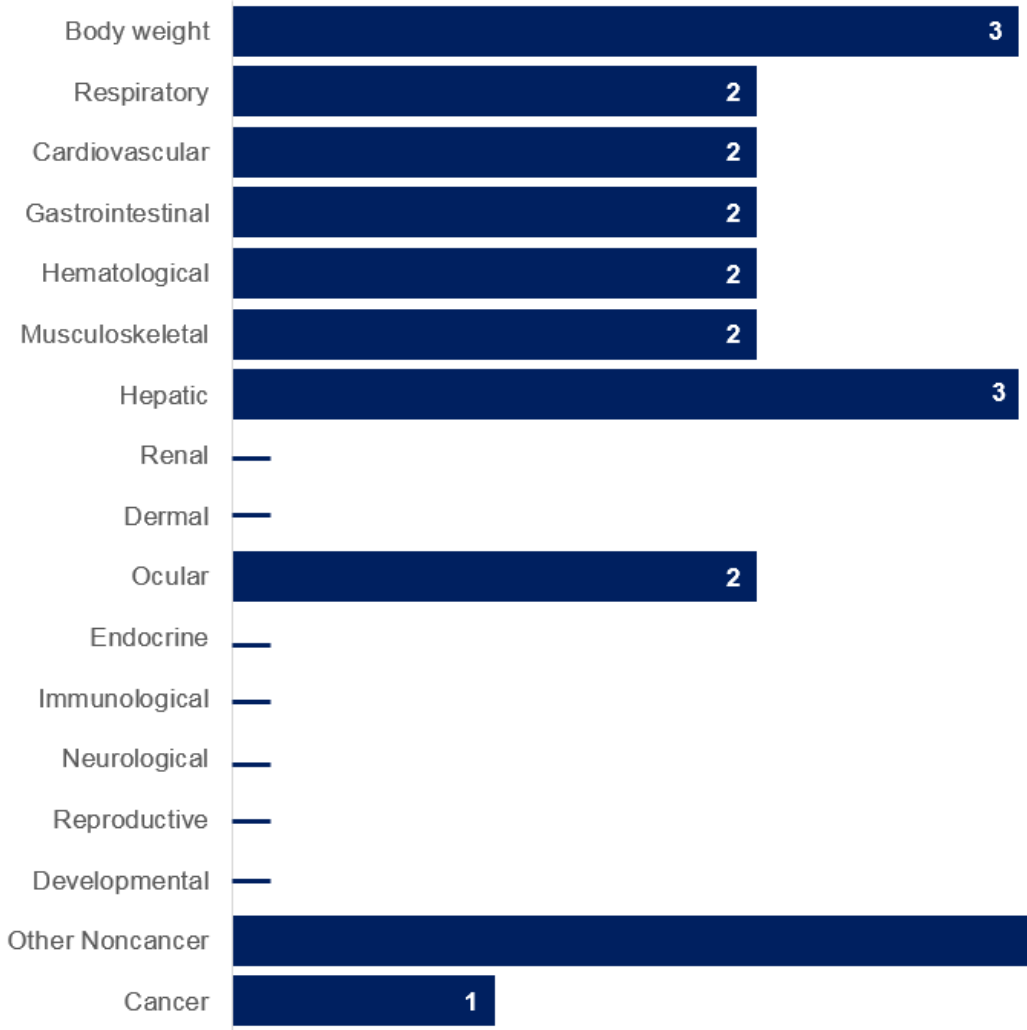
The health effects of *N*-nitrosodiphenylamine have been evaluated only in animal studies. As illustrated in Figure 2-1, all of the health effects data come from a limited number of oral exposure studies that examined the effects of *N*-nitrosodiphenylamine in rats and mice. One chronic-duration study that examined the major organs and tissues of rats and mice provided most of the information. The most examined endpoint was the urinary bladder.

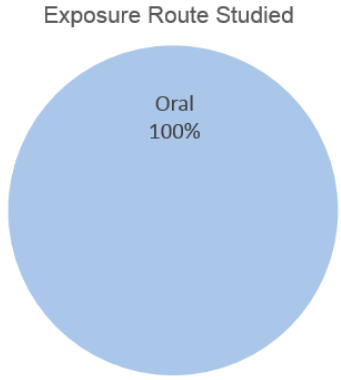
The animal studies suggest one sensitive target of *N*-nitrosodiphenylamine toxicity:

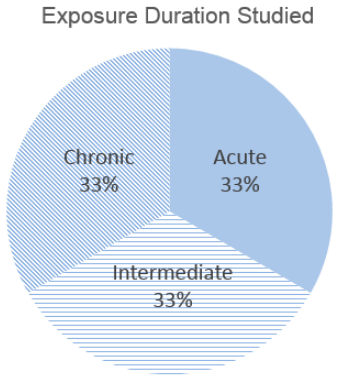
- **Other Noncancer Endpoints (Urinary Bladder):** Urinary bladder effects were reported in rats and mice. In rats, there was evidence of urinary bladder alterations already after 2 weeks of exposure. After lifetime exposure, urinary lesions in rats developed into bladder carcinoma. No inference to human health can be made based on the limited animal data available.

Figure 2-1. Overview of the Number of Studies Examining *N*-Nitrosodiphenylamine Health Effects

Most studies examined the potential body weight, hepatic, and other noncancer effects of *N*-nitrosodiphenylamine
All studies evaluated health effects in **animals** (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 23 studies include those finding no effect. Most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to *N*-Nitrosodiphenylamine – 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 (Fischer 344, F)	5 days to 2 weeks (F)	0, 15, 60, 123, 183, 251	HP, OW	Other noncancer (urinary bladder)	123	183		Increased relative urinary bladder weight (44% after 5 days and 28% after 2 weeks); histopathologic changes in the bladder: increased mitosis (6/10 after 5 days and 2 weeks), infiltrate-mixed cells (10/10 after 5 days, and diffuse hyperplasia (5/10 after 2 weeks)
Dodd et al. 2013									
2	Mouse (Swiss Webster) 10 M	4 days 1 time/day (GO)	0, 350	HP	Hepatic	350			No histopathological alterations in the liver
Nishie et al. 1972									
INTERMEDIATE EXPOSURE									
3	Rat (Fischer-344, F)	4–13 weeks (F)	0, 15, 60, 123, 183, 251	HP, OW	Other noncancer (urinary bladder)	60	123		Histopathologic changes in the bladder: infiltrate-mixed cells (6/10 after 4 weeks, 8/10 after 13 weeks) and diffuse hyperplasia (7/10 after 4 weeks, 9/10 after 13 weeks)
Dodd et al. 2013									
4	Rat F344 5 M, 5 F	8–11 weeks 7 days/week ad lib (F)	M: 0, 50, 100, 150, 200, 300, 400, 500 F: 0, 200, 400, 800, 1,200, 1,600, 2,300	BW, LE	Death			800F	2/5 died
					Bd Wt	150M	200M		>10% reduction in body weight
NCI 1979									

Table 2-1. Levels of Significant Exposure to *N*-Nitrosodiphenylamine – 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
CHRONIC EXPOSURE									
5	Rat F344 20–50 M, 20–50 F	100 weeks 7 days/week (F)	0, 50, 200	BW, HP, LE	Death			200	30% mortality in females
					Bd Wt		50		>10% reduction in body weight
					Resp	200			
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Musc/skel	200			
					Hepatic	200			
					Ocular		50 F		Corneal opacity in females at 50 mg/kg/day and males at 200 mg/kg/day
					Other noncancer (urinary bladder)		50	200	Bladder epithelial hyperplasia at 50 mg/kg; squamous metaplasia at 200 mg/kg
					Cancer			200	CEL – bladder tumors
Cardy et al. 1979; NCI 1979									
6	Mouse B6C3F1 20–50 M, 20–50 F	98–101 weeks 7 days/week (F)	M: 0, 1,300, 2,600 F: 0, 301, 711	BW, HP, LE	Death			711	38% mortality in females
					Bd Wt			301 F	Body weight reduced by approximately 40% in females and 15% in males
					Resp	2,600			
					Cardio	2,600			
					Gastro	2,600			
					Hemato	2,600			
					Musc/skel	2,600			

Table 2-1. Levels of Significant Exposure to *N*-Nitrosodiphenylamine – 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
					Hepatic	2,600			
					Ocular	2,600			
					Other noncancer (urinary bladder)		301 (F)		Inflammation of bladder and bladder epithelial hyperplasia in females at 301 mg/kg/day and in males at 1,300 mg/kg/day
Cardy et al. 1979; NCI 1979									

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

ad lib = ad libitum; Bd Wt or BW = body weight; Cardio – cardiovascular; CEL = Cancer Effect Level; (F) = food; F = female(s); Gastro = gastrointestinal; (GO) = gavage in oil; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; OW = organ weight; Resp = respiratory

Figure 2-2. Levels of Significant Exposure to *N*-Nitrosodiphenylamine – Oral

Acute (≤ 14 days)

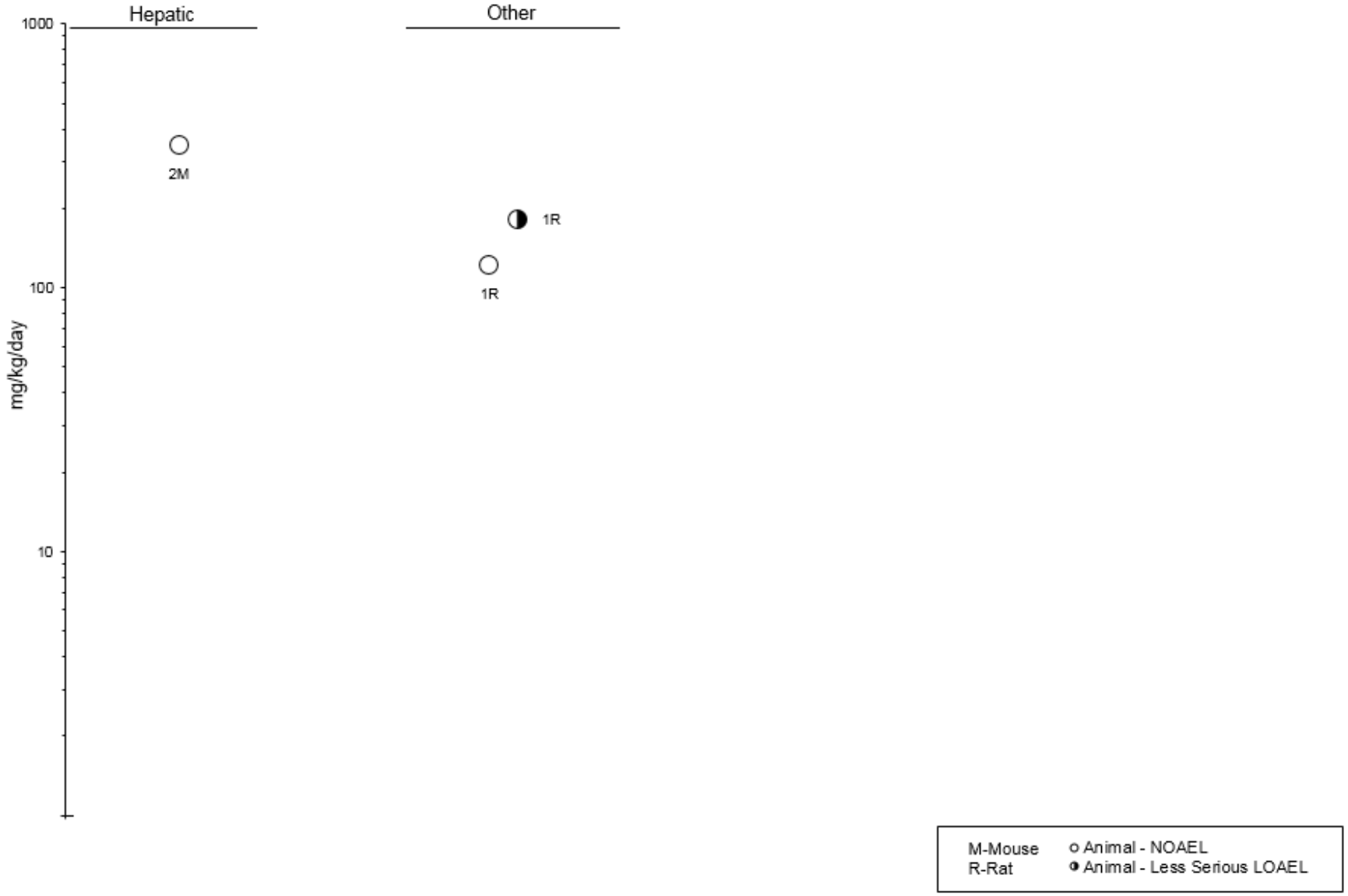


Figure 2-2. Levels of Significant Exposure to *N*-Nitrosodiphenylamine – Oral
Intermediate (15-364 days)

