TOXICOLOGICAL PROFILE FOR N-NITROSODIMETHYLAMINE

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

In collaboration with
U.S. Environmental Protection Agency (EPA)

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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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Acting Administrator
Agency for Toxic Substances and
Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS N-NITROSODIMETHYhYMINE?

N-Nitrosodimethylamine is commonly known as NDMA. It is a yellow liquid which has no distinct odor. It is produced in the U.S. only for use as a research chemical. NDMA was used to make rocket fuel, but this use was stopped after unusually high levels of this compound were found in air, water, and soil samples collected near a rocket fuel manufacturing plant. NDMA is, however, unintentionally formed during various manufacturing processes at many industrial sites and in air, water and soil from reactions involving other chemicals called alkylamines. Alkylamines are both natural and man-made compounds which are found widely distributed throughout the environment.

NDMA does not persist in the environment. When NDMA is released into the atmosphere, it breaks down in sunlight in a matter of minutes. When released to soil surfaces, NDMA may evaporate into air, break down upon exposure to sunlight, or sink into deeper soil. NDMA should break down within a few months in deep soil. When NDMA is released into water, it may break down upon exposure to sunlight or break down by natural biological processes. The rate of breakdown in water is not known. More information can be found in Chapters 3, 4 and 5.

1.2 HOW MIGHT I BE EXPOSED TO N-NITROSODIMETHYLAMINE?

Information suggests that the general population may be exposed to NDMA from a wide variety of sources, including environmental, consumer, and occupational sources. At this time, NDMA has been found in at least 1 out of 1177 hazardous waste sites on the National Priorities List (NPL) in the United States. Under certain conditions, NDMA may be found in outdoor air, surface waters (rivers and lakes, for example), and soil. The primary sources of human exposure to NDMA are tobacco smoke, chewing tobacco, diet [cured meats (particularly bacon), beer, fish, cheese, and other food items], toiletry and cosmetic products (for example, shampoos and cleansers), interior air of cars, and various other household goods, such as detergents and pesticides. In addition, NDMA can form in the stomach during digestion of alkylamine-containing foods. Alkylamines are naturally occurring compounds which are found in some drugs and in a variety of foods. Infants may be exposed to NDMA from the use of rubber baby bottle nipples and pacifiers which may contain very small amounts of NDMA, from ingestion of contaminated infant formulas, and from breast milk of some nursing mothers. Very low levels of NDMA have been found in some samples of human breast milk. Occupational exposure may happen in a large number of places including industries such as tanneries, pesticide manufacturing plants, rubber and tire manufacturing plants, alkylamine manufacture/use industries, fish processing industries, foundries, and dye manufacturing plants. Researchers making or handling NDMA may also be exposed to this compound if It passes through the rubber gloves they wear during laboratory work. NDMA

has been found in groundwater samples, in amounts of 10 parts NDMA per billion parts of water, at one or more hazardous waste sites on the National Priorities List (NPL). No information is available about contamination of soil, drinking water, irrigation water, sewers, storm drains, or the human food chain with NDMA near NPL sites. For more information, refer to Chapter 5.

1.3 HOW CAN N-NITROSODIMETHYIAMINE ENTER AND LEAVE MY BODY?

NDMA can enter the body when a person breathes air that contains NDMA or when a person eats food or drinks water contaminated with NDMA. NDMA can also enter the body through the skin after contact with rubber articles that contain NDMA. Experiments in animals have shown that after being given by mouth, NDMA enters the bloodstream and goes to many organs of the body in a matter of minutes. In the liver, NDMA is broken down into other substances, most of which leave the body within 24 hours in air exhaled from the lungs and in urine, along with the NDMA that is not broken down. Little is known about what happens to NDMA that enters the body through the skin or through contaminated air. Although vapors of NDMA are broken down within minutes after exposure to sunlight, if NDMA is spilled at a waste site and evaporates, a person nearby can be exposed to NDMA before it disappears from the air. The most important and probably the most harmful way of coming into contact with NDMA seems to be by eating contaminated food or drinking contaminated water. Further information on how NDMA can enter and leave the body can be found in Chapter 2.

1.4 HOW CAN N-NITROSODIMETHYUMINE AFFECT MY HEALTH?

NDMA is very harmful to the liver of animals and humans. People who were intentionally poisoned on one or several occasions with unknown levels of NDMA in beverage or food died of severe liver damage accompanied by internal bleeding. Animals that ate food, drank water, or breathed air containing high levels of NDMA over a period of days or several weeks also developed serious, non-cancerous, liver disease. When rats, mice, hamsters, and other animals ate food, drank water, or breathed air containing lower levels of NDMA for periods more than several weeks, liver cancer and lung cancer as well non-cancerous liver damage occurred. The high level short-term and low level long-term exposures that caused non-cancerous liver damage and/or cancer in animals also usually resulted in internal bleeding and death. Although there are no reports of NDMA causing cancer in humans, it is reasonable to expect that exposure to NDMA by eating, drinking, or breathing could cause cancer in humans. Mice that were fed NDMA during pregnancy had offspring that were born dead or died shortly after birth. However, it is not known whether NDMA could cause the death of human babies whose mothers are exposed during pregnancy. It should be realized that exposure to NDMA does not mean that any effect on health will definitely occur.

1. PUBLIC HEALTH STATEMENT

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO NITROSODIMETHWAMINE?

The presence of NDMA can be detected in blood and urine by a test, but this test is not usually available and has not been used as a test for human exposure or to predict possible health effects.

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

The amounts of N-nitrosodimethylamine in air, drinking water, and food that cause known health effects other than cancer in humans and animals are summarized in Tables l-l, l-2, l-3, and 1-4. These amounts are expressed as parts of NDMA per million parts of air, water, or food (ppm). As seen in Tables l-1 and l-3, the amounts of NDMA in air, water, or food that result in health effects in humans are unknown. As seen in Table 1-2, short-term exposure of animals to air containing NDMA produces liver damage and death. Toxic effects of long-term exposures of animals to air containing NDMA are unknown. As seen in Table l-4, short-term or long-term exposure of animals to water or food containing NDMA is also associated with serious effects, such as liver disease and death. More information on levels of NDMA that cause harmful effects in animals is presented in Chapter 2.

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

The Federal government has issued guidelines and rules to protect human health from exposure to NDMA in water and in food. The U.S. Environmental Protection Agency (EPA) has set limits on the amounts of NDMA in water such as lakes and streams. The EPA controls the release of NDMA. Releases or spills of one pound or more of NDMA must be reported to the National Response Center. The Food and Drug Administration (FDA) has set a limit of 10 parts of NDMA per billion parts of barley malt (ppb). Further information on Federal and state regulations can be found in Chapter 7.

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

1. PUBLIC HEALTH STATEMENT

TABLE 1-1. Human Health Effects from Breathing N-Nitrosodimethylamine*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term human exposure to air containing specific levels of NDMA are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term human exposure to air containing specific levels of NDMA are not known.

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

TABLE 1-2. Animal Health Effects from Breathing N-Nitrosodimethylamine

Short-term Exposure (less than or equal to 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects*
16	4 hour	Liver damage and death in dogs.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term animal exposure to air containing specific levels of NDMA 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.

TABLE 1-3. Human Health Effects from Eating or Drinking N-Nitrosodimethylamine*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from short-term human exposure to food containing specific levels of NDMA are not known.
Levels in Water (ppm)		The health effects resulting from short-term human exposure to water containing specific levels of NDMA are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects
		The health effects resulting from long-term human exposure to food containing specific levels of NDMA are not known.
Levels in Water (ppm)		The health effects resulting from long-term human exposure to water containing specific levels of NDMA are not known.

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

TABLE 1-4. Animal Health Effects from Eating or Drinking N-Nitrosodimethylamine

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
75	1 week	Liver damage in rats.
Levels in Water (ppm)		
20	1 day	Liver damage in hamsters.
50	1 week	Death in mice.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppm)	Length of Exposure	Description of Effects*
50	5 months	Liver damage in mice.
100	62-93 days	Death in rats.
Levels in Water (ppm)		
5.5	30 weeks	Death in rats.
20	28 days	Liver damage in hamsters.

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

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 NDMA. Its purpose is to present levels of significant exposure for NDMA 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 NDMA 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.

