

**TOXICOLOGICAL PROFILE FOR
N-NITROSODIPHENYLAMINE**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry**

April 1993

DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for *N*-nitrosodiphenylamine was released on December 1988. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, on October 17, 1990, and on October 17, 1991. A revised list of 275 substances was published on October 28, 1992.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following:

- (A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.
- (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 which present a significant risk to human health of acute, subacute, and chronic health effects.
- (C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

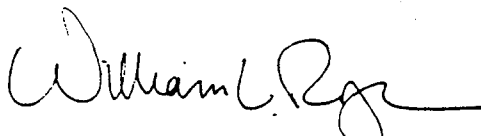
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. 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 protection of public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

Foreword

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 our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

A handwritten signature in black ink, appearing to read "William L. Roper". The signature is fluid and cursive, with a long horizontal stroke at the end.

William L. Roper, M.D., M.P.H.
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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.
2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.
3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about *N*-nitrosodiphenylamine and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,300 sites on its National Priorities List (NPL). *N*-Nitrosodiphenylamine has been found in at least 172 of these sites. However, we do not know how many of the 1,300 NPL sites have been evaluated for *N*-nitrosodiphenylamine. As EPA evaluates more sites, the number of sites at which *N*-nitrosodiphenylamine is found may change. This information is important for you to know because *N*-nitrosodiphenylamine may cause harmful health effects and because these sites are potential or actual sources of human exposure to *N*-nitrosodiphenylamine.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as *N*-nitrosodiphenylamine, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS *N*-NITROSODIPHENYLAMINE?

N-Nitrosodiphenylamine is an orange-brown or yellow solid. It evaporates slowly to the air and can attach to dust particles and travel with the wind. It can dissolve in water and attach to soil. It breaks down to other substances, but we do not know whether these substances are harmful to humans. We have not found *N*-nitrosodiphenylamine in drinking water, foods, or in the air we breathe. However, it is in the water and soil near some hazardous waste sites. We do not know whether *N*-nitrosodiphenylamine is found in the air near hazardous waste sites or in food grown near such sites.

We do not know if *N*-nitrosodiphenylamine occurs naturally in the environment, but some scientific evidence suggests that tiny organisms too small to be seen without the aid of a microscope may make it. It can be man-made and is used to make rubber products such as tires. It is sometimes used to make other chemicals. In the early 1980s most U.S. rubber manufacturers replaced it with more efficient chemicals. Only one manufacturer

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in the United States produces *N*-nitrosodiphenylamine. See Chapter 3 for more information on the physical and chemical properties of *N*-nitrosodiphenylamine. See Chapter 4 for more information on its production, import, use, and disposal.

1.2 WHAT HAPPENS TO *N*-NITROSODIPHENYLAMINE WHEN IT ENTERS THE ENVIRONMENT?

N-Nitrosodiphenylamine can enter the environment by evaporating to the air from waste sites. It can also leak into the ground from waste sites and dissolve into the groundwater and surface water. Industrial discharge releases *N*-nitrosodiphenylamine into water. *N*-Nitrosodiphenylamine can also bind to soil. In laboratory tests, most *N*-nitrosodiphenylamine disappears from water and soil within several weeks. Organisms that live in the water take it up to a limited degree. We do not know if land animals or plants take it up. It is believed that the chemical breaks down to other products. We do not know what the breakdown products are or if they are harmful to humans. However, it has not been found in the drinking water, food, or air with which you would normally come in contact. Chapters 4 and 5 contain more information on what happens to this chemical when it enters the environment.

1.3 HOW MIGHT I BE EXPOSED TO *N*-NITROSODIPHENYLAMINE?

There is no available information to show that *N*-nitrosodiphenylamine exists in the soil, air, food, or water with which you would normally come in contact. Therefore, you are not likely to be exposed to it.

Workers who were or are involved in the production or use of *N*-nitrosodiphenylamine may have been exposed to the chemical. Occupational data from 1981 to 1983 show that an estimated 1,093 workers employed at 137 plants might have been exposed to it. Today, since only one company makes it, fewer workers are exposed. Current exposure may also include contact with *N*-nitrosodiphenylamine at hazardous waste sites. It has been found in 3.6% of underground water samples and 0.7% of aboveground water samples taken at hazardous waste sites. See Chapter 5 for more information on how you might be exposed to *N*-nitrosodiphenylamine.

1.4 HOW CAN *N*-NITROSODIPHENYLAMINE ENTER AND LEAVE MY BODY?

Substances can generally enter your bloodstream if you breathe them in the air, eat or drink them, or get them on your skin. We do not know if *N*-nitrosodiphenylamine can enter your body through the lungs. Evidence from animal studies shows that *N*-nitrosodiphenylamine enters the bloodstream after animals swallow water or food containing it. This information suggests that it is likely to enter your body if you, are

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exposed to it by mouth. Animal studies also suggest that *N*-nitrosodiphenylamine can enter your body if it gets on your skin. If you live near a hazardous waste site, *N*-nitrosodiphenylamine could enter your body if you drink water containing it or possibly if you breathe it in the air. Children could also be exposed by eating or touching dirt that has *N*-nitrosodiphenylamine in it. If you work with *N*-nitrosodiphenylamine, you could be exposed to it by breathing small particles of it in the air or getting it on your skin. Animals break *N*-nitrosodiphenylamine down into other substances that can also harm their health. We expect that humans break it down by similar means.

An animal study showed that some *N*-nitrosodiphenylamine rapidly leaves the body in urine. Some probably also leaves the body in feces. It probably leaves the human body in a similar manner. We do not know how long it takes for all *N*-nitrosodiphenylamine to leave the body.

It is most likely to enter your body if you come into contact with it in air, water, or soil at hazardous waste sites containing it. For more information on how it enters and leaves your body see Chapter 2.

1.5 HOW CAN *N*-NITROSODIPHENYLAMINE AFFECT MY HEALTH?

We do not have enough information to know how *N*-nitrosodiphenylamine will affect your health.

We know very little about the health effects of exposure to *N*-nitrosodiphenylamine in animals, except that swallowing large doses can cause death. Animals given *N*-nitrosodiphenylamine in their diets for long periods developed swelling, cancer of the bladder, and changes in body weight. We do not know whether these effects would occur in humans. We also do not know if it can affect pregnancy or cause birth defects. EPA considers *N*-nitrosodiphenylamine to be a possible cancer-causing substance in humans because of the health effects seen in some animals. The International Agency for Research on Cancer (IARC) concluded that there are not enough data to determine whether *N*-nitrosodiphenylamine causes cancer in humans. IARC also concluded that there is limited evidence indicating that *N*-nitrosodiphenylamine causes cancer in experimental animals.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO *N*-NITROSODIPHENYLAMINE?

There are no tests available to determine if you have been exposed to *N*-nitrosodiphenylamine. There are tests to detect *N*-nitrosodiphenylamine and its breakdown products in

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the blood and urine of exposed animals, but these tests have not been used for people. Refer to Chapters 2 and 6 for more information on these tests in animals.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has taken steps to protect you from *N*-nitrosodiphenylamine. If amounts over 100 pounds are released to the environment, the National Response Center of the federal government must be told immediately. According to EPA, the amount of *N*-nitrosodiphenylamine in water (lakes, rivers, etc.) should be limited to 49,000 nanograms (one billionth of a gram) per liter of water or less. At these amounts, EPA estimates that your risk of getting cancer is very low. The amount in drinking water should be 700 micrograms (one millionth of a gram) per liter or less.

Chapter 7 contains more information on recommendations to protect human health.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

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 of the toxicology of *N*-nitrosodiphenylamine and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for *N*-nitrosodiphenylamine based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of *N*-nitrosodiphenylamine are indicated in Figure 2-1. Because cancer effects could occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2. HEALTH EFFECTS

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to *N*-nitrosodiphenylamine.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal/ocular effects in humans or animals after inhalation exposure to *N*-nitrosodiphenylamine.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to *N*-nitrosodiphenylamine.

Rats exposed to 350-400 mg/m³ Vulkalent A (*N*-nitrosodiphenylamine) dust for 2 hours per 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.

2.2.1.3 Immunological Effects

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

Reduced phagocytic activity of the leukocytes was reported in rats exposed to 350-400 mg/m³ Vulkalent A (*N*-nitrosodiphenylamine) dust for 2 hours per 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 2.2.1.2.

2.2.1.4 Neurological Effects

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

A lengthening of the chronaxie of the extensors of the rear extremities was observed in rats exposed to 350-400 mg/m³ Vulkalent A (*N*-nitrosodiphenylamine) dust for 2 hours per 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 2.2.1.2.

2. HEALTH EFFECTS

No studies were located regarding the following health effects in humans or animals after inhalation exposure to *N*-nitrosodiphenylamine:

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to *N*-nitrosodiphenylamine.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to *N*-nitrosodiphenylamine.

Only two studies on the acute oral toxicity of *N*-nitrosodiphenylamine in animals were located. Acute oral LD₅₀ values of 3,000 mg/kg 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 per 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

2. HEALTH EFFECTS

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.

All reliable LOAEL values for death in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans after oral exposure to *N*-nitrosodiphenylamine. The highest NOAEL values and all reliable LOAEL values for systemic effects in rats and mice following acute, intermediate, and chronic exposure are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. 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).

Cardiovascular Effects. No treatment-related histological effects of the heart 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.

Gastrointestinal Effects. 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.

Hematological Effects. 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). No functional studies were performed that might provide data supporting the histological evidence.

