

TOXICOLOGICAL PROFILE FOR
N-NITROSODI-n-PROPYLAMINE

Agency for Toxic Substances and Disease Registry (ATSDR)
U.S. Public Health Service

In collaboration with
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FOREWORD

The Superfund Amendments and Reauthorization Act 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 (also known as SARA) 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 most significant hazardous substances were published in the Federal Register on April 17, 1987, and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

- (A) An examination, summary and interpretation of available toxicological information and epidemiological evaluations on the 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, or chronic health effects, and
- (C) Where appropriate, an 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, but no less often than every 3 years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that

describes a hazardous substance's toxicological properties. Other literature is 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 statement is material that presents 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, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

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. We plan to revise these documents as additional data become available.

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, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS N-NITROSODI-n-PROPYLAMINE?

N-Nitrosodi-n-propylamine is a yellow liquid at room temperature that does not dissolve in water and evaporates slowly. It is a man-made chemical made in small amounts for use in research. There is no evidence that N-nitrosodi-n-propylamine exists naturally in soil, air, food, or water. Small amounts of N-nitrosodi-n-propylamine are produced as a side reaction during some manufacturing processes, as a contaminant in some commonly available weed killers (dinitroaniline-based), and during the manufacture of some rubber products. When exposed to sunlight, N-nitrosodi-n-propylamine usually does not last for more than a day. Without sunlight (e.g., in water deeper than sunlight reaches or in subsurface soil) N-nitrosodi-n-propylamine breaks down slowly. It takes between 14 and 80 days for one-half of any certain amount of N-nitrosodi-n-propylamine to break down when it is released to the subsurface soil. More information can be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO N-NITROSODI-n-PROPYLAMINE?

Persons may be exposed to N-nitrosodi-n-propylamine by eating foods treated with nitrite preservatives (e.g., cheeses, cured meats) and drinking certain alcoholic beverages. N-Nitrosodi-n-propylamine forms in the stomach during digestion of nitrite-treated foods and foods that contain certain amines, particularly di-n-propylamine. Amines occur in some medicines and in a variety of foods. Levels of N-nitrosodi-n-propylamine found in food and alcoholic beverages range between 0.03 parts per billion (ppb) in fried, salt-preserved fish to 30 ppb in cheese. The general population may be exposed to N-nitrosodi-n-propylamine in cigarette smoke. Workers making molded rubber products have been exposed to levels of N-nitrosodi-n-propylamine in workroom air that were measured in parts of compound per trillion parts (ppt) of air. Workers applying contaminated weed killers may also be exposed to extremely low (ppt) levels of N-nitrosodi-n-propylamine. At this time, N-nitrosodi-n-propylamine has been found in at least 1 of 1177 hazardous waste sites on the National Priorities List (NPL) in the United States. Workers and the general population at these sites could possibly be exposed to this compound by skin contact, breathing, and eating contaminated items. For more information, refer to Chapter 5.

1.3 HOW CAN N-NITROSODI-n-PROPYLAMINE ENTER AND LEAVE MY BODY?

N-Nitrosodi-n-propylamine can enter the body when a person breathes air that contains N-nitrosodi-n-propylamine, or eats food or drinks water contaminated with N-nitrosodi-n-propylamine. N-nitrosodi-n-propylamine is not likely to get into your body unless you eat certain foods, drink alcoholic beverages, or are exposed to it at a waste disposal site by breathing N-nitrosodi-n-propylamine vapors. It is likely that N-nitrosodi-n-propylamine can enter the body by direct skin contact with wastes,

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pesticides, or soil that contains it. Experiments with animals suggest that if N-nitrosodi-n-propylamine enters the body, it will be broken down into other compounds and will leave the body in the urine. More information on how N-nitrosodi-n-propylamine can enter and leave your body is given in Chapter 2.

1.4 HOW CAN N-NITROSODI-n-PROPYLAMINE AFFECT MY HEALTH?

The effects of short- or long-term exposures to N-nitrosodi-n-propylamine on human health have not been studied. Little is known about the health effects of short exposures to N-nitrosodi-n-propylamine in experimental animals except that eating or drinking certain amounts of this chemical can cause liver disease and death. Long-term exposure of experimental animals to N-nitrosodi-n-propylamine in food or drinking water causes cancer of the liver, esophagus, and nasal cavities. Although human studies are not available, the animal evidence indicates that it is reasonable to expect that exposure to N-nitrosodi-n-propylamine by eating or drinking could cause liver disease and cancer in humans. It is not known whether other effects, such as birth defects, occur in animals or could occur in humans exposed to N-nitrosodi-n-propylamine by eating or drinking. It is also not known whether exposure to N-nitrosodi-n-propylamine by breathing contaminated air or contact with the skin can affect the health of animals or humans. Liver disease and cancer due to exposure to N-nitrosodi-n-propylamine by breathing or skin contact are, however, a possibility and a health concern. More information on the health effects of N-nitrosodi-n-propylamine is given in Chapter 2.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO N-NITROSODI-n-PROPYLAMINE?

The presence of N-nitrosodi-n-propylamine in blood and urine can be measured by chemical analysis, but this analysis is not usually available at your doctor's office and has not been used to test for human exposure or to predict possible health effects. These considerations are discussed in more detail in Chapter 2.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Tables 1-1 through 1-4 show the relationship between exposure to N-nitrosodi-n-propylamine and known health effects. As indicated in Tables 1-1 and 1-2, nothing is known about the health effects on humans or animals of breathing N-nitrosodi-n-propylamine. Also, nothing is known about the health effects in humans of eating food or drinking water containing N-nitrosodi-n-propylamine (Table 1-3). A Minimal Risk Level (MRL) is also included in Table 1-3. This MRL was derived from animal data for short-term exposure as described in Chapter 2 and in Table 2-1. The MRL provides a basis for comparison with levels that people might encounter in drinking water. If a person is exposed to N-nitrosodi-n-propylamine at an amount

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TABLE 1-1. Human Health Effects from Breathing
N-Nitrosodi-n-propylamine*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of humans to air containing N-nitrosodi-n-propylamine are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term exposure of humans to air containing N-nitrosodi-n-propylamine are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

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TABLE 1-2. Animal Health Effects from Breathing
N-Nitrosodi-n-propylamine

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of animals to air containing N-nitrosodi-n-propylamine are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term exposure of animals to air containing N-nitrosodi-n-propylamine are not known.

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TABLE 1-3. Human Health Effects from Eating or Drinking
N-Nitrosodi-n-propylamine*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of humans to food containing N-nitroso-di-n-propylamine are not known.
<u>Levels in Water (ppm)</u>		
3.3		Minimal risk level (based on animal data; see Section 1.6 for discussion).
Long-term Exposure (greater than 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term exposure of humans to food containing N-nitroso-di-n-propylamine are not known.
<u>Levels in Water</u>		
		The health effects resulting from long-term exposure of humans to food containing N-nitrosodi-n-propylamine are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

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TABLE 1-4. Animal Health Effects from Eating or Drinking
N-Nitrosodi-n-propylamine

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food (ppm)</u>		
308	4 days	Liver injury in mice.
<u>Levels in Water (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
3429	once	Liver injury and death in rats.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term animal exposure to food containing specific levels of N-nitrosodi-n-propylamine are not known.
<u>Levels in Water</u>		The health effects resulting from long-term animal exposure to water containing specific levels of N-nitrosodi-n-propylamine are not known.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

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below the MRL, it is not expected that harmful (noncancer) health effects will occur. Because this level is based on information that is currently available, some uncertainty is always associated with it. Also, because the method for deriving MRLs does not use any information about cancer, an MRL does not imply anything about the presence, absence, or level of risk of cancer. The levels of N-nitrosodi-n-propylamine in food and drinking water linked with known health effects in animals are given in Table 1-4. It is not known whether skin contact with N-nitrosodi-n-propylamine can affect the health of humans or animals. More information on levels of exposure linked with adverse health effects can be found in Chapter 2.

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

The EPA controls the release of N-nitrosodi-n-propylamine. It is proposed that releases or spills of 10 pounds or more of N-nitrosodi-n-propylamine must be reported to the National Response Center.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have more questions or concerns, please contact your State Health or Environmental Department or:

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to N-nitrosodi-n-propylamine. Its purpose is to present levels of significant exposure for N-nitrosodi-n-propylamine based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of N-nitrosodi-n-propylamine and (2) a depiction of significant exposure levels associated with various adverse health effects.

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 data in this section are 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, intermediate, and chronic.

Levels of significant exposure for each exposure route and duration (for which data exist) 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, determine whether or not the intensity of the effects varies 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 on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund 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) are of interest to health professionals and citizens alike.

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For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited. Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one 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 end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1980a), uncertainties are associated with the techniques.

2.2.1 Inhalation Exposure

No studies were located regarding the following effects in humans or animals following inhalation exposure to N-nitrosodi-n-propylamine:

- 2.2.1.1 Death
- 2.2.1.2 Systemic Effects
- 2.2.1.3 Neurological Effects
- 2.2.1.4 Immunological Effects
- 2.2.1.5 Developmental Effects
- 2.2.1.6 Reproductive Effects
- 2.2.1.7 Genotoxic Effects
- 2.2.1.8 Cancer
- 2.2.2 Oral Exposure
 - 2.2.2.1 Death

No studies were located regarding lethality in humans following oral exposure to N-nitrosodi-n-propylamine.

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

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Table 2-1 and Figure 2-1. No short-term studies of N-nitrosodi-n-propylamine administered in drinking water were located; therefore, the dose level of 480 mg/kg, which was administered by gavage in water (Druckrey et al. 1967), was converted to an equivalent concentration of 3400 ppm in water for presentation in Table 1-4.

Decreased longevity occurred in rats that were treated with N-nitrosodi-n-propylamine at doses of 6.3 mg/kg/day (females) or 12.6 mg/kg/day (males) by gavage for 2 days/week for 30 weeks (Lijinsky and Reuber 1983), or 5.1 mg/kg/day (males) via drinking water for 5 days/week for 30 weeks (Lijinsky and Taylor 1978, 1979). Mortality in the Lijinsky and Reuber (1983) study was 92-100% after 40-60 weeks compared to 5-10% after 100 weeks in controls; comparable data were reported by Lijinsky and Taylor (1978, 1979) for the treated rats but a control group was not used. The mortality in these studies was due to tumor development (see Section 2.2.2.8, Oral exposure, Cancer). The 5.1, 6.3 and 12.6 mg/kg/day doses are serious LOAEL values for lethality in rats due to intermediate duration oral exposure and are recorded in Table 2-1 and plotted in Figure 2-1. No studies were located regarding survival in animals following chronic oral exposure to N-nitrosodi-n-propylamine.