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

2.2.1.1 Death

At least two human deaths following inhalation of NDMA have been reported in the literature. One was a male chemist who was involved in the production of NDMA and was exposed to an unknown level of fumes for about two weeks, and subsequently to an unknown level of fumes during cleanup of a spilled flask (Freund 1937). The subject became ill 6 days later, showed abdominal distention, large amounts of yellow ascitic fluid, a tender and enlarged liver and enlarged spleen, and died 6 weeks after the last exposure. The other death was that of a male worker who was exposed to unknown concentrations of NDMA in an automobile factory. Autopsy of this subject showed a cirrhotic liver with areas of regeneration (Hamilton and Hardy 1974).

The lethality of inhaled NDMA has been evaluated in several acute duration studies with animals. Four-hour single exposure LC_{50} values of 78 ppm (95% confidence limits of 68 and 90 ppm) and 57 ppm (95% confidence limits of 51 and 64 ppm) were determined for rats and mice, respectively (Jacobson et al. 1955). The observation time in these assays was 14 days. The cause of death was not specified but liver damage and hemorrhage in various abdominal tissues were predominant pathologic findings. Druckrey (1967) reported that the "LD_{50}" for rats exposed to NDMA by inhalation for one hour is 37 mg/kg. The air concentration corresponding to this dose is not reported but a value of 925 ppm can be calculated from information provided in the report; confidence in this value is low, however, because this information is ambiguously reported. Two of three dogs that were exposed to 16 ppm NDMA for 4 hours died or were moribund by the second day (Jacobson et al. 1955). All dogs that were similarly exposed to 43-144 ppm died or were moribund after 1-3 days. The 57 ppm mouse and 78 ppm rat LC_{50} values are presented in the acute duration category in Table 2-1 and Figure 2-1. The Druckrey (1967) rat value is not included in Table 2-1 and Figure 2-1 due to uncertainty regarding its validity. The 16 ppm concentration represents a LOAEL for lethality in dogs due to acute duration inhalation

TABLE 2-1. Levels of Significant Exposure to N-Nitrosodimethylamine - Inhalation

Graph Key	Species	Exposure Frequency/ Duration	Effect	NOAEL[b] (ppm)	LOAEL[a] (Effect) Less Serious (ppm)	LOAEL[a] (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	rat	4 hr, once				78 (LC_{50})	Jacobson et al. 1955
2	mouse	4 hr, once				57 (LC_{50})	Jacobson et al. 1955
3	dog	4 hr, once				16 (death)	Jacobson et al. 1955
Systemic							
4	rat	4 hr, once	Hepatic			78 (hemorrhagic necrosis)	Jacobson et al. 1955
5	mouse	4 hr, once	Hepatic			57 (hemorrhagic necrosis)	Jacobson et al. 1955
6	dog	4 hr, once	Hemato			16 (increased clotting time)	Jacobson et al. 1055
7	dog	4 hr, once	Hepatic			16 (hemorrhagic necrosis)	Jacobson et al. 1955
CHRONIC EXPOSURE							
Cancer							
8	rat	life, 2 d/wk, 30 min/d				50 (CEL[c]) (nasal tumors)	Druckrey et al. 1967
9	rat	25 mo, continuous				0.07 (CEL) (liver, lung, kidney tumors)	Moiseev and Benemanski 1975
10	mouse	17 mo, continuous				0.07 (CEL) (liver, lung, kidney tumors)	Moiseev and Benemanski 1975

[a]NOAEL - No Observed Adverse Effect Level
[b]LOAEL - Lowest Observed Adverse Effect Level
[c]CEL - Cancer Effect Level

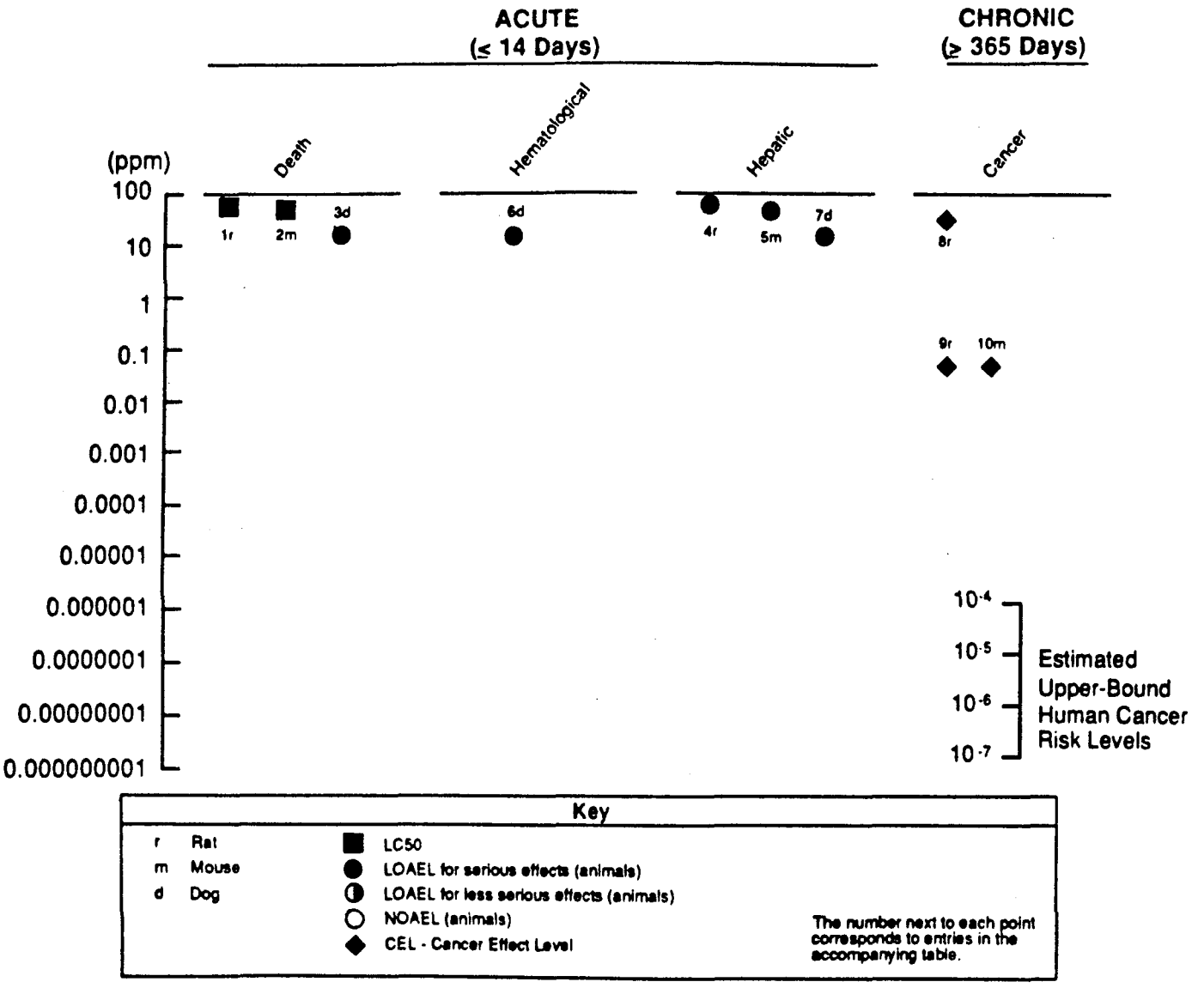

FIGURE 2-1. Levels of Significant Exposure to N-Nitrosodimethylamine - Inhalation

exposure (Table 2-l and Figure 2-l). The concentration of 16 ppm in air (Jacobson et al. 1955) is presented in Table l-2.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal or renal effects in humans or animals following inhalation exposure to NDMA.

Respiratory Effects. Freund (1937) observed small hemorrhages in the bronchi and trachea of a person who died from accidental exposure to vapors of NDMA (Section 2.2.1.1).

No studies were located regarding respiratory effects in animals following.inhalation exposure to NDMA.

Cardiovascular Effects. Subpericardial hemorrhage was observed in a person who died from accidental exposure to vapors of NDMA (Freund 1937) (Section 2.2.1.1).

No studies were located regarding cardiovascular effects in animals following inhalation exposure to NDMA.

Gastrointestinal Effects. Gastrointestinal hemorrhage was observed in a person who died from accidental exposure to vapors of NDMA (Freund 1937) (Section 2.2.1.1).

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to NDMA.

Hematological Effects. No studies were located regarding hematological effects in humans following inhalation exposure to NDMA.