TABLE 2-1. Levels of Significant Exposure to N-Nitrosodiphenylamine - Oral

Key to figure ^a	Species	Route	Exposure duration/frequency	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE								
Systemic								
1	Mouse	(G0)	4 d 1x/d	Hepatic	350			Nishie et al. 1972
INTERMEDIATE EXPOSURE								
Death								
2	Rat	(F)	8-11 wk 7d/wk ad lib				800 (2/5 died)	NCI 1979
Systemic								
3	Rat	(F)	8-11 wk	Other	150	200 (>10% reduction in body weight)		NCI 1979
CHRONIC EXPOSURE								
Death								
4	Rat	(F)	100 wk 7d/wk				200 (30% mortality in females)	NCI 1979
5	Mouse	(F)	98- 101 wk 7d/wk				711 (38% mortality in females)	NCI 1979

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
6	Rat	(F) 100 wk 7d/wk	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal	200 200 200 200 200 200	50 (bladder epithelial hyperplasia)	200 (squamous metaplasia)	Cardy et al. 1979; NCI 1979
			Derm/oc		200 (corneal opacity in males)		
					50 (corneal opacity in females)		
			Other		50 (body weight reduced >10%)		
7	Mouse	(F) 98- 101 wk 7d/wk	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal	2600 2600 2600 2600 2600 2600	301 (inflammation of bladder and bladder epithelial hyperplasia in females)		Cardy et al. 1979; NCI 1979
					1300 (inflammation of bladder and bladder epithelial hyperplasia in males)		
			Derm/oc	2600			
			Other		301 (body weight reduced approximately 40% in females)		
					1300 (body weight reduced approximately 15% in males)		

TABLE 2-1 (Continued)

Key to figure ^a	Species	Exposure duration/frequency	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kd/day)	
Cancer							
8	Rat	(F) 100 wk 7d/wk				200 (CEL - bladder tumors)	Cardy et al. 1979

^aThe number corresponds to entries in Figure 2-1.

ad lib = ad libitum; Cardio = cardiovascular; CEL = Cancer Effect Level; d = day(s); Derm/oc = dermal/ocular; (F) = food; Gastro = gastrointestinal; (GO) = gavage in oil; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

FIGURE 2-1. Levels of Significant Exposure to *N*-Nitrosodiphenylamine - Oral

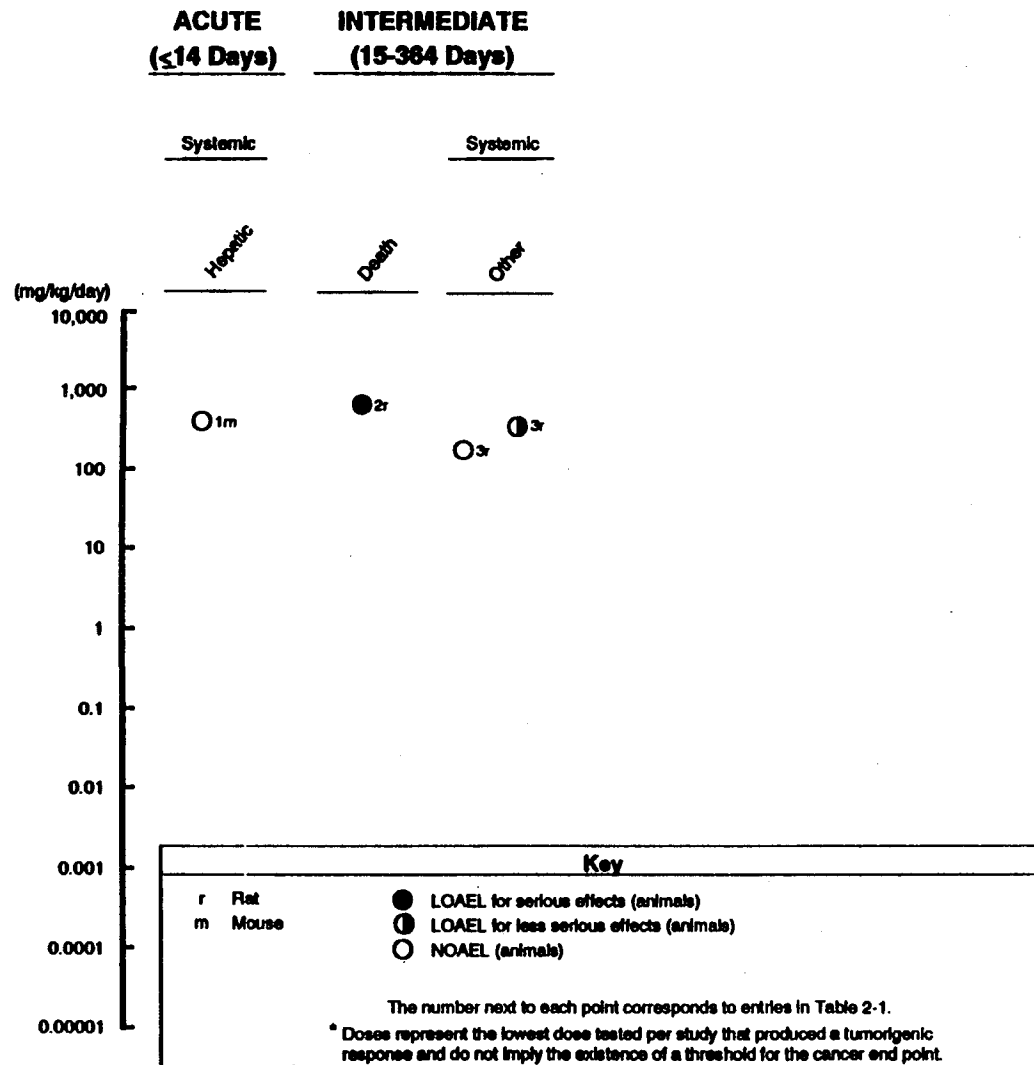
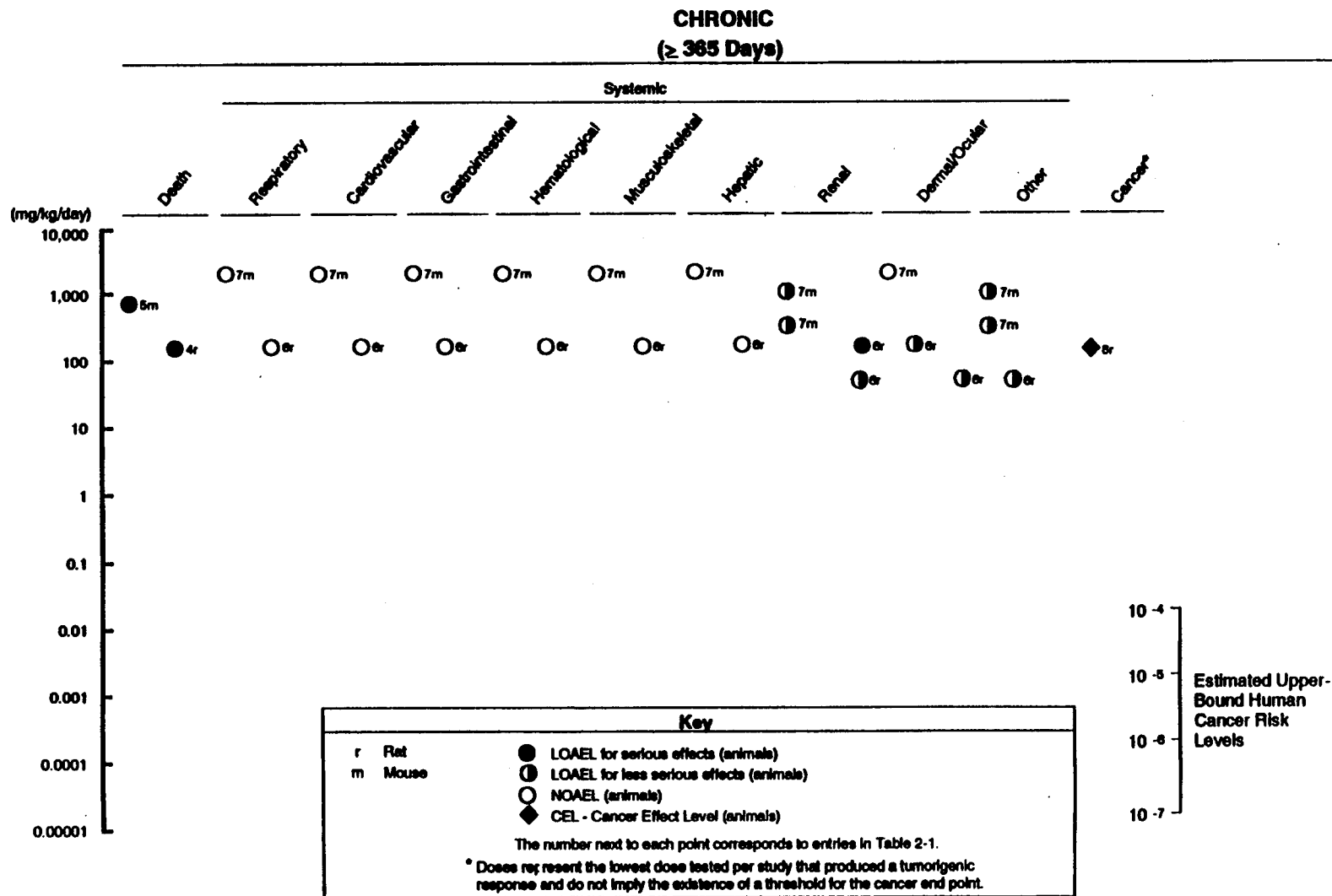


FIGURE 2-1 (Continued)



2. HEALTH EFFECTS

Musculoskeletal Effects. No treatment-related histological effects of the musculoskeletal system were reported in a chronic study of rats and mice administered *N*-nitrosodiphenylamine in their food (NCI 1979). The specific tissues examined were not reported and no studies of function were performed.

Hepatic Effects. 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 cells. Electron microscopy also revealed blebs, hypertrophy, and pleomorphism of the mitochondria. A NOAEL of 350 mg/kg/day was identified for hepatic effects, since no hepatic lesions were revealed by light microscopy.

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*-nitrosodiphenylamine) for 4 months (Zhilova and Kasparov 1966). The limitations of this study are described in the discussion of renal effects in Section 2.2.2.2.

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.

Renal Effects. 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 g-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.

Data from chronic-duration studies in rats and mice indicate that the bladder is a target organ for chronic oral exposure to *N*-nitrosodiphenylamine. 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 2.2.2.8).

2. HEALTH EFFECTS

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 2.2.2.1 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, lowdose, 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.

Dermal/Ocular Effects. 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 authors 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.

Other Systemic Effects. In an intermediate-duration range-finding study, rats showed a decrease in body weight of >10% 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 does not appear to be related to treatment (NCI 1979). No histopathological lesions were observed in the salivary glands, pituitary, adrenals, or thyroid of rats and mice chronically exposed to *N*-nitrosodiphenylamine in their food (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.

2.2.2.3 immunological Effects

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

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.

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2.2.2.4 Neurological Effects

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

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.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in either humans or animals after oral exposure to *N*-nitrosodiphenylamine.

2.2.2.6 Reproductive Effects

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

No treatment-related histological effects of the testes, prostate, uterus, or ovaries 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.