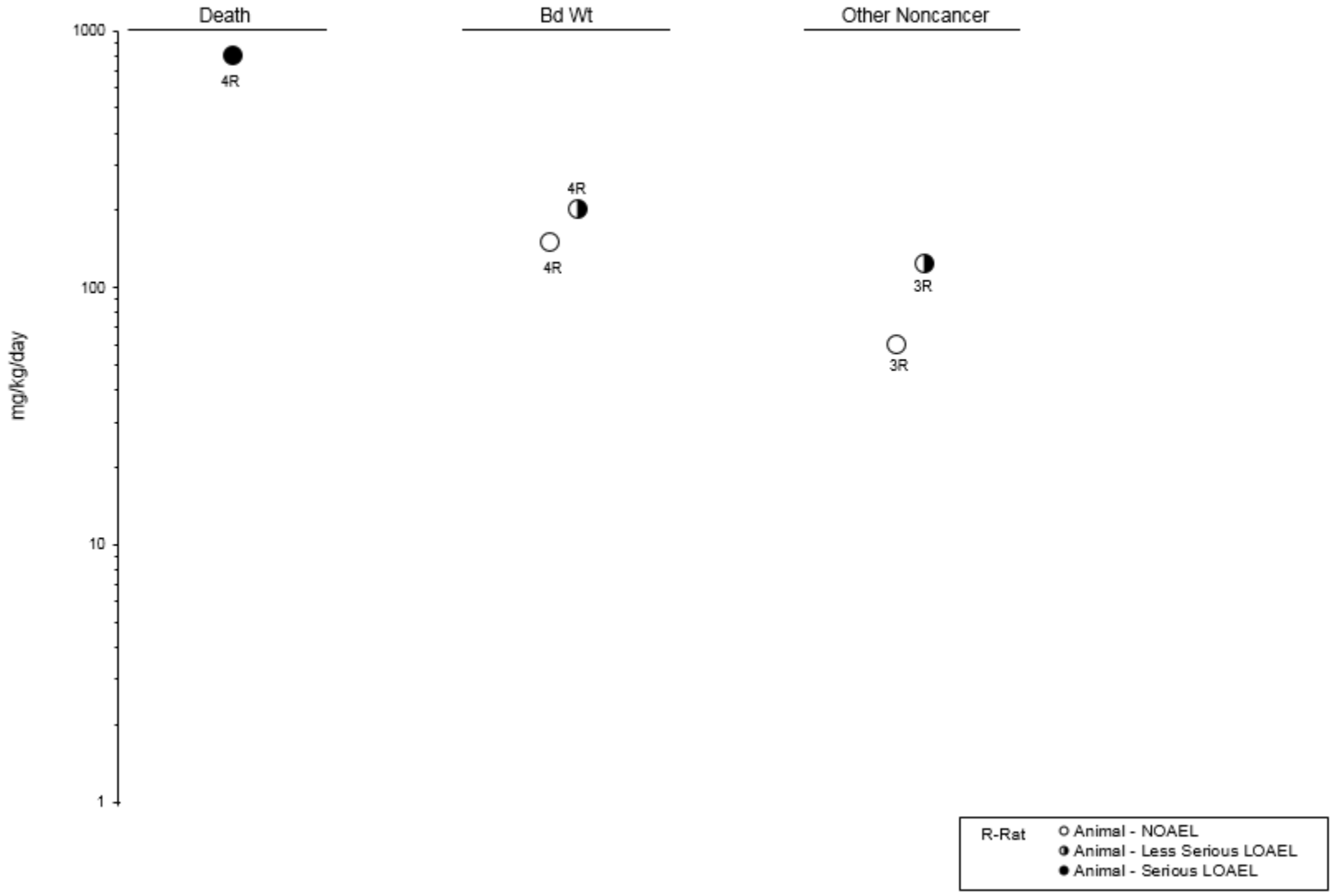
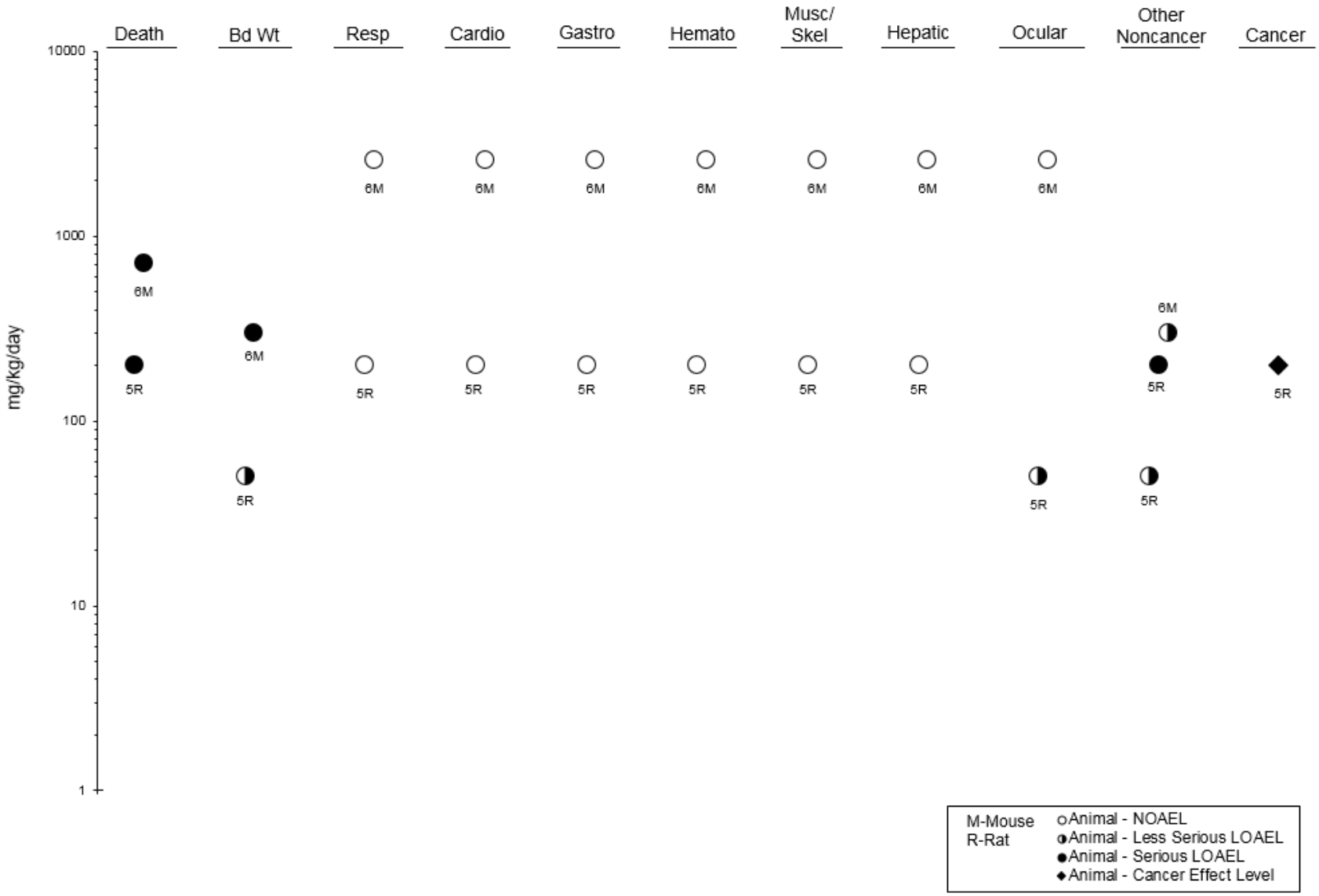


Figure 2-2. Levels of Significant Exposure to *N*-Nitrosodiphenylamine – Oral

Chronic (≥365 days)



2.2 DEATH

No studies were located regarding death in humans or animals after inhalation or dermal exposure to *N*-nitrosodiphenylamine, or in humans following oral exposure to this substance.

Only two studies on the acute oral toxicity of *N*-nitrosodiphenylamine in animals were located. Acute oral LD_{50} values of 3,000 and 3,850 mg/kg were determined for rats (Druckrey et al. 1967) and mice (Zhilova and Kasparov 1966), respectively. However, details on the methodology for these experiments were limited and detailed data were not presented.

Data from an intermediate-duration, range-finding study provide lethality data for intermediate exposure (NCI 1979). Groups of five Fischer-344 rats of each sex and five B6C3F1 mice of each sex were used in these studies. Male rats were fed diets containing 0–500 mg/kg/day of *N*-nitrosodiphenylamine for 11 weeks, and female rats were fed diets containing 0–2,300 mg/kg/day for 8 weeks. No deaths occurred in exposed male rats or in female rats given doses of <800 mg/kg/day (NOAEL of 500 mg/kg/day for male rats and 400 mg/kg/day for female rats). Two of five female rats died at 800 mg/kg/day (a LOAEL), and mortality was 100% at dietary levels of >800 mg/kg/day. In another intermediate-duration study, *N*-nitrosodiphenylamine in an aqueous methylcellulose vehicle was administered by gavage to 25 male Wistar rats at a dose of 3.1 mg/kg/day, 5 days/week, for 45 weeks (Argus and Hoch-Ligeti 1961). All rats survived until termination of the study at 53 weeks. This study provides limited information since no control groups were used and only one concentration was tested. The doses of *N*-nitrosodiphenylamine incorporated into the diet of male and female mice ranged from 0 to 5,980 mg/kg/day for 8 weeks (NCI 1979). All mice survived at all dietary levels including the highest tested. These data indicate that rats are more sensitive to the lethal effects of *N*-nitrosodiphenylamine than are mice since the dose that produced 100% mortality in rats had no effect on survival in mice.

Decreased survival was observed in rats and mice chronically exposed to *N*-nitrosodiphenylamine in their diet for 98–101 weeks (Cardy et al. 1979; NCI 1979). As in the intermediate-duration study, rats were found to be more sensitive to the lethal effects of the chemical than mice. The females of both species were more sensitive to the lethal effects of chronic exposure to *N*-nitrosodiphenylamine than the males. Fischer-344 rats of both sexes were fed diets that contained 50 or 200 mg/kg/day of *N*-nitrosodiphenylamine for 101 weeks. Male B6C3F1 mice were fed diets that contained 1,300 or 2,600 mg/kg/day for 101 weeks. Female B6C3F1 mice were initially fed diets containing 650 or 1,300 mg/kg/day, but these were reduced to 130 and 520 mg/kg/day at 38 weeks because of the drastic reduction in body weight

experienced at the higher doses. The reduced doses were continued for 60 additional weeks. The time-weighted average (TWA) concentrations for female mice over the 98 total weeks of the experiment were calculated to be 301 and 711 mg/kg/day. There were no significant treatment-related effects on survival in the male rats or male mice (NOAELs of 200 and 2,600 mg/kg/day for male rats and male mice, respectively). Survival was dose-related in the female rats, with a marginal reduction in survival at 50 mg/kg/day (NOAEL) and a more marked reduction at 200 mg/kg/day (LOAEL). In female mice, there was no dose-related survival trend; however, survival in the high-dose group was greatly reduced (LOAEL of 711 mg/kg/day) compared with that in low-dose (NOAEL of 30 mg/kg/day) and control groups.

2.3 BODY WEIGHT

In an intermediate-duration, range-finding study, rats showed a decrease in body weight of >l0% at doses of 200 mg/kg/day or more in their food (NCI 1979). Mean body weight in male rats was 12% less than the controls at 200 mg/kg/day and 16% less than the controls at the high dose (500 mg/kg/day). Mean body weight in female rats was 14% less than in the control group at the lowest dose (200 mg/kg/day) and was 37% less than the control group at the highest dose (800 mg/kg/day) at which animals survived (only two of five survived at this dose). The decreased body weight may not be indicative of an adverse effect because it is not clearly related to dose, and the pathologic data do not show tissue damage. However, full evaluation of the significance of the body weight depression is precluded because of the lack of food consumption data. The LOAEL for male and female rats was 200 mg/kg/day. A NOAEL of 150 mg/kg/day was determined for male rats. Body weights in mice exposed to concentrations of 0–5,980 mg/kg/day for 8 weeks were decreased (<14% depression) in a sporadic manner that did not appear to be related to treatment (NCI 1979).

Dose-related decreases in body weight were also reported in a chronic study (NCI 1979). Both exposure groups of rats and mice showed reduced body weight gain and reduced terminal body weight compared to control groups. A LOAEL of 50 mg/kg/day was determined for male and female rats. LOAELs of 301 and 1,300 mg/kg/day for reduced body weight were determined for female and male mice, respectively.

2.4 RESPIRATORY

No studies were located regarding respiratory effects in humans after inhalation exposure to *N*-nitroso-diphenylamine.

Rats exposed to 350-400 mg/m^3 Vulkalent A (*N*-nitrosodiphenylamine) dust for 2 hours/day were observed to have catarrhal bronchitis of the lungs (Zhilova and Kasparov 1966). Interpretation of the results of this study is not possible because of severe limitations in the experimental procedure and presentation of data. The limitations include insufficient reporting of experimental details and data, use of unspecified strains and an undefined control group, and lack of statistical analyses.

In an intermediate-duration gavage study, *N*-nitrosodiphenylamine in an aqueous methylcellulose vehicle was administered to 25 male Wistar rats at a dose of 3.1 mg/kg/day, 5 days/week, for 45 weeks (Argus and Hoch-Ligeti 1961). The rats were killed after an additional 8-week observation period. Histological examination of the lungs revealed peribronchial lymphocytic infiltration, which the authors described as common in older rats. Squamous metaplasia of the bronchial epithelium, particularly in areas of bronchiectasis, was observed in some of the lungs. Peribronchial pneumonia and emphysema were observed in rabbits administered 20 mg/kg Vulkalent A (*N*-nitrosodiphenylamine) intragastrically for 4 months (Zhilova and Kasparov 1966). It could not be determined if the respiratory effects observed in these studies were associated with *N*-nitrosodiphenylamine exposure since incidences were not reported and control groups either were not used or were not clearly defined. However, no treatment-related histological lesions of the lungs, bronchi, or trachea were observed in intermediate- and chronic-duration studies in which rats and mice were administered doses as high as 5,980 mg/kg/day for periods up to 101 weeks (NCI 1979).