Hematological determinations were performed in dogs that were exposed to 16-144 ppm NDMA for 4 hours (Jacobson et al. 1955). Increased coagulation time, increased prothrombin time, increased plasma cholinesterase levels and leukopenia occurred following exposure to all concentrations. There was no evidence of intravascular hemolysis. As indicated in Section 2.2.1.1, the concentrations producing these effects were lethal. Pathologic examination of the dogs showed bloody ascites and hemorrhage in the liver and other abdominal tissues, Due to the clinical evidence of impaired blood coagulation and the possibility that the hemorrhagic effects were related to impaired coagulation, 16 ppm is a LOAEL for hematological effects due to acute inhalation exposure (Table 2-l and Figure 2-l).

Hepatic Effects. Four cases of liver disease in humans resulting from inhalation exposure to NDMA have been described in the literature. Two of the subjects died; these cases are discussed in Section 2.2.1.1. Of the subjects who did not die, one was a chemist who was exposed to unknown concentrations of fumes and experienced exhaustion, headache, cramps in the

abdomen, soreness on the left side, nausea and vomiting for at least two years (Freund, 1937). The second case was an automobile factory worker who was exposed to unknown levels of NDMA and became violently ill with jaundice and ascites (Hamilton and Hardy 1974).

Hepatotoxicity is a predominant effect of high concentrations of inhaled NDMA in animals. Pathologic examination of dogs following exposure to 16-144 ppm NDMA for 4 hours showed marked necrosis and varying degrees of hemorrhage in the liver (Jacobson et al. 1955). Related effects at all concentrations included increased bilirubin levels and increased sulfobromophthalein retention. As indicated in Section 2.2.1.1, the concentrations producing these effects were lethal. Jacobson et al. (1955) also indicated that necrosis and hemorrhage occurred in the liver of rats and mice that were exposed to lethal concentrations of NDMA for 4 hours; as indicated in Section 2.2.1.1, LC_{50} values for the rats and mice are 78 and 57 ppm, respectively. The 16 ppm, 57 and 78 ppm concentrations represent LOAELs for hepatic effects due to acute inhalation exposure and are presented in Table 2-l and Figure 2-l. The concentration of 16 ppm in air (Jacobson et al. 1955) is presented in Table l-2.

Dennal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans following inhalation exposure to NDMA.

Limited information is available regarding dermal or ocular effects of inhaled NDMA. Doolittle et al. (1984) reported that the only toxic signs observed in rats exposed to 500 or 1000 ppm for 4 hours were reddened eyes and piloerection. The only additional information reported in this study pertained to genotoxic effects. Although high concentrations of NDMA vapor are likely to be irritating, the significance of the reddened eyes and piloerection cannot be determined because it is not specified if the effects occurred at both concentrations and prevalence is not indicated. As indicated in Section 2.2.1.1, acute exposure to much lower concentrations of NDMA was lethal for rats, mice and dogs. The lack of mortality in rats at the higher concentrations in the Doolittle et al. (1984) study may be attributable to the fact that the animals were killed immediately following exposure and consequently not observed for subsequent death.

No studies were located regarding the following effects in humans or animals following inhalation exposure to NDMA:

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following inhalation exposure to NDMA.

Rats exposed to 500 or 1000 ppm of NDMA in the air for 4 hours showed chemically induced DNA repair in epithelial cells in the nasal turbinates and trachea. DNA repair was also evident in hepatocytes, indicating that the substance entered the general circulation. No DNA repair was seen in the pachytene spermatocytes, indicating that NDMA either did not reach the testes in high enough concentrations, or that the testes could not metabolically activate the compound (Doolittle et al. 1984). It should be noted that the exposures in this study are likely to have been lethal if the rats had.been observed following treatment; as indicated in Section 2.2.1.1, 4-hour exposure to much lower concentrations of NDMA was lethal for rats, mice and dogs in other studies.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans following inhalation exposure to NDMA.

The carcinogenicity of inhaled NDMA has been evaluated in two studies. Twice weekly 30-minute exposures to 50 or 100 ppm NDMA vapor for life produced malignant nasal cavity tumors in rats (Druckrey et al. 1967). The incidence of tumors was 67% in each group, and the time to induce tumors in 50% of the rats was 400 days. Group sizes were small (12 and 6 animals at 50 and 100 ppm, respectively), control data were not reported, and additional information regarding longevity was not provided. The 50 ppm concentration is included in Table 2-l and Figure 2-l as an effect level for cancer (cancer effect level, CEL) in rats due to intermittent inhalation exposure of chronic duration.

Rats and mice that were continuously exposed to 0.07 ppm NDMA for 25 and 17 months, respectively, developed significantly increased incidences of lung, liver and kidney tumors (Moiseev and Benemanski 1975). Tumor types included various adenomas, carcinomas, and sarcomas in the lung, liver and kidneys, and hemangiomas in the liver, but the types were not tabulated according to species or concentration. Induction of nasal tumors was not reported. Exposure to 0.002 ppm NDMA according to the same schedule did not produce significantly increased incidences of tumors in either species. Since the tumors associated with exposure to 0.07 ppm NDMA are consistent with those produced by NDMA in oral and injection studies and the study is reported adequately otherwise, 0.07 ppm is considered to be a CEL for rats and mice due to continuous inhalation exposure of chronic duration (Table 2-1, Figure 2-l).

EPA has adopted the oral carcinogenicity slope factor (BH) of 51 $(mg/kg/day)^{-1}$ (see Section 2.2.2.8) as the slope factor for inhalation (EPA

1988a). The oral slope factor was converted to a unit risk for inhalation of 1.4×10^{-2} $(\bullet g/m^3)^{-1}$, which is equivalent to 42.4 $(ppm)^{-1}$. Using this unit risk, the concentrations associated with upper bound lifetime cancer risk levels of 10^{-4} to 10^{-7} are calculated to be 2.36×10^{-6} to 2.36×10^{-9} ppm, respectively. The cancer risk levels are plotted in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

At least three human deaths following oral exposure to NDMA have been reported in the literature. One of the fatalities was a woman who was apparently poisoned over a two-year period by her husband (Fussgaenger and Ditschuneit 1980, Pedal et al. 1982). It was estimated by the authors that she received at least 4 doses as high as 250-300 mg each, for a total dose of less than 1.5 gram; the mean daily dose was estimated to be 50 •g/kg. Both clinical and autopsy findings indicated that she died of hepatic failure. Two other people (an adult male and a l-year-old boy) died within days after consuming lemonade tainted with unknown quantities of NDMA (Kimbrough 1982, Cooper and Kimbrough 1980). Based on animal studies, the authors estimated that the adult might have received about 1.3 gm, and the boy might have received about 300 mg. In both cases, clinical and autopsy findings primarily showed liver failure and cerebral hemorrhage.

Single dose lethality studies have been conducted in which NDMA was administered to rats and cats by gavage. Druckrey et al. (1967) determined a LD_{50} of 40 mg/kg for rats. This value was determined using an unspecified graphic technique, and confidence limits and specific mortality data were not reported. All of 12 rats that were treated with 40 mg/kg in a skin grafting (immunology) experiment died by day 21, but the stress of skin graft rejection may have contributed to mortality (Waynforth and Magee 1974). Jenkins et al. (1985) reported that single 25 mg doses of NDMA resulted in 100% mortality in an unspecified number of rats, but it is unclear if this is dose per kg body weight or dose per total body weight. Single doses of 15 and 20 mg/kg were not lethal for nonpregnant rats but 23 mg/kg was estimated to be the LD_{50} for pregnant rats (Nishie 1983). The LD_{50} for the pregnant rats was extrapolated using mortality of 18-day pregnant rats given single oral doses of 15 or 20 mg NDMA/kg. A dose of 10 mg/kg did not produce deaths in rats within 48 hours (Sumi and Miyakawa 1983). Two of 6 cats died when treated with 50 mg NDMA/kg (Maduagwu and Basir 1980). The NOAEL and appropriate LOAEL values for lethality from these single dose studies are included in the acute duration category in Table 2-2 and Figure 2-2. The 40 mg/kg and 23 mg/kg rat LD_{50}s are also presented in Table 2-2 and Figure 2-2.