2.2.2.2 Systemic Effects

No studies were located regarding systemic effects in humans following oral exposure to N-nitrosodi-n-propylamine.

Hepatic Effects. Pathologic examinations of rats that received single lethal doses of various nitrosamines, including N-nitrosodi-n-propylamine, showed centrilobular necrosis and fatty degeneration of the liver (Druckrey et al. 1967). Specific doses of N-nitrosodi-n-propylamine that produced these effects were not reported, but the LD₅₀ was determined to be 480 mg/kg; this dose is indicated in Table 2-1 and Figure 2-1 as a serious LOAEL for hepatic effects in rats due to acute oral exposure. No short-term studies of N-nitrosodi-n-propylamine administered in drinking water were located; therefore, the dose level of 480 mg/kg, which was administered by gavage in water (Druckrey et al. 1967), was converted to an equivalent concentration of 3400 ppm in water for presentation in Table 1-4.

Nishie et al. (1972) determined pentobarbital sleeping time (PST) in mice that were treated by gavage with single doses or with four consecutive daily doses of various nitrosamines, including N-nitrosodi-n-propylamine. Doses of N-nitrosodi-n-propylamine were 160 mg/kg/day in the single dose study and 40 mg/kg/day in the four-day study. N-nitrosodi-n-propylamine treatment resulted in significantly prolonged PST in both studies. Liver histology was evaluated in the four-day study, but results of the histologic examinations were not reported specifically for any of the nitrosamines. Hepatic histological alterations attributed to unspecified nitrosamines included hepatocyte swelling and necrosis in the centrilobular areas; due to the inadequately reported data, it cannot be determined whether N-nitrosodi-

TABLE 2-1. Levels of Significant Exposure to N-Nitrosodi-n-propylamine - Oral

Graph Key	Species ^a	Route	Duration/ Frequency Exposure	Effect	NOAEL ^b (mg/kg/day)	LOAEL ^c (Effect)		Reference
						Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE								
Death								
1	rat	(G)	one dose				480 (LD ₅₀)	Druckrey et al. 1967
Systemic								
2	mouse	(W)	1 wk, daily	Hepatic	9.5 ^d			Tyndall et al. 1978
3	mouse	(G)	4 d, once/day	Hepatic		40 (increased PST)		Nishie et al. 1972
4	rat	(G)	one dose	Hepatic			480 (necrosis)	Druckrey et al. 1967
INTERMEDIATE EXPOSURE								
Death								
5	rat	(W)	30 wk, 5 d/wk				5.1 (decreased longevity)	Lijinsky and Taylor 1978, 1979
6	rat (male)	(G)	30 wk, 2 d/wk				12.6 (decreased longevity)	Lijinsky and Reuber 1983
7	rat (female)	(G)	30 wk, 2 d/wk				6.3 (decreased longevity)	Lijinsky and Reuber 1983
Cancer								
8	rat	(W)	30 wk, 5 d/wk				2.6 (CEL ^e -esophagus, forestomach tumors)	Lijinsky and Reuber 1981
9	rat	(G)	30 wk, 2 d/wk				6.3 (CEL ^e -liver, nasal, esophagus tumors)	Lijinsky and Reuber 1983

TABLE 2-1 (continued)

Graph Key	Species ^a	Route	Duration/ Frequency Exposure	Effect	NOAEL ^b (mg/kg/day)	LOAEL ^c (Effect)		Reference
						Less Serious (mg/kg/day)	Serious (mg/kg/day)	
10	rat	(F)	life, daily				4 (CEL ^e -liver carcinoma)	Druckrey et al. 1967
11	mouse	(G)	50 wk, 2 d/wk				1 (CEL ^e -forestomach, pulmonary tumors)	Griciute et al. 1982

^aG - gavage, W - water, F - feed

^bNOAEL - No Observed Adverse Effect Level

^cLOAEL - Lowest Observed Adverse Effect Level

^dUsed to derive acute oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in a MRL of 0.095 mg/kg/day. This MRL has been converted to an equivalent concentration in water (3.3 ppm) for presentation in Table 1-3.

^eCEL - Cancer Effect Level

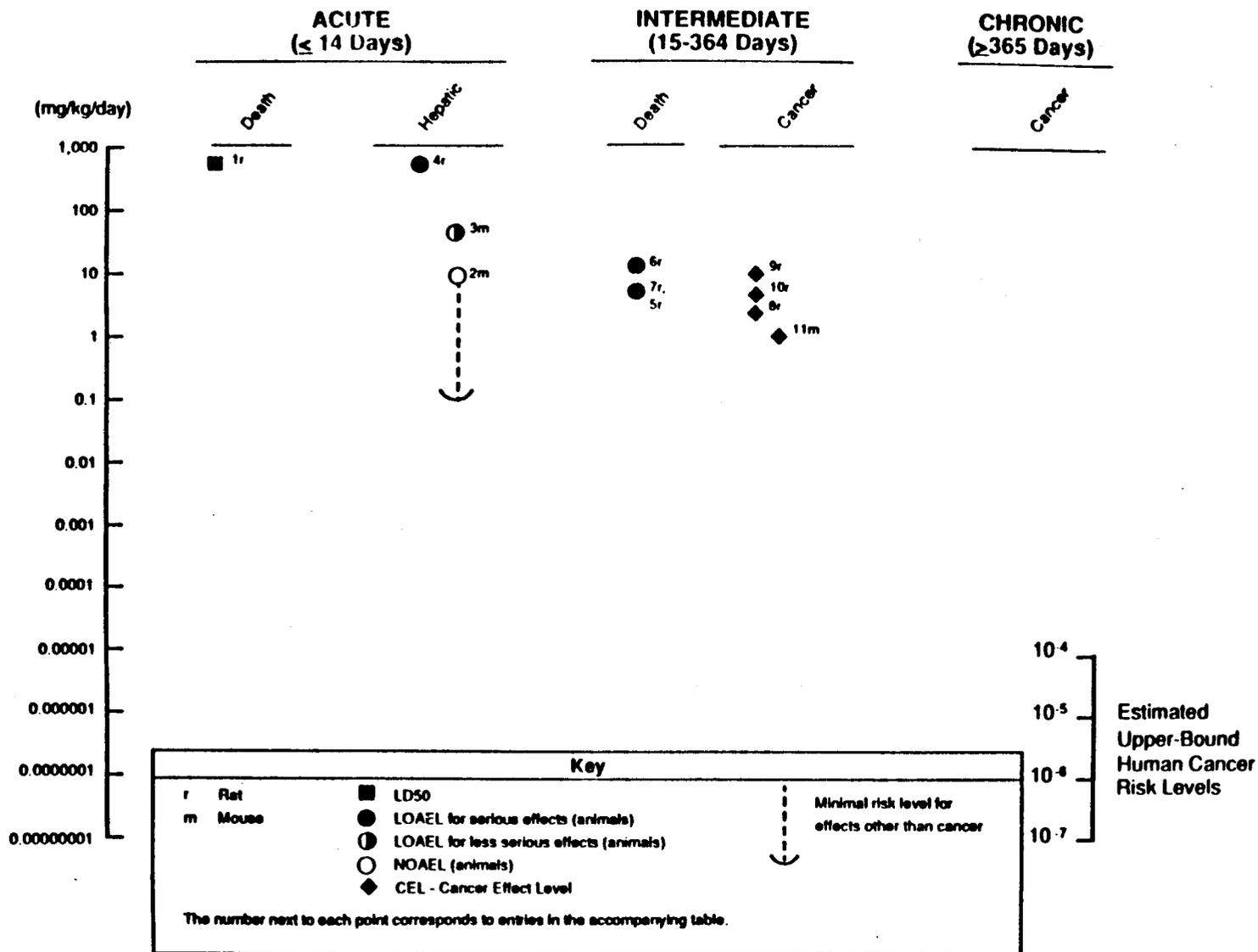


FIGURE 2-1. Levels of Significant Exposure to N-Nitrosodi-n-propylamine - Oral

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n-propylamine was among the nitrosamines that produced these effects. However, considering the aforementioned findings for nitrosamines in general as well as evidence for hepatotoxicity of N-nitrosodi-n-propylamine and other nitrosamines from other studies, the increase in PST provides an indirect indication of adverse liver effects. Therefore, since N-nitrosodi-n-propylamine markedly increased PST in the four-day study, 40 mg/kg/day can be regarded as a LOAEL for less serious hepatic effects due to acute oral exposure (Table 2-1 and Figure 2-1). No short-term studies of N-nitrosodi-n-propylamine administered in food were located; therefore, the dose level of 40 mg/kg/day, which was administered by gavage in olive oil (Nishie et al. 1972), was converted to an equivalent concentration of 308 ppm in food for presentation in Table 1-4.

Liver histology and activities of liver-associated serum enzymes (SGOT, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl-transferase) were unaltered in mice exposed to 9.5 mg/kg/day via drinking water for one week (Tyndall et al. 1978). This dose represents a NOAEL for hepatic effects due to acute duration exposure (Table 2-1 and Figure 2-1). Because this NOAEL is lower than the 40 mg/kg/day LOAEL for hepatic effects (Nishie et al. 1972), it can be used as the basis for an acute MRL (Figure 2-1). Based on this value, an acute oral MRL of 0.095 mg/kg/day was calculated, as described in the footnote in Table 2-1. This MRL has been converted to an equivalent concentration in drinking water (3.3 ppm) for presentation in Table 1-3.

Other Effects. Plasma esterase profiles were examined in mice exposed to various carcinogenic, weakly carcinogenic and noncarcinogenic chemicals in the drinking water for one week (Tyndall et al. 1978). N-nitrosodi-n-propylamine, administered at a dose 9.5 mg/kg/day, produced esterase alterations that were similar to those produced by other N-nitrosodialkylamines. The alterations were not accompanied by weight loss, altered liver-associated serum enzymes or histologic effects. This study was conducted to determine whether altered esterase patterns in plasma would provide a more sensitive indicator of exposure to a carcinogenic chemical than standard clinical chemistry tests. It was concluded that it is not known if the altered esterase profiles that were observed for N-nitrosodi-n-propylamine and the other carcinogens are related to carcinogenicity, toxicity or metabolism. Since the biological significance of the altered esterase profiles is unknown, it cannot be determined if 9.5 mg/kg/day represents a NOAEL or LOAEL for serum chemistry alterations due to acute oral exposure.