2.5 CARDIOVASCULAR

No human studies have evaluated the cardiovascular toxicity of *N*-nitrosodiphenylamine. No information was located regarding cardiovascular effects in animals following inhalation or dermal exposure to *N*-nitrosodiphenylamine.

No treatment-related histological effects of the heart were reported in a chronic oral study of rats and mice administered *N*-nitrosodiphenylamine in their food (NCI 1979). No functional studies were performed that might provide data supporting the histological evidence.

2.6 GASTROINTESTINAL

No human studies have evaluated the gastrointestinal toxicity of *N*-nitrosodiphenylamine. No information was located regarding gastrointestinal effects in animals following inhalation or dermal exposure to *N*-nitrosodiphenylamine.

No treatment-related histological effects of the gastrointestinal system (esophagus, stomach, intestines, pancreas) were reported in a chronic study of rats and mice administered *N*-nitrosodiphenylamine in their food (NCI 1979). No functional studies were performed that might provide data supporting the histological evidence.

2.7 HEMATOLOGICAL

No human studies have evaluated the hematological toxicity of *N*-nitrosodiphenylamine. No information was located regarding hematological effects in animals following inhalation or dermal exposure to *N*-nitrosodiphenylamine.

No treatment-related histological effects of the bone marrow were reported in a chronic study of rats and mice administered *N*-nitrosodiphenylamine in their food (NCI 1979). Hematological tests were not conducted in the NCI (1979) study. No data were available from acute- or intermediate-duration oral exposures in animals.

2.8 MUSCULOSKELETAL

No human studies have evaluated the musculoskeletal toxicity of *N*-nitrosodiphenylamine.

No treatment-related histological effects of the musculoskeletal system were reported in a chronic oral study of rats and mice administered *N*-nitrosodiphenylamine in the food (NCI 1979). The specific tissues examined in that study were not reported. No data were available from acute- or intermediate-duration oral exposures in animals.

2.9 HEPATIC

No information was located regarding hepatic effects in humans exposed to *N*-nitrosodiphenylamine.

The limited data available indicate that the liver is not a target organ for *N*-nitrosodiphenylamine toxicity. In an acute study of hepatotoxicity (Nishie et al. 1972), mice given 350 mg/kg/day of *N*-nitrosodiphenylamine for 4 consecutive days preceding, or one dose 24 hours prior to, pentobarbital administration had effects characteristic of liver enzyme induction. These effects consisted of significantly decreased pentobarbital sleeping time and increased amounts of smooth endoplasmic reticulum among granules of glycogen in the liver cell. Electron microscopy also revealed blebs, hypertrophy, and pleomorphism of the mitochondria. A NOAEL of 350 mg/kg/day was identified for hepatic effects, since light microscopy examination did not reveal hepatic lesions.

Studies in male mice showed that administration of a single intraperitoneal dose of 20 mg/kg various *N*-nitroso compounds significantly altered the activities of both phase I and phase II metabolic enzymes in the liver (Sheweita and Mostafa 1996a, 1996b). *N*-Nitrosodiphenylamine decreased cytochrome P-450 by 54%, and arylhydrocarbon hydroxylase by 64%, and increased dimethylnitrosamine *N*-demethylase by 42%, cytochrome b_5 content by 159%, and NADPH-cytochrome *c* reductase by 57% (Sheweita and Mostafa 1996a). *N*-nitrosodiphenylamine also increased the activity of glutathione reductase by 50% and glutathione-S-transferase by 60% (Sheweita and Mostafa 1996b).

In an 8-week feeding study in rats and mice (NCI 1979), the only gross or histopathological effect reported for the liver was pigmentation of Kupffer's cells in the hepatic sinusoids in male mice that received 5,980 mg/kg/day of *N*-nitrosodiphenylamine. However, according to the tabular data presented, only female mice received this dose; the highest dose in male mice was reported as 2,860 mg/kg/day. There is no way to determine which data are incorrect. In any case, the pigmentation was presumed to reflect phagocytic activity by the Kupffer's cells. It was not considered to be adverse because only trace amounts occurred, there were no signs of toxicity or other histological alterations, and survival was not affected. In addition, no adverse liver effects were reported in rats from the same study (NCI 1979) even though rats appear more sensitive to the toxic effects of *N*-nitrosodiphenylamine than mice. Fatty and granular degeneration of the liver was reported in rabbits given 20 mg/kg Vulkalent A (*N*-nitroso-diphenylamine) for 4 months (Zhilova and Kasparov 1966). The limitations of this study are described in the discussion of renal effects in Section 2.10.

Chronic studies conducted by NCI (1979) revealed no treatment-related histological effects on the livers of exposed rats and mice. Only histological data are available and no studies of function, which might have revealed more subtle changes, were performed.

No data were available from inhalation or dermal exposure studies in animals.

2.10 RENAL

No information was located regarding renal effects in humans exposed to *N*-nitrosodiphenylamine. No data were located regarding effects in animals following inhalation or dermal exposure to *N*-nitroso-diphenylamine.

In an intermediate-duration gavage study, *N*-nitrosodiphenylamine in an aqueous methylcellulose vehicle was administered to 25 male Wistar rats at a dose of 3.1 mg/kg/day, 5 days/week, for 45 weeks (Argus and Hoch-Ligeti 1961). The rats were killed after an additional 8-week observation period. Histological examination of the kidneys revealed albuminous precipitation in the tubules of "many" kidneys. The significance of this finding in the kidneys is uncertain because incidences were not reported and control groups were not included. Albuminous degeneration of the epithelium of the kidneys was also observed in rabbits administered 20 mg/kg for 4 months (the frequency of administration was not specified) (Zhilova and Kasparov 1966). This experiment was severely limited because the strains used were not specified, the nature of control groups was uncertain, there were no statistical analyses of data, information on critical experimental details was lacking, and no quantitative data were presented.

2.11 DERMAL

No data were located regarding dermal effects in humans following dermal exposure to *N*-nitroso-diphenylamine or in animals following inhalation or oral exposure to *N*-nitrosodiphenylamine.

A single dermal study was located in which mice had 0.1 mL of a 0.1% solution of *N*-nitrosodiphenyl-amine painted on the intrascapular region once per week for 20 weeks (Iversen 1980). The investigator reported that all painted animals had small skin ulcerations and scarring. However, the significance of the results cannot be determined because it was not clear if these data included the control animals painted with the acetone solvent or only the experimental animals. Another limitation of the experiment is the use of only one dose.

2.12 OCULAR

No data were located regarding ocular effects in humans following direct contact of the eye with *N*-nitrosodiphenylamine or following oral exposure to *N*-nitrosodiphenylamine in animals following inhalation or oral exposure to *N*-nitrosodiphenylamine.

Following chronic exposure to *N*-nitrosodiphenylamine, grossly observable corneal opacity occurred at higher incidences in the high-dose male rats (15/50) and low-dose female rats (16/50) than in the corresponding control males (0/20) and control females (1/20) (NCI 1979). While the investigators concluded that this effect may have been related to treatment, the results should be viewed with caution. Incidences in the low-dose males and high-dose females were not reported, and no histopathological findings were recorded for the cornea.

2.13 ENDOCRINE

No data were located regarding endocrine effects in humans following exposure to *N*-nitrosodiphenylamine or in animals following inhalation or dermal exposure to *N*-nitrosodiphenylamine.

No histopathological lesions were observed in the salivary glands, pituitary, adrenals, or thyroid of rats or mice chronically exposed to *N*-nitrosodiphenylamine in their food (NCI 1979).

N-Nitrosodiphenylamine did not exhibit estrogenic properties in an *in vitro* assay in yeast (Nishihara et al. 2000). However, in a similar assay, *N*-nitrosodiphenylamine showed anti-androgenic activity by competitively binding to the androgen receptor against 5α-dihydrotestosterone and decreasing the level of androgen receptor protein (Hari et al. 2006).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after exposure to *N*-nitrosodiphenylamine.

Reduced phagocytic activity of the leukocytes was reported in rats exposed to 350–400 mg/m^3 Vulkalent A (*N*-nitrosodiphenylamine) dust for 2 hours/day for 20 days (Zhilova and Kasparov 1966). Interpretation of these results is not possible because of severe limitations in the experimental procedure. These limitations are discussed in Section 2.4. No treatment-related histological effects of the

immunological system (spleen, lymph nodes, thymus) were reported in a chronic study of rats and mice administered *N*-nitrosodiphenylamine in their food (NCI 1979). No functional studies were performed that might provide data supporting the histological evidence.

2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans after exposure to *N*-nitrosodiphenylamine.

Lengthening of the chronaxie of the entensors of the rear extremities was reported in rats exposed to 350–400 mg/m^3 Vulkalent A (*N*-nitrosodiphenylamine) dust for 2 hours/day for 20 days (Zhilova and Kasparov 1966). Interpretation of these results is not possible because of severe limitations in the experimental procedure. These limitations are discussed in Section 2.4. No treatment-related histological effects were reported in the brains of rats and mice chronically exposed to *N*-nitrosodiphenylamine in their food (NCI 1979). No functional studies were performed that might provide data supporting the histological evidence.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans following exposure to *N*-nitrosodiphenylamine.

No treatment-related histological effects of the testes, prostate, uterus, or ovaries were reported in chronic studies that might provide data supporting the histological evidence study of rats and mice administered *N*-nitrosodiphenylamine in their food (NCI 1979). No functional studies were performed that might provide data supporting the histological evidence. No data are available in animals following inhalation or dermal exposure to *N*-nitrosodiphenylamine.

2.17 DEVELOPMENTAL

No data are available regarding developmental effects in humans or in animals following exposure to *N*-nitrosodiphenylamine.

2.18 OTHER NONCANCER

Data from oral studies in rats and mice indicate that the bladder is a target organ for chronic oral exposure to *N*-nitrosodiphenylamine. Exposure of male rats to 183 mg/kg/day *N*-nitrosodiphenylamine in the food for 2 weeks significantly increased the incidence of mixed cell infiltrate and diffuse hyperplasia in the transitional epithelium of the urinary bladder; no significant changes were reported at 123 mg/kg/day (Dodd et al. 2013). Continued exposure for up to 13 weeks resulted in similar lesions in rats exposed to 123 mg/kg/day *N*-nitrosodiphenylamine, but not in rats dosed with 60 mg/kg/day (Dodd et al. 2013). Absolute and relative bladder weight were significantly increased in rats dosed with ≥183 mg/kg/day, but no significant changes were reported at 123 mg/kg/day. Epithelial hyperplasia of the urinary bladder increased in frequency with dose in both male and female rats given doses of 50 and 200 mg/kg/day *N*-nitrosodiphenylamine in their diet for approximately 2 years (Cardy et al. 1979; NCI 1979). Squamous metaplasia of the bladder, a more serious lesion, occurred at low incidences and only in the high-dose animals. It is likely that the bladder hyperplasia and metaplasia were preneoplastic effects since transitional cell carcinoma also occurred in the high-dose rats (see Section 2.19).

Effects on the bladder from chronic exposure to *N*-nitrosodiphenylamine also occurred in mice (Cardy et al. 1979; NCI 1979). Male mice received 1,300 or 2,600 mg/kg/day *N*-nitrosodiphenylamine in the diet for 101 weeks, and females received 301 or 711 mg/kg/day (TWA concentrations) in the diet for 98 weeks (see Section 2.2 for details of female dosing). Incidences of submucosal inflammation of the urinary bladder in the control, low-dose, and high-dose groups were 0/18, 12/49, and 31/46, respectively, in the males and 0/18, 31/47, and 30/38, respectively, in the females. The inflammatory response was associated with connective tissue degeneration in the submucosa. Epithelial hyperplasia of the bladder in the control, low-dose, and high-dose groups occurred in 0/18, 2/49, and 7/46 males, respectively, and 0/18, 3/47, and 6/38 females respectively, but increased incidences of bladder neoplasms were not statistically significant. LOAELs of 1,300 and 301 mg/kg/day were identified for inflammation of the bladder submucosa in males and females, respectively.

2.19 CANCER

No information was located regarding cancer effects in humans following oral or dermal exposure to *N*-nitrosodiphenylamine or in animals following inhalation exposure.

Straif et al. (2000) published the results of a study of cancer occurrence among German workers exposed to nitrosamines (*N*-nitrosodiphenylamine among them) in the rubber industry. The cohort consisted of

8,933 workers hired after January 1959 and followed up for mortality from January 1st 1981 until December 31st 1991. *N*-Nitrosodiphenylamine had been used as a retarder until early 1980, but specific exposure concentrations to this chemical in the air were not available. Hazard rate ratios calculated for high exposure (>15 µg/m^3) to total nitrosamines showed significantly elevated risks for cancers of the esophagus and oral cavity and pharynx compared to the upper boundary for a low exposure category (<2.5 µg/m^3). In this study, the specific role of *N*-nitrosodiphenylamine, if any, cannot be determined.

One intermediate-duration study was located in which 25 male Wistar rats received *N*-nitrosodiphenylamine in an aqueous methylcellulose vehicle by gavage at a dose of 11.63 mg/kg/day, 5 days/week, for 45 weeks (Argus and Hoch-Ligeti 1961). No tumors were found in the treated animals. Histological examinations were limited to the liver, spleen, kidneys, lungs, and organs with gross abnormalities.