Rats, guinea pigs, cats and monkeys that were treated with NDMA by gavage at a dose of 5 mg/kg/day for 11 days experienced 30-40% mortality;

TABLE 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine - Oral

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
ACUTE EXPOSURE								
Death								
1	rat	(G)	once				40 (LD_{50})	Druckrey et al. 1967
2, 3	rat	(G)	once		20 (non-pregnant rats)		23 (LD_{50}) (pregnant rats)	Nishie 1983
4	rat	(G)	5-11 days, daily				5 (decreased survival)	Maduagwu and Bassir 1980
5	rat	(G)	once		10			Sumi and Miyakawa 1983
6	rat	(G)	6 days, daily				8 (decreased survival)	McGiven and Ireton 1972
7	mouse	(W)	1 wk daily				9.5 (decreased survival)	Terracini et al. 1966
8	gn pig	(G)	5-11 days, daily				5 (decreased survival)	Maduagwu and Bassir 1980
9	hamster	(W)	1, 2, 4, 7 or 14 d, daily		4.0			Ungar 1984
10	cat	(G)	5-11 days, daily				5 (decreased survival)	Maduagwu and Bassir 1980
11	cat	(G)	once				50 (death)	Maduagwu and Bassir 1980
12	monkey	(G)	5-11 days, daily				5 (decreased survival)	Maduagwu and Bassir 1980

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
Systemic								
13	rat	(G)	once	Hepatic		2.5 (degeneration)		Jenkins et al. 1985
14	rat	(G)	once	Hepatic			20 (necrosis)	Nishie 1983
15	rat	(G)	once	Other (thyroid)	20			Nishie 1983
16	rat	(G)	once	Hepatic			8 (necrosis)	Sumi and Miuakawa 1983
17	rat	(F)	1 or 2 wk, daily	Hepatic			3.75 (necrosis)	Khanna and Puri 1966
18, 19	rat	(G)	once	Hepatic	0.7	1.9 (vacuolation)		Korsrud et al. 1973
20	rat	(G)	5-11 d, daily	Hepatic			5 (necrosis)	Maduagwu and Bassir 1980
21	gn pig	(G)	5-11 d, daily	Hepatic			5 (necrosis)	Maduagwu and Bassir 1980
22	hamster	(W)	1, 2, 4, 7 or 14 d, daily	Hepatic		4.0 (portal venopathy)		Ungar 1984
23	cat	(G)	5-11 d, daily	Hepatic			5 (necrosis)	Maduagwu and Bassir 1980
24	monkey	(G)	5-11 d, daily	Hepatic			5 (necrosis)	Maduagwu and Bassir 1980
Immunological								
25	rat	(G)	once		40			Waynforth and Magee 1974

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
Developmental								
26	rat	(G)	once, G d 15, or 20				20 (decreased fetal weight)	Nishie 1983
Cancer								
27	mouse	(W)	1 wk, daily				9.5 (CEL[d]) (kidney, lung)	Terracini et al. 1966
INTERMEDIATE EXPOSURE								
Death								
28	rat	(G)	30 d, daily		1			Maduagwu and Bassir 1980
29, 30	rat	(F)	24-110 d daily		2.5		5.0 (death)	Barnes and Magee 1954
31	rat	(F)	40 wk, daily				3.9 (decreased survival)	Magee and Barnes 1956
32	rat	(W)	30 wk, 5 d/wk				0.32 (decreased survival)	Lijinsky and Reuber 1984
33	rat	(G)	30 wk, 2 d/wk				6.0 (decreased survival)	Lijinsky et al. 1987
34	mouse	(W)	49 d, daily				1.8 (decreased survival)	Clapp and Toya 1970
35	mouse	(F)	5 mo, daily				5.26 (decreased survival)	Takayama and Oota 1965
36	mouse	(W)	13 wk, daily				1.9 (decreased survival)	Den Engelse et al. 1974

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
37	mouse	(W)	224 d, daily		0.4			Clapp and Toya 1970
38	mouse	(W)	38 wk, daily				1.19 (decreased survival)	Terracini et al. 1966
39	gn pig	(G)	30 d, daily		1			Maduagwu and Bassir 1980
40	hamster	(G)	4 wk, 1 d/wk				10.7 (decreased survival)	Lijinsky et al. 1987
41	hamster	(G)	20 wk, 1 d/wk				5.4 (decreased survival	Lijinsky et al. 1987
42	hamster	(W)	8, 12 or 16 wk, daily				4.0 (death)	Ungar 1986
43	hamster	(W)	28 d, daily		4.0			Ungar 1984
44	cat	(G)	30 d, daily				1 (decreased survival)	Maduagwu and Bassir 1980
45	monkey	(G)	30 d, daily		1			Maduagwu and Bassir 1980
46	mink	(F)	32-34 d, daily				0.32 (decreased survival)	Carter et al. 1969
Systemic								
47	rat	(F)	40 wk, daily	Hepatic			3.9 (necrosis)	Magee and Barnes 1956
48, 49	rat	(F)	62-110 d daily		2.5		5.0 (necrosis)	Barnes and Magee 1954

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
50	rat	(F)	4,8 or 12 wk, daily	Hepatic			3.75 (necrosis)	Khanna and Puri 1966
51	rat	(G)	30 d, daily	Hepatic		1 (vacuolation)		Maduagwu and Bassir 1980
52	mouse	(F)	16-92d, daily	Hepatic			13 (hemorrhage/ necrosis)	Otsuka and Kuwahara 1971
53	mouse	(W)	1-4 wk, daily	Hepatic			5.0 (hemorrhage)	Anderson et al. 1986
54	mouse	(F)	5 mo, daily	Hepatic			5.26 (hemorrhage/ necrosis)	Takayama and Oota 1965
55	gn pig	(G)	30 d, daily	Hepatic			1 (necrosis)	Maduagwu and Bassir 1980
56	rabbit	(F)	22 wk, daily	Hepatic		1.6 (fibrosis)		Magee and Barnes 1956
57	hamster	(W)	8, 12 or 16 wk, daily	Hepatic		4.0 (portal venopathy)		Ungar 1986
58	hamster	(W)	28 d, daily	Hepatic		4.0 (portal venopathy)		Ungar 1984
59	dog	(C)	3 wk, 2 d/w (consec)	Hepatic			2.5 (necrosis)	Strombeck et al. 1983
60	cat	(G)	30 d, daily	Hepatic			1 (necrosis)	Maduagwu and Bassir 1980
61	monkey	(G)	30 d, daily	Hepatic			1 (necrosis)	Maduagwu and Bassir 1980
62	mink	(F)	122 d, daily	Hepatic		0.13 (venopathy)		Koppang and Rimeslatten 1976

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
63	mink	(F)	32-34 d, daily	Hepatic			0.32 (necrosis)	Carter et al. 1969
Developmental								
64	mouse	(W)	75 d, gestation				0.02 (perinatal death)	Anderson et al. 1978
Cancer								
65	rat	(F)	40 wk, daily				3.9 (CEL[d]) (liver)	Magee and Barnes 1956
66	rat	(W)	30 wk, 5 d/wk				0.3 (CEL[d]) (liver)	Keefer et al. 1973
67	rat	(W)	30 wk, 5 d/wk				0.32(CEL[d]) (liver)	Lijinsky and Reuber 1984
68	rat	(G)	30 wk, 2 d/wk				6.0 (CEL[d]) (liver, lung, kidney)	Lijinsky et al. 1987
69	mouse	(W)	49 d, daily				1.8 (CEL[d]) (liver, lung)	Clapp and Toya 1970
70	mouse	(W)	38 wk, daily				1.19 (CEL[d]) (liver, lung, kidney)	Terracini et al. 1966
71	mouse	(W)	224 d, daily				0.4 (CEL[d]) (liver)	Clapp and Toya 1970
72	mouse	(F)	10 mo, daily				9.04 (CEL[d]) (liver, lung)	Takayama and Oota 1965
73	mouse	(F)	16-92 d, daily				13 (CEL[d]) (lung)	Otsuka and Kuwahara 1971
74	mouse	(G)	50 wk, 2 d/wk				1 (CEL[d]) (liver)	Griciute et al. 1981