No studies were located regarding the following effects in humans or animals following oral exposure to N-nitrosodi-n-propylamine:

2.2.2.3 Immunological Effects

2.2.2.4 Neurological Effects

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2.2.2.5 Developmental Effects

2.2.2.6 Reproductive Effects

2.2.2.7 Genotoxic Effects

Single doses of N-nitrosodi-n-propylamine, administered by gavage, produced fragmentation of liver DNA in rats (Brambilla et al. 1981, 1987a). Doses ranged from 0.31 to 25 mg/kg and the effect was dose-related.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to N-nitrosodi-n-propylamine.

The carcinogenicity of N-nitrosodi-n-propylamine has been demonstrated unequivocally in oral studies. High incidences of liver carcinomas, nasal cavity carcinomas, esophageal carcinomas and papillomas, forestomach tumors or tongue tumors occurred in rats that were exposed to N-nitrosodi-n-propylamine by gavage at doses of 6.3 or 12.6 mg/kg/day for 2 days/week for 30 weeks (Lijinsky and Reuber 1983), via drinking water at a dose of 2.6 mg/kg/day for 5 days/week for 30 weeks (Lijinsky and Reuber 1981), via drinking water at a dose of 5.1 mg/kg/day for 5 days/week for 30 weeks (Lijinsky and Reuber 1981; Lijinsky and Taylor 1978, 1979), and via diet daily at reported doses of 4-30 mg/kg/day for life (survival duration not specified) (Druckrey et al. 1967). Tumor incidences in the liver, nasal cavity, esophagus and forestomach were generally in the range of 60-100%, and tongue tumor incidences ranged from 30-40%. The Lijinsky and Reuber (1983) study was the only study that used control groups; no tumors occurred in the control rats at any of the sites in which tumors developed in the treated rats. The lack of controls in the other studies is not considered to be a serious deficiency due to the high tumor incidences. As indicated in Section 2.2.2.1 (Oral exposure, Death), tumor development in all of the rat studies was life-shortening.

The lowest drinking water and gavage doses of N-nitrosodi-n-propylamine that were carcinogenic to rats are 2.6 mg/kg/day (Lijinsky and Reuber 1981) and 6.3 mg/kg/day (Lijinsky and Reuber 1983), respectively; these are intermediate duration effect levels for carcinogenicity (cancer effects levels, CELs) because exposure durations were 30 weeks (Table 2-1 and Figure 2-1). The lowest dose tested in the study of Druckrey et al. (1967) (4 mg/kg/day) is also presented in Table 2-1 and Figure 2-1 in the intermediate duration category as this study is used as the basis for a carcinogenic potency factor for N-nitrosodi-n-propylamine (EPA 1988). The 4 mg/kg/day dose from the Druckrey et al. (1967) study is considered to be the lowest CEL due to intermediate duration exposure because (1) time to tumor data suggest that survival was generally less than one year, and (2) survival was less than one year in the other cancer studies which used

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similar or lower doses. Although a carcinogenic potency factor is based on this study, it should be recognized that the study is limited by small numbers of treated rats, no controls and unreported specific tumor incidences. Using hepatocellular carcinoma response data from this study, EPA (1988) derived and verified an oral slope factor (BH) of 7.0 (mg/kg/day)⁻¹ for N-nitrosodi-n-propylamine. Using this slope factor the doses associated with upper bound lifetime cancer risk levels of 10⁻⁴ to 10⁻⁷ are calculated to be 1.4 x 10⁻⁵ to 1.4 x 10⁻⁸ mg/kg/day, respectively. The cancer risk levels are plotted in Figure 2-1 in the chronic duration category because they represent lifetime risks for humans.

In an oral carcinogenicity study conducted with mice, the animals received an estimated N-nitrosodi-n-propylamine dose of 1 mg/kg by gavage, twice a week for 50 weeks (Griciute et al. 1982). Incidences of forestomach papillomas, forestomach carcinomas and pulmonary adenomas were significantly higher than in mice that were similarly treated with 40% ethanol; a vehicle (water) control was not used. The 1 mg/kg/day dose from the Griciute et al. (1982) study represents an intermediate duration CEL in mice (Table 2-1 and Figure 2-1).

2.2.3 Dermal Exposure

No studies were located regarding the following effects in humans or animals following dermal exposure to N-nitrosodi-n-propylamine:

- 2.2.3.1 Death
- 2.2.3.2 Systemic Effects
- 2.2.3.3 Neurological Effects
- 2.2.3.4 Immunological Effects
- 2.2.3.5 Developmental Effects
- 2.2.3.6 Reproductive Effects
- 2.2.3.7 Genotoxic Effects
- 2.2.3.8 Cancer

2.3 RELEVANCE TO PUBLIC HEALTH

Death. Information regarding death of humans following exposure to N-nitrosodi-n-propylamine by any route was not found. Case reports indicate that intentional oral and accidental inhalation exposures to unknown levels of N-nitrosodimethylamine, however, have resulted in deaths in humans (Barnes and Magee 1954, Cooper and Kimbrough 1980, Freund 1937, Fussgaenger and Ditschuneit 1980, Pedal et al. 1982); these deaths apparently were due

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to hepatotoxicity. Limited data are available for acute lethality in N-nitrosodi-n-propylamine-exposed animals. In the only acute study that used a natural route of exposure, an oral LD₅₀ value of 480 mg/kg was determined for rats (Druckrey et al. 1967). Subcutaneous injection LD₅₀ values have been determined for N-nitrosodi-n-propylamine in various species; these are consistent with the oral LD₅₀ and include 487.2 mg/kg for rats (Reznik et al. 1975), 689 mg/kg for mice (Dickhaus et al. 1977) and 600 mg/kg for hamsters (Pour et al. 1973). Pathologic examinations revealed centrilobular liver necrosis and hemorrhages in the lungs, stomach, kidneys and/or heart.

Oral administration of N-nitrosodi-n-propylamine at doses ranging from 5.1-12.6 mg/kg/day, on 2 or 5 days a week for 30 weeks, produced high mortality in rats (Lijinsky and Reuber 1983; Lijinsky and Taylor 1978, 1979). Once-weekly subcutaneous injections of similar doses of N-nitrosodin-propylamine to rats (≤ 24.4 mg/kg) (Reznik et al. 1975), mice (≥ 34.5 mg/kg) (Dickhaus et al. 1977) and hamsters (≥ 3.75 mg/kg) (Pour et al. 1973, Althoff et al. 1973a,b) also were life-shortening (average survival times of 27-54 weeks). Weekly intraperitoneal injection of 40 mg/kg N-nitrosodi-n-propylamine produced deaths in monkeys after an average period of 28 months (Adamson and Sieber 1979, 1983). Mortality in the above studies is dose-related and due to tumor development.

The available lethality data indicate that deaths resulting from acute exposure to N-nitrosodi-n-propylamine are due primarily to hepatotoxicity, that deaths resulting from repeated exposure to N-nitrosodi-n-propylamine are due to tumors occurring primarily in the liver, and that causes of death and lethal doses are similar in different species. The causes of death produced by N-nitrosodi-n-propylamine also are consistent with those produced by other dialkylnitrosamines (Magee et al. 1976).

Systemic Effects. Information regarding systemic effects in humans following exposure to N-nitrosodi-n-propylamine was not found. Very limited information is available for systemic effects of N-nitrosodi-n-propylamine in animals because interest in this compound has focused overwhelmingly on carcinogenicity.

As indicated in the previous subsection (see Death above), lethal single oral or subcutaneous doses of N-nitrosodi-n-propylamine produced hepatic necrosis and hemorrhagic lesions in the liver and other internal tissues in rats and hamsters (Druckrey et al. 1967, Pour et al. 1973, Reznik et al. 1975). Similar effects were reported by Nishie et al. (1972), who observed that gavage doses of 40 mg/kg/day for 4 consecutive days produced swelling of hepatocytes and possibly necrosis in the centrilobular area of the liver in mice. Hepatotoxicity and hemorrhagic lesions in the liver and other internal tissues are also the primary acute effects of other dialkylnitrosamine compounds (Magee et al. 1976). Based on data for other dialkylnitrosamines, it can be inferred that systemic effects of intermediate or chronic duration exposure to N-nitrosodi-n-propylamine are likely to include acute-type responses and preneoplastic alterations.

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Although it is apparent that N-nitrosodi-n-propylamine produces hepatotoxicity and hemorrhages in the lungs, stomach, kidney and heart at acute lethal doses in animals, there is only limited information regarding the threshold for these effects following acute exposure and documentation of these effects following intermediate or chronic duration exposure is not available. Although human data are not available, human fatalities due to intentional oral and accidental inhalation exposures to unknown levels of N-nitrosodimethylamine have been described in case reports in which hemorrhagic, necrotic and cirrhotic alterations in the liver and diffuse internal bleeding were observed (Barnes and Magee 1954; Cooper and Kimbrough 1980; Freund 1937; Fussgaenger and Ditschuneits 1980; Pedal et al. 1982). The available information for N-nitrosodi-n-propylamine and related nitrosamines therefore indicates that N-nitrosodi-n-propylamine is likely to produce characteristic hepatic and/or hemorrhagic effects in humans exposed orally or by inhalation. Systemic effects of N-nitrosodi-n-propylamine may result from dermal exposure, since evidence indicates that dermal absorption of N-nitrosodi-n-propylamine is likely (Section 2.6.1.3, Absorption, Dermal exposure).

Developmental Effects. Limited information regarding developmental effects of N-nitrosodi-n-propylamine in humans or in animals is available from subcutaneous injection transplacental carcinogenesis studies with hamsters (Althoff et al. 1977a; Althoff and Grandjean 1979). Injection of a single dose of 100 mg N-nitrosodi-n-propylamine/kg on day 8, 10, 12, or 14 of gestation did not produce gross malformations in the offspring but the scope of the examination was not specified. However, transplacental carcinogenicity was observed in the offspring of dams treated with N-nitrosodi-n-propylamine. There were no treatment-related effects on litter size but postnatal mortality in the first four weeks was increased (Althoff et al. 1977a). Transplacental transport of N-nitrosodi-n-propylamine by the hamsters was demonstrated by detection of the chemical in the placenta, fetus and amniotic fluid. No studies were located demonstrating that N-nitrosodi-n-propylamine crosses the placenta in humans and it is not known whether N-nitrosodi-n-propylamine can cause developmental effects in humans. It is relevant to note, however, that limited evidence indicates that N-nitrosodimethylamine is fetotoxic but not teratogenic. Also, it has been estimated from studies with rodents that drugs with a molecular weight of less than 1,000 can readily cross the placenta (Mirkin 1973); the molecular weight of N-nitrosodi-n-propylamine is 130.2.