Rats were more sensitive than mice to the carcinogenic effects of *N*-nitrosodiphenylamine according to an NCI (1979) study. *N*-Nitrosodiphenylamine was administered in the diet to Fischer-344 rats and B6C3F1 mice (50/sex/strain) with the matched control groups consisting of 20 untreated rats and mice of each sex (Cardy et al. 1979; NCI 1979). Comprehensive gross and histopathological examinations were conducted on animals that died during the study and on all animals that survived to the end of the study. The highest incidence of tumors was found in the urinary bladder of rats.

Rats received 50 and 200 mg/kg/day *N*-nitrosodiphenylamine in the diet for 100 weeks (Cardy et al. 1979; NCI 1979). A significant increase ($p<0.001$) in the incidence of transitional cell carcinomas in the urinary bladder occurred in rats receiving the highest dose (an increase of 38% in males and 86% in females) compared to the controls. An increase in fibromas of the integumentary system (i.e., subcutis and skin) occurred in male rats, but this increase was not statistically significant. The investigators noted that the occurrence of fibromas was probably associated with treatment because integumentary system fibromas were rare in historical controls at the same laboratory. The results of the study are sufficient to conclude that *N*-nitrosodiphenylamine is carcinogenic in male and female Fischer-344 rats. The EPA (IRIS 2002) has classified *N*-nitrosodiphenylamine in Group B2, probable human carcinogen. IARC has classified *N*-nitrosodiphenylamine in Group 3, not classifiable as to its carcinogenicity to humans (IARC 2017).

An earlier study reported negative results in rats; however, uncertainties are associated with the study because the bladders were not routinely examined, smaller groups of rats were studied, and doses were lower than those provided by the NCI (1979) dietary levels. *N*-Nitrosodiphenylamine was administered

to 20 BD rats of unspecified sex in drinking water that provided a daily dose of 120 mg/kg and a total dose of 65,000 mg/kg (Druckrey et al. 1967). Histopathologic examinations consisting of gross evaluation of the liver, brain, and unspecified organs were conducted after 700 days, but there was no evidence of tumors in the treated animals.

Male B6C3F1 mice were fed 1,300 or 2,600 mg/kg/day *N*-nitrosodiphenylamine for 101 weeks (Cardy et al. 1979; NCI 1979). Female $B6C3F_1$ mice initially received 650 or 1,300 mg/kg/day for 38 weeks, but because of an excessive reduction in mean weight gain, dosing was discontinued for 3 weeks and then resumed at 130 or 520 mg/kg/day for 60 weeks. TWAs of 301 and 711 mg/kg/day were determined for the low- and high-dose females, respectively. Transitional cell carcinoma of the bladder was reported in a low-dose male and female, as well as transitional cell papilloma in a high-dose male. However, there was no statistically significant increase in tumor incidence in the treated animals. The authors concluded that *N*-nitrosodiphenylamine was not carcinogenic in mice under the test conditions used.

B6C3F1 and B6AKF1 mice (18 sex/strain) initially received 1,000 mg/kg/day of *N*-nitrosodiphenylamine in dimethyl sulfoxide by gavage from 7 to 28 days of age, and subsequently in the diet at a concentration of 490 mg/kg/day until 81 or 83 weeks of age (Innes et al. 1969; NCI 1968). Negative and positive controls were tested. An increased incidence of hepatomas, of borderline statistical significance, was observed in only 6 of 18 treated B6C3F1 males. The histological examinations in this study were usually limited to the chest contents, liver, spleen, kidneys, adrenals, stomach, intestines, and genital organs. The bladder was not examined, so it is possible that results similar to those of the NCI (1979) study might have been obtained had the bladder been examined. The equivocal liver results from the early NCI (1968) study might be explained by the high percentage of liver neoplasms (30 and 20% in male and female control groups, respectively) found in all groups of B6C3F1 mice in the later NCI (1979) study. This strain of mice may have a genetic tendency towards liver lesions.

Single weekly 0.1-mL applications of a 1% solution of *N*-nitrosodiphenylamine (33 mg/kg/week) in acetone were placed on the intrascapular region of 16 male and 24 female hairless hr/hr Oslo strain mice for 20 weeks (Iversen 1980). Gross and histological examinations were performed on the lungs and palpable lesions of surviving animals (14 males, 21 females) following 80 weeks of observation. The only tumors detected were lung adenomas in three of the treated males. The study was limited because the treatment duration was short, the frequency was low, only one low exposure level was tested, histopathological examinations were limited, and control data were not available.

The mechanism by which *N*-nitrosodiphenylamine induces bladder cancer in rats has not been elucidated but it does not appear to involve direct alkylation. Instead, there is some evidence that a mechanism involving transnitrosation may play a role. Further details regarding this potential mechanism are presented below in Section 2.20

2.20 GENOTOXIC

No epidemiology or case studies were available for genotoxicity of *N*-nitrosodiphenylamine in humans. The only human data regarding the genotoxic effects of this chemical come from *in vitro* assays for deoxyribonucleic acid (DNA) damage and sister chromatid exchange. Human fibroblasts were used to test for DNA damage from metabolically activated *N*-nitrosodiphenylamine (Agrelo and Amos 1981; Martin and McDermid 1981; Snyder and Matheson 1985). Only one of the three studies produced a positive response (see Table 2-3). A positive but statistically insignificant response was noted for increased sister chromatid exchange frequency in human lymphocytes after exposure to activated *N*-nitrosodiphenylamine (Lindahl- Kiessling et al. 1989). It is difficult to draw conclusions for humans from these data. However, from these and other studies it appears that *N*-nitrosodiphenylamine is not a human clastogen.

In vivo animal studies involving mice and rats consistently show negative results for DNA damage, micronuclei, DNA synthesis inhibition, and abnormal sperm morphology (Table 2-2). A gene mutation study (wing spot test) and a recessive lethal study involving *Drosophila melanogaster* both produced negative results as well (Negishi et al. 1991; Vogel et al. 1981). However, in a host-mediated assay, a positive response for DNA damage was observed in *Escherichia coli* that were injected along with *N*-nitrosodiphenylamine into the abdomina of male *D. melanogaster* (Knasmuller et al. 1990). The most commonly tested route of exposure for these studies was intraperitoneal injection in mice (McFee et al. 1989; Salamone et al. 1981; Topham 1981; Tsuchimoto and Matter 1981). Oral exposure was tested in only three studies (Brambilla et al. 1987; Friedman and Staub 1976; McFee et al. 1989). From this information, *N*-nitrosodiphenylamine does not appear to be genotoxic to intact animal systems.

Table 2-2. Genotoxicity of *N*-Nitrosodiphenylamine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammalian cells			
Rat (liver nuclei)	DNA damage	–	Brambilla et al. 1987
Mouse (bone marrow cells)	Micronucleus assay	–	McFee at al. 1989

Table 2-2. Genotoxicity of *N*-Nitrosodiphenylamine *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse (bone marrow cells)	Micronucleus assay	–	Salamone et al. 1981
Mouse (bone marrow cells)	Micronucleus assay	–	Tsuchimoto and Matter 1981
Mouse (testicular cells)	DNA synthesis inhibition	–	Friedman and Staub 1976
Mouse (cauda epididymis)	Abnormal spermal morphology	–	Topham 1981
Non-mammalian cells			
Drosophilia melanogaster (wing spot test)	Gene mutation	–	Negishi et al. 1991
D. melanogaster (recessive lethal test)	Gene mutation	–	Vogel et al. 1981
Escherichia coli (host-mediated assay)	DNA damage	+	Knasmuller et al. 1990

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

Data from *in vitro* studies using prokaryotic and eukaryotic organisms and cultured mammalian cells are presented in Table 2-3. Responses were negative in the majority of the gene mutation studies. However, two *Salmonella typhimurium* assays detected gene mutations after exposure to metabolically activated *N*-nitrosodiphenylamine (Khudoley et al. 1987; Zielenska and Guttenplan 1988) and one study reported weakly positive results for gene mutation in the absence of metabolic activation (Kubo et al. 2002). *N*-Nitrosodiphenylamine exhibited no effect on mitotic crossing-over and gene conversion in *Saccharomyces cerevisiae* (Jagannath et al. 1981; Kassinova et al. 1981; Sharp and Parry 1981a). Chromosomal aberration assays for Chinese hamster fibroblasts and Don cells were inconclusive (Abe and Sasaki 1977; Ishidate and Odashima 1977). Sister chromatid exchange was unaffected in hamster ovary cells (Evans and Mitchell 1981; Perry and Thomson 1981), but a positive response for sister chromatid exchange was noted in hamster Don cells after exposure to *N*-nitrosodiphenylamine that had not been metabolically activated (Abe and Sasaki 1977). Micronuclei were not induced in Chinese hamster ovary cells either with or without the addition of metabolic activation (Phelps et al. 2002). In a cellular transformation assay in mouse BALB/c cells, a weak positive result was reported in the presence of metabolic activation (Mathews et al. 1993). Tests for DNA damage have produced mixed results among prokaryotes and fungi. Among mammalian hepatocytes, however, the results for DNA damage were positive. As mentioned previously, only one study involving cultured human fibroblasts was positive for DNA damage (Snyder and Matheson 1985).

Table 2-3. Genotoxicity of *N*-Nitrosodiphenylamine *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Prokaryotic organisms				
Salmonella typhimurium (pour plate and premincubation assay)	Gene mutation	–	NA	Araki et al. 1984
S. typhimurium (Ames assay)	Gene mutation	–	–[a]	Crebelli et al. 1984
S. typhimurium (Ames assay)	Gene mutation	NA	–	Ichinotsubo et al. 1981
S. typhimurium (Ames assay)	Gene mutation	+	NA	Khudoley et al. 1987
S. typhimurium (Ames assay)	Gene mutation	–	(+)	Kubo et al. 2002
S. typhimurium (modified Ames assay)	Gene mutation	–	–	Probst et al. 1981
S. typhimurium (Ames assay)	Gene mutation	–	NA	Raineri et al. 1981
S. typhimurium (Ames assay)	Gene mutation	–	–	Wagner et al. 2012
S. typhimurium (liquid preincubation assay)	Gene mutation	+	NA	Zielenska and Guttenplan 1988
S. typhimurium (umu assay)	Gene mutation	–	NA	Degirmenci et al. 2000
Escherichia coli (pour plate and preincubation assay)	Gene mutation	–	NA	Araki et al. 1984
E. coli (reverse mutation preincubation)	Gene mutation	–	–	Matsushima et al. 1981
E. coli (modified Ames assay)	Gene mutation	–	–	Probst et al. 1981
S. typhimurium (umu gene response)	DNA damage	–	NA	Shimada et al. 1989
E. coli (differential killing test)	DNA damage	+	NA	Green 1981
E. coli (rec assay)	DNA damage	–	NA	Mamber et al. 1983
E. coli (disc diffusion and liquid suspensión assay)	DNA damage	–	NA	Rosenkranz et al. 1981
E. coli (differential killing test)	DNA damage	–	+	Tweats 1981
Bacillus subtilis (rec assay)	DNA damage	–	+	Kada 1981
Eukaryotic organisms, non-mammalian				
Schizosaccharomyces pombe (forward mutation assay)	Gene mutation	–	–	Loprieno 1981
Saccharomyces cerevisiae (rep-test)	DNA damage	NA	–	Kassinova et al. 1981
S. cerevisiae (rad assay)	DNA damage	–	+	Sharp and Parry 1981b

Table 2-3. Genotoxicity of *N*-Nitrosodiphenylamine *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
S. cerevisiae (ade2 locus assay)	Mitotic crossing over	–	–	Kassinova et al. 1981
S. cerevisiae (his4, trp5 assay)	Mitotic gene conversion	–	–	Sharp and Parry 1981a
S. cerevisiae (ade2, trp5 assay)	Mitotic gene conversion	–	–	Jagannath et al. 1981
Mammalian cells				
Rat (embryo cells)	Gene mutation	–	–	Mishra et al. 1978
Chinese hamster (V79 cells)	Gene mutation	–	–	Jones and Huberman 1980
Chinese hamster (V79 cells)	Gene mutation	–	–	Kuroki et al. 1977
Mouse (lymphoma cells)	Gene mutation	–	–	Clive et al. 1979
Mouse (lymphoma cells)	Gene mutation	–	–	Jotz and Mitchell 1981
Mouse (lymphoma cells)	Gene mutation	–	–	Oberly et al. 1984
Human (fibroblasts)	DNA damage	–	NA	Agrelo and Amos 1981
Human (fibroblasts)	DNA damage	–	NA	Martin and McDermid 1981
Human (fibroblasts)	DNA damage	+	NA	Snyder and Matheson 1985
Rat (hepatocytes)	DNA damage	+	NA	Althaus et al. 1982
Rat (hepatocytes)	DNA damage	+	NA	Althaus and Pitot 1983
Rat (hepatocytes)	DNA damage	+	NA	Bradley et al.1982
Rat (hepatocytes)	DNA damage	+	NA	Probst et al. 1981
Rat (hepatocytes)	DNA damage	+	NA	Sina et al. 1983
Chinese hamster (hepatocytes)	DNA damage	+	NA	McQueen et al.1983
Mouse (hepatocytes)	DNA damage	+	NA	McQueen et al.1983
Mouse (BALB/c cells)	Cellular transformation	–	(+)	Matthews et al. 1993
Phelps et al. 2002	Micronucleus assay	–	–	Phelps et al. 2002
Chinese hamster (Don cells)	Chromosomal aberrations	NA	±	Abe and Sasaki 1977
Chinese hamster (fibroblasts)	Chromosomal aberrations	NA	±	Ishidate and Odashima 1977
Human (lymphocytes)	Sister chromatid exchange	(+)	NA	Lindahl-Kiessling et al. 1989
Chinese hamster (ovary cells)	Sister chromatid exchange	–	–	Evans and Mitchell 1981
Chinese hamster (Don cells)	Sister chromatid exchange	NA	+	Abe and Sasaki 1977

Table 2-3. Genotoxicity of *N*-Nitrosodiphenylamine *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Chinese hamster (ovary cells)	Sister chromatid exchange	–	–	Perry and Thomson 1981

[a]A positive response was observed after *in vitro* nitrosation.