2.2.2.7 Genotoxic Effects

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

Male mice given oral doses of *N*-nitrosodiphenylamine at 500 mg/kg showed no significant signs of testicular deoxyribonucleic acid (DNA) synthesis depression (Friedman and Staub 1976). Negative results were also obtained in a liver DNA fragmentation test in which male Sprague-Dawley rats were exposed to 540 mg/kg of *N*-nitrosodiphenylamine (Brambilla et al. 1987).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to *N*-nitrosodiphenylamine.

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 per 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 of Fischer-344 rats and B6C3F₁ mice (50/sex/strain) with the matched control groups consisting of 20 untreated rats and mice of each sex

2. HEALTH EFFECTS

(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 authors believe that the occurrence of these fibromas was 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. A carcinogenic potency factor for humans (q_1^*) of $4.92 \times 10^3 (\text{mg/kg/day})^{-1}$ has been calculated by EPA (EPA 1980b) based on these findings. Using this q_1^* estimated doses corresponding to individual lifetime upper-bound limits for increased risk of cancer have been calculated. These levels, 2×10^{-2} and 2×10^{-5} mg/kg/day, for increased risk in 1/10,000 and 1/100,000 people, respectively, are displayed graphically in Figure 2-1.

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 B6C3F₁ 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 (18sex/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.

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IARC has concluded that no evaluation of the carcinogenicity of *N*-nitrosodiphenylamine to humans is currently possible, and there is limited evidence for the carcinogenicity of *N*-nitrosodiphenylamine in experimental animals (IARC 1982a; 1987).

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to *N*-nitrosodiphenylamine.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to *N*-nitrosodiphenylamine.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after dermal exposure to *N*-nitrosodiphenylamine.

A single dermal study was located in which mice had 0.1 mL of a 0.1% solution of *N*-nitrosodiphenylamine painted on the intrascapular region once per week for 20 weeks (Iversen 1980). The author 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.

No studies were located regarding the following health effects in humans or animals after dermal exposure to *N*-nitrosodiphenylamine:

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after dermal exposure to *N*-nitrosodiphenylamine.

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.

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2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

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

2.3.1.2 Oral Exposure

Specific information on the rate and extent of absorption of *N*-nitrosodiphenylamine in humans or animals following oral exposure is not available. The appearance of metabolites in the urine of rats and in the serum of guinea pigs following oral administration provides indirect evidence of gastrointestinal absorption of *N*-nitrosodiphenylamine (Appel et al. 19%; Tatsumi et al. 1983). Furthermore, the occurrence of systemic effects in rats and mice in oral carcinogenicity studies suggests that *N*-nitrosodiphenylamine is absorbed through the gastrointestinal tract in these animals (Cardy et al. 1979; NCI 1979).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of *N*-nitrosodiphenylamine in humans after dermal exposure.

The appearance of lung adenomas in a dermal carcinogenicity study with mice provides indirect evidence of dermal absorption of *N*-nitrosodiphenylamine (Iversen 1980).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution of *N*-nitrosodiphenylamine in humans or animals after inhalation exposure.

2.3.2.2 Oral Exposure

No studies were located regarding distribution of *N*-nitrosodiphenylamine in humans or animals after oral exposure.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of *N*-nitrosodiphenylamine in humans or animals after dermal exposure.

2. HEALTH EFFECTS

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

No studies were located regarding metabolism of *N*-nitrosodiphenylamine in humans or animals after inhalation exposure.

2.3.3.2 Oral Exposure

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

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). A single dose of *N*-nitrosodiphenylamine in corn oil (1,000 mg/kg) was administered to female Wistar rats. Nitrate was identified as the major urinary metabolite, while nitrite, diphenylamine, and a monohydroxydiphenylamine were found in smaller amounts. The conclusion is that *N*-nitrosodiphenylamine is denitrosated to diphenylamine and nitric oxide. The nitric oxide is then converted into nitrite and nitrate. Nitrite is 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 conclude 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 2-2.

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).

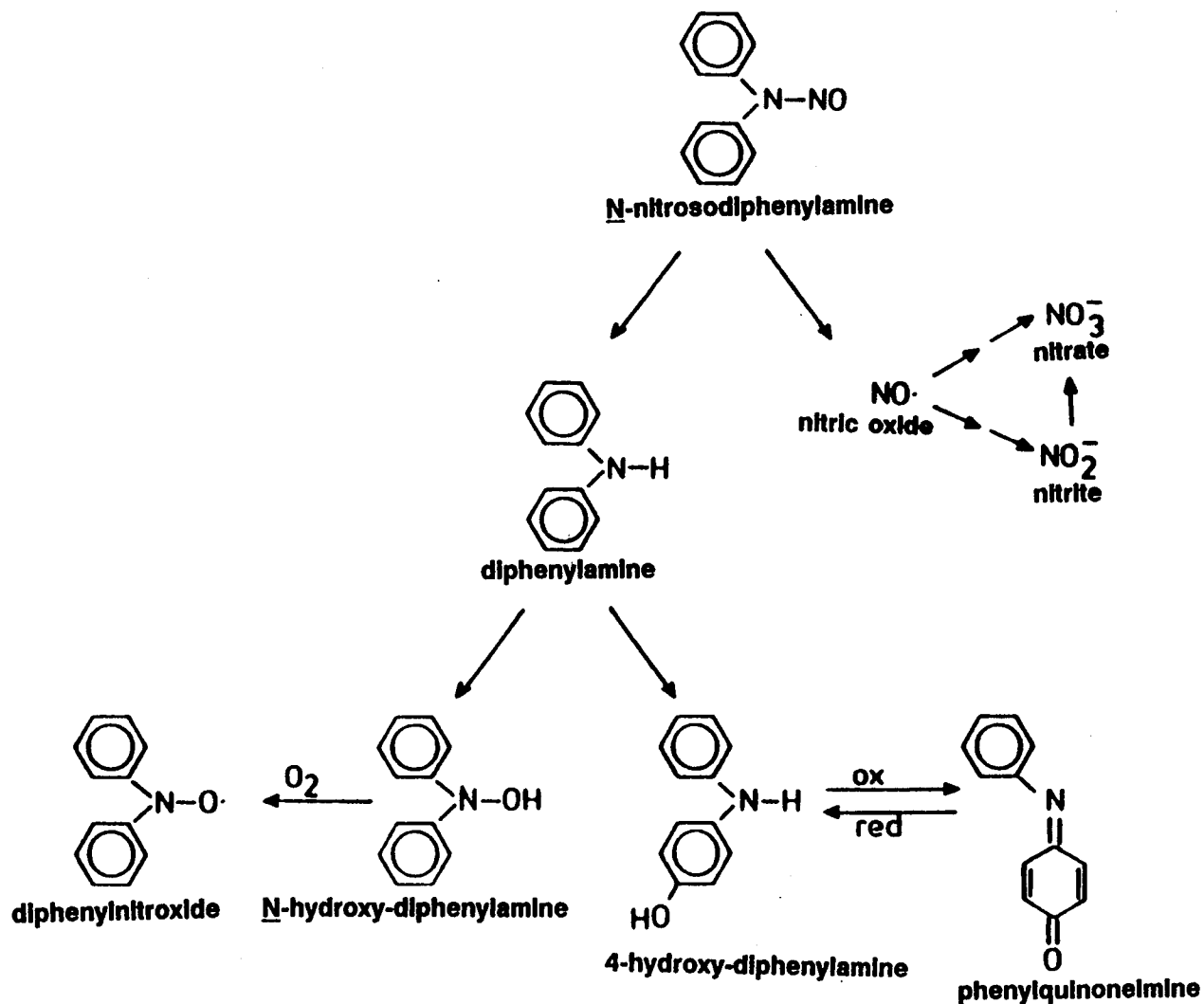
Transnitrosation of proline by *N*-nitrosodiphenylamine occurred in male BD VI rats that were orally administered 28.28 mg/kg *N*-nitrosodiphenylamine and 50 μ mol proline by gavage (Ohshima et al. 1982). The excretion of *N*-nitrosoproline was 15-fold higher than in the controls. Co-administration of 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.

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism of *N*-nitrosodiphenylamine in humans or animals after dermal exposure.

FIGURE 2-2. Metabolic Pathways for N-Nitrosodiphenylamine*



*Adapted from Appel et al. 1987b

2. HEALTH EFFECTS

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion of *N*-nitrosodiphenylamine in humans or animals after inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located regarding excretion of *iV*-nitrosodiphenylamine in humans after oral 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.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of *N*-nitrosodiphenylamine in humans or animals after dermal exposure.

2.3.4.4 Other Routes of Exposure

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.

2.4 RELEVANCE TO PUBLIC HEALTH

The general population is probably not exposed to *N*-nitrosodiphenylamine. *N*-Nitrosodiphenylamine is not a naturally occurring substance and is no longer manufactured in the United States. Although it has been shown to be produced by cultures of microorganisms under laboratory conditions, the extent to which this may occur in the environment is unknown. Available data indicate that it is not likely to be found

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in air, water, or soil except in contaminated areas. The major routes of exposure to *N*-nitrosodiphenylamine for humans living near hazardous waste sites are probably via inhalation of airborne dust particles or ingestion of contaminated water. The result of direct skin contact with soil contaminated with *N*-nitrosodiphenylamine is unclear.

No information was located regarding toxic effects in humans following acute, intermediate, or chronic inhalation exposure to *N*-nitrosodiphenylamine; no occupational studies or case reports were located. Extremely limited animal data suggest that the primary target of inhalation exposure to *N*-nitrosodiphenylamine is the respiratory system. There may also be some immunological and neurological effects.

No information was located regarding toxic effects in humans following acute, intermediate, or chronic oral exposure to *N*-nitrosodiphenylamine. Limited animal studies give data primarily on intermediate and chronic exposure. The target organ of *N*-nitrosodiphenylamine toxicity in rats, and possibly in mice, is the urinary bladder, although minor hepatic and ocular alterations have also been reported.

Chronic studies have reported that tumors occurred in rats and mice following a lifetime exposure to *N*-nitrosodiphenylamine in the diet. At lower doses, tumors were not evident. IARC has concluded that no evaluation of the carcinogenicity of *N*-nitrosodiphenylamine to humans is currently possible, and there is limited evidence for the carcinogenicity of *N*-nitrosodiphenylamine in experimental animals (IARC 1982a; 1587). Negative results have been found in in vivo tests and in vitro gene mutation and chromosome assays. However, there are conflicting results in in vitro human fibroblast DNA damage assays.

No information was located regarding toxic effects in humans following acute, intermediate, or chronic dermal exposure to *N*-nitrosodiphenylamine. Animal studies of poor quality found that *N*-nitrosodiphenylamine can irritate the skin.