Genotoxic Effects. No studies were located regarding the genotoxicity of N-nitrosodi-n-propylamine in humans by the inhalation, oral or dermal routes. Fragmentation of DNA was observed, however, in human hepatocytes cultured in the presence of N-nitrosodi-n-propylamine (Brambilla et al. 1987b).

Genotoxicity of N-nitrosodi-n-propylamine has been demonstrated consistently in numerous in vitro studies. As indicated in Table 2-2,

TABLE 2-2. Genotoxicity of N-Nitrosodi-n-Propylamine In Vitro

Endpoint	Species (Test System)	Result		References
		With Activation	Without Activation	
Gene mutation	<u>Salmonella typhimurium</u>	+	-	Yahagi et al. 1977, Bartsch et al. 1976, 1980, McMahon et al. 1979, Rao et al. 1979, Araki et al. 1984, Phillipson and Ioannides 1985, Guttenplan and Hu 1984, Guttenplan 1987, Moore et al. 1985, Dahl 1985, Rao et al. 1982, Probst et al. 1981
	<u>Escherichia coli</u>	+	-	McMahon et al. 1979, Araki et al. 1984, Nakajima et al. 1974, Rao et al. 1981, 1982
	Mouse lymphoma L5178Y cells	+	-	Amacher et al. 1979, Amacher and Paillet 1982, 1983,
	Chinese hamster V79 cells	+	-	Kuroki et al. 1977, Bartsch et al. 1980, Jones and Huberman 1980, Langenbach 1986
DNA fragmentation	Rat hepatocytes	+	NT	Bradley and Dysart 1981a,b, Bradley et al. 1982, Parodi et al. 1982
	Human hepatocytes	+	NR	Brambilla et al. 1987b
Unscheduled DNA synthesis	Rat hepatocytes	+	NT	Probst et al. 1981
	HeLa cells	+	-	Martin et al. 1978
DNA repair	Rat hepatocytes	+	NT	Yamazaki et al. 1985
Chromosome aberrations	Chinese hamster fibroblasts	+	-	Kaneko et al. 1978
	Chinese hamster lung cells	(+)	-	Matsuoka et al. 1979

NT = not tested; NR = not reported

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N-nitrosodi-n-propylamine was mutagenic in bacteria (Salmonella Typhimurium, Escherichia coli) and mammalian cells (mouse lymphoma L5178Y, Chinese hamster V79), caused DNA effects (fragmentation, unscheduled synthesis, repair) in rat hepatocytes, and chromosome aberrations in Chinese hamster cells. The in vitro assays generally required addition of an exogenous metabolic activation system for expression of effects; this is consistent with the apparent indirect carcinogenicity of N-nitrosodi-n-propylamine. Single doses of N-nitrosodi-n-propylamine produced DNA fragmentation in rats treated orally and sister chromatid exchange and DNA synthesis suppression in mice treated by intraperitoneal injection (Table 2-3). In addition, intraperitoneal injection (133 mg/kg) of N-nitrosodi-n-propylamine to rats results in propylation of DNA and RNA, an event regarded as critical in the initiation of carcinogenesis by this and related alkylating agents (Park et al. 1980).

The weight of evidence indicates that N-nitrosodi-n-propylamine is genotoxic in mammalian cells. The effect observed in the study with human hepatocytes (DNA fragmentation) (Brambilla et al. 1987b) is consistent with the results of other assays, particularly the in vitro and in vivo rat hepatocyte DNA fragmentation assays (Table 2-2 and 2-3). Given the type and weight of genotoxicity evidence, one can predict that N-nitrosodi-n-propylamine poses a genotoxic threat to humans.

Cancer. Information regarding the carcinogenicity of N-nitrosodi-n-propylamine in humans was not located. In animals, carcinogenicity of N-nitrosodi-n-propylamine has been demonstrated in several species in all studies that have been conducted. In rats observed for life, daily or partial weekly (2 days/week or 5 days/week) oral exposure produced tumors primarily in the liver, nasal cavity and esophagus (Druckrey et al. 1967; Lijinsky and Reuber 1981, 1983; Lijinsky and Taylor 1978, 1979). In mice, increased incidences of forestomach tumors occurred as a result of twice weekly orally treatment for 50 weeks (Griciute et al. 1982). Weekly subcutaneous injections of N-nitrosodi-n-propylamine to rats (Althoff et al. 1973b, Reznik et al. 1975), mice (Dickhaus et al. 1977) and hamsters (Althoff et al. 1973a, 1977b; Pour et al. 1973, 1974) for life produced high incidences of tumors primarily in the nasal cavity and other parts of the respiratory system, but also in the liver and esophagus. Subcutaneous injection of single 100 mg/kg doses of N-nitrosodi-n-propylamine into hamsters during gestation induced tumors; primarily in the respiratory and digestive tracts, in the dams and offspring (Althoff et al. 1977a; Althoff and Grandjean 1979). Weekly intraperitoneal injections of 40 mg N-nitrosodi-n-propylamine produced death due to hepatocellular carcinomas in monkeys after an average duration of 28 months (Adamson and Sieber 1979, 1983).

Overall, there is conclusive evidence that N-nitrosodi-n-propylamine is carcinogenic in animals. The carcinogenicity of N-nitrosodi-n-propylamine may be related to alkylation of DNA. It is important to recognize that cancer was observed in the oral and injection studies after durations as short as 20-30 weeks, and that once weekly oral exposures and single

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TABLE 2-3. Genotoxicity of N-Nitrosodi-n-propylamine In Vivo

Endpoint	Species (Test System)	Result	References
DNA alkylation	Rat liver	+	Park et al. 1980
DNA fragmentation	Rat hepatocytes	+	Brambilla et al. 1981, 1987a
Suppressed DNA synthesis	Mouse liver and renal epithelial cells	+	Amlacher and Rudolph 1981
Sister chromatid exchange	Mouse bone marrow cells	+	Parodi et al. 1983

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exposure by injection were sufficient to induce cancer. Based on the evidence of carcinogenicity in animals, it is reasonable to anticipate that N-nitrosodi-n-propylamine will be carcinogenic in humans.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

There is no known association between levels of N-nitrosodi-n-propylamine or its metabolites in human tissues and fluids and health effects of N-nitrosodi-n-propylamine. N-nitrosodi-n-propylamine was detected in the liver of 1 of 4 deceased subjects (Cooper et al. 1987). As indicated in Section 2.6.2 (Distribution), the cause of death is not attributable to N-nitrosodi-n-propylamine.

2.5 LEVELS IN THE ENVIRONMENT ASSOCIATED WITH LEVELS IN HUMAN TISSUES AND/OR HEALTH EFFECTS

There is no known association between levels of N-nitrosodi-n-propylamine in the environment and levels of N-nitrosodi-n-propylamine or its metabolites in human tissues and fluids or health effects of N-nitrosodi-n-propylamine.

2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

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

2.6.1.2 Oral Exposure

No studies were located regarding absorption in humans following oral exposure to N-nitrosodi-n-propylamine.

Specific information regarding absorption in animals following oral exposure to N-nitrosodi-n-propylamine was not located. Gastrointestinal absorption of N-nitrosodi-n-propylamine by rodents is indicated by the occurrence of metabolites in the urine following oral treatment (Section 2.3.1.3) and systemic effects in oral carcinogenicity and toxicity studies (Section 2.2). Other nitrosamines are rapidly absorbed from the gastrointestinal tract after oral exposure. Diaz Gomez et al. (1977) found that less than 2% of radiolabelled dimethylnitrosamine could be recovered

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from the stomach and intestine of rats 15 minutes after administration. Also in rats, Lijinsky et al. (1981) and Preussmann et al. (1978) estimated absorption rates of 25% and 70% of the dose for N-nitrosodiethanolamine, respectively (estimates are from urinary excretion).

2.6.1.3 Dermal Exposure

No studies were located regarding absorption in humans following dermal exposure to N-nitrosodi-n-propylamine. However, absorption of N-nitroso-di-n-propylamine through human skin *in vivo* (Edwards et al. 1979) and *in vitro* (Bronaugh et al. 1979, 1981) has been demonstrated.

Diffusion of N-nitroso-di-n-propylamine through rat skin *in vitro* has been demonstrated (Wishnok et al. 1982). Information regarding dermal absorption of N-nitroso-di-n-propylamine by animals *in vivo* was not located in the reviewed literature. Dermal absorption of N-nitrosodiethanolamine has been determined in pigs (Marzulli et al. 1981), monkeys (Marzulli et al. 1981), and rats (Airolidi et al. 1984; Lijinsky et al. 1981). The degree of absorption varied greatly (4-78%) depending on the site of the application and the vehicle used. Based on the data for N-nitrosodi-n-propylamine and N-nitrosodiethanolamine, it is likely that N-nitrosodi-n-propylamine will be absorbed following dermal exposure.

2.6.2 Distribution

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

Transplacental transport of N-nitrosodi-n-propylamine was shown in pregnant hamsters (Althoff et al. 1977a, Althoff and Grandjean 1979). After a single 100 mg/kg subcutaneous injection, N-nitrosodi-n-propylamine was detected in the maternal blood, placenta, fetus, and amniotic fluid. The concentration of the chemical in maternal blood reached a maximum at 45 and 90 minutes after the injection, whereas a single peak at 90 minutes was observed in the fetus. Analysis for metabolites was not conducted, but 1.6% of the unchanged compound was found in the placenta and 1.3% in the fetus at day 14 of gestation. Detection of O⁶-methylguanine in human placental DNA by immunoassay indicates that nitrosamines, as a group, can reach the placenta in humans (Foiles et al. 1988).

Limited data are available regarding the distribution of related nitrosamines. Daugherty and Klapp (1976) reported that after oral administration of ¹⁴C-N-nitrosodimethylamine to mice radioactivity could be

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

2.6.3 Metabolism

No studies were located regarding metabolism in humans following exposure to N-nitrosodi-n-propylamine. .