+ = positive results; (+) = weakly positive results; – = negative results; ± = inconclusive or equivocal; DNA; deoxyribonucleic acid; NA: not applicable

Most of the positive *in vitro* responses occurred in cases where exogenous metabolic activation was involved. This suggests that if *N*-nitrosodiphenylamine has genotoxic potential, the potential may arise from its metabolites. In fact, many *N*-nitroso compounds are thought to exert their mutagenic and carcinogenic effects through intermediates derived from alpha-carbon hydroxylation; these intermediates can alkylate DNA (Magee et al. 1976; Preussman and Stewart 1984; Schut and Castonguay 1984). However, since *N*-nitrosodiphenylamine is not susceptible to alpha-carbon oxidation, it presumably exerts its action by some mechanism other than direct alkylation. Some researchers have speculated that the carcinogenicity of *N*-nitrosodiphenylamine is due to transnitrosation with carcinogenic *N*-nitroso derivative(s) formation (NCI 1979; Preussmann and Stewart 1984; Raineri et al. 1981). An example of the reaction can be found in the formation of nitrosamines by nitrosation of dietary amines. This theory is supported by a *Salmonella* Ames test in which *N*-nitrosodiphenylamine was found to be mutagenic in strains TA98 and TA100 only after it was nitrosated *in vitro*; significantly positive responses were observed in systems without activation (Crebelli el al. 1984). Alternatively, transnitrosation could occur from *N*-nitrosodiphenylamine to another compound. Evidence exists for transnitrosation by *N*-nitroso-diphenylamine *in vivo*; transnitrosation from *N*-nitrosodiphenylamine to proline occurred in rats when the compounds were coadministered orally (Ohshima et al. 1982). The transnitrosation mechanism is consistent with the negative results obtained for *N*-nitrosodiphenylamine in assays for mutagenicity (with or without metabolic activation) and the positive results obtained in the NCI (1979) dietary carcinogenesis study in rats.

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

3.1 TOXICOKINETICS

No studies were located regarding *N*-nitrosodiphenylamine in humans. Limited information available in animals is summarized below.

- *N*-nitrosodiphenylamine is absorbed through the gastrointestinal tract, but quantitative data are not available.
- No distribution data are available.
- Limited data suggest that the main metabolic pathway for *N*-nitrosodiphenylamine is cytochrome P-450-dependent denitrosation and ring hydroxylation in the liver.
- In animals, *N*-nitrosodiphenylamine was eliminated primarily in the urine and the main metabolite appeared to be nitrate.

3.1.1 Absorption

No studies were located regarding absorption of *N*-nitrosodiphenylamine in humans following any route of exposure or in animals following inhalation exposure.

The appearance of metabolites in the urine of rats and in the serum of rats and guinea pigs following oral administration provides indirect evidence of gastrointestinal absorption of *N*-nitrosodiphenylamine (Appel et al. 1984; Dodd et al. 2013; Tatsumi et al. 1983). Furthermore, the occurrence of systemic effects in rats and mice in oral studies suggests that *N*-nitrosodiphenylamine is absorbed through the gastrointestinal tract in these animals (Cardy et al. 1979; Dodd et al. 2013; NCI 1979).

3.1.2 Distribution

No studies were located regarding distribution of *N*-nitrosodiphenylamine in humans or animals following any route of exposure.

3.1.3 Metabolism

No studies were located regarding metabolism of *N*-nitrosodiphenylamine in humans.

In experiments with animals, the reaction in which *N*-nitrosodiphenylamine is denitrosated to diphenylamine and nitric oxide seems to be the first step in the metabolic activation of *N*-nitrosodiphenylamine (Appel et al. 1984). Following administration of a single dose of *N*-nitrosodiphenylamine in corn oil (1,000 mg/kg) to female Wistar rats, nitrate was identified as the major urinary metabolite, while nitrite, diphenylamine, and a monohydroxydiphenylamine were found in smaller amounts. These results suggested that *N*-nitrosodiphenylamine is denitrosated to diphenylamine and nitric oxide and then the nitric oxide is converted into nitrite and nitrate. Nitrite can be oxidized in substantial amounts to nitrate (Appel et al. 1984).

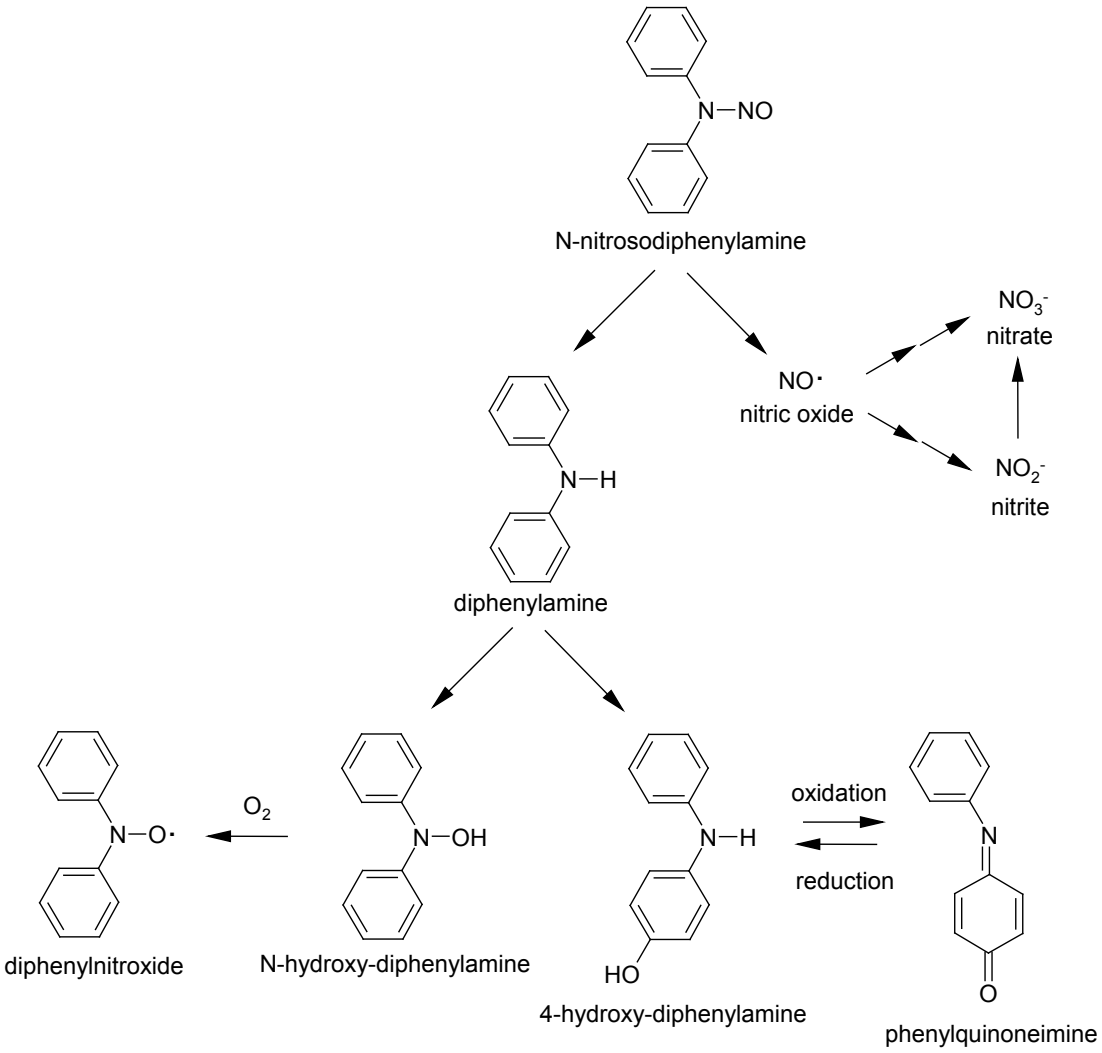
In vitro studies investigated the metabolism of *N*-nitrosodiphenylamine in phenobarbital-induced mouse liver microsomes (Appel et al. 1987a, 1987b, 1987c). The metabolites found were diphenylamine, 4-hydroxydiphenylamine, and its oxidized product, the corresponding quinoneimine. The authors concluded that diphenylamine undergoes ring hydroxylation to form 4-hydroxydiphenylamine, which is oxidized to the quinoneimine. Since *N*-hydroxylation is recognized as the initial step in the bioactivation of carcinogenic arylamines, the *N*-hydroxy derivative of diphenylamine may be a potential metabolite. This possible metabolite, however, has not been detected using microsomal incubation. A postulated metabolic scheme based on these data is presented in Figure 3-1.

In vitro studies conducted with rat and mouse liver cytochrome *P*-450 demonstrated the denitrosation of *N*-nitrosodiphenylamine (Appel et al. 1979; Schrenk et al. 1982; Wakabayashi et al. 1982).

Transnitrosation of proline by *N*-nitrosodiphenylamine occurred in male BD VI rats that were orally administered 28.28 mg/kg *N*-nitrosodiphenylamine and 50 μmol proline by gavage (Ohshima et al. 1982). The excretion of *N*-nitrosoproline was 15-fold higher than in the controls. Co-administration of thiocyanate had a catalytic effect, which resulted in a 58-fold increase in the urinary levels of *N*-nitrosoproline.

N-Nitrosodiphenylamine can undergo reductive metabolism by liver aldehyde oxidase under anaerobic conditions (Tatsumi et al. 1983). Guinea pigs received oral dosages (200 mg/kg) of *N*-nitrosodiphenylamine. Just before and 3 hours after administration of *N*-nitrosodiphenylamine, the guinea pigs were treated with oral dosages (50 mg/kg) of acetaldehyde (an electron donor). Acetaldehyde diphenylhydrazone was identified as a plasma metabolite.

Figure 3-1. Metabolic Pathways for *N*-Nitrosodiphenylamine



Source: Appel et al. 1987b

3.1.4 Excretion

No studies were located regarding excretion of *N*-nitrosodiphenylamine in humans following any route of exposure or in animals following inhalation and dermal exposure.

One study was located that investigated excretion in animals. After oral administration of a single 1,000-mg/kg dose of *N*-nitrosodiphenylamine to female Wistar rats, the maximum urinary excretion of nitrate and nitrite was found 24–48 hours after administration (Appel et al. 1984). Within 36 hours of administration, 24.8 and 1.4% of the administered dose of *N*-nitrosodiphenylamine was excreted as nitrate

and nitrite, respectively. Ninety-six hours after administration, about 30% of the administered dose had been eliminated as nitrite and nitrate.

In female Wistar rats, the maximum urinary nitrate or nitrite excretion was found in the 24 hours following intraperitoneal administration of 500 mg/kg *N*-nitrosodiphenylamine (Appel et al. 1984). This is a more rapid elimination than that following oral dosing. Ninety-six hours after administration, approximately 50% of the administered dose was detected as nitrate and nitrite—almost twice as much as was found after oral administration. Diphenylamine and hydroxydiphenylamine were also present as urinary metabolites. The rate of denitrosation after intraperitoneal injection was considerably higher than after oral administration. This was probably due to an altered availability of *N*-nitrosodiphenylamine to the liver.

Results from a study of rats, rabbits, and guinea pigs receiving 50 mg/kg *N*-nitrosodiphenylamine through intraperitoneal injection suggested that the rate of excretion of *N*-nitrosodiphenylamine into the bile and elimination of the chemical from the bile varies among species (Atawodi and Maduagwu 1990). Guinea pigs showed the most rapid excretion of *N*-nitrosodiphenylamine into the bile. Rabbits had the slowest excretion of *N*-nitrosodiphenylamine into the bile, but the most rapid elimination of the chemical from the bile. Both excretion to and elimination from bile were comparatively slow in the rat. The half-lives for *N*-nitrosodiphenylamine elimination from bile for these species are as follows: 95 minutes for rabbits, 240 minutes for guinea pigs, and 510 minutes for rats.

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 model has been developed for *N*-nitrosodiphenylamine.

3.1.6 Animal-to-Human Extrapolations

There is virtually no information on the toxicity of *N*-nitrosodiphenylamine in humans and there are limited data in animals, so predicting possible adverse health outcomes in humans based on results from animal studies would be highly speculative and inappropriate.

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*-nitrosodiphenylamine are discussed in Section 5.7, Populations with Potentially High Exposures.

It is difficult to determine persons with increased risk because there are limited data on the toxicity of *N*-nitrosodiphenylamine. People who have bladder dysfunction or disease may be more susceptible since the primary effect of *N*-nitrosodiphenylamine in animals is bladder cancer.

The alterations in activities of phase I and phase II metabolic enzymes in the liver by *N*-nitroso-diphenylamine (Sheweita and Mostafa 1996a, 1996b) may affect the metabolism of other chemicals. Whether this will result in increased or reduced toxicity of a particular chemical will depend on the specific enzymes involved and whether metabolism leads to production of an active metabolite or is a detoxifying reaction.