No inhalation MRLs were derived because no human data and no reliable animal data exist. For the same reasons, no oral MRLs were derived for intermediate or acute exposure. No oral MRL was derived for chronic exposure because no human data exists and the only effects observed in a reliable animal study (epithelial hyperplasia and squamous metaplasia of the urinary bladder, seen in NCI 1979) were considered to be preneoplastic. No MRLs were derived for acute, intermediate, or chronic dermal exposure to *N*-nitrosodiphenylamine because appropriate MRL methodology has not been developed for this route.

Death. Although there have been no deaths reported in humans from *N*-nitrosodiphenylamine exposure, animal data suggest that fatalities can occur at high doses. Rats have been shown to be more susceptible to *N*-nitrosodiphenylamine toxicity than mice. Chronic studies by NCI (1979) found decreased survival in mice exposed to 711 mg/kg and in rats exposed to 200 mg/kg. An oral rat LD₅₀ of 3,000 mg/kg was reported by Druckrey et al. (1967). There were no studies regarding lethality following inhalation exposure, which is assumed to be a likely route of exposure in humans.

Systemic Effects

Only limited histopathological data from an oral chronic-duration animal study are available for respiratory, cardiovascular, gastrointestinal, hematological, and musculoskeletal effects (NCI 1979). No pathological changes related to treatment were found in tissues from these systems that were analyzed. The significance of exposure in humans cannot be determined from these data.

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Hepatic Effects. Evidence suggests that *N*-nitrosodiphenylamine may cause slight, but not major, damage to the liver at high oral doses in animals. An intermediate-duration study revealed pigmentation of Kupffer's cells in hepatic sinusoids in mice exposed to *N*-nitrosodiphenylamine in the diet. Electron microscopic examination revealed an increased number of smooth endoplasmic reticula distributed among glycogen granules, blebs, hypertrophy, and pleomorphism of the mitochondria in Swiss-Webster mice treated with *N*-nitrosodiphenylamine for 4 days (Nishie et al. 1972). These changes are believed to be representative of liver enzyme induction. Since there were no studies available to evaluate hepatotoxicity following inhalation exposure and there are no human data, judgments regarding the significance of these results for humans cannot be made.

Renal Effects. The urinary bladder is considered the target organ of *N*-nitrosodiphenylamine toxicity in animals. However, no data are available regarding bladder toxicity in humans. Data regarding the effects of acute exposure are not available, but chronic studies have reported toxic effects in the bladder of *N*-nitrosodiphenylamine-treated animals. Epithelial hyperplasia and a small degree of squamous metaplasia were evident in a few rats fed 50 and 200 mg/kg for 100 weeks (NCI 1979). There was a high incidence, of submucosal inflammation, as well as a minimal incidence of epithelial hyperplasia, of the urinary bladder in mice receiving 130-2,600 mg/kg *N*-nitrosodiphenylamine in the diet (NCI 1979). There is no information to indicate whether adverse bladder effects would occur in humans after exposure to *N*-nitrosodiphenylamine. However, other nitrosamines have been shown to adversely affect the bladder, and there is evidence to suggest that bladder cancer rates are higher in the rubber industry (the main industry using *N*-nitrosodiphenylamine) than in the general population (Boyland et al. 1968; NCI 1979).

Dermal/Ocular Effects. A chronic oral study reported grossly observable corneal opacity in 15 of 50 male rats exposed to 200 mg/kg and 16 of 50 female rats exposed to 50 mg/kg (Cardy et al. 1979; NCI 1979). There is no information on whether exposure to this chemical may produce similar effects in humans. People living near hazardous waste sites could be at risk if the water supply were contaminated.

Other Systemic Effects. Decreases in body weight were observed in rats exposed to oral doses of *N*-nitrosodiphenylamine for intermediate and chronic durations, and in mice exposed chronically to the chemical (NCI 1979). The decrease was >10% in rats exposed to levels of ≥ 200 mg/kg/day for 11 weeks, and the decrease was much more significant in females at 800 mg/kg/day (39% decrease relative to controls), the dose at which survival was also significantly decreased. The significance of body weight depression for humans cannot be determined from this study, and no additional data exist by which to assess the relevance to human health.

Immunological Effects. Limited histopathological data from a chronic animal study do not show adverse immunological effects due to oral exposure to *N*-nitrosodiphenylamine (NCI 1979). The relevance to human exposure cannot be determined from these data.

Neurological Effects. Limited histopathological data from a chronic animal study do not show adverse neurological effects due to oral exposure to *N*-nitrosodiphenylamine (NCI 1979). The relevance to human exposure cannot be determined from these data.

Developmental Effects. No studies were located regarding developmental effects in humans or animals after inhalation, oral, or dermal exposure to *N*-nitrosodiphenylamine. Since no information is available, the relevance to human exposure cannot be determined.

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Reproductive Effects. Limited histopathological data from a chronic animal study do not show adverse reproductive effects due to oral exposure to *N*-nitrosodiphenylamine (NCI 1979). The relevance to human exposure cannot be determined from these data.

Genotoxic Effects. 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 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 2-2). 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 (see Table 2-3). A recessive lethal study involving *Drosophila melanogaster* produced a negative result as well (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 *Drosophila 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.

Data from *in vitro* studies using prokaryotic and eukaryotic organisms and cultured mammalian cells are presented in Table 2-3. The response has been negative for the majority of gene mutation studies. However, two *Salmonella* assays detected gene mutations after exposure to metabolically activated *N*-nitrosodiphenylamine (Khudoley et al. 1987; Zielenska and Guttenplan 1988). *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). Tests for DNA damage have produced mixed results among prokaryotes and fungi. Among mammalian hepatocytes, however, the results for DNA damage have been positive. As mentioned previously, only one study involving cultured human fibroblasts was positive for DNA damage (Snyder and Matheson 1985).

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 speculate 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

TABLE 2-2. Genotoxicity of *N*-Nitrosodiphenylamine In Vitro

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<u>Salmonella typhimurium</u> (Ames assay)	Gene mutation	-	No data	Raineri et al. 1981
<u>S. typhimurium</u> (Ames assay)	Gene mutation	+	No data	Khudoley et al. 1987
<u>S. typhimurium</u> (liquid preincubation assay)	Gene mutation	+	No data	Zielenska and Guttenplan 1988
<u>S. typhimurium</u> (modified Ames assay)	Gene mutation	-	-	Probst et al. 1981
<u>S. typhimurium</u> (Ames assay)	Gene mutation	No data	-	Ichinotsubo et al. 1981
<u>S. typhimurium</u> (pour plate and preincubation assay)	Gene mutation	-	No data	Araki et al. 1984
<u>S. typhimurium</u> (Ames assay)	Gene mutation	-	- ^a	Crebelli et al. 1984
<u>Escherichia coli</u> (pour plate and preincubation assay)	Gene mutation	-	No data	Araki et al. 1984
<u>E. coli</u> (reverse mutation preincubation)	Gene mutation	-	-	Matsushima et al. 1981
<u>E. coli</u> (modified Ames assay)	Gene mutation	-	-	Probst et al. 1981
<u>S. typhimurium</u> (<u>umu</u> gene response)	DNA damage	-	No data	Shimada et al. 1989
<u>E. coli</u> (differential killing test)	DNA damage	+	No data	Green 1981
<u>E. coli</u> (differential killing test)	DNA damage	-	+	Tweats 1981
<u>E. coli</u> (rec assay)	DNA damage	-	No data	Mamber et al. 1983
<u>E. coli</u> (disc diffusion and liquid suspension assay)	DNA damage	-	-	Rosenkranz et al. 1981
<u>Bacillus subtilis</u> (rec assay)	DNA damage	-	+	Kada 1981

TABLE 2-2 (Continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Eukaryotic organisms:				
Fungi:				
<u>Schizosaccharomyces pombe</u> (forward mutation assay)	Gene mutation	-	-	Loprieno 1981
<u>Saccharomyces cerevisiae</u> (rep-test)	DNA damage	No data	-	Kassinova et al. 1981
<u>S. cerevisiae</u> (rad assay)	DNA damage	-	+	Sharp and Parry 1981b
<u>S. cerevisiae</u> (ade2 locus assay)	Mitotic crossing-over	-	-	Kassinova et al. 1981
<u>S. cerevisiae</u> (his4, trp5 assay)	Mitotic gene conversion	-	-	Sharp and Parry 1981a
<u>S. cerevisiae</u> (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	-	-	Kuroki et al. 1977
Chinese hamster (V79 cells)	Gene mutation	-	-	Jones and Huberman 1980
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
Rat (hepatocytes)	DNA damage	+	NA	Althaus et al. 1982
Rat (hepatocytes)	DNA damage	+	NA	Probst et al. 1981
Rat (hepatocytes)	DNA damage	+	NA	Sina et al. 1983
Rat (hepatocytes)	DNA damage	+	NA	Bradley et al. 1982
Rat (hepatocytes)	DNA damage	+	NA	Althaus and Pitot 1983

TABLE 2-2 (Continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Mammalian cells (Cont.):				
Chinese hamster (hepatocytes)	DNA damage	+	NA	McQueen et al. 1983
Mouse (hepatocytes)	DNA damage	+	NA	McQueen et al. 1983
Human (fibroblasts)	DNA damage	+	No data	Snyder and Matheson 1985
Human (fibroblasts)	DNA damage	-	No data	Agrelo and Amos 1981
Human (fibroblasts)	DNA damage	-	No data	Martin and McDermid 1981
Chinese hamster (Don cells)	Chromosomal aberrations	No data	+/-	Abe and Sasaki 1977
Chinese hamster (fibroblasts)	Chromosomal aberrations	No data	+/-	Ishidate and Odashima 1977
Chinese hamster (ovary cells)	Sister chromatid exchange	-	-	Evans and Mitchell 1981
Chinese hamster (ovary cells)	Sister chromatid exchange	-	-	Perry and Thomson 1981
Chinese hamster (Don cells)	Sister chromatid exchange	No data	+	Abe and Sasaki 1977
Human (lymphocytes)	Sister chromatid exchange	(+)	No data	Lindahl-Kiessling et al. 1989

^aA positive response was observed after in vitro nitrosation.