In vitro and in vivo studies with rodents have been conducted that provide evidence that N-nitrosodi-n-propylamine can be metabolized via oxidation at the alpha, beta and gamma carbon positions (Figure 2-2). Alpha carbon oxidation (hydroxylation) is regarded as the primary pathway, resulting in formation of propionaldehyde and 1-propanol and 2-propanol as metabolites (Farrelly et al. 1984; Park and Archer 1978; Park et al. 1977). 1-Propanol and 2-propanol are formed via propyldiazohydroxide and a propyl cation (carbonium ion). It is generally believed that the carbonium ions can also react with nucleic acids to form propylated adducts, but Park et al. (1980) have suggested that propylation takes place via a bimolecular reaction. However, reaction of DNA with propylnitrosourea (a direct acting equivalent of N-nitrosodi-n-propylamine) results in formation of n-propyl and isopropyl DNA adducts, suggesting carbonium ions are involved. Alkylation of nucleic acids and proteins by metabolites of nitrosamines has been suggested as the mechanism responsible for the toxic and carcinogenic properties of these substances.

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

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

Documented and postulated metabolites of N-nitrosodi-n-propylamine have been shown to be carcinogenic in hamsters and rats (IARC 1978). These include N-nitroso-bis-(2-hydroxy-n-propyl)amine, N-nitroso-2-oxo-n-

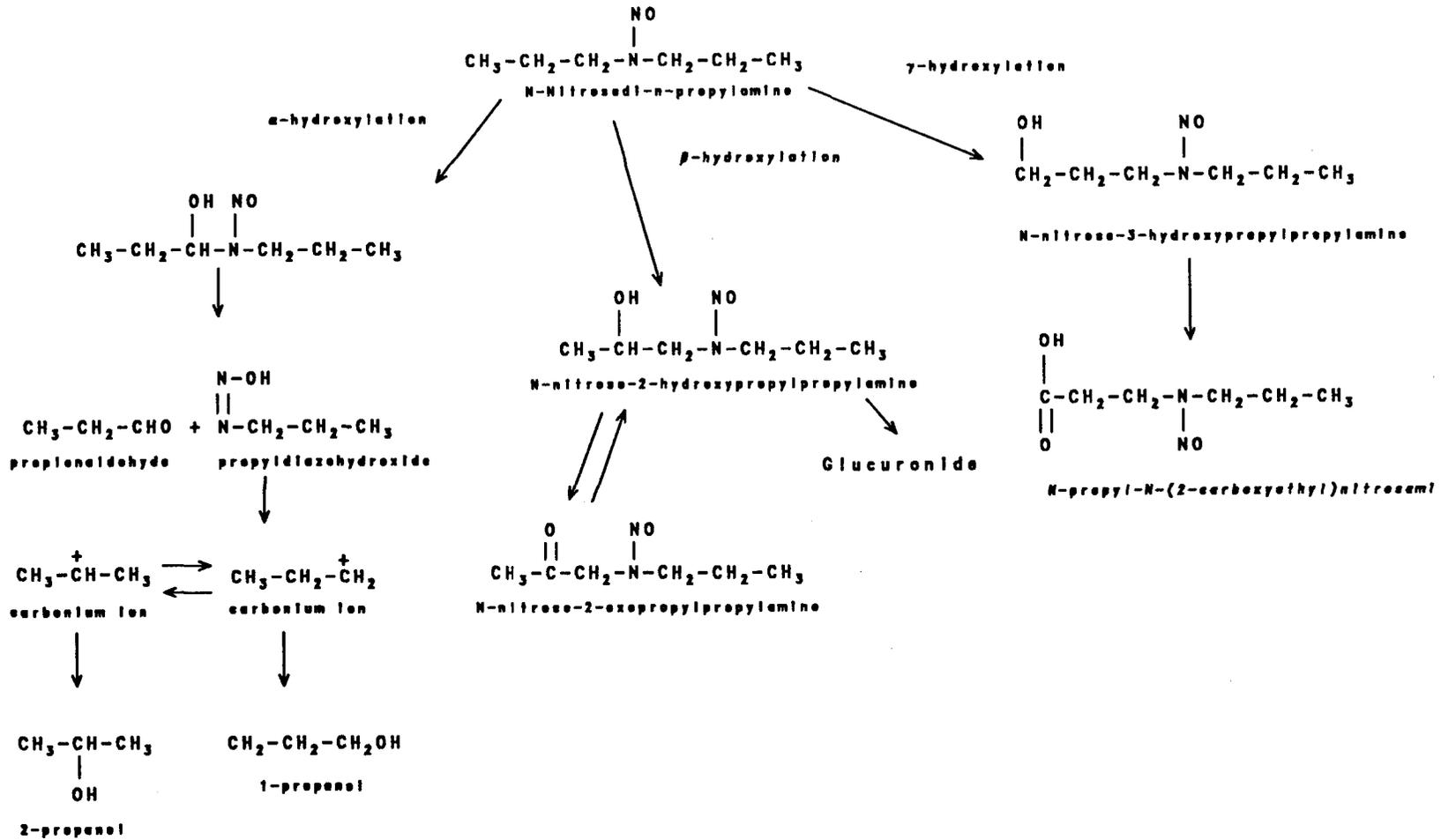


FIGURE 2-2. Metabolism of N-Nitrosodi-n-propylamine

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propylpropylamine, N-nitroso-bis(2-oxo-n-propyl)amine and N-nitroso-bis(2-acetoxy-n-propyl)amine. Main tumor sites of many of these metabolites include those associated with N-nitrosodi-n-propylamine treatment (Section 2.2.2.8, Oral exposure, Cancer).

2.6.4 Excretion

2.6.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals following inhalation exposure to N-nitrosodi-n-propylamine.

2.6.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to N-nitrosodi-n-propylamine.

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

2.6.4.3 Dermal Exposure

No studies were located regarding excretion in humans following dermal exposure to N-nitrosodi-n-propylamine.

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

2.7 INTERACTIONS WITH OTHER CHEMICALS

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

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2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations with unusual susceptibility to health effects of N-nitrosodi-n-propylamine have been identified. However, heavy consumers of alcoholic beverages might be considered to be a susceptible population based on a single report in which ethanol was shown to potentiate the carcinogenicity of N-nitrosodi-n-propylamine in mice (Griciute et al. 1982).

2.9 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of N-nitrosodi-n-propylamine is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

2.9.1 Existing Information on Health Effects of N-Nitrosodi-n-propylamine

Information regarding health effects of N-nitrosodi-n-propylamine in humans is not available. Health effects of N-nitrosodi-n-propylamine in animals have been investigated only in oral exposure studies. As indicated in Figure 2-3, animal oral data are available for lethality, acute systemic effects, genotoxicity and cancer. These data indicate that the acute toxicity of N-nitrosodi-n-propylamine is attributable to hepatic effects and that intermediate duration exposure is life-shortening due to cancer.

2.9.2 Data Needs

Single Dose Exposure. Information on lethality (LD_{50}) and severe systemic effects in rats are available from one single dose oral study. Similar information is available from single dose subcutaneous injection studies with rats, mice and hamsters. Another oral study reported a nonlethal effect (increased pentobarbital sleeping time) but none of the other studies reported non-lethal doses or attempted to identify dose-response data for other subtle systemic effects. Additional single dose oral studies would provide better information on thresholds for lethality and systemic toxicity as well as interspecies differences. Inhalation and dermal studies with N-nitrosodi-n-propylamine have not been conducted; single dose studies involving exposure by these routes would provide information on lethality, systemic effects and skin and eye irritation.

2. HEALTH EFFECTS

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Carcinogenic
		Acute	Intermed.	Chronic						
Inhalation										
Oral										
Dermal										

HUMAN

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Carcinogenic
		Acute	Intermed.	Chronic						
Inhalation										
Oral	●	●						●	●	
Dermal										

ANIMAL

● Existing Studies

FIGURE 2-3. Existing Information on Health Effects of N-Nitrosodi-n-propylamine

2. HEALTH EFFECTS

Repeated Dose Exposure. Oral studies provide limited information on the threshold for hepatotoxicity in mice. Several intermediate duration oral studies with rats, one limited oral study with mice and injection studies with rats, mice, hamsters and monkeys provide survival data but no information on effects other than cancer. Additional short-term repeated dose oral studies (e.g., 14-28 day studies) in various species could provide additional information on systemic effects, particularly dose-response characterization of hepatic/hemorrhagic effects. Repeated dose inhalation studies are lacking and could provide useful information regarding lethality and systemic effects.

Chronic Exposure and Carcinogenicity. Chronic oral toxicity data for N-nitrosodi-n-propylamine are not available because treated animals have died of cancer within one year of treatment. Animals treated with doses lower than those used in the intermediate duration studies may survive chronic exposure and provide information on nonneoplastic effects. With the exception of a single study with mice, species other than rat have not been tested for carcinogenicity by the oral route.

Genotoxicity. The genotoxicity of N-nitrosodi-n-propylamine is documented but only one in vivo study used an environmentally relevant route of exposure (oral), and only two studies (in vitro) evaluated human cells. Additional studies, particularly types providing information on the potential for heritable mutations in humans, would add to the data base on genotoxicity.

Reproductive Toxicity. Information on the reproductive toxicity of N-nitrosodi-n-propylamine is not available. Histological examinations of reproductive organs of animals exposed in subchronic and chronic studies would provide relevant data. Multigenerational or continuous breeding studies would provide further information regarding reproductive effects of N-nitrosodi-n-propylamine in animals, which may be related to possible reproductive effects in humans.

Developmental Toxicity. Some data on developmental toxicity are available from single-dose subcutaneous injection studies with hamsters. Developmental effects of N-nitrosodi-n-propylamine have not been investigated in animals exposed by natural routes. Developmental studies in animals by natural routes of exposure would provide information on possible developmentally toxic effects, including transplacental carcinogenicity, that might be relevant to humans. These studies should include postnatal evaluations for neonatal mortality, as well as for tumor incidence in adult animals.

Immunotoxicity. Histological examination of organs and tissues of the immunological system from animals exposed in subchronic and chronic studies would provide relevant information as immunotoxicity data for N-nitrosodi-n-propylamine are not available. Specific immunotoxicity tests or a battery of immunotoxicity tests would provide a better assessment of possible

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immunotoxic effects. Sensitization tests in animals might provide information on whether there is likely to be an allergic response to N-nitrosodi-n-propylamine. Although the low molecular weight of N-nitrosodi-n-propylamine would probably preclude activity as an antigen by itself, it is possible that a higher molecular weight moiety resulting from alkylation of proteins by N-nitrosodi-n-propylamine could produce an allergic response.