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
75	mouse	(F)	5 mo, daily				5.26 (CEL[d]) (liver, lung, kidney)	Takayama and Oota 1965
76	hamster	(G)	20 wk, 1 d/wk				5.4 (CEL[d]) (liver)	Lijinsky et al. 1987
77	hamster	(G)	6.5 wk, 2 d/wk				5.4 (CEL[d]) (liver)	Lijinsky et al. 1987
78	hamster	(G)	4 wk, 1 d/wk				10.7 (CEL[d]) (liver)	Lijinsky et al. 1987
79	hamster	(W)	12 or 16 wk, daily				4.0 (CEL[d]) (liver)	Ungar 1986
CHRONIC EXPOSURE								
Death								
80	rat	(F)	54 wk		0.5			Terao et al. 1978
81	mouse	(W)	406 d, daily				0.43 (decreased survival)	Clapp and Toya 1970
82	mink	(F)	321-670 d daily				0.1 (decreased survival)	Koppang and Rimmeslatten 1976
Systemic								
83	rat	(F)	54 wk	Hepatic	0.5			Terao et al. 1978
84	rat	(F)	96 wk, daily	Hepatic	0.5			Arai et al. 1979
85	mink	(F)	321-670 d daily	Hepatic			0.1 (venopathy, focal necrosis)	Koppang and Rimmeslatten 1976

TABLE 2-2 (continued)

Graph Key	Species	Route[a]	Exposure Frequency/ Duration	Effect	NOAEL[b] (mg/kg/day)	LOAEL[c] (Effect) Less Serious	LOAEL[c] (Effect) Serious	Reference
Cancer								
86	rat	(F)	54 wk daily				0.5 (CEL[d]) (testes)	Terao et al. 1978
87	rat	(F)	96 wk, daily				0.05 (CEL[d]) (liver)	Arai et al. 1979
88	rat	(F)	96 wk, daily				10 (CEL[d]) (liver)	Ito et al. 1982
89	rat	(W)	life, daily				0.02 (CEL[d]) (liver)	Peto et al. 1984
90	mouse	(W)	life, daily				0.43 (CEL[d]) (liver, lung)	Clapp and Toya 1970
91	mink	(F)	321-607 d daily				0.1 (CEL[d]) (liver)	Koppang and Rimeslatten 1976

[a]G - gavage, F - diet, W - drinking water, C - capsule
[b]NOAEL - No Observed Adverse Effect Level
[c]LOAEL - Lowest Observed Adverse Effect Level
[d]CEL - Cancer Effect Level