- = negative result; + = positive result; (+) = weakly or insignificantly positive; +/- = inconclusive; DNA = deoxyribonucleic acid; NA = not applicable

TABLE 2-3. Genotoxicity of *N*-Nitrosodiphenylamine In Vivo

Species (test system)	End point	Results	Reference
Nonmammalian cells:			
<u><i>Drosophila melanogaster</i></u> (recessive lethal test)	Gene mutation	-	Vogel et al. 1981
Host-mediated assays:			
<u><i>Escherichia coli</i></u> (<i>D. melanogaster</i> host-mediated assay)	DNA damager	+	Knasmuller et al. 1990
Mammalian cells:			
Rat (liver nuclei)	DNA damage	-	Brambilla et al. 1987
Mouse (bone marrow cells)	Micronuclei	-	McFee et al. 1989
Mouse (bone marrow cells)	Micronuclei	-	Salamone et al. 1981
Mouse (bone marrow cells)	Micronuclei	-	Tsuchimoto and Matter 1981
Mouse (testicular cells)	DNA synthesis inhibition	-	Friedman and Staub 1976
Mouse (cauda epididymis)	Abnormal spermal morphology	-	Topham 1981

- = negative result; DNA = deoxyribonucleic acid

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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 (Crchelli et al. 1984). Alternatively, transnitrosation could occur from *N*-nitrosodiphenylamine to another compound. Evidence exists for transnitrosation by *N*-nitrosodiphenylamine *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.

Cancer. The only neoplastic lesion shown to be significantly correlated with *N*-nitrosodiphenylamine exposure was an increase of bladder transitional cell carcinoma in rats (Cardy et al. 1979; NCI 1979). The difference was significant at only the higher of the two doses tested. Increases in other neoplastic lesions, including cancers of the integumentary system and liver, were found in orally exposed rats and mice (Cardy et al. 1979); Innes et al. 1969; NCI 1968, 1979), but the increases were not statistically significant. Some early studies reported no treatment-related tumors in orally exposed rats (Argus and Hoch-Ligeti 1961; Druckrey et al. 1967); however, the bladder was not routinely examined in these studies. A nonsignificant increase in reticulum cell sarcomas was reported in 28-day-old mice subcutaneously injected with 1.000 mg/kg *N*-nitrosodiphenylamine and observed for 18 months (Innes et al. 1969; NCI 1968). EPA has calculated a q_1^* of 4.92×10^{-3} (mg/kg/day)⁻¹ based on the bladder cancer in rats. According to EPA's Integrated Risk Information System (IRIS) database, *N*-nitrosodiphenylamine is a probable human carcinogen (class B2). According to IARC, *N*-nitrosodiphenylamine is a level 3 chemical, meaning there is not enough data to determine the potential carcinogenicity of this compound (IARC 1987). Given the equivocal nature of the data from most of these studies and the lack of information for humans, no statements regarding the possible carcinogenicity of *N*-nitrosodiphenylamine in humans can be made.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to *N*-nitrosodiphenylamine are discussed in Section 2.5.1.

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

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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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by *N*-nitrosodiphenylamine are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to *N*-Nitrosodiphenylamine

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, ninety-six 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.

2.5.2 Biomarkers Used to Characterize Effects Caused by *N*-Nitrosodiphenylamine

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 (50 mg/kg/day), and the effect is only observable post-mortem. 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.

2.6 INTERACTIONS WITH OTHER CHEMICALS

N-Nitrosodiphenylamine was mutagenic in 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.

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2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to *N*-nitrosodiphenylamine than will most persons exposed to the same level of *N*-nitrosodiphenylamine in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

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

The induction of the hepatic microsomal enzymes, such as the mixed function oxidases, by *N*-nitrosodiphenylamine may affect the metabolism of some drugs and alcohol. The efficacy of prescription drugs may be altered because of the increased rate of metabolism.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to *N*-nitrosodiphenylamine. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to *N*-nitrosodiphenylamine. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Human exposure to *N*-nitrosodiphenylamine may occur by inhalation, ingestion, or dermal contact. The major routes of exposure to *N*-nitrosodiphenylamine for individuals living near hazardous waste sites are inhalation of airborne dust particles or ingestion of contaminated water. There is little actual experience in treatment of persons exposed to this compound. However, general recommendations for reducing absorption of *N*-nitrosodiphenylamine following acute exposure include removal from the source of exposure. In the case of inhalation exposure, the patient is moved to fresh air. If the eyes are exposed, they are irrigated with copious amounts of water. If dermal contact has occurred, contaminated clothing is removed and the exposed area is thoroughly washed with soap and water (HSDB 1992).

Following oral exposure, prevention of the absorption of *N*-nitrosodiphenylamine is imperative. The method used for reducing peak absorption is dependent on the amount ingested, the time since ingestion, and the patient's condition. Emesis may be considered unless the patient is comatose, is convulsing, or has lost the gag reflex. Caution concerning the use of this method stems from the risk of aspiration of vomit into the lungs. Gastric lavage may be used as an alternative to emesis. Endotracheal intubation may be performed to reduce the risk of aspiration pneumonia. Administration of a charcoal slurry, aqueous or mixed with saline cathartic or sorbitol, has also been suggested (HSDB 1992).

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2.8.2 Reducing Body Burden

There are no data regarding methods to enhance elimination of *N*-nitrosodiphenylamine. As in methods used with other chemicals, hemodialysis might be useful following acute intoxication, but no data were located regarding this possibility. After a single oral dose of *N*-nitrosodiphenylamine, the maximum urinary excretion of its metabolites (nitrate and nitrite) was found within 24-48 hours. The metabolites of *N*-nitrosodiphenylamine have been associated with hepatic and renal toxicity. No information was located on the bioaccumulation of *N*-nitrosodiphenylamine or its metabolites. However, there are data that indicate *N*-nitrosodiphenylamine has a low potential for bioaccumulation, based on the log K_{OW} (see Section 53.1).

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Based on a multicompartamental pharmacokinetic model, Kadlubar et al. (1991) predicted that DNA adduct formation by 4-aminodiphenyl in the bladder epithelial cells would decrease with increasing frequency of voiding. A similar situation may exist with *N*-nitrosodiphenylamine. Since this compound causes bladder cancer in rats (Cardy et al. 1979; NCI 1979), increased voiding frequency might similarly mitigate its effects.

Like *N*-nitrosodiphenylamine, its metabolite diphenylamine has been associated with nephrotoxic effects. However, no information on the mechanism of action for nephrotoxicity of either chemical was located. Results from Wakabayashi et al. (1982) suggest that the carcinogenic effects of *N*-nitrosodiphenylamine may be due to interaction with other compounds. This study found that although *N*-nitrosodiphenylamine is not mutagenic in *Salmonella typhimurium* TA98, it is mutagenic in the presence of norharman (β -carboline). Norharman has been found in a tobacco smoke, a tryptophan pyrolysate, and cooked foods. The effect was not due to transnitrosation, since a similar effect was seen with diphenylamine. However, other authors have suggested that transnitrosation of or by *N*-nitrosodiphenylamine could be mechanistically important. Since the mechanism of *N*-nitrosodiphenylamine carcinogenicity is unknown, no methods can be suggested for interfering with it.

Since there is no evidence that *N*-nitrosodiphenylamine bioaccumulates, the best mitigation would be to reduce absorption. If the carcinogenic metabolite were identified, it would be possible to consider interfering with its generation. However the metabolite is not known, and the metabolic enzymes involved have not been identified.

2.9 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 the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of *N*-nitrosodiphenylamine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health 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.

2. HEALTH EFFECTS

2.9.1 Existing Information on Health Effects of *N*-Nitrosodiphenylamine

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to *N*-nitrosodiphenylamine are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of *N*-nitrosodiphenylamine. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as “data needs” information (i.e., data gaps that must necessarily be filled).

No human data were located for *N*-nitrosodiphenylamine. The animal data on this chemical are limited. Most of the studies investigate the potential carcinogenicity of *N*-nitrosodiphenylamine following oral exposure; however, one dermal study provides information on the toxicity and carcinogenicity of the compound by this route. Oral data on toxicity come primarily from a carcinogenicity study in rats and mice conducted by the National Cancer Institute (NCI). Most of the data are based on extensive histological examination of tissues from exposed animals, although body weight and survival information were also provided. Several studies on the oral carcinogenicity of the chemical were located.

2.9.2 Identification of Data Needs

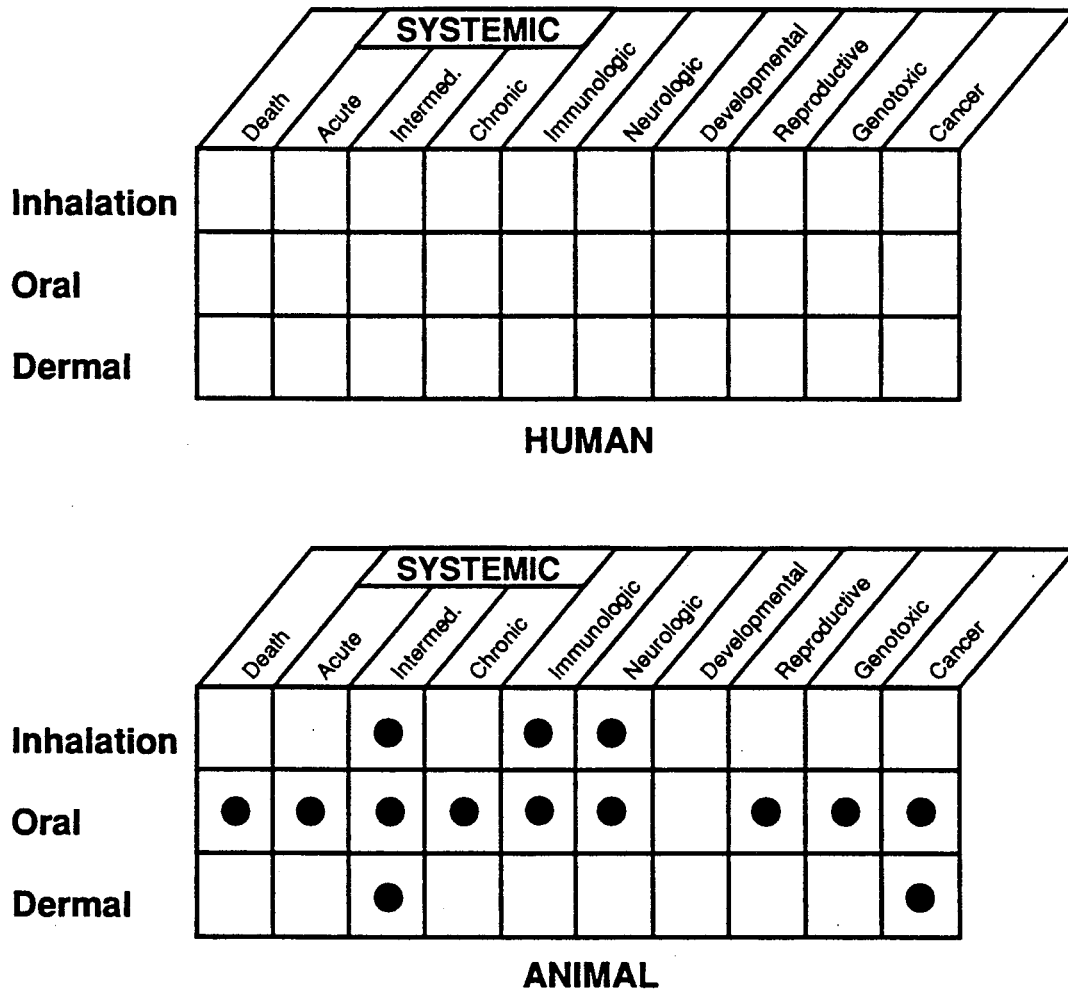
Acute-Duration Exposure. No cases of accidental or intentional poisonings were available to evaluate acute exposure in humans. There was a paucity of animal data, especially in animals exposed via inhalation or dermal routes. Enzyme induction in the liver was observed in mice receiving *N*-nitrosodiphenylamine by oral gavage for 4 days (Nishie et al. 1972). An acute oral LD₅₀ was established for rats, but no inhalation LC₅₀ or dermal LD₅₀ studies were available (Druckrey et al. 1967). Insufficient information prevented the derivation of an acute-duration oral MRL. Pharmacokinetic data were not available to support the identification of target organs across routes of exposure. Inhalation and dermal data in mammalian species would be useful for determining possible effects of acute exposures in the population. The potential exists for the occurrence of acute exposure to *N*-nitrosodiphenylamine in populations near hazardous waste sites and accidental spills.