Neurotoxicity. Information on the neurotoxicity of N-nitrosodi-n-propylamine is not available. A battery of tests for neurotoxicity would provide further information of neurotoxicity in animals, which then might be related to possible neurotoxic effects in humans.

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

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

Biomarkers of Disease. No disease states in humans produced by exposure to N-nitrosodi-n-propylamine are known. If epidemiological studies are conducted that correlate exposure with diseases, it may be possible to identify subtle changes, such as altered blood chemistry indices, associated with a particular disease state.

Disease Registries. Diseases in humans produced by exposure to N-nitrosodi-n-propylamine are not known. If epidemiological studies identify particular diseases produced by N-nitrosodi-n-propylamine, it may be possible to determine the number of people affected and the factors associated with identifying the disease in certain populations, such as, those with exposure to high levels near hazardous waste sites.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of N-nitrosodi-n-propylamine from environmental media. The lack of data concerning levels in human tissues and fluids does not necessarily indicate a lack of bioavailability since the monitoring literature reports that N-nitrosodi-n-propylamine is present in some foods, water, beverages and workroom air. It is, therefore, important to determine if N-nitrosodi-n-propylamine can be absorbed by humans from

2. HEALTH EFFECTS

environmental samples. An understanding of the bioavailability of N-nitrosodi-n-propylamine from environmental media may be obtained by studying the biological fluids of individuals exposed to N-nitrosodi-n-propylamine in the workplace or through the ingestion of N-nitrosodi-n-propylamine-containing foods and beverages such as cheeses, cured meats, and whiskey. Limited information is available regarding absorption parameters of N-nitrosodi-n-propylamine in experimental animals. However, one could assume, based on data obtained with other nitrosamines, that N-nitrosodi-n-propylamine would be readily absorbed from the gastrointestinal tract if ingested from contaminated soil.

Food Chain Bioaccumulation. No studies were available concerning food chain bioaccumulation of N-nitrosodi-n-propylamine from environmental media. The monitoring literature indicates that N-nitrosodi-n-propylamine has been detected in samples of cooked fish and meat; however, occurrence of N-nitrosodi-n-propylamine in these samples was not the result of bioaccumulation, but was the result of formation resulting from preservation and/or cooking. Various studies have also shown that N-nitrosamines, such as N-nitrosodi-n-propylamine, form in the gastrointestinal tract during digestion of foods containing secondary amines. Estimation techniques have been used to determine that N-nitrosodi-n-propylamine would not bioaccumulate in lipids of fish (see Section 5.3.1, Transport and Partitioning). Based on this limited amount of information it is speculated that human exposure to N-nitrosodi-n-propylamine through diet is not the result of food chain bioaccumulation. Monitoring for the accumulation of N-nitrosodi-n-propylamine in organisms from several trophic levels could be used to support this conclusion.

Absorption, Distribution, Metabolism, Excretion. The general metabolic pathways of N-nitrosodi-n-propylamine in animals have been identified, but the relative contribution of the pathways in vivo, particularly following exposure by natural routes, is inadequately characterized. The identity of the alkylating agent(s) associated with carcinogenesis is unclear. Information is available regarding absorption and distribution of N-nitrosodi-n-propylamine. Evidence from other nitrosamines indicates that a number of factors (e.g., species, route of exposure, dosing schedule) appear to determine the organ specificity and the severity of the effects induced by these compounds. Therefore, to fully characterize the pharmacokinetics of N-nitrosodi-n-propylamine, studies of absorption, distribution, metabolism, and excretion in animals following exposure by all three routes are needed.

Comparative Toxicokinetics. The toxic and carcinogenic effects of N-nitrosodi-n-propylamine are attributable to activity of metabolites but no data are available to determine if there are quantitative differences in metabolism among species. Information from other nitrosamines suggests that there are species-characteristic tumors induced by nitrosamines. This seems to be the reflection of differences in metabolic activities (and also repair mechanisms) existing among animal species; therefore, caution must be

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exercised when extrapolating possible effects in humans. Although toxicity and carcinogenicity of N-nitrosodi-n-propylamine has been demonstrated in rodents and monkeys, the animal species that serves as the best model for extrapolating results to humans may be difficult to identify.

2.9.3 On-going Studies

No on-going studies of N-nitrosodi-n-propylamine were identified.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of N-nitrosodi-n-propylamine are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of N-nitrosodi-n-propylamine are presented in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of N-Nitrosodi-n-Propylamine

	Value	Reference
Chemical name	1-Propanamine, N-nitroso-N-propyl	CAS 1988
Synonyms	N-nitrosodipropylamine; N,N-dipropylnitrosamine; N-Nitroso-N-di-n-propylamine; NDPA; DPNA; DPN	SANSS 1988; HSDB 1988
Trade name(s)	Not available	
Chemical formula	C ₆ H ₁₄ N ₂ O	CAS 1988
Chemical structure	$ \begin{array}{c} \text{CH}_3\text{-CH}_2\text{-CH}_2 \\ \quad \quad \quad \backslash \\ \quad \quad \quad \text{N-N=O} \\ \quad \quad \quad / \\ \text{CH}_3\text{-CH}_2\text{-CH}_2 \end{array} $	SANSS 1988
Identification numbers:		
CAS Registry	621-64-7	CAS 1988
NIOSH RTECS	JL9700000	RTECS 1988
EPA Hazardous Waste	U111	RTECS 1988
OHM-TADS	8300201	OHM-TADS 1988
DOT/UN/NA/IMCO	Not available	
HSDB	5108	HSDB 1988
NCI	Not available	

CAS = Chemical Abstract Service

NIOSH = National Institute for Occupational Safety and Health

RTECS = Registry of Toxic Effects of Chemical Substances

EPA = Environmental Protection Agency

OHM-TADS = Oil and Hazardous Materials - Technical Assistance Data Base

DOT/UN/NA/IMCO = Department of Transportation/United Nations/North

America/International Maritime Consultive Organization

HSDB = Hazardous Substances Data Bank

NCI = National Cancer Institute

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Chemical and Physical Properties of
N-Nitrosodi-n-Propylamine

Property	Value	Reference
Molecular weight	130.19	Weast 1983
Color	Yellow	IARC 1978
Physical state	Liquid	IARC 1978
Melting point	6.6°C (estimated) -12°C (estimated)	Lyman 1985 EPA 1986a
Boiling point	206°C	Weast 1983
Specific gravity, 20/4°C	0.9163	Weast 1983
Odor	Not available	
Odor threshold		
Water	Not available	
Air	Not available	
Solubility		
Water	9,894 mg/L (23-25°C)	Mirvish et al. 1976
Organic solvents	Soluble in alcohol, ether, other organic solvents	Weast 1983; IARC 1978
Partition coefficient		
Log octanol/water	1.36	Hansch and Leo 1985
Log K _{oc}	2.11 (estimated)	
Vapor pressure	0.086 mm Hg (20°C) (estimated)	Klein 1982
Henry's Law constant	1.47x10 ⁻⁶ atm-m ³ /mole at 20°C (estimated from vapor pressure and water solubility data)	
Autoignition temperature	Not available	

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2 (continued)

Property	Value	Reference
Flashpoint	Not available	
Flammability limits in air	Not available ^a	
Conversion factors		
ppm (v/v) to mg/m ³ in air (20°C)	ppm (v/v) x 5.41 = mg/m ³	
mg/m ³ to ppm (v/v) in air (20°C)	mg/m ³ x 0.185 = ppm (v/v)	

^aVapor probably does not form an explosive mixture with air at ordinary temperatures (OHM-TADS 1988).

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

N-Nitrosodi-n-propylamine is not produced for commercial use in the United States (HSDB 1988). The public portion of the EPA TSCA Production File indicates that The Ames Laboratories in Milford, CT prepared <1000 pounds during 1977, and that Eastman-Kodak in Rochester, NY prepared none during 1977, although it had the capability to do so and had prepared small research quantities in the past (EPA 1977). N-nitrosodi-n-propylamine may be produced as an impurity in the pesticides trifluralin, isopropalin, and oryzalin (Cohen et al. 1978, Wotherspoon and Hindle 1988). N-Nitrosodi-n-propylamine can be prepared by the reaction of nitrous acid with di-n-propylamine (HSDB 1988).

4.2 IMPORT

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

4.3 USE

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

4.4 DISPOSAL

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

4.5 ADEQUACY OF THE DATA BASE

Section 104 (i) (5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of N-nitrosodi-n-propylamine is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

4.5.1 Data Needs

Production, Use, Release, and Disposal. Uses, methods of synthesis, and methods of disposal are described in the literature and there does not appear to be a need for further information in these topics. Lack of information pertaining to the import of this compound is to be expected since this compound has no commercial significance and it is doubtful that research quantities would be imported rather than prepared by laboratories in the United States. Data regarding the amount of N-nitrosodi-n-propylamine released to air, water, and soil are needed in order to establish potential sources of exposure and levels of exposure from environmental media. In particular, releases from hazardous waste landfills and industries in which this compound is inadvertently formed should be established in order to determine whether people living in the vicinity of these sites are exposed to elevated levels of this compound. According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Information on the production and environmental sources of di-n-propylamine, tri-n-propylamine and the N-oxide of tri-n-propylamine is needed due to the possible presence of N-nitrosodi-n-propylamine as a contaminant, and the possibility of inadvertent formation of N-nitrosodi-n-propylamine from reaction to these compounds with ubiquitous nitrate. There is also a need to investigate whether N-nitrosodi-n-propylamine occurs in waste sites where these precursor compounds are disposed due to occurrences as an impurity or in situ formation.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

N-nitrosodi-n-propylamine is not an industrially or commercially important chemical. It is produced in small, laboratory-scale quantities for research purposes. It is also produced inadvertently during certain manufacturing processes, occurring as an impurity in some dinitroaniline pesticides and during manufacture of some extruded rubber products. Nitrosodi-n-propylamine could also be present in certain secondary amines (di-n-propylamine, tri-n-propylamine and the N-oxide of tri-n-propylamine) as an impurity or due to inadvertent nitrosation of these amines in industrial processes other than those mentioned above. Low levels of Nitrosodi-n-propylamine may be released to the environment from contaminated products, from industrial sites of inadvertent production or from disposal of wastes containing this chemical. N-nitrosodi-n-propylamine could also be released to the environment from waste disposal sites where the precursor secondary amines have been discharged, but the potential for human exposure from nitrosation of precursors at waste sites has not been evaluated.