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*-nitrosodiphenylamine 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*-nitrosodiphenylamine 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*-nitrosodiphenylamine 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

N-Nitrosodiphenylamine can be detected and quantitated in the blood, serum, and urine of animals, with the lowest detection limits for serum (Pylypiw and Harrington 1981). Limited animal data suggest that

suspected metabolites of *N*-nitrosodiphenylamine can also be detected in the urine. However, these methods do not appear to have been used to test humans for exposure and no monitoring data for *N*-nitrosodiphenylamine were located. Therefore, no conclusion regarding the usefulness of these potential biomarkers in humans can be made, although it is reasonable to assume that they can indicate exposure. There are no other known biomarkers of exposure to *N*-nitrosodiphenylamine.

There are no data on how long *N*-nitrosodiphenylamine persists in the body of humans or animals. In one study, 96 hours after the administration of an oral dose, 30% of the dose had been eliminated in the urine (Appel et al. 1984). However, it is not known how much was eliminated in the feces or by other routes and how much was retained in the body. No data are available regarding the exposure levels that would result in levels detectable in body fluids.

3.3.2 Biomarkers of Effect

Based on data in rats and mice, the target organ appears to be the urinary bladder. Observed effects consist of epithelial hyperplasia and squamous metaplasia of the bladder (NCI 1979). These effects were seen at the lowest dose tested (15 mg/kg/day), and the effect is only observable postmortem. In addition, these effects can occur from other circumstances such as disease, exposure to drugs, and exposure to other chemicals, and are not unique to *N*-nitrosodiphenylamine. Therefore, they are not useful as specific biomarkers of effect for *N*-nitrosodiphenylamine. There are so few data available on the chemical that it is difficult to associate specific symptoms with exposure to *N*-nitrosodiphenylamine.

3.4 INTERACTIONS WITH OTHER CHEMICALS

N-Nitrosodiphenylamine was mutagenic in *Salmonella* strains TA98 and TA1535, but not TA100, in preincubation assays with rat liver S-Y fractions only in the presence of the comutagen norharman (9H-pyrido-[3,4b]indole) (Nagao and Takahashi 1981; Wakabayashi et al. 1981, 1982).

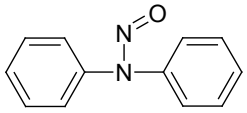
In mice treated with *N*-nitrosodiphenylamine prior to pentobarbital administration, pentobarbital sleeping time was significantly shortened compared to control mice given only the corn oil vehicle (Nishie et al. 1972). This was believed to be due to induction of liver enzymes that could metabolize pentobarbital.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information on the chemical identity of *N*-Nitrosodiphenylamine is provided in Table 4-1.

Table 4-1. Chemical Identity of *N*-Nitrosodiphenylamine

Characteristic	Information	Reference
Chemical name	*N*-Nitrosodiphenylamine	HSDB 1990
Synonym(s) and registered trade name(s)	Benzenamine; diphenyl- nitrosamine; diphenylamine, *N*-nitroso; *N*-nitroso-N-phenylaniline; diphenyl-N-nitrosamine; N,N-diphenyl- nitrosamine; NDPA:, NDPHA; nitrous diphenylamide; Retarder J; Redax; Vulkalent A; Vultrol; Vulcatard A; Curetard A; Delac J; Naugard TJB; TJB	OHM/TADS 1990
Chemical formula	$C_{12}H_{10}N_2O$	HSDC 1990
Chemical structure		IARC 1982a
Identification numbers:		
CAS Registry	86-30-6	HSDB 1990

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information on the physical and chemical properties of *N*-Nitrosodiphenylamine is provided in Table 4-2.

Table 4-2. Physical and Chemical Properties of *N*-Nitrosodiphenylamine

Property	Information	Reference
Molecular weight	198.23	HSDB 1990
Color	Orange-brown; yellow	HSDB 1990
Physical state	Amorphous solid; plates	HSDB 1990
Melting point	66.5°C	HSDB 1990
Boiling point	No data	
Density at 25°C	1.23 g/cm^3	IARC 1982a
Odor	No data	

Table 4-2. Physical and Chemical Properties of *N*-Nitrosodiphenylamine

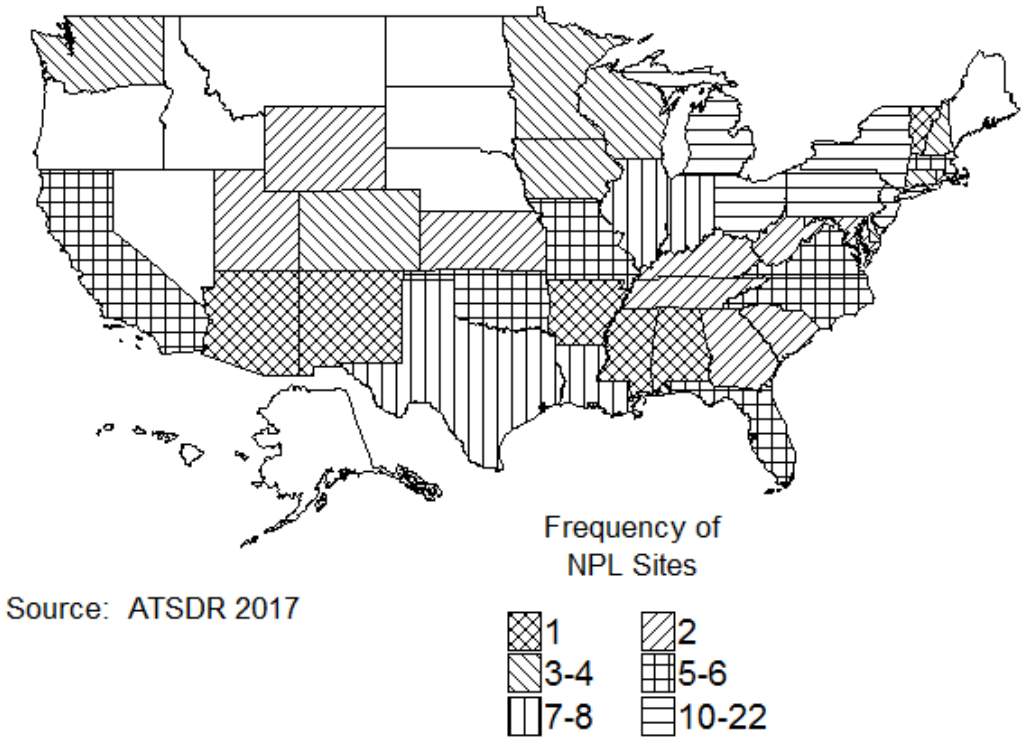
Odor threshold:	No data	
Water		
Air		
Solubility:		
Water at 25°C	40 mg/L	EPA 1982a
Organic solvents	Miscible with acetone, benzene, ethanol, ethylene dichloride	HSDB 1990
Partition coefficients:		
Log K_{ow}	2.57–3.13	Banerjee et al. 1980
Log K_{oc}	2.92–3.26	Lyman et al. 1982
Vapor pressure at 25°C	0.1 mmHg	HSDB 1990
Henry's law constant at 25°C	6.6×10^{-4} atm-m^3/mol	EPA 1982a
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors	1 mg/L=123.5 ppm; 1 ppm=8.1 mg/m^3 at 25°C, 760 mmHg	Clayton 1978
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

N-Nitrosodiphenylamine has been identified in at least 199 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*-nitrosodiphenylamine has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. The 199 sites are located within the United States.

Figure 5-1. Number of NPL Sites with *N*-Nitrosodiphenylamine Contamination



- *N*-Nitrosodiphenylamine has not been found in air, drinking water, or foods, so it is unlikely that the general public will be exposed to this chemical.
- Persons living near facilities producing, or waste sites containing, diphenylamine may have a higher risk of exposure to *N*-nitrosodiphenylamine via microbial production of the chemical.
- *N*-Nitrosodiphenylamine has been produced by reacting diphenylamine and sodium nitrite in water that has been acidified with sulfuric acid.
- *N*-Nitrosodiphenylamine is used as a vulcanization retardant in rubber compounds used to make tires.

- *N*-Nitrosodiphenylamine can be released to air from waste sites. In air, it is decomposed by sunlight. It also can react with other chemicals; the half-life for this reaction is 7 hours.
- In laboratory test, most *N*-nitrosodiphenylamine disappears from water and soil within several weeks.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

N-Nitrosodiphenylamine is not known to occur naturally in the environment (IARC 1982a). However, there is evidence to indicate that microorganisms produce the chemical under laboratory conditions (Ayanaba and Alexander 1973). It is possible that this may take place under environmental conditions also. *N*-Nitrosodiphenylamine has been produced by reacting diphenylamine and sodium nitrite in water that has been acidified with sulfuric acid (NIOSH 1983). The *N*-nitrosodiphenylamine is then separated from the aqueous layer, drained, dried on hot rollers, and packed as the final product into drums.

N-Nitrosodiphenylamine had been produced commercially in the United States since 1945 (IARC 1982a). U.S. production volumes peaked in 1974 at 3.2 million pounds and gradually declined to 0.4 million pounds in 1980. The decline in production was due to the availability of new and more efficient chemicals for its applications in the rubber-processing industry (Taylor 1982). Production volumes are not available after 1980 (USITC 1985, 1986, 1987, 1988).

According to the Toxics Release Inventory (TRI), there is one facility in the United States that manufactured or processed *N*-nitrosodiphenylamine in 2016 (TRI16 2017). See Table 5-1 for more details. The data listed in the TRI should he used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
LA	1	10,000	99,999	2, 3, 10

[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

Imports of *N*-nitrosodiphenylamine through principal U.S. customs districts increased from 52,000 pounds in 1977 to 110,000 pounds in 1982 (USITC 1978a, 1983). Current import and export data for *N*-nitrosodiphenylamine are not available.

5.2.3 Use

N-Nitrosodiphenylamine was primarily used as a retardant in the rubber-processing industry (HSDB 1990). Retardants are chemicals that prevent the premature vulcanization of rubber compounds during certain rubber-processing steps such as mixing and calendaring. *N*-Nitrosodiphenylamine was generally used with the sulfenamide accelerators in tire compounds. The use of *N*-nitrosodiphenylamine as a retardant had the following undesirable side effects: gaseous decomposition products of *N*-nitroso-diphenylamine during vulcanization cause porosity in thick cross-section extrusions; *N*-nitrosodiphenyl-amine is a nitrosating agent of secondary amines, which are suspected to be animal carcinogens; it is slightly staining; and it is not efficient in the presence of alkyl-atyl or dialkyl-substituted *p*-phenylene-diamine antidegradants (Taylor 1982).

N-Nitrosodiphenylamine was also used as an intermediate in the manufacture of *p*-nitrosodiphenylamine. *p*-Nitrosodiphenylamine can be reduced to *N*-phenyl-*p*-phenylenediamine, which is also a rubber-processing chemical and an intermediate in the production of other rubber-processing chemicals (OHM/TADS 1990).

5.2.4 Disposal

Product residues and sorbent media containing *N*-nitrosodiphenylamine can be packaged in 17H epoxy-lined drums and disposed of at an EPA-approved site. The compound can be destroyed by high-temperature rotary kiln or fluidized bed incineration with scrubbing equipment (NO_X scrubber) or acid hydrolysis (HSDB 1990).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 11 pounds of *N*-nitrosodiphenylamine to the atmosphere from one facility reporting to TRI) domestic manufacturing and processing facilities in 2016, accounted for 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.

N-Nitrosodiphenylamine may he released to the atmosphere from sewage sludge incinerators (Gerstle 1988) or from hazardous waste sites. Release of *N*-nitrosodiphenylamine to the environment can occur from effluent discharges generated from its production and use.

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
LA	1	11	0	0	0	0	11	0	11
Total	1	11	0	0	0	0	11	0	11

[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)

5.3.2 Water

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

N-Nitrosodiphenylamine may be released in industrial waste water (Rhoades et al. 1980). There is also evidence suggesting that some microorganisms produce *N*-nitrosodiphenylamine from diphenylamine and nitrate or nitrite in the environment (Ayanaba and Alexander 1973). Although this has only been shown for pure cultures under laboratory conditions, it may be a natural source of *N*-nitrosodiphenylamine in the environment.

5.3.3 Soil

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

There is evidence suggesting that *N*-nitrosodiphenylamine might be produced by some microorganisms under certain environmental conditions (Ayanaba and Alexander 1973).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. *N*-Nitrosodiphenylamine has a vapor pressure of 0.1 mmHg at 25°C (HSDB 1990). It should exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981).

Water. *N*-Nitrosodiphenylamine is soluble in water (40 mg/L) (EPA 1982a). The Henry's law constant for *N*-nitrosodiphenylamine ($6.6x10^{-4}$ atm-m^3/mol) (EPA 1982a) indicates that volatilization from water will be slow but significant transport process (Lyman et al. 1982).

Sediment and Soil. The soil sorption coefficient (K_{oc}) for *N*-nitrosodiphenylamine was estimated to range from 830 to 1,830 (Lyman et al. 1982). This K_{oc} range is indicative of low mobility in soil; therefore, significant leaching is not expected to occur in most types of soil (Swann et al. 1983). In the aquatic environment, substantial partitioning from the water column to sediment and suspended particulate organic matter may occur.

Other Media. The logarithm of n-octanol/water partition coefficient (log K_{ow}) is a useful preliminary indicator of potential bioaccumulation of a compound. The log K_{ow} for *N*-nitrosodiphenylamine was estimated to range from 2.57 to 3.13, indicating a low potential for bioaccumulation (Banerjee et al. 1980; Barrows et al. 1980). An experimental bioconcentration factor of 217 was determined for *N*-nitrosodiphenylamine based on a continuous 14-day exposure study of bluegill sunfish with a mean *N*-nitrosodiphenylamine water concentration of 9.21 ppb (Barrows et al. 1980). The half-life of *N*-nitrosodiphenylamine in the fish was found to be <1 day when the fish were placed in pollutant-free water after the exposure period. The relatively low experimental bioconcentration potential and short half-life of *N*-nitrosodiphenylamine indicate that biomagnification in the aquatic food chain is not a major environmental fate process (Barrows et al. 1980).