Intermediate-Duration Exposure. 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). 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 identify target organs and use several different animal species would be very helpful in determining potential adverse health effects in humans.

Chronic-Duration Exposure and Cancer. 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 corneal 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.

2. HEALTH EFFECTS

FIGURE 2-3. Existing Information on Health Effects of *N*-Nitrosodiphenylamine



● Existing Studies

2. HEALTH EFFECTS

No information was available on the carcinogenic potential of *N*-nitrosodiphenylamine in humans. Although conflicting cancer results have been seen in chronic bioassay there are enough oral exposure data to indicate that this chemical is carcinogenic in rats, primarily in the bladder. The only pertinent study of carcinogenicity following dermal exposure in mice lacked information that is critical for a thorough evaluation. The histological examinations were limited and no controls were used. Kinetic data suggest that *N*-nitrosodiphenylamine may be absorbed through the skin (Iversen 1980). More data concerning the actual risk of cancer from dermal exposure are needed since a possible route of exposure to humans is from contaminated soil.

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. 1987); 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. Reproductive organ pathology could be examined in a 90-day study recommended under intermediateduration exposure.

Developmental Toxicity. There were no studies evaluating developmental effects in humans or animals. Data regarding potential developmental effects would be useful. Information is also lacking on the kinetics of *N*-nitrosodiphenylamine, such as its distribution and whether it is likely to cross the placenta.

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.

Epidemiological and Human Dosimetry Studies. There are no epidemiological studies available on *N*-nitrosodiphenylamine. 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. Rubber workers in cohort studies could be used as a potentially exposed population, although the generally low levels of the chemical that have been measured in the occupational

2. HEALTH EFFECTS

air space would make quantifying this relationship difficult. 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 gave indirect evidence that *N*-nitrosodiphenylamine was absorbed following administration of a single oral dose (Appel et al. 1984; Tatsumi et al. 1983) and during chronic oral exposure (Cardy et al. 1979; 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. Chronic oral studies have reported alterations in specific organs in animals (Cardy et al. 1979; 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.

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.

Mitigation of Effects. 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

2. HEALTH EFFECTS

that orally administered *N*-nitrosodiphenylamine is absorbed (Appel et al. 1984; Cardy et al. 1979; 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 5.3.1). 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.

2.9.3 On-going Studies

No on-going studies were located for *N*-nitrosodiphenylamine.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

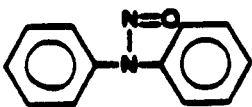
The chemical identity of *N*-nitrosodiphenylamine is shown in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of *N*-nitrosodiphenylamine are shown in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of *N*-Nitrosodiphenylamine

Characteristic	Information	Reference
Chemical name	<i>N</i> -Nitrosodiphenylamine	HSDB 1990
Synonym(s)	Benzenamine; diphenyl-nitrosamine; diphenylamine, <i>N</i> -nitroso; <i>N</i> -nitroso- <i>N</i> -phenylaniline; diphenyl- <i>N</i> -nitrosamine; <i>N,N</i> -diphenyl-nitrosamine; NDPA; NDPHA; nitrous diphenylamide	OHM/TADS 1990
Registered trade name(s)	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 ₂ O	HSDB 1990
Chemical structure		IARC 1982a
Identification numbers:		
CAS registry	86-30-6	HSDB 1990
NIOSH RTECS	JJ9800000	HSDB 1990
EPA hazardous waste	No data	
OHM/TADS	8300186	OHM/TADS 1990
DOT/UN/NA/IMCO shipping	No data	
HSDB	2875	HSDB 1990
NCI	C02880	HSDB 1990

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. 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	
Odor threshold	No data	
Solubility:		
Water at 25°C	40 mg/L	EPA 1982a
Organic solvent(s)	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	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 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), the two facilities in the United States that manufactured or processed *N*-nitrosodiphenylamine in 1988 were Arkansas Eastman Company (Batesville, Arkansas) and Uniroyal Chemical Company, Inc. (Geismar, Louisiana) (see Table 4-1) (TRI88 1990). The data listed in the TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. In 1990, however, Uniroyal Chemical Company, Inc., was reportedly the only facility in the United States producing *N*-nitrosodiphenylamine (SRI 1990).

4.2 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.

4.3 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*-nitrosodiphenylamine during vulcanization cause porosity in thick cross-section extrusions; *N*-nitrosodiphenylamine 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-aryl or dialkyl-substituted *p*-phenylenediamine 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).

4.4 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

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

rotary kiln or fluidized bed incineration with scrubbing equipment (NO_x scrubber) or acid hydrolysis (HSDB 1990).

TABLE 4-1. Facilities That Manufacture or Process N-Nitrosodiphenylamine^a

Facility	Location ^b	Range of maximum amounts on site in pounds	Activities and uses
Arkansas Eastman Co.	Batesville, AR	1,000-9,999	Produce; for on-site use/processing; as a reactant
Uniroyal Chemical Co. Inc.	Geismar, LA	10,000-99,999	Produce; for on-site use/processing

^aDerived from TRI88 (1990)

^bPost office state abbreviations used

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

N-Nitrosodiphenylamine is used as a vulcanization retardant in rubber compounds used to make tires. There is some evidence to suggest it is produced by microorganisms in the environment. In 1988 it was being produced and used by two manufacturers in the United States (TRIM 1990). Currently, only one manufacturer in the United States produces and uses *N*-nitrosodiphenylamine (SRI 1090). Releases to the environment occur from effluent discharges generated from its production and use and from leachate at hazardous waste sites.

N-Nitrosodiphenylamine exists in the vapor phase in the atmosphere. It is subject to volatilization from water. Significant leaching is not expected to occur because of its low soil mobility. In the aquatic environment, *N*-nitrosodiphenylamine partitions from the water column to sediments and suspended particulate organic matter. It is subject to photolysis and biodegradation. Biomagnification in the aquatic food chain is not considered to be a major environmental fate process since *N*-nitrosodiphenylamine has a low potential for bioaccumulation in aquatic organisms.

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 has been identified in 172 of the 1,300 NPL hazardous waste sites (HAZDAT 1992). The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

N-Nitrosodiphenylamine may be 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.

5.2.2 Water

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. *N*-Nitrosodiphenylamine was detected in an estimated 3.6% of the groundwater and 0.71% of the surface water samples analyzed at NPL sites included in EPA's Contract Laboratory Program (CLP). Estimated geometric mean concentrations of 7.8 ppb in groundwater and 9.4 ppb in surface water were reported in the positive samples (CLPSD 1989). Note that the information used from the CLP Statistical Database (CLPSD) includes data from NPL sites only. According to the Toxics Release Inventory (TRI), an estimated total of at least 27 pounds of *N*-nitrosodiphenylamine was released to water from manufacturing and processing facilities in the United States in 1988 (TRI88 1990). Table 5-1 lists the amounts released from these facilities. The data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process N-Nitrosodiphenylamine^a

Facility	Location ^b	Reported amounts released in pounds						
		Air	Underground injection	Water	Land	Total environment ^c	POTW transfer	Off-site waste transfer
Arkansas Eastman Co.	Batesville, AR	0	0	27	0	27	0	300
Uniroyal Chemical Co. Inc.	Geismar, LA	0	34,000	0	0	34,000	0	0
Totals		0	34,000	27	0	34027	0	300

^aDerived from TRI88 (1990)

^bPost office state abbreviations used

^cThe sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

POTW = publicly owned treatment works

5. POTENTIAL FOR HUMAN EXPOSURE

5.2.3 Soil

N-Nitrosodiphenylamine potentially can be released to soil from leachate at hazardous waste sites, underground injection wells, or off-site waste transfer (TRISS 1990). There is also evidence suggesting it might be produced by some microorganisms under certain environmental conditions (Ayanaba and Alexander 1973). However, *N*-nitrosodiphenylamine was not detected in soil samples at any of the NPL sites included in the CLPSD (CLPSD 1989).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

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).

N-Nitrosodiphenylamine is soluble in water (40 mg/L) (EPA 1982a). The Henry's law constant for *N*-nitrosodiphenylamine (6.6×10^{-4} atm-m³/mol) (EPA 1982a) indicates that volatilization from water will be a slow but significant transport process (Lyman et al. 1982).

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.

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 less than 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).

5.3.2 Transformation and Degradation

5.3.2.1 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).

5. POTENTIAL FOR HUMAN EXPOSURE

5.3.2.2 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 11 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.

5.3.2.3 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).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

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

5.4.2 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).

5.4.3 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).

5.4.4 Other Environmental Media

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

5. POTENTIAL FOR HUMAN EXPOSURE

5.5 GENERAL POPULATION AND OCCUPATIONAL 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 $\mu\text{g}/\text{m}^3$ (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, and three tire plants (Fajen et al. 1979, 1980).