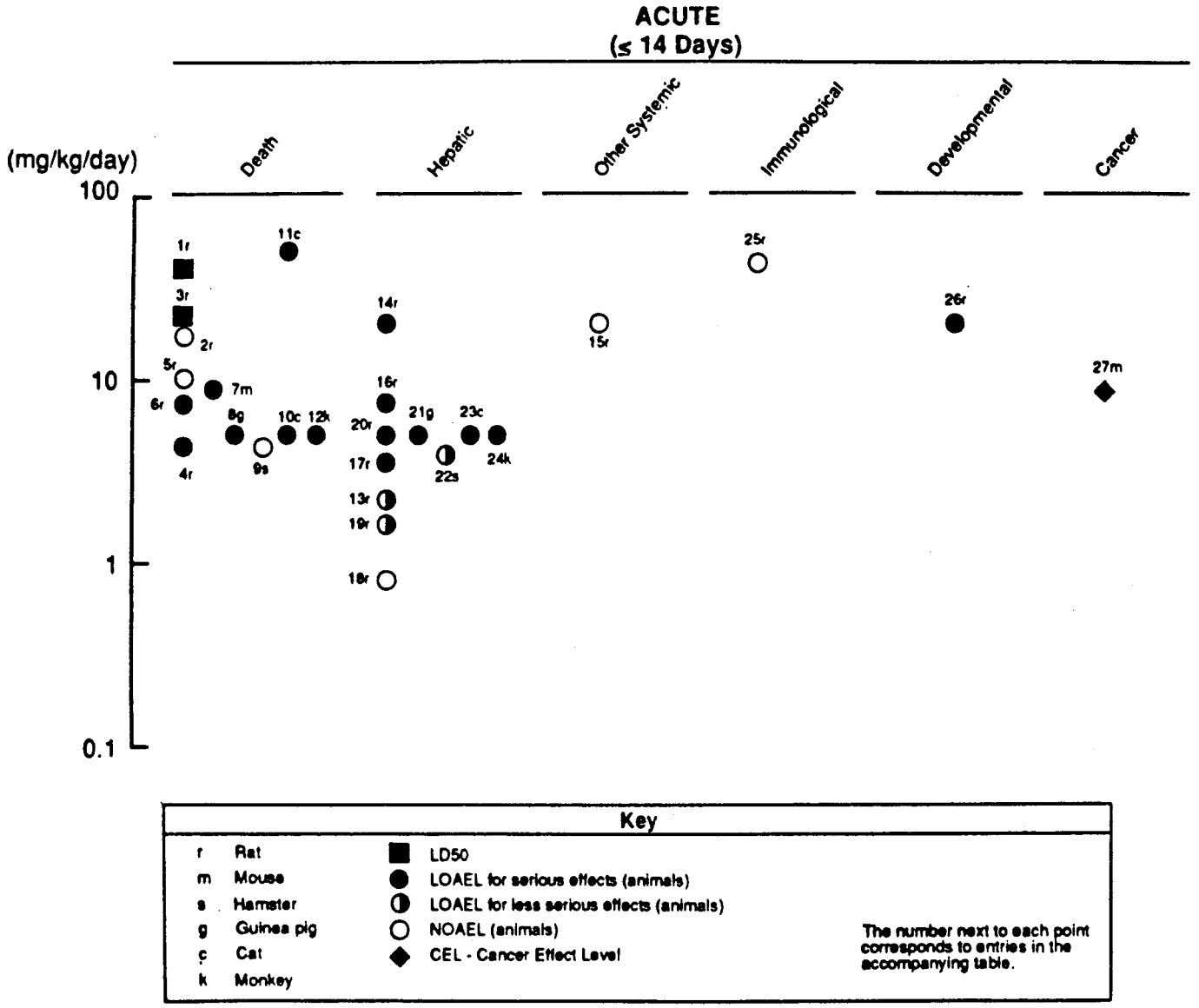

FIGURE 2-2. Levels of Significant Exposure to N-Nitrosodimethylamine - Oral

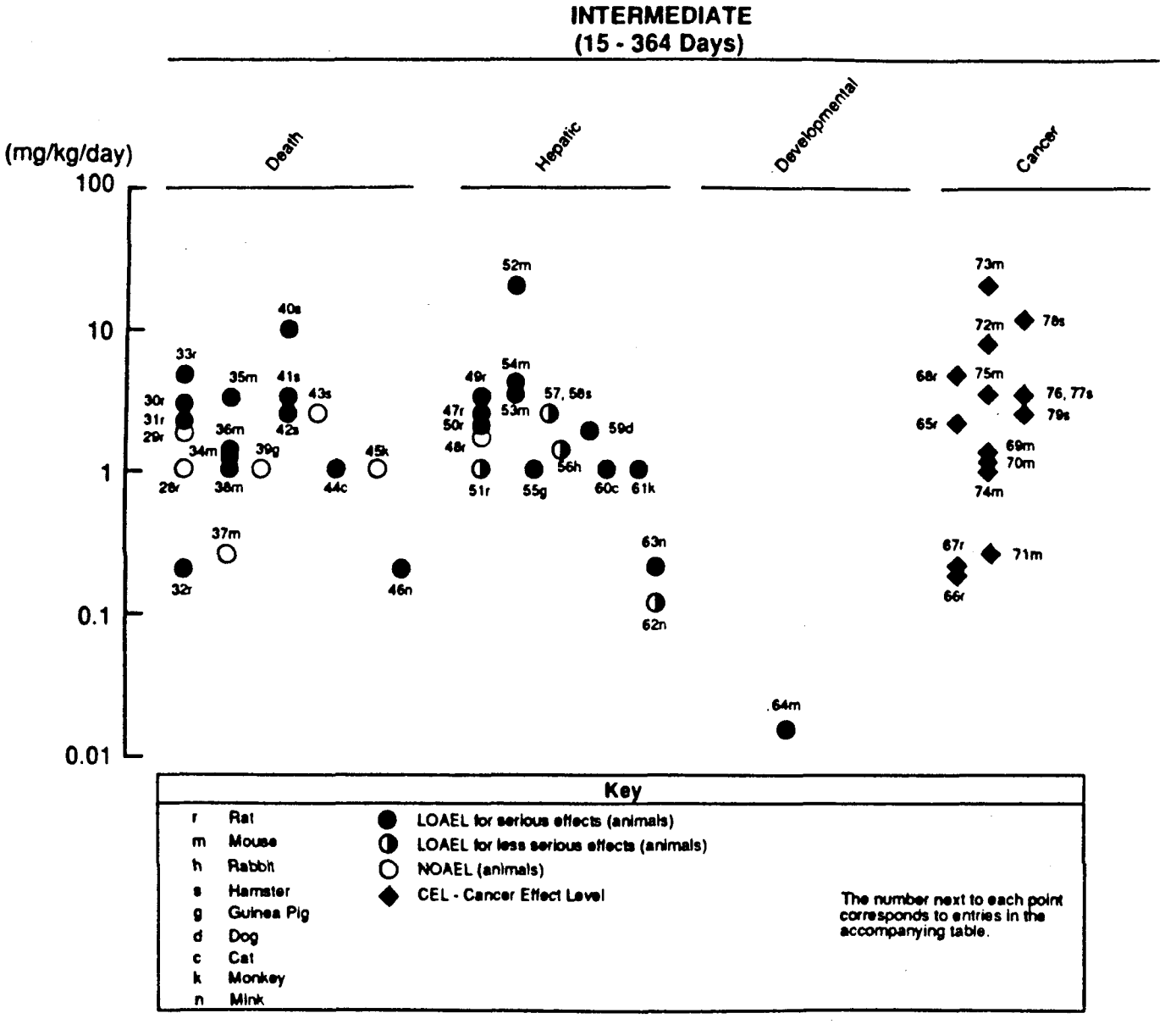

FIGURE 2-2 (continued)

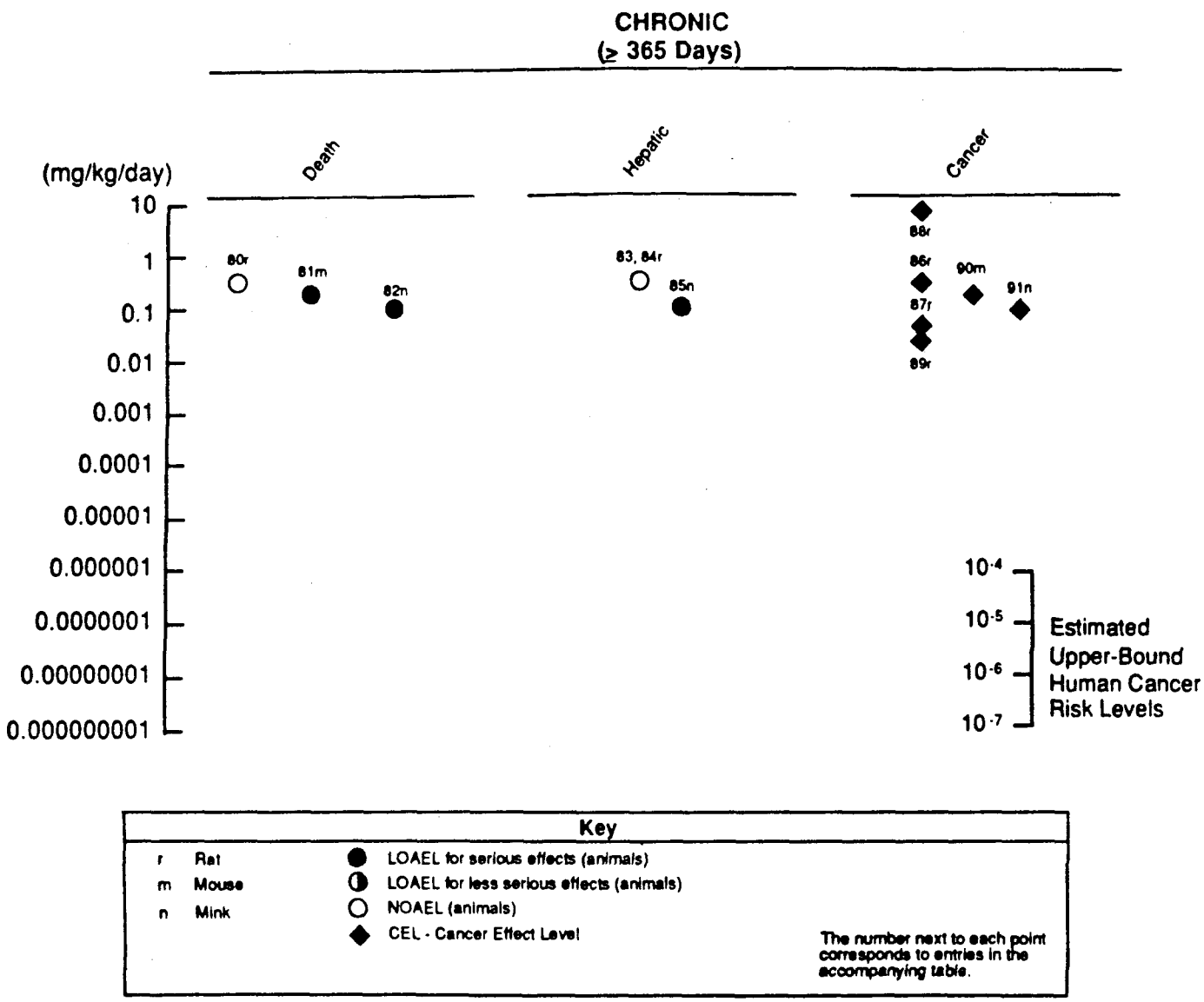

FIGURE 2-2 (continued)

mean survival times were 5-11 days (Maduagwu and Bassir 1980). Rats treated by gavage daily with 8 mg/kg NDMA for 6 days experienced 10% mortality within one month (McGiven and Ireton 1972). Administration of NDMA in the drinking water at a daily dose of 9.5 mg/kg for one week resulted in decreased survival in mice (Terracini et al. 1966). Administration of a daily dose of 4 mg/kg/day in the drinking water of hamsters for 1, 2, 4, 7 or 14 days did not result in mortality (Ungar 1984). The hamster NOAEL value and all LOAEL values for lethality from these repeated exposure studies are recorded in Table 2-2 and plotted in Figure 2-2. The mouse dose of 9.5 mg/kg/day was calculated from the administered concentration of 50 ppm in water (Terracini et al. 1966); this concentration is presented in Table l-4 for short-term exposure.

Numerous oral studies in which NDMA was administered for intermediate durations (15-365 days) have been conducted. Deaths resulting from intermediate duration exposure to NDMA were usually attributed to liver toxicity or carcinogenicity. Representative lethal and nonlethal intermediate duration exposures in various species are presented below.

In rats, decreased survival resulted when 0.32 mg NDMA/kg was given in the drinking water for 5 days/week for 30 weeks (Lijinsky and Reuber 1984), and when 6 mg/kg was administered by gavage for 2 days/week for 30 weeks (Lijinsky et al. 1987). Control groups were not included in the latter study but there was 100% mortality by 40 weeks after cessation of treatment. Barnes and Magee (1954) administered NDMA in the diet to small numbers of rats (6/group); 2.5 mg/kg/day produced no deaths, 5 mg/kg/day produced 100% mortality after 62-93 days, and 10 mg/kg/day produced 100% mortality after 34-37 days. Rats treated with 3.9 mg/kg/day in the diet for 40 weeks also had high mortality (Magee and Barnes 1956). Daily exposure to 1 mg/kg/day by gavage for 30 days had no effect on survival of rats (Maduagwu and Bassir 1980). Jenkins et al. (1985) observed mortality in rats that received 2.5 mg doses of NDMA by gavage for 4 days/week for 9 weeks, but it is unclear if this is dose per kg body weight or dose per total body weight. The NOAEL values and all reliable LOAEL values for lethality in rats from these intermediate duration studies are recorded in Table 2-2 and plotted in Figure 2-2. The rat dose of 5 mg/kg/day was calculated from the administered concentration of 100 ppm in diet (Barnes and Magee 1954); this concentration is presented in Table l-4 for long-term exposure. The rat dose of 0.32 mg/kg/day was calculated from the administered concentration of 5.5 ppm in water (Lijinsky and Reuber 1984); this concentration is also presented in Table l-4 for long-term exposure.