5.4.2 Transformation and Degradation

Air. *N*-Nitrosodiphenylamine absorbs sunlight, suggesting a potential for direct photolysis in a sunlit environment (EPA 1979). Irradiation experiments using a benzene solution of *N*-nitrosodiphenylamine have shown that *N*-nitrosodiphenylamine is photodecomposed at sunlight wavelengths (Sharma et al. 1986). The rate at which photolysis occurs was not determined. *N*-Nitrosodiphenylamine also reacts with hydroxyl radicals in the atmosphere. An estimated half-life for this reaction is 7 hours (HSDB 1990).

Water. The major environmental fate process for *N*-nitrosodiphenylamine in water is biodegradation. A static-culture flask-screening biodegradability test was performed using domestic waste water as the microbial inoculum and 5 and 10 ppm of *N*-nitrosodiphenylamine as the test compound (Tabak et al. 1981). At the end of 7 days, 87% degradation was achieved in the original culture dosed with 5 ppm, and 47% degradation was achieved in the original culture dosed with 10 ppm. After the second 7-day incubation period, 100% degradation was achieved in the first subculture dosed with 5 ppm, while 63% degradation was achieved in the first subculture dosed with 10 ppm. After the fourth 7-day incubation period, 98% degradation was achieved by the third subculture dosed with 20 ppm. These results showed that *N*-nitrosodiphenylamine was degradable, with rapid microbial adaptation at concentrations of 5 ppm and with more gradual microbial adaptation at concentrations of 10 ppm (Tabak et al. 1981). No studies were located regarding hydrolysis and oxidation of *N*-nitrosodiphenylamine.

Sediment and Soil. Biodegradation is the major environmental fate process for *N*-nitrosodiphenylamine in soil. In laboratory tests using a sandy loam soil, 68% of added *N*-nitrosodiphenylamine was degraded after 30 days of incubation, but amending the soil with wheat straw (to increase microbial activity) resulted in complete disappearance of added *N*-nitrosodiphenylamine in 10 days (Mallik and Tesfai 1981).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to *N*-nitrosodiphenylamine depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of *N*-nitrosodiphenylamine 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*-nitrosodiphenylamine 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 and biological media.

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

Media	Detection limit	Reference
Air	NR	Fajen et al. 1979, 1980; NIOSH 1983
Water	NR	Rhoades et al. 1980
Soil	NR	NIOSH 1983
Blood and serum	0.01 ppm[b]	Pylpiw and Harrington 1981
Urine	0.1 ppm[b]	Pylpiw and Harrington 1981

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]Actual data are for N-nitroso-N-methylaniline; authors indicate that N-nitrosodiphenylamine yielded comparable results

NR = not reported

Detections of *N*-nitrosodiphenylamine in air, water, and soil at NPL sites are summarized in Table 5-4.

Table 5-4. *N*-Nitrosodiphenylamine 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)	22	32.5	7,370	37	21
Soil (ppb)	2,500	3,000	18,600	30	23
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

No data were located regarding the levels of *N*-nitrosodiphenylamine in air.

5.5.2 Water

No data were located regarding the levels of *N*-nitrosodiphenylamine in drinking water. Only one positive detection was found for ambient surface waters. *N*-Nitrosodiphenylamine was detected (no

concentration reported) in the Cuyahoga River, which feeds Lake Erie (Great Lakes Water Quality Board 1983).

5.5.3 Sediment and Soil

N-Nitrosodiphenylamine was measured at a concentration of 47 mg/kg (47,000 ppb) in a soil sample collected in 1978 near a manufacturing facility (NIOSH 1983). It has also been detected (no concentration reported) in the soil-sediment-water complex of the Love Canal near Niagara Falls, New York (Hauser and Bromberg 1982).

5.5.4 Other Media

No reports of *N*-nitrosodiphenylamine detection in food or other environmental media were found in the available literature.

5.6 GENERAL POPULATION EXPOSURE

The general population does not appear to be exposed to any background levels of *N*-nitrosodiphenylamine. No data were located regarding levels of *N*-nitrosodiphenylamine in air, drinking water, or foods.

The National Occupational Exposure Survey (NOES), conducted by NIOSH from 1981 to 1983 estimated that 1,093 workers employed at 137 plants were potentially exposed to *N*-nitrosodiphenylamine in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration. or duration of exposure to *N*-nitrosodiphenylamine. The survey provides only estimates of workers potentially exposed to chemicals in the workplace.

N-Nitrosodiphenylamine was detected in the workplace air of an Ohio tire chemical factory in the spring of 1978. The concentrations of *N*-nitrosodiphenylamine ranged from 0 to 47 µg/m^3 (0–6 ppb) (Fajen et al. 1979, 1980). A scraping from a staircase in the factory contained 15,000 ppm of *N*-nitrosodiphenylamine. Additional monitoring conducted in Ohio during the spring of 1978 found no detectable levels of *N*-nitrosodiphenylamine in the workplace air of an industrial rubber products factory, an aircraft tire factory, a synthetic rubber and latex factory, or three tire plants (Fajen et al. 1979, 1980).

Levels of *N*-nitrosodiphenylamine ranging from not detectable to 12.35 µg/m^3 (1.5 ppb) in workplace air samples were found at a Kelly-Springfield tire plant in 1979 in the United States (NIOSH 1984). Levels

ranging from below detectable limits (5 ng per sample) to 160 ng/m^3 (0.02 ppb) were found in the breathing zone of curing press operators at a Uniroyal plant in Mishawaka, Indiana (NIOSH 1982).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers involved in the production and use of *N*-nitrosodiphenylamine may constitute a group at risk because of the potential for occupational exposure. Persons living near a production facility or a hazardous waste site containing *N*-nitrosodiphenylamine may have a higher risk of exposure to *N*-nitrosodiphenylamine resulting from contact with contaminated air, drinking water, or soil. If microorganisms are found to nitrosate diphenylamine *in situ*, then workers exposed to this chemical may be at higher risk of *N*-nitrosodiphenylamine exposure. Persons living near facilities producing, or waste sites containing, diphenylamine might also be at increased risk of exposure to *N*-nitrosodiphenylamine via microbial production of the chemical.

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 Information on Health Effects

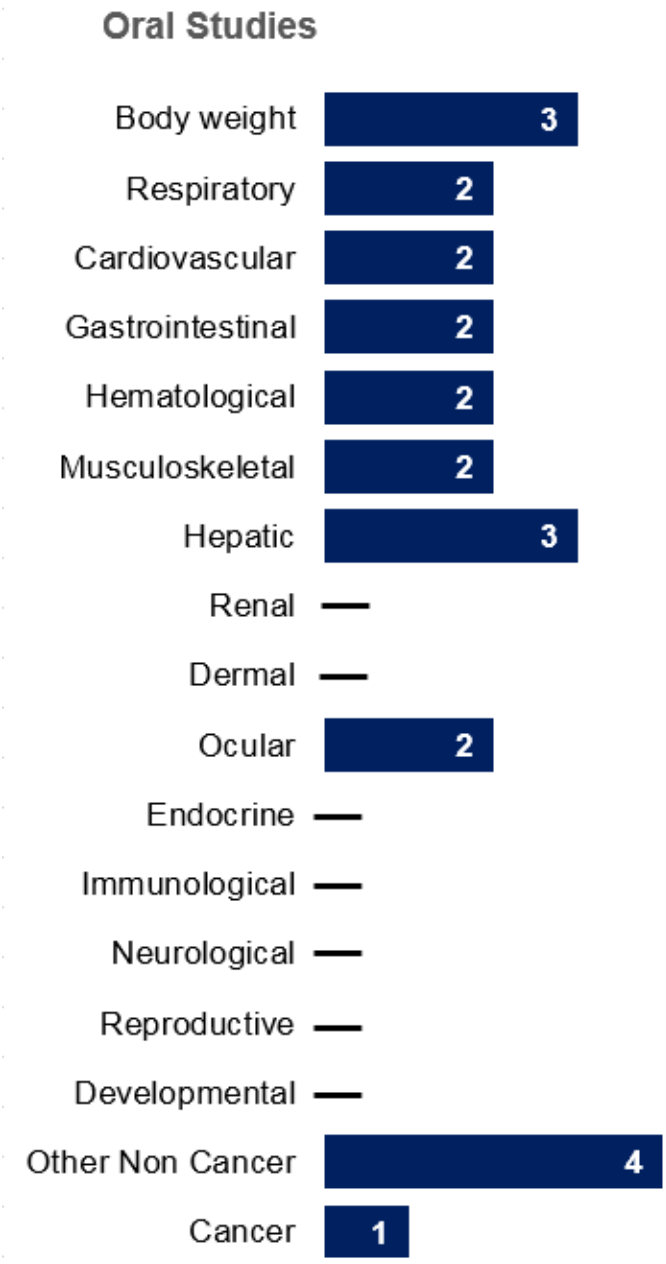
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to *N*-nitrosodiphenylamine that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of *N*-nitrosodiphenylamine.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

6.2 Identification of Data Needs

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

Figure 6-1. Summary of Existing Health Effects Studies on *N*-Nitrosodiphenylamine by Route and Endpoint*

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



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

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

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

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

Health Effects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.3 Ongoing Studies

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

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Table 7-1. Regulations and Guidelines Applicable to *N*-Nitrosodiphenylamine

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		WHO 2017
	Guideline value	0.0001 mg/L (0.1 µg/L)[a]	
FDA	EAFUS	No data[b]	FDA 2013
	Cancer		
ACGIH	Carcinogenicity classification	No data	ACGIH 2016
HHS	Carcinogenicity classification	No data	NTP 2016
EPA			
	Carcinogenicity classification	B2[c,d]	IRIS 2002
	Oral slope factor	4.9×10^{-3} $(mg/kg/day)^{-1}$	
IARC	Carcinogenicity classification	Group 3[e]	IARC 2017
	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

Table 7-1. Regulations and Guidelines Applicable to *N*-Nitrosodiphenylamine

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]	5.5 mg/m^3	
	PAC-2[f]	60 mg/m^3	
	PAC-3[f]	360 mg/m^3	

[a]Based on hepatic biliary cystadenomas in female rats, the most sensitive carcinogenic end-point, observed in a drinking-water study, using a multistage model.
[b]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.
[c]Group B2: probable human carcinogen.
[d]Based on increased incidence of bladder tumors in male and female rats and reticulum cell sarcomas in mice, and structural relationship to carcinogenic nitrosamines.
[e]Group 3: not classifiable as to its carcinogenicity to humans.
[f]Definitions of PAC terminology are available from U.S. 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 value; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the 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 F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *N*-Nitrosodiphenylamine
CAS Numbers: 86-30-6
Date: April 1993
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 located.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *N*-Nitrosodiphenylamine
CAS Numbers: 86-30-6
Date: April 1993
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 located.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *N*-Nitrosodiphenylamine
CAS Numbers: 86-30-6
Date: April 1993
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 located.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *N*-Nitrosodiphenylamine
CAS Numbers: 86-30-6
Date: April 1993
March 2017—Updated literature search
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 oral toxicity of *N*-nitrosodiphenylamine has been examined in a dietary exposure study in rats (Dodd et al. 2013) and in a mouse gavage study (Nishie et al. 1972); both studies only examined a limited number of potential toxicity targets. Dodd et al. (2013) reported diffuse hyperplasia in the urinary bladder of rats exposed to 183 mg/kg/day for 2 weeks. Nishie et al. (1972) reported that no histological alterations were observed in the livers of mice administered 350 mg/kg/day *N*-nitrosodiphenylamine for 4 days. The urinary bladder has been identified as the most sensitive target following intermediate- and chronic-duration oral exposure; however, the observed hyperplasia was not considered a suitable basis for an MRL because the lesion was considered preneoplastic.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *N*-Nitrosodiphenylamine
CAS Numbers: 86-30-6
Date: April 1993
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: Two studies have evaluated the oral toxicity of *N*-nitrosodiphenylamine following intermediate-duration oral exposure (Dodd et al. 2013; NCI 1979). Both studies have examined a limited number of endpoints. Dodd et al. (2013) reported diffuse hyperplasia in the urinary bladder of rats exposed via the diet to 123 mg/kg/day *N*-nitrosodiphenylamine for at least 4 weeks. NCI (1979) reported decreases in body weight gain in rats exposed to 200 mg/kg/day via the diet for 8–11 weeks. Although the identification of the urinary bladder as a sensitive target of toxicity is supported by chronic-duration oral studies, the observed hyperplasia was considered a pre-neoplastic lesions and was not considered suitable for derivation of an MRL.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** *N*-Nitrosodiphenylamine
CAS Numbers: 86-30-6
Date: April 1993
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: The chronic-duration oral database for *N*-nitrosodiphenylamine consists of a study of rats and mice exposed via the diet for 100 weeks (Cardy et al. 1979; NCI 1979). The observed effects included urinary bladder epithelial hyperplasia and corneal opacities in rats exposed to 50 mg/kg/day, urinary bladder squamous metaplasia in rats exposed to 200 mg/kg/day, and decreases in body weight and inflammation and epithelial hyperplasia in the urinary bladder of mice exposed to 301 mg/kg/day. No other adverse effects were reported in the wide range of tissues examined. These data, supported by similar findings following acute and intermediate oral exposure, suggested that the urinary bladder is the most sensitive target of toxicity. The epithelial hyperplasia was not considered a suitable basis for an MRL because the lesion was considered preneoplastic.