Levels of *N*-nitrosodiphenylamine ranging from not detectable to 12.35 $\mu\text{g}/\text{m}^3$ (1.5 ppb) in workplace air samples were detected 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 detected in the breathing zone of curing press operators at a Uniroyal plant in Mishawaka, Indiana (NIOSH 1982).

5.6 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.

5.7 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 health effects (and techniques for developing methods to determine such health effects) of *N*-nitrosodiphenylamine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the

5. POTENTIAL FOR HUMAN EXPOSURE

identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

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, and Release and Disposal. *N*-Nitrosodiphenylamine is currently produced and used by one manufacturer in the United States (SRI 1990). 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.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1988, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

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 levels were, 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

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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.

Exposure Registries. No exposure registries for *N*-nitrosodiphenylamine were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this substance.

5.7.2 On-going Studies

No on-going studies were located for *N*-nitrosodiphenylamine.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring *N*-nitrosodiphenylamine in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify *N*-nitrosodiphenylamine. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect *N*-nitrosodiphenylamine in environmental samples are the methods approved by federal organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Analytical methods exist for measuring *N*-nitrosodiphenylamine and its metabolites in the serum, blood, and urine of animals. However, because the data are very limited, a comparison of the methods cannot be made. The methods used are differential pulse polarography (DPP), thermal energy analyzer (TEA) (Pylypiw and Harrington 1981), high-performance liquid chromatography (HPLC) combined with detection by ultraviolet (UV) or UV-visible (UV-VIS) detection, or gas chromatography (GC) with detection by mass spectrometry (MS) (Appel et al. 1984; Tatsumi et al. 1983). Preparation steps for DPP and TEA include the addition of a buffer to the sample, which is then passed-through a *Sep-Pac*® cartridge. The cartridge is washed with methanol (for DPP) or methylene chloride [for TEA], diluted with a buffer, concentrated under nitrogen (for TEA), and analyzed by DPP or TEA. Results were included only for *N*-nitroso-*N*-methylaniline. The authors stated that results for *N*-nitrosodiphenylamine were comparable (Pylypiw and Harrington 1981). Detection limits obtained using DPP analysis for blood, serum, and urine were 0.5, 0.05, and 0.1 ppm, respectively. Recovery was good for all sample types, ranging from 85% to 101%; precision was excellent (<5%). Better sensitivity was obtained using TEA rather than the DPP. Detection limits obtained using TEA analysis for blood and serum were both 0.01 ppm. Recovery was good for both sample types, ranging from 82% to 96%; precision was excellent (<3%) (Pylypiw and Harrington 1981). No information was given on sensitivity, precision, or recovery using HPLC/UV, HPLC/UV-VIS, or GC/MS (Appel et al. 1984; Tatsumi et al. 1983). Table 6-1 gives a summary of the methods available for analyzing for *N*-nitrosodiphenylamine in biological materials.

6.2 ENVIRONMENTAL SAMPLES

Methods exist for measuring *N*-nitrosodiphenylamine in air, water, soil, and foods. The most common methods used are GC and HPLC combined with detection by TEA, flame-ionization detector (FID), or MS. Methods for analyzing for *N*-nitrosodiphenylamine in environmental samples are summarized in Table 6-2.

N-Nitrosodiphenylamine is measured in air samples using GC/TEA and HPLC/TEA (NIOSH 1983). Air samples are collected with a ThermoSorb®/N air sampling cartridge designed specifically for collection of airborne *N*-nitrosamines. A polar solvent (acetone, methanol, or methanol/dichloromethane) is then backflushed through the cartridge. The eluate is examined using GC/TEA and HPLC/TEA. The TEA has been specifically designed for the detection of *N*-nitroso compounds in the ppb range. TEA is not totally specific for *N*-nitroso compounds. Additional confirmation of positive results can be obtained by the use of HPLC/TEA. Specific sensitivity, recovery, and precision data were not reported. A group in Czechoslovakia reported 100% recovery of *N*-nitrosodiphenylamine from air samples using a silica gel

TABLE 6-1. Analytical Methods for Determining *N*-Nitrosodiphenylamine in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, serum, urine	A buffered solution containing the sample is passed through a Sep-Pac® cartridge. The cartridge is washed with methanol or methylene chloride, concentrated under nitrogen (for TEA).	DPP	0.5 ppm (blood), 0.05 ppm (serum), 0.1 ppm (urine)	93-99 (blood), 85-90 (serum)	Pylypiw and Harrington 1981 ^a
		TEA	0.01 ppm (blood and serum)	82-84 (blood), 88-90 (serum)	
Blood (<i>N</i> -nitrosodiphenylamine and metabolites)	Blood sample centrifuged; serum extraction.	HPLC/UV GC/MS	NR NR	NR NR	Tatsumi et al. 1983
Urine (metabolites)	Extracted with dichloromethane; concentrated.	HPLC/UV-VIS	NR	NR	Appel et al. 1984

^aActual data are for *N*-nitroso-*N*-methylaniline. Authors indicate that *N*-nitrosodiphenylamine yielded comparable results.

DPP = differential pulse polarography; GC = gas chromatography; HPLC = high-performance liquid chromatography; MS = mass spectrometry; NR = not reported; TEA = thermal energy analysis; UV = ultraviolet detection; UV-VIS = ultraviolet-visible detection

TABLE 6-2. Analytical Methods for Determining N-Nitrosodiphenylamine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Samples collected with ThermoSorb®/N air sampling cartridge. Extraction with acetone, methanol, or methanol/dichloromethane.	GC/TEA HPLC/TEA	NR	NR	Fajen et al. 1979, 1980; NIOSH 1983
Waste water	Extraction with methylene chloride, column clean-up with Alumina®; dry over sodium sulfate; concentrate; solvent exchange to methanol.	GC/TEA GC/FID	NR	86 (TEA) 98 (FID)	Rhoades et al. 1980
Water	Extraction with methylene chloride, column clean-up, dry over sodium sulfate; concentrate; solvent exchange to methanol.	GC/MS HRGC/MS		68 (GC/MS) 89 (HRGC/MS)	Eichelberger et al. 1983
Soil	Extraction with appropriate solvent; concentration.	GC/TEA HPLC/TEA	NR	NR	NIOSH 1983
Foods (vodka)	Extraction with dichloromethane; dry over sodium sulfate; concentrate; redissolve in dichloromethane.	HPLC/TEA	NR	60	Fine et al. 1976

FID = flame ionization detection; GC = gas chromatography; HPLC = high-performance liquid chromatography; HRGC = high-resolution gas chromatography; MS = mass spectrometry; NR = not reported; TEA = thermal energy analysis

6. ANALYTICAL METHODS

column for collecting the sample and eluting with ethanol (Mejstrik et al. 1989). Precision and sensitivity were not reported, and experimental details were limited.

N-Nitrosodiphenylamine is measured in water samples using GC/TEA, HPLC/TEA, GC/FID, and high-resolution gas chromatography (HRGC)/MS (Eichelberger et al. 1983; NIOSH 1983; Rhoades et al. 1980).

Sample preparation steps involve extraction with methylene chloride, column clean-up with Florisil[®] or Alumina[®], drying over sodium sulfate, and concentration in a Kuderna-Danish[®] evaporator with solvent exchange to methanol. *N*-Nitrosodiphenylamine decomposes thermally in the hot gas chromatograph injection port to nitric oxide and diphenylamine and is measured as diphenylamine. Therefore, this compound cannot be accurately measured in a sample unless it is first separated from diphenylamine prior to GC. Florisil[®] or Alumina[®] column clean-up is usually employed for this separation (Eichelberger et al. 1983; Rhoades et al. 1980). Average recovery using GC/TEA without Alumina[®] column clean-up was 86% while average recovery using GC/FID with Alumina[®] column clean-up was 98%. Sensitivity was not reported (Rhoades et al. 1980). Recovery using GC/MS was 68%. Greater accuracy was obtained using HRGCMS (89%). Precision for both of these methods was adequate (13-14%). Sensitivity was not reported (Eichelberger et al. 1983).

N-Nitrosodiphenylamine can be measured in soil using GC/TEA and HPLC/TEA (NIOSH 1983). Sample preparation involves extraction with an appropriate solvent and concentration. Precision, accuracy, and sensitivity for these methods were not reported.

N-Nitrosodiphenylamine has been measured in foods using HPLC/TEA (Fine et al. 1976). Preparation steps for liquor samples involve extraction with dichloromethane, drying over sodium sulfate, concentration under a vacuum, and redissolving in dichloromethane. Recovery for this method is fair (60%). Sensitivity and precision were not reported.

6.3 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 health effects (and techniques for developing methods to determine such health effects) of *N*-nitrosodiphenylamine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health 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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No human studies were located regarding methods for determining levels of the compound in blood, serum, or urine. Animal data on the determination of *N*-nitrosodiphenylamine and its metabolites in these media are very limited (Appel et al. 1984; Pylypiw and Harrington 1981; Tatsumi et al. 1983). Sensitivity is in the ppm range (Pylypiw and

6. ANALYTICAL METHODS

Harrington 1981). More information on the sensitivity, accuracy, and precision obtained for these methods is needed to evaluate the value of using levels of *N*-nitrosodiphenylamine as an indicator of exposure. The lack of human data for evaluation of these methods makes it difficult to assess whether these methods are sensitive for measuring background levels in the population and levels at which health effects might occur.

Currently, no biomarkers of effect have been identified for *N*-nitrosodiphenylamine.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media.

Data on the methods used for determining *N*-nitrosodiphenylamine in air (Mejstrik et al. 1989), water (Eichelberger et al. 1983; NIOSH 1983; Rhoades et al. 1983), soil (NIOSH 1983), and foods (Fine et al. 1976) are very limited. More information on the accuracy, precision, and sensitivity for these methods is needed to determine if these methods are sensitive enough to measure background levels in the environment, as well as levels at which health effects might occur. Research investigating the relationship between levels measured in air, water, soil, and foods and observed health effects could increase our confidence in existing methods and/or indicate where improvements are needed.

6.3.2 On-going Studies

No on-going studies were located for *N*-nitrosodiphenylamine.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding *N*-nitrosodiphenylamine in air, water, and other media are summarized in Table 7-1.