In intermediate duration studies with mice, decreased survival resulted from treatment with doses of 1.8 mg/kg/day via drinking water for 49 days (Clapp and Toya 1970), 1.9 mg/kg/day via drinking water for 13 weeks (Den Engelse et al. 1974), 1.19 mg/kg/day via drinking water for 38 weeks (Terracini et al. 1966) and 5.26 mg/kg/day via diet for 5 months (Takayama and Oota 1965). Mice that received 0.4 mg/kg/day in drinking water for 224 days did not experience significantly decreased survival (Clapp and Toya

1970). The NOAEL value and all LOAEL values for lethality in mice from these intermediate duration studies are recorded in Table 2-2 and plotted in Figure 2-2.

Survival data for intermediate oral exposure to NDMA are available for species other than rat and mouse. Daily gavage exposure to 1 mg NDMA/kg for 30 days caused decreased survival in cats but not guinea pigs or monkeys (Maduagwu and Bassir 1980). In hamsters, daily administration of 4 mg/kg/day in the drinking water for 8, 12, or 16 weeks resulted in occasional moribundity (Ungar 1986), while no lethality resulted from daily administration of the same dose for 28 days (Ungar 1984); this dose is a NOAEL or LOAEL for lethality depending on duration of exposure. Once weekly gavage treatment with a dose of 10.7 mg/kg for 4 weeks or 5.4 mg/kg for 20 weeks was lethal for hamsters (Lijinsky et al. 1987). Mink that were given doses of 0.32 or 0.63 mg/kg/day in the diet died after 23-34 days of treatment (Carter et al. 1969), but low numbers of animals were tested (three per dose). Mink fed a contaminated diet that provided approximately 0.18 mg NDMA/kg/day died (Martin0 et al. 1988), but there is uncertainty about the dietary concentration of NDMA used to calculate the dose. The mink that were examined in this study were from a commercial breeding colony that died during a 2 month period; durations of exposure were not specified. The NOAEL values and all reliable LOAEL values for lethality in these intermediate duration studies are recorded in Table 2-2 and plotted in Figure 2-2.

Chronic lethality data are available for NDMA-exposed rats, mice and mink. Survival of rats that received 0.5 mg/kg/day of NDMA in the diet for 54 weeks (Terao et al. 1978) was not affected. Decreased survival occurred in mice that were exposed to 0.43 mg/kg/day in the drinking water for life (average 406 days) (Clapp and Toya 1970). Mink appear to be particularly sensitive to NDMA as mortality resulted from ingestion of 0.1 mg/kg/day in the diet for 321-670 days (Koppang and Rimeslatten 1976). The NOAEL value and LOAEL values for lethality in these chronic duration studies are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal or dermal/ocular effects in humans or animals following oral exposure to NDMA.

Respiratory Effects. Petechial and larger hemorrhages were observed in the lungs of two people following lethal poisoning with NDMA (Kimbrough 1982) (Section 2.2.2.1).

Macroscopic congestion was noted in the lungs of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for l-12 weeks (Khanna and Puri 1966). The adversity of the congestion cannot be determined because results of lung histological examinations were not reported. No studies were

located regarding respiratory effects in animals due to chronic duration oral exposure.

Cardiovascular Effects. Myocardial and endocardial bleeding was observed in a person following lethal poisoning with NDMA (Kimbrough 1982) (Section 2.2.2.1).

Macroscopic congestion was noted in the myocardium of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for l-12 weeks (Khanna and Puri 1966). The adversity of the congestion cannot be determined because results of heart histological examinations were not reported. No studies were located regarding cardiovascular effects in animals due to chronic duration exposure.

Gastrointestinal Effects. Gastrointestinal hemorrhage occurred in humans following lethal poisoning with NDMA (Kimbrough 1982, Pedal et al. 1982) (Section 2.2.2.1).

NDMA produced similar gastrointestinal effects in animals. Barnes and Magee (1954) observed occasional hemorrhage into the gastrointestinal tract in rats that died from treatment with a single 50 mg/kg dose of NDMA by gavage , or with 10 mg/kg/day doses in the diet for 34-37 days. The numbers of animals examined were unspecified (single dose study) or small (6 in the diet study), and frequency of occurrence was not indicated. Gastrointestinal hemorrhages were also observed in mink that ingested 0.32 or 0.63 mg NDMA/kg/day via diet for 23-34 days (Carter et al. 1969). Only three mink per dose were treated, the hemorrhages occurred in a total of three mink, and the dose(s) that the affected mink received was not specified. The cause of the hemorrhages in the mink was attributed to gastric and duodenal erosions. No studies were located regarding gastrointestinal effects in animals due to chronic duration exposure.

Hepatic Effects. Five members of a family who consumed unknown quantities of NDMA in lemonade became ill with nausea and vomiting associated with acute liver disease, generalized bleeding and low platelet counts (Kimbrough 1982, Cooper and Kimbrough 1980). As indicated in Section 2.2.2.1, two of these people died; the other three were released from a hospital 4-21 days after admission. Another fatality due to ingestion of NDMA was attributed to liver failure (Fussgaenger and Ditschuneit 1980, Pedal et al. 1982) (Section 2.2.2.1). Autopsies of the subjects described above showed that the primary effects were hemorrhagic and cirrhotic changes in the liver and necrosis and hemorrhage in other internal organs.

Hepatotoxicity of NDMA has been described and investigated in numerous oral studies of acute, intermediate and chronic duration in several animal species. Hepatotoxicity is the most prominent and characteristic systemic effect of NDMA, resulting in centrilobular necrosis and hemorrhage often leading to hemorrhagic ascites.

2. HEALTH EFFECTS

In acute studies, characteristic hepatotoxic alterations, as indicated above, occurred in rats following single gavage doses as low as 20 and 8 mg/kg (Nishie 1983, Sumi and Miyakawa 1983), and following daily doses of 3.75 mg/kg in the diet for 1 or 2 weeks (Khanna and Puri 1966). These doses therefore are LOAELs for serious hepatic effects. Jenkins et al. (1985) observed degenerative alterations in the livers of rats following a single 2.5 mg/kg gavage dose of NDMA. As these alterations (collapse of reticulum network in the centrilobular areas followed by regeneration) were nonnecrotic and did not result in loss of the lobular architecture, the 2.5 mg/kg dose is a LOAEL for less serious hepatic effects. Single gavage doses of 1.9 mg/kg and 0.7 mg/kg are a LOAEL for less serious hepatic effects and a NOAEL, respectively, for rats, as nonnecrotic histologic alterations (clumping and slight vacuolation of cells in the central vein area) occurred at 1.9 mg/kg and no alterations occurred at 0.7 mg/kg (Korsrud et al. 1973),. Daily gavage exposure to 5 mg/kg for 5-11 days produced hemorrhagic necrosis in rats, guinea pigs, cats and monkeys (Maduagwu and Bassir 1980). Hamsters that ingested daily doses of 4 mg/kg/day in the drinking water for 1, 2, 4, 7 or 14 days showed portal venopathy, a less serious hepatic effect (Ungar 1984). The NOAEL value and LOAEL values for hepatic effects in these acute duration studies are recorded in Table 2-2 and plotted in Figure 2-2. The rat diet dose of 3.75 mg/kg/day was calculated from the administered concentration of 75 ppm in food (Khanna and Puri 1966); this concentration is presented in Table l-4 for short-term exposure. The hamster drinking water dose of 4 mg/kg/day was calculated from the administered concentration of 20 ppm in water (Ungar 1984); this concentration is also presented in Table l-4 for short-term exposure.

In intermediate duration studies with rats, characteristic hepatic effects (described previously) were produced by treatment with NDMA doses of 3.75 mg/kg/day in the diet for 4-12 weeks (Khanna and Puri 1966), 5 mg/kg/day in the diet for 62-95 days (Barnes and Magee 1954), and 3.9 mg/kg/day in the diet for 40 weeks (Magee and Barnes 1956). Jenkins et al. (1985) observed cirrhosis in rats that received 2.5 mg doses of NDMA by gavage for 4 days/week for 9 weeks, but it is unclear if this is dose per kg body weight or dose per total body weight. A dose of 1 mg/kg/day administered by gavage for 30 days produced centrilobular congestion and vacuolation of hepatocytes without necrosis in rats (Maduagwu and Bassir 1980), indicating that this dose is a LOAEL for less serious hepatic effects. Hepatic alterations were not observed in rats treated with 2.5 mg/kg/day in the diet for 110 days (Barnes and Magee 1954). The NOAEL and all LOAEL values for hepatic effects in rats from these intermediate duration studies are recorded in Table 2-2 and plotted in Figure 2-2.