Agency Contact (Chemical Manager): Obaid Faroon, DVM, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR *N*-NITROSODIPHENYLAMINE

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*-nitrosodiphenylamine.

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*-nitrosodiphenylamine. 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*-nitrosodiphenylamine 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*-nitrosodiphenylamine are presented in Table B-1.

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

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

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

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for *N*-nitrosodiphenylamine (ATSDR 1993), thus, the literature search was restricted to studies published between January 1991 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*-nitrosodiphenylamine. 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*-nitroso-diphenylamine 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.

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	((AP2V89J1DA[rn] OR 86-30-6[rn] OR N-nitrosodiphenylamine[supplementary concept] OR N-nitrosodiphenylamine[nm]) AND (1991/01/01 : 3000[dp] OR 1991/01/01 : 3000[mhda])) OR (("Curetard A"[tw] OR "Delac J"[tw] OR "Difenylnitrosamin"[tw] OR "Diphenyl N-nitrosoamine"[tw] OR "N-nitroso-Diphenylamine"[tw] OR "Diphenylnitrosamin"[tw] OR "Diphenylnitrosamine"[tw] OR "N, N-Diphenylnitrosamine"[tw] OR "N-Nitroso-N-phenylaniline"[tw] OR "N-Nitroso-N-phenylbenzenamine"[tw] OR "N-Nitrosodifenylamin"[tw] OR "N-Nitrosodiphenylamine"[tw] OR "Naugard TJB"[tw] OR "Nitrosodiphenylamine"[tw] OR "Ortard"[tw] OR "Redax"[tw] OR "Retarder J"[tw] OR "Sconoc"[tw] OR "Vulcalent A"[tw] OR "Vulcatard A"[tw] OR "Vulkalent A"[tw] OR "Vultrol"[tw]) AND (1991/01/01 : 3000[dp] OR 1991/01/01 : 3000[crdat] OR 1991/01/01 : 3000[edat]))
Toxline	
03/2017	("curetard a" OR "delac j" OR "difenylnitrosamin" OR "diphenyl n-nitrosoamine" OR "n-nitroso-diphenylamine" OR "diphenylnitrosamin" OR "diphenylnitrosamine" OR "n n-diphenylnitrosamine" OR "n-nitroso-n-phenylaniline" OR "n-nitroso-n-phenylbenzenamine" OR "n-nitrosodifenylamin" OR "n-nitrosodiphenylamine" OR "naugard tjb" OR "nitrosodiphenylamine" OR "ortard" OR "redax" OR "retarder j" OR "sconoc" OR "vulcalent a" OR "vulcatard a" OR "vulkalent a" OR "vultrol" OR 86-30-6 [rn]) AND 1991:2017 [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 13:04:45 ON 20 MAR 2017 L1 1016 SEA 86-30-6 L2 994 SEA L1 NOT TSCATS/FS L3 965 SEA L2 NOT PATENT/DT L4 376 SEA L3 AND PY>=1991 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?)

Table B-2. Database Query Strings

Database search date	Query string
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	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 269 SEA L4 AND L37
	L39 16 SEA L38 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L40 26 SEA L38 AND BIOSIS/FS L41 208 SEA L38 AND CAPLUS/FS L42 19 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L43 236 DUP REM L39 L40 L42 L41 (33 DUPLICATES REMOVED) SAVE TEMP L43 PHENYL/A L*** DEL 16 S L38 AND MEDLINE/FS L*** DEL 16 S L38 AND MEDLINE/FS L44 16 SEA L43 L*** DEL 26 S L38 AND BIOSIS/FS L*** DEL 26 S L38 AND BIOSIS/FS L45 22 SEA L43 L*** DEL 208 S L38 AND CAPLUS/FS L*** DEL 208 S L38 AND CAPLUS/FS L46 180 SEA L43 L*** DEL 19 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 19 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L47 18 SEA L43 L48 220 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS 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: 86-30-6
NTP	
03/2017	86-30-6 Diphenyl N-nitrosoamine N-nitroso-Diphenylamine Diphenylnitrosamin Diphenylnitrosamine N,N-Diphenylnitrosamine N-Nitroso-N-phenylaniline N-Nitroso-N-phenylbenzenamine N-Nitrosodifenylamin N-Nitrosodiphenylamine Nitrosodiphenylamine
NIH RePORTER	
05/2017	Active projects, 2012-2017 "Curetard A" OR "Delac J" OR "Difenylnitrosamin" OR "Diphenyl N-nitrosoamine" OR "N-nitroso-Diphenylamine" OR "Diphenylnitrosamin" OR "Diphenylnitrosamine" OR "N,N-Diphenylnitrosamine" OR "N-Nitroso-N-phenylaniline" OR "N-Nitroso-N-phenylbenzenamine" OR "N-Nitrosodifenylamin" OR "N-Nitrosodiphenylamine" OR "Naugard TJB" OR "Nitrosodiphenylamine" OR "Ortard" OR "Redax" OR "Retarder J" OR "Sconoc" OR "Vulcalent A" OR "Vulcatard A" OR "Vulkalent A" OR "Vultrol"

Table B-3. Strategies to Augment the Literature Search

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

[a]Several 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): 302
- Number of records identified from other strategies: 24
- Total number of records to undergo literature screening: 326

B.1.2 Literature Screening

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

- 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.

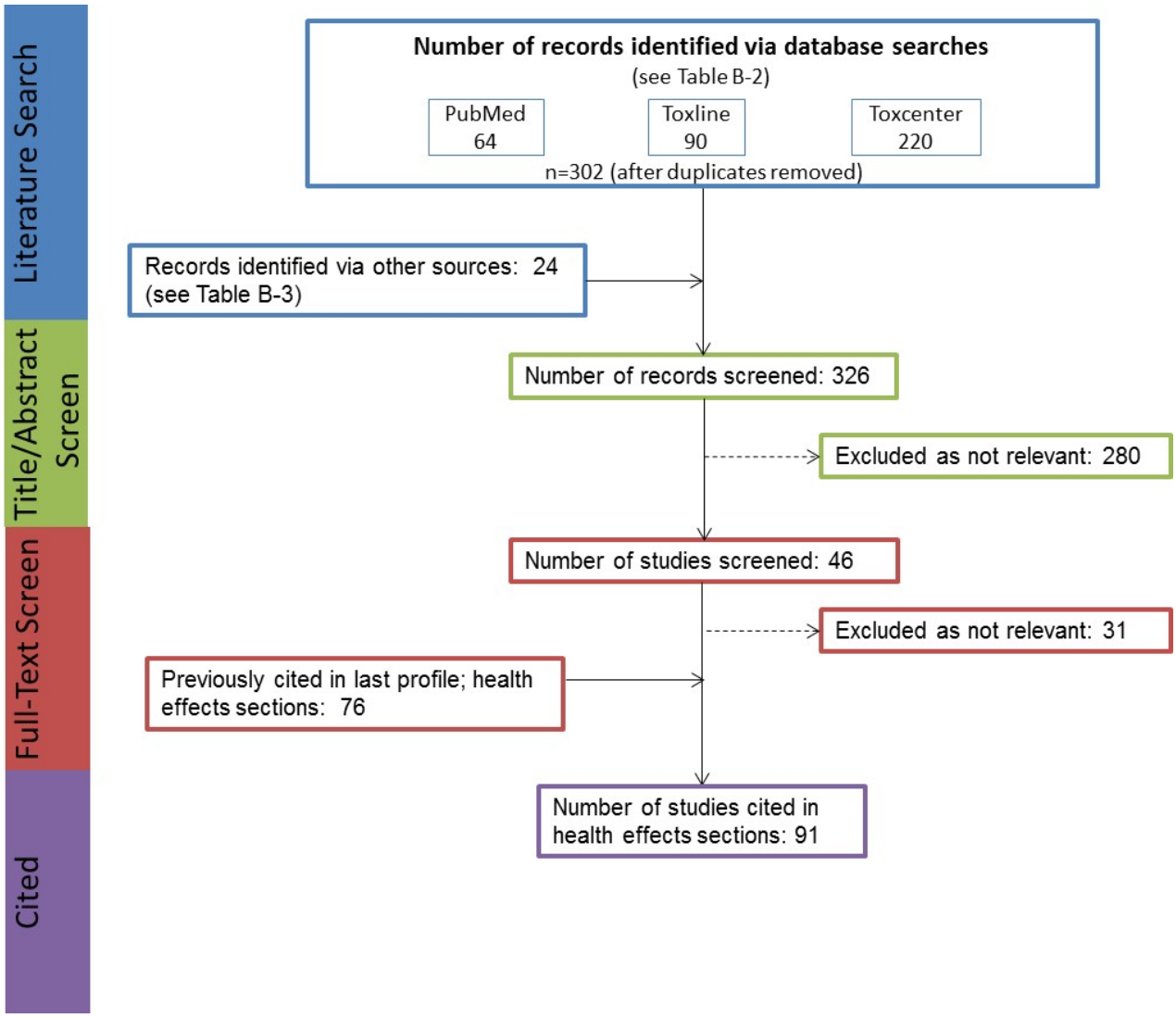
- Number of titles and abstracts screened: 326
- Number of studies considered relevant and moved to the next step: 46

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: 46
- Number of studies cited in the health effects sections of the existing toxicological profile (April, 1993): 76
- Total number of studies cited in the health effects sections of the updated profile: 91

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*-Nitrosodiphenylamine



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.

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

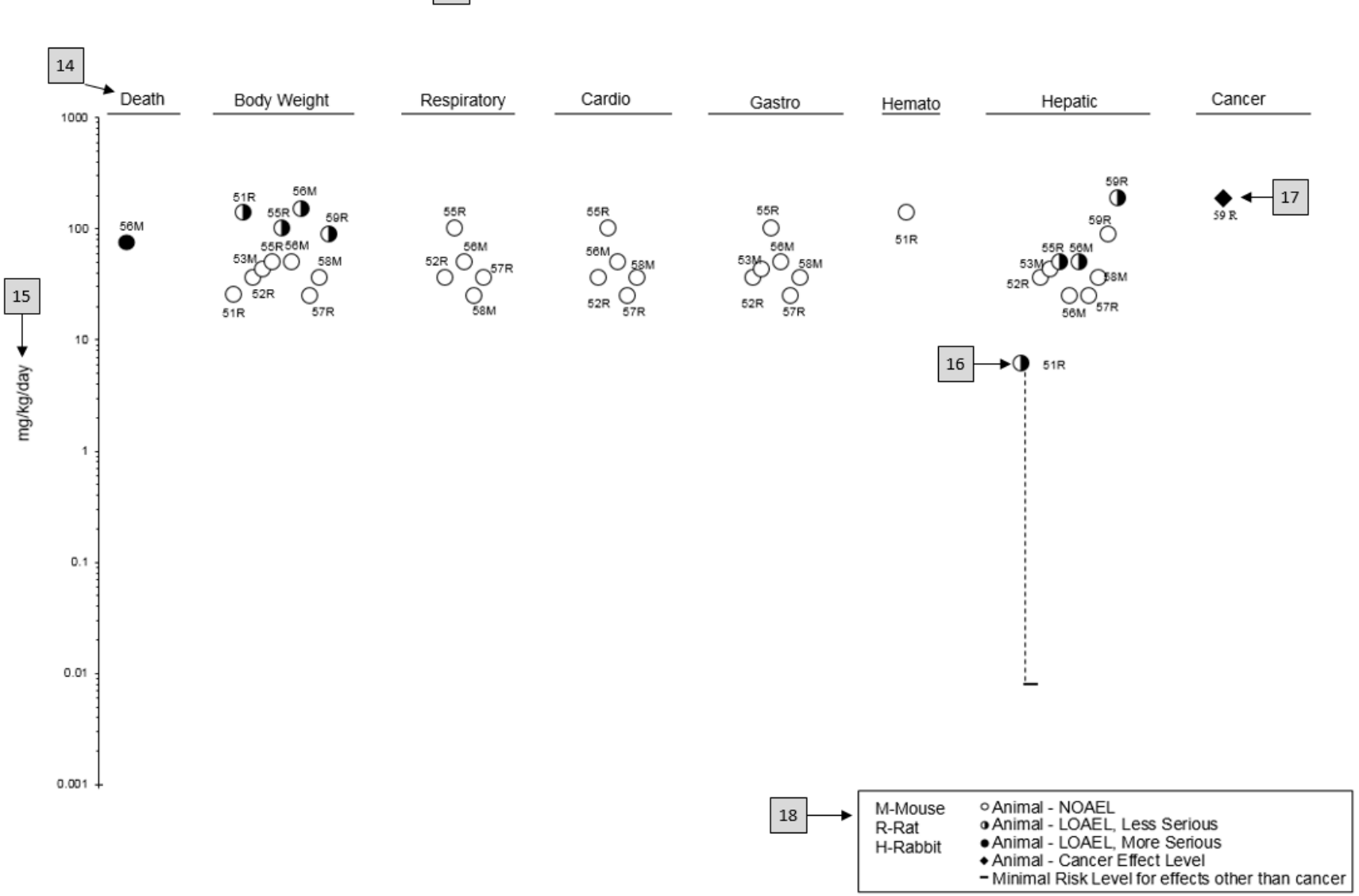
[a]The number corresponds to entries in Figure 2-x.

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

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

APPENDIX C

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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).

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
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

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

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
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

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