EPA has not derived an inhalation reference concentration or an oral reference dose for *N*-nitrosodiphenylamine (IRIS 1990). The quantitative estimate of carcinogenic risk from oral exposure is 4.9×10^{-3} mg/kg/day (IRIS 1990), based on transitional cell carcinomas of the bladder in rats exposed to *N*-nitrosodiphenylamine in the diet (NCI 1979). *N*-Nitrosodiphenylamine has a weight-of-evidence classification of B2, which indicates a probable human carcinogen (IRIS 1990).

N-Nitrosodiphenylamine is on the list of chemicals appearing in “Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986” (EPA 1987, 1988).

7. REGULATIONS AND ADVISORIES

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

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
IARC	Carcinogenic classification	Group 3 ^a	IARC 1987
<u>NATIONAL</u>			
Regulations:			
a. Water:			
EPA OSW	Designated as a toxic pollutant under Section 307(a)(1) of the Clean Water Act; detected in treated effluents from a small number of discharge sources and uniquely related to those sources	Yes	EPA 1989b (40 CFR 401.15); EPA 1987d
	Hazard ranking	Low	EPA 1986b
	Groundwater monitoring requirement	Yes	EPA 1987b (40 CFR 264, Appendix IX); EPA 1987c
b. Other:			
EPA OERR	Reportable quantity	100 pounds	EPA 1985a (40 CFR 302); EPA 1985b
EPA OTS	Toxic chemical release reporting; Community Right-to-Know	Yes	EPA 1988 (40 CFR 372); EPA 1987e
Guidelines:			
a. Water:			
	Ambient water quality criteria for protection of human health ^b		
	Ingesting water and organisms:		EPA 1980b
	10 ⁻⁵	49,000 ng/L	
	10 ⁻⁶	4,900 ng/L	
	10 ⁻⁷	490 ng/L	
	Ingesting organisms only:		EPA 1980b
	10 ⁻⁵	161,000 ng/L	
	10 ⁻⁶	16,100 ng/L	
	10 ⁻⁷	1,610 ng/L	
	Drinking water concentrations:		IRIS 1990
	10 ⁻⁴	700 µg/L	
	10 ⁻⁵	70 µg/L	
	10 ⁻⁶	7 µg/L	
b. Other:			
EPA	Carcinogen classification	B2 ^c	IRIS 1990
	Unit risk (air)	No data	EPA 1990
	Unit risk (water)	1.4×10 ⁻⁷ (µg/L) ⁻¹	EPA 1990

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE			
Regulations and Guidelines:			
a. Air:			
Maryland	Acceptable ambient air concentrations	0.00	NATICH 1991
Wisconsin	Hazardous air contaminants without acceptable ambient concentrations requiring application of best available control technology	250 pounds/year	CELDS 1990
b. Water:			
	Drinking water quality guidelines and standards		FSTRAC 1988
Kansas		71 µg/L	
Minnesota		71.1 µg/L	
California	Toxic materials limitations-- objectives for protection of human health (30-day average)	2.5 µg/L	CELDS 1990
Indiana	Water quality continuous criteria concentration for human health (4-day average): Outside mixing zone Point of water intake	161 mg/L 49 mg/L	CELDS 1990
Wisconsin	Human cancer criteria Public water supply: Warm water sport fish communities Cold water communities Great Lakes communities Non-water supply: Warm water sport fish communities Cold water communities Warm water forage and limited forage fish communities and limited aquatic life	45 µg/L 24 µg/L 24 µg/L 120 µg/L 36 µg/L 14,000 µg/L	DNR 1987
c. Other:			
Wisconsin	Designated as a toxic pollutant	Yes	CELDS 1990

^aGroup 3: not classifiable as to human carcinogenicity

^bBecause of its carcinogenic potential, the EPA-recommended concentration for N-nitrosodiphenylamine in ambient water is zero. However, because attainment of this level may not be possible, levels that correspond to upper-bound incremental lifetime cancer risks of 10^{-5} , 10^{-6} , and 10^{-7} are estimated.

^cGroup B2: possible human carcinogen

EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

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 (K_d) -- The amount of a chemical adsorbed by a 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.

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.

Cancer Effect Level (CEL) -- The lowest dose of 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.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Clastogen -- A substance which causes a break in the DNA molecule that is observable at the chromosome level.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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.

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 insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance 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) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

9. GLOSSARY

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

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

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 which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀) -- 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 is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀) -- 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 dose 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.

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

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of 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. Effects may be produced at this dose, but 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.

9. GLOSSARY

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g/L}$ for water, mg/kg/day for food, and $\mu\text{g/m}^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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 chemical. 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.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

9. GLOSSARY

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. 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.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

- (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. 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.
- (2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported

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- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the “System” column of the LSE table.
- (4) Key to Figure 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 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two “18r” data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18, rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day).
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. “Other” refers to <any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.
- (8) NOAEL A No Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation h4RL of 0.005 ppm (see footnote “b”).
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful 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 end point used to quantify the adverse effect accompanies the LOAEL. The “Less Serious” respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.
- (10) Reference The complete reference citation is given in Chapter 8 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

APPENDIX A**LEGEND****See LSE Figure 2-1**

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

- (13) Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.
- (15) Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale “y” axis. Inhalation exposure is reported in mg/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 1% NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).
- (17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q₁*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure ^a	Species	Exposure frequency/duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓ Rat	6 ↓ 13 wk 5d/wk 6hr/d	7 ↓ Resp	8 ↓ 3 ^b	9 ↓ 10 (hyperplasia)		10 ↓ Nitschke et al. 1981
4 → 18							

CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				11 ↓ 20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

^a The number corresponds to entries in Figure 2-1.

12 → ^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

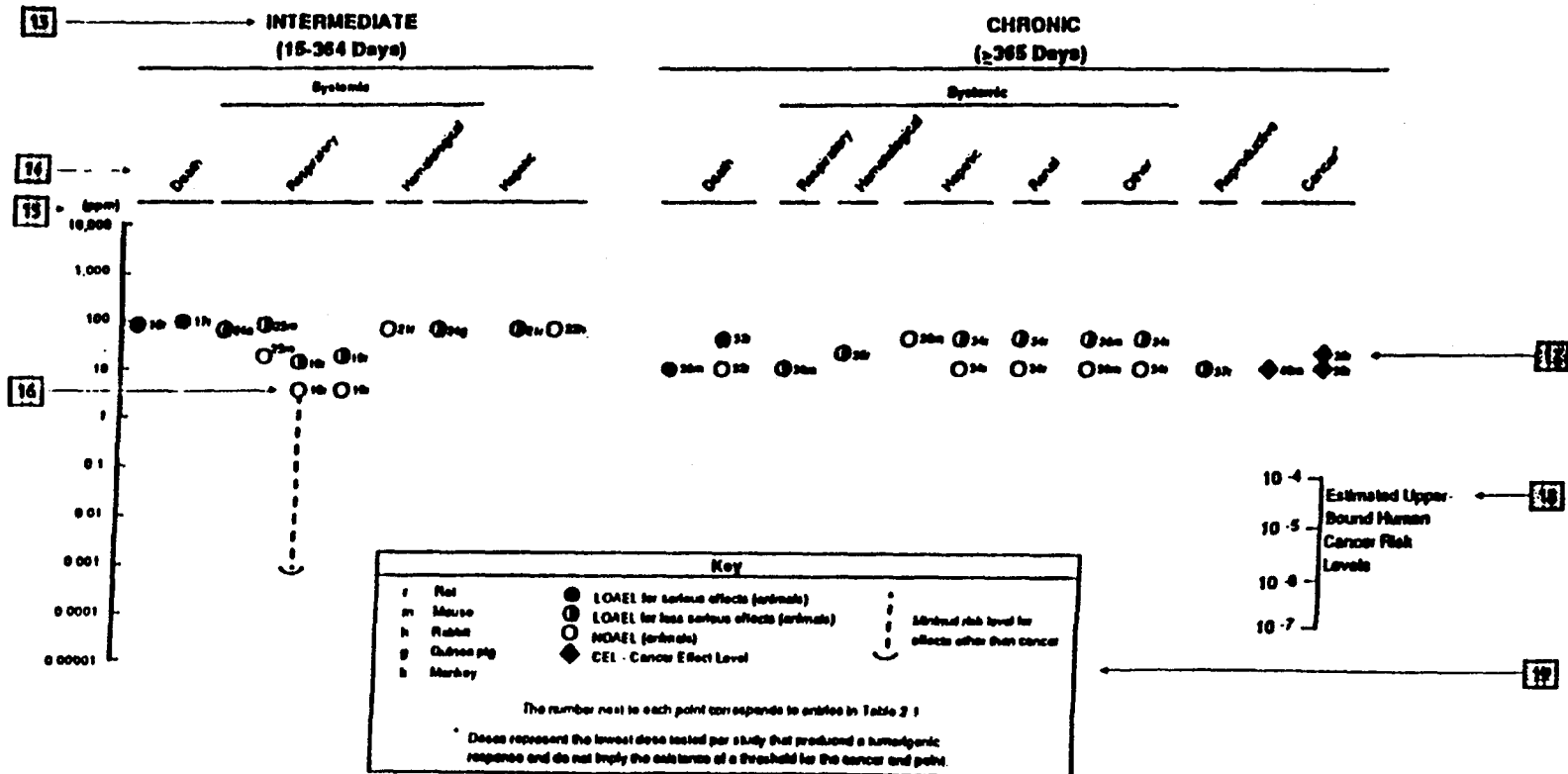


FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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Chapter 2 (Section 2.4)**Relevance to Public Health**

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points 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?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRL 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. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Chemicals” and 2.7, “Populations that are Unusually Susceptible” 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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

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To derive an MRL, ATSDR generally selects the end point 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used 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 adjusted 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 LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	<i>Department of Labor</i>
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F ₁	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K _d	adsorption ratio
kg	<i>kilogram</i>
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter

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LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

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STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
\geq	greater than or equal to
=	equal to
<	less than
\leq	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for *N*-nitrosodiphenylamine. The panel consisted of the following members: Dr. Rajender Abraham, Abraham Associates, Ltd., Albany, New York; Dr. Martin Alexander, Professor of Soil Microbiology, Cornell University, Ithaca, New York; Dr. Brent Burton, Associate Professor of Emergency Medicine, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Peter Lacouture, Associate Director, Clinical Research, The Purdue Frederick Company, Norwalk, Connecticut; Dr. Frederick Oehme, Director, Comparative Toxicology Laboratories, Kansas State University, Manhattan, Kansas; and Dr. Raymond Smith, Professor of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska. These experts collectively have knowledge of *N*-nitrosodiphenylamine's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