N-Nitrosodi-n-propylamine is not expected to be a persistent environmental contaminant. If released to the ambient atmosphere, it should be degraded by direct photolysis and/or reaction with sunlight-produced hydroxyl radicals (overall half-life typically on the order of several hours). In water with significant exposure to sunlight, N-nitrosodi-n-propylamine would be subject to rapid photolysis (half-life about 2-3 hours). On soil surfaces, N-nitrosodi-n-propylamine would be subject to rapid removal by photolysis and volatilization. The volatilization half-life of N-nitrosodi-n-propylamine from soil surfaces after spray application of a dinitroaniline herbicide was found to be between 2 to 6 hours. In subsurface soil and in water beyond the penetration of sunlight, N-nitrosodi-n-propylamine would be susceptible to biodegradation under both aerobic and anaerobic conditions. In subsurface soil, the half-life of N-nitrosodi-n-propylamine has been found to range from 14 to 40 days under aerobic conditions and 47 to 80 days under anaerobic conditions. At this time, N-nitrosodi-n-propylamine has been found in at least 1 of 1177 hazardous waste sites on the National Priorities List (NPL) in the United States (VIEW Database 1989).

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

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

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

5.2.2 Water

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

5.2.3 Soil

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

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

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

5. POTENTIAL FOR HUMAN EXPOSURE

estimated vapor pressure of N-nitrosodi-n-propylamine [0.086 mm Hg at 25°C (see Table 3-2)] indicates that this compound should not partition from the vapor phase to particulates in the atmosphere.

Using linear regression equations based on $\log K_{ow}$ data [$\log K_{ow} = 1.36$ (see Table 3-2)], a bioconcentration factor of 6 and an adsorption coefficient (K_{oc}) of 129 have been estimated for N-nitrosodi-n-propylamine (Bysshe 1982; Hansch and Leo 1985; Lyman 1982). These values indicate that bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments in water would not be important fate processes. The low Henry's Law constant for N-nitrosodi-n-propylamine [1.47×10^{-6} atm-m³/mol (see Table 3-2)] suggests that volatilization would be a relatively insignificant fate process in water.

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

5.3.2 Transformation and Degradation

5.3.2.1 Air

In the atmosphere, N-nitrosodi-n-propylamine vapor would be rapidly degraded by direct photolysis and/or reaction with photochemically-generated hydroxyl radicals. Crosby et al. (1980) determined a pseudo-first order half-life of 5 to 7 hours for photolysis of N-nitrosodi-n-propylamine vapor in air exposed to sunlight. Although experimental conditions did not closely simulate environmental conditions (the concentration of N-nitrosodi-n-propylamine was relatively high), results of this study did indicate that N-nitrosodi-n-propylamine is susceptible to rapid photolysis. The half-life for the reaction of N-nitrosodi-n-propylamine vapor with photochemically-generated hydroxyl radicals has been estimated to be about 16 hours in typical ambient air. This value is based on a reaction rate constant of 2.42×10^{-11} cm³/molecules-sec at 25°C which was estimated using the method of Atkinson (1987).

5.3.2.2 Water

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

5. POTENTIAL FOR HUMAN EXPOSURE

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

5.3.2.3 Soil

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

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

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

5.4.2 Water

No data were available regarding the monitoring and detection of N-nitrosodi-n-propylamine in ambient surface water, groundwater, or drinking water in the United States except at EPA National Priorities List (NPL) hazardous waste sites. There were only a couple of monitoring studies available pertaining to the occurrence N-nitrosodi-n-propylamine in treated wastewater. In a survey of 32 U.S. textile plants, N-nitrosodi-n-propylamine was detected at concentrations of 2-20 $\mu\text{g/L}$ in 2 out of 32 samples of secondary effluent, while no detectable levels were found in samples of raw wastewater from these same plants (Rawlings and Samfield 1979). This suggests that N-nitrosodi-n-propylamine was formed during the treatment process. N-nitrosodi-n-propylamine has also been detected at a maximum concentration of 1.2 $\mu\text{g/L}$ in the final effluent from a German chemical manufacturing plant involved in the manufacture and/or use of amines (Hartmetz and Slemrova 1980). A survey of stormwater runoff samples collected from 15 cities geographically located across the U.S. revealed

5. POTENTIAL FOR HUMAN EXPOSURE

that N-nitrosodi-n-propylamine is not a typical contaminant of stormwater runoff (Cole et al. 1984). Water samples collected from agricultural fields immediately following application of the pesticide trifluralin contained no detectable levels of N-nitrosodi-n-propylamine (detection limit 0.01-0.02 µg/L) (Ross et al. 1978, West and Day 1979).

5.4.3 Soil

Soil samples collected from agricultural fields immediately following application of the pesticide trifluralin contained no detectable levels of N-nitrosodi-n-propylamine (detection limit 0.2-1 ng/g) (Ross et al. 1978, West and Day 1979). It has been detected in at least 1 of 1177 NPL hazardous waste sites (VIEW 1989).

5.4.4 Other Media

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

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

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5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

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

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

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

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

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5.7 ADEQUACY OF THE DATA BASE

Section 104 (i) (5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of N-nitrosodi-n-propylamine is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

5.7.1 Data Needs

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

Environmental Fate. Data are available to establish, in general, the environmental fate of N-nitrosodi-n-propylamine. It has been predicted that in surface waters, beyond the reach of sunlight, N-nitrosodi-n-propylamine would be subject to slow microbial degradation; however, data are needed to determine its degradation rate in unlit surface water under aerobic or anaerobic conditions. Natural water grab sample biodegradation studies and soil metabolism studies carried out in the dark under both aerobic and anaerobic conditions would be useful in establishing the persistence of N-nitrosodi-n-propylamine in the environment. The dominant removal mechanisms for N-nitrosodi-n-propylamine in air are expected to be photolysis and reaction with photochemically generated hydroxyl radicals; however, no data are available concerning the reaction pathway and the products of these types of reactions. These types of data would be useful in establishing what happens to this compound when it is released to the environment.

Exposure Levels in Environmental Media. Data are needed to relate the levels of N-nitrosodi-n-propylamine found at hazardous waste landfills to

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

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

Exposure Registries. An exposure registry currently is not available. The development of a registry for exposures would provide a useful reference tool in assessing exposure levels and frequency. In addition, a registry would allow an assessment of the variations in exposure concentrations from, for example, geography, season, regulatory actions, presence of hazardous waste landfills, or manufacturing facilities. These assessment would, in turn, provide a better understanding of the needs for some type of research or data acquisition based on current exposure concentrations. Occupational exposure to this compound is mainly through its inadvertent formation, so an occupational exposure registry would be difficult to obtain.

5.7.2 On-going Studies

There is no indication that there are any studies currently in progress which are related to the level of N-nitrosodi-n-propylamine in environmental media, environmental fate of N-nitrosodi-n-propylamine, or general population or occupational exposure to N-nitrosodi-n-propylamine.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

Methods used for the analysis of N-nitrosodi-n-propylamine in biological samples are shown in Table 6-1. The use of vacuum distillation at low temperature (60-70°C) and trapping the distillate in dry ice/acetone bath is the preferred method for the isolation of the compound from biological matrices. Because of its selectivity and sensitivity, methods using Thermal Energy Analyzer (TEA) detectors are selected for quantification of this compound. In cases where analysis of multiple pollutants are necessary, mass spectrometric detectors, in spite of their lower sensitivity for nitrosodi-n-propylamine, may be favored over the TEA detector.

6.2 ENVIRONMENTAL SAMPLES

Methods used for the analysis of N-nitrosodi-n-propylamine in environmental samples are given in Table 6-2. Two pretreatment methods are most suitable for the analysis of this compound in environmental samples. When the matrix is not too complex, as in the case of drinking water, surface water, groundwater and wastewater, solvent extraction is the preferred method. With more complex matrices as soil and foodstuffs, vacuum distillation and cold trapping is more suitable. The three methods commonly used for the quantification of this compound in environmental samples are mass spectrometry, nitrogen-phosphorus detectors (NPD) and TEA in chemiluminescence mode. Each of these detectors has its own advantages and disadvantages. When a high sensitivity is required, a method using a TEA detector may be the method of choice. For multipollutant analysis in a single sample, mass spectrometry may be more suitable. Nitrogen-phosphorus detectors, on the other hand, may be more cost-effective and will provide reasonable specificity and sensitivity for nitroso compounds. A Hall detector in the pyrolytic mode may be preferable over NPD detectors because it may require less sample clean-up (Rhoades et al. 1980).

6.3 ADEQUACY OF THE DATA BASE

Section 104 (i) (5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of N-nitrosodi-n-propylamine is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects (and techniques for developing methods to determine such health effects). The following discussion highlights the availability, or absence, of exposure and toxicity information applicable to human health assessment. A statement of the

TABLE 6-1. Analytical Methods for N-Nitrosodi-n-propylamine in Biological Samples

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Urine	Extracted with solvent, cleaned by washing with water, extract dried, concentrated, and subjected to acid catalyzed denitrosation and reaction of evolved NO with ozone.	Chemiluminescence detection	0.05 µg/L (for 100 mL sample)	65% at 11 ppb	Drescher and Frank 1978
Postmortem tissues (brain, liver, kidneys, and pancreas)	Organs mixed with KOH and ammonium sulfamate homogenized, vacuum-distilled distillate solvent extracted and concentrated. Concentrate derivatized for ECD only.	GC-ECD and GC-TEA	<0.5 µg/kg (for 50 g sample)	77-88% (GC-ECD)	Cooper et al. 1987
Liver, kidney, and blood	Organs mixed with sulfuric acid and ammonium sulfamate homogenized and extracted with solvent and concentrated.	GC-TEA	0.6 ng/kg	91% (liver) 96% (kidney) 83% (blood)	Maki 1980
Urine, blood, feces, saliva and gastric contents	Homogenized sample mixed with paraffin or glycerol, water and sodium hydroxide, vacuum distilled at low temperature. Distillate extracted on-column or by shaking with solvent and extract concentrated.	GC-TEA	0.05-0.5 µg/kg	79% (for urine)	Eisenbrand et al. 1983

GC = Gas chromatography; ECD = electron capture detected; TEA = thermal energy analyzer

TABLE 6-2. Analytical Methods for N-Nitrosodi-n-propylamine in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Occupational air	Sorbed onto ThermoSorb/N, desorbed by CH ₂ Cl ₂ /CH ₃ IG	HRGC-MS	<0.1 µg/m ³ (monitoring NO ⁺) <0.04 µg/m ³ (monitoring parent ion)	NG	Cooper 1987
Water and wastewater	Solvent extracted, acid washed, column chromatographic cleanup	GC-NPD; GC-reductive HECD GC-TEA (EPA Method 607))	0.46 µg/L (GC-NPD)	61% at 9 µg/L	EPA 1982
	Solvent extracted, acid washed, column chromatographic cleanup	GC-NPD (collaborative study on EPA Method 607)	0.46 µg/L (clean water) 0.36-0.74 µg/L (wastewater)	82% at 1.22 µg/L 84% at 26.7 µg/L 92% at 1.22 µg/L 94% at 26.7 µg/L	Millar et al. 1984
	Solvent extraction under basic condition, solvent concentrated	GC-MS (EPA Method 625)	NG	68% (reagent water) 76% (wastewater)	EPA 1982
Water	Solvent extracted, water washed and concentrated, acid catalyzed denitrosation and reaction evolved NO with ozone	Chemiluminescence detection	0.05 µg/L (for 100 mL sample)	61% at 11 ppb (11 µg/L)	Drescher and Frank 1978
	Direct injection	HPLC separation, resolved nitrosoamine photolyzed to nitrite and detected colorimetrically	NG	NG (suggested screening method)	MacMillan 1983
Waste and wastewater	Solvent extraction, column chromatographic cleanup, if necessary, and concentration	GC-AFID (nitrogen mode) GC-Hall (pyrolytic mode) GC-TEA	NG	54-103% (AFID) 73-108% (Hall) 78-104% (TEA) at 1.2 µg/L	Rhoades et al. 1980
	Solvent extraction under neutral condition, solvent concentrated	HRGC-MS (EPA Method 625.1)	<10 µg/L	67% at 20 µg/L	Eichelberger et al. 1983
Groundwater	Solvent extraction at pH 11, solvent concentrated	GC-MS (EPA CLP Method)	10 µg/L	NG	EPA 1987, Fisk 1986

TABLE 6-2 (continued)

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Groundwater	Solvent extraction, column chromatographic cleanup, concentration of extract	GC-MS (EPA Method 8250)	NG	79% at 19 µg/L	EPA 1986b
	Solvent extraction, column chromatographic cleanup, concentration of extract	HRGC-MS (EPA Method 8270)	10 µg/L	79% at 19 µg/L	EPA 1986b
Soil	Aqueous extract subjected to combined distillation and solvent extraction, and extract concentrated	GC-FID	0.025 µg/g	81-87%	Pancholy 1976
	Homogenized sample mixed with paraffin or glycerol, water and NaOH, vacuum distilled at low temperature. Distillate extracted on-column or by shaking with solvent and extract concentrated	GC-TEA	0.05-0.5 µg/g	71%	Eisenbrand et al. 1983
	Sample solvent extracted, washed with water and concentrated concentrate, subjected to acid catalyzed nitrosation and evolved NO reacted with ozone	Chemiluminescence detection	0.05 µg/kg	69% at 11 ppb (11 µg/kg)	Drescher and Frank 1978
Soil/sediment	Solvent extracted, column chromatographic cleanup if necessary, extract concentrated	GC-MS (EPA CLP Method)	330 µg/kg	NG	EPA 1987, Fisk 1986
Soil, sludge or solid waste	Solvent extracted by Soxhlet or or sonication, extract subjected to column chromatographic cleanup, concentration of extract	GC-MS (EPA Method 8250)	NG	NG	EPA 1986b
Soil, sludge or solid waste	Solvent extracted by Soxhlet or or sonication, extract cleaned by column chromatography and concentrated	HRGC-MS (EPA Method 8270)	660 µg/kg	NG	EPA 1986b
Whiskey and beer	Sample mixed with paraffin or glycerol, water and NaOH vacuum distilled at low temperature. Distillate solvent extracted and concentrated	GC-TEA	0.05-0.5 µg/L	77-86%	Eisenbrand et al. 1983

TABLE 6-2 (continued)

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Beans and fish	Blended sample distilled by freeze drying, extracted in solvent and concentrated	GC-FID	3 µg/g	90.6-99.4%	Du Plessis and Nunn 1972
Cooked bacon	Alkaline sample vacuum distilled, trapped in liquid N ₂ , extracted with solvent and concentrated	GC-TEA	NG	82% at 10 µg/kg	Greenfield et al. 1982
Canned tuna, corned beef, soya bean oil, deep fried fish, and french fries	Vacuum distillation from mineral oil extraction with solvent and concentrated	GC-TEA	5 µg/kg	95-100%	Fine et al. 1975
Rubber nipple	Sliced sample extracted with solvent and extract concentrated	HPLC-TEA with a cold trap	NG	NG	Rühl and Reusch 1985
	Sliced sample solvent extracted, solution made alkaline and distilled. Aqueous distillate solvent extracted and concentrated	GC-TEA with a cold trap	NG	10-120%	Gray and Stachiw 1987
Cosmetic products	Sample mixed with aqueous ammonium sulfamate and cleaned with CHCl ₃ . The aqueous solution cleaned up by a HPLC pre column	HPLC-DPP	0.2 ppb	NG	Vohra and Harrington 1981

NG = Not given; HRGC = high resolution gas chromatography, MS = mass spectrometry; NPD = nitrogen-phosphorus detector, HECD = Hall electrolytic conductivity detector, TEA = thermal energy analyzer; GC = gas chromatography; HPLC = high pressure liquid chromatography; AFID = alkali flame ionization detector; FID = flame ionization detector; DPP = differential pulse polanography

6. ANALYTICAL METHODS

relevance of identified data needs is also included. In a separate effort, ATSDR, in collaboration with NTP and EPA, will prioritize data needs across chemicals that have been profiled.

6.3.1 Data Needs

Methods for Determining Parent Compound and Metabolites in Biological Materials. Analytical methods of suitable sensitivity and specificity are available for the quantification of N-nitrosodi-n-propylamine in biological samples. The study of the levels of the parent compound in human blood, urine or other biological matrices can be useful in deriving a correlation between the level of this compound found in the environment and those found in human tissue and body fluid. Such correlation studies are not available for N-nitrosodi-n-propylamine. The changes in metabolite concentrations with time in human blood, urine, or other appropriate biological medium may be useful in estimating its rate of metabolism in humans. In some instances, a metabolite may be useful in correlating the exposed doses to the human body burden. Such studies on the levels of metabolites in human biological matrices are not available for this compound, although metabolic products of this compound from animal and in vitro studies have been identified (see Subsection 2.6.3) and analytical methods for their quantification are available.

Methods for Biomarkers of Exposure. No known biomarker for exposure to N-nitrosodi-n-propylamine has been identified (see Subsection 2.9.2). 7-Methyldeoxyguanosine and O6-methyldeoxyguanosine adducts are formed as a result of exposure to methylated nitrosoamines. Immunological assays are available for the determination of these adducts (Degan et al. 1988, Foiles et al. 1988). If propyl-substituted deoxyguanosine adducts are formed from N-nitrosodi-n-propylamine by similar reaction, it could be used as a biomarker for N-nitrosodi-n-propylamine exposure. If such a biomarker were available and a correlation were found between the level of the biomarker and exposure, it could be used as a measure of exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods of suitable sensitivity and specificity are available for the quantification of this compound in environmental samples. The levels of this compound in different environmental media can be used to indicate exposure of humans to this compound through the inhalation of air and ingestion of drinking water and foods containing N-nitrosodi-n-propylamine. If a correlation with human tissue or body fluid levels were available, the intake levels from different environmental sources could be used to estimate the body burden of the chemical in humans. Although the products of biotic and abiotic processes of this compound in the environment are adequately known, no systemic study is available that measured the concentrations of its degradation products in the environment. In instances where the product(s) of an environmental reaction is more toxic than the parent compound, it is important that the level of the degradation products in the environment be known. However, the

6. ANALYTICAL METHODS

degradation products of this compound in environmental media are less toxic compounds, namely n-propylamine, di-n-propylamine etc. (see Subsection 5.3.2). The analytical methods for the determination of the levels of these and other environmental degradation products of N-nitrosodi-n-propylamine are available.

6.3.2 On-going Studies

No significant on-going studies are in progress for the development of analytical methodologies for this compound in environmental or biological samples.

7. REGULATIONS AND ADVISORIES

International, National and State regulations and guidelines pertinent to human exposure to N-nitrosodi-n-propylamine are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

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

Agency	Description	Value	Reference
INTERNATIONAL			
WHO	Cancer classification	Group 2B ^a	IARC 1987
NATIONAL			
<u>Regulations</u>			
EPA OERR	Reportable quantity	10 lbs (proposed)	40 CFR 117 and 302
<u>Guidelines</u>			
EPA	Oral slope factor	7.0 (mg/kg/day) ⁻¹	EPA 1988
EPA	Cancer classification	Group B2 ^b	EPA 1988
STATE			
<u>Regulations</u>			
State of Kentucky	Ambient air quality standard	Best available control technology	State of Kentucky 1986

^aPossibly carcinogenic to humans.^bProbable human carcinogen.

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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 time period.

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

Carcinogen -- A chemical capable of inducing cancer.

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

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.

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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.

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_(L0) (LC_{L0}) -- 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_(L0) (LD_{L0}) -- 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.

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

LT₅₀ (lethal time) -- 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.

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

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

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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 a chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- That dose of chemical at which there are 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.

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

ql* - - The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually g/L for water, mg/kg/day for food, and g/m³ 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 lb 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-h 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.

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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.

TD₅₀ (toxic dose) -- 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.

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-h workday or 40-h workweek.

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 humans, (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: PEER REVIEW

A peer review panel was assembled for N-nitrosodi-n-propylamine. The panel consisted of the following members: Dr. Edmond LaVoie, College of Pharmacy, Rutgers University; Dr. Raymond Smith, Instructor, Department of Pathology and Microbiology, University of Nebraska Medical Center; Dr. Frank Lu, Private Consultant, Miami, FL; and Dr. Vincent Garry, Laboratory of Medicine and Pathology, University of Minnesota. These experts collectively have knowledge of N-nitrosodi-n-propylamine'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 the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has 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 their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.