Characteristic liver alterations (described previously) occurred in mice that were treated with NDMA doses of 5.0 mg/kg/day in the drinking water for l-4 weeks (Anderson et al. 1986), 13 mg/kg/day in the diet for 16-92 days (Otsuka and Kuwahara 1971) and 5.26 mg/kg/day in the diet for 5 months (Takayama and Oota 1965). These LOAELs for hepatic effects in mice due to intermediate duration exposure are included in Table 2-2 and plotted

in Figure 2-2. The mouse dose of 5.26 mg/kg/day was calculated from the administered concentration of 50 ppm in food (Takayama and Oota 1965); this concentration is presented in Table 1-4 for long-term exposure.

Liver effects resulting from intermediate duration oral exposure have been observed in species .other than rat and mouse. Treatment with 1 mg/kg/day by gavage for 30 days was hepatotoxic for guinea pigs, cats and monkeys (Maduagwa and Basir 1980). Necrotic alterations occurred in dogs treated with 2.5 mg/kg by capsule on 2 days/week for 3 weeks (Strombeck et al. 1983). Fibrotic and proliferative alterations without necrosis or hemorrhage were observed in rabbits treated with an average NDMA dose of 1.6 mg/kg/day in the diet for 22 weeks (Magee and Barnes 1956), indicating that this dose is a less serious LOAEL for hepatic effects. Occlusive alterations in the portal veins developed in hamsters that received daily 4 mg/kg doses in the drinking water for 28 days or 8, 12 or 16 weeks (Ungar 1984, 1986), indicating that this dose is also a less serious LOAEL for hepatic effects. Similar hepatic venopathy occurred in mink exposed to 0.13-0.15 mg/kg/day in the diet for 122 days (Koppang and Rimeslatten 1976). Mink that were given doses of 0.32 or 0.63 mg/kg/day in the diet for 23-34 days had widespread liver necrosis (Carter et al. 1969), but low numbers of animals were tested (three per dose). Liver necrosis was also observed in mink that ingested 0.18 mg/kg/day via diet (Martin0 et al. 1988); limitations of this study, discussed in Section 2.2.2.1, include uncertainty regarding exposure duration and concentration. All reliable LOAEL values for hepatic effects due to intermediate duration exposure in these studies are recorded in Table 2-2 and plotted in Figure 2-2. The hamster drinking water dose of 4 mg/kg/day was calculated from the administered concentration of 20 ppm in water (Ungar 1984, 1986); this concentration is presented in Table 1-4 for long-term exposure. It should be noted that this water concentration (20 ppm) is higher than the water concentration associated with death (5.5 ppm) due to long-term exposure reported in Table 1-4. The apparent discrepancy in these values is attributable to differences in species sensitivity and length of exposure (rats exposed for 30 weeks, hamsters exposed for 28 days).

In chronic duration studies, characteristic hepatotoxic alterations (described previously) were not observed in rats that were treated with 0.5 mg/kg/day NDMA in the diet for 54 weeks (Terao et al. 1978) or 96 weeks (Arai et al. 1979). Alterations in mink that ingested 0.1 mg/kg/day doses of NDMA in the diet for 321-670 days included occlusive changes in the hepatic veins with focal necrosis (Koppang and Rimeslatten 1976). Data regarding hepatic effects of chronic oral NDMA exposure in other species were not found in the available literature. The NOAEL values and LOAEL value for hepatic effects due to chronic exposure in these studies are recorded in Table 2-2 and plotted in Figure 2-2.

Although hepatotoxicity is the primary effect of NDMA and has been demonstrated in all tested species, calculation of MRLs for NDMA is precluded by insufficient data defining the threshold region (i.e., NOAELs)

for intermediate and chronic exposures, particularly for species which appear to be particularly sensitive (e.g., mink) and because serious effects (perinatal death) occurred in a developmental study (see Section 2.2.2.5) at a dose lower than any NOAELS for liver effects.

Renal Effects. No studies were located regarding renal effects in humans following oral exposure to NDMA.

Limited information is available regarding renal effects of orallyadministered NDMA in animals. In a study by Nishie (1983), pregnant and nonpregnant rats were treated with a single NDMA dose of 15 or 20 mg/kg/day by gavage. An unspecified number of deceased animals (dose and pregnancy state not indicated) had distal tubule necrosis two days following treatment, and surviving rats had normal kidneys. Macroscopic congestion was noted in kidneys of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for l-12 weeks (Khanna and Puri 1966). The adversity of the congestion cannot be determined because results of kidney histological examinations were not reported. Moderate tubule congestion with other effects (glomerulus dilatation, slightly thickened Bowman's capsule) were observed in mink that ingested 0.18 mg/kg/day via diet (Martin0 et al. 1988); limitations of this study, discussed in Section 2.2.2.1, include uncertainty regarding exposure duration and concentration.

Other Systemic Effects. Adrenal relative weight and mitotic count were increased in rats following a single 20 mg/kg gavage dose of NDMA (Nishie et al. 1983). Other results of the adrenal histological examinations were not described, precluding assessment of adversity of the increased adrenal weight, There was no effect on thyroid weight or histology in the same study. It therefore is appropriate to regard 20 mg/kg as a NOAEL for thyroid effects in rats due to acute oral exposure (Table 2-2 and Figure 2-2). Macroscopic congestion was noted in spleens of rats that were administered 3.75 mg/kg/day doses of NDMA in the diet for l-12 weeks (Khanna and Puri 1966). The adversity of the congestion cannot be determined because results of spleen histological examinations were not reported.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans following oral exposure to NDMA.

Limited information is available regarding immunological effects of orally-administered NDMA in animals. Skin graft survival time and white blood cell count were not reduced in rats that received a single 40 mg/kg dose of NDMA by gavage, indicating that treatment was not immunosuppressive (Waynforth and Magee 1974). The dose reported was near the LD50 for rats, but all of the animals died by day 21; it is indicated that the high mortality may partially reflect the stress of skin graft rejection. Although treatment resulted in 100% mortality, this dose represents a NOAEL for immunological effects due to acute duration oral exposure (Table 2-2 and

Figure 2-2). No studies were located regarding immunological effects in animals following intermediate or chronic duration exposure to NDMA.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to NDMA.

Dogs treated with 2.5 mg NDMA/kg/day by capsule on 2 consecutive days/week for 3 weeks experienced marked central nervous system (CNS) depression (Strombeck et al. 1983). The significance of this observation cannot be ascertained since it was not characterized further. As these dogs developed liver necrosis and hepatic insufficiency, it is possible that the CNS depression is secondary to liver damage rather than a direct neurological effect of NDMA.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to NDMA.

Evidence indicates that orally-administered NDMA is a developmental toxicant in animals. Fetuses of rats that received single 20 mg/kg doses of NDMA by gavage on days 15 or 20 of gestation had significantly decreased body weights, but fetal survival data were not reported (Nishie 1983). This dose was also toxic to the dams as indicated by reduced body weight, hepatotoxicity and mortality. Other investigators have reported fetal mortality in rats that were treated with a single 30 mg/kg dose of NDMA by gavage on various days during the first 12 days (Aleksandrov 1974) or 15 days (Napalkov and Alexandrov 1968) of gestation. In other studies, NDMA reportedly caused fetal deaths in rats when administered in the diet at a dose of 5 mg/kg/day from an unspecified day in early pregnancy (treatment duration not indicated) (Bhattacharyya 1965), by gavage at a dose of 2.9 mg/kg/day during the first or second weeks of gestation (Napalkov and Alekandrov 1968), or by gavage at a dose of 1.4 mg/kg/day throughout gestation until days 17-21 (not specified) (Napalkov and Alekandrov 1968). Teratogenic effects were not observed in the studies of Aleksandrov (1974) and Napalkov and Alekandrov (1968), and not eva1uated.i.n the studies of Nishie (1983) and Bhattacharyya (1965). Evaluation of the studies of Bhattacharyya (1965), Napalkov and Alekandrov (1968) and Aleksandrov (1974) is complicated by insufficient information regarding experimental design and results; deficiencies include lack of control data, lack of maternal toxicity data, use of pooled data and/or uncertain treatment schedule. Due to these limitations, there is low confidence in the doses associated with fetotoxicity in these studies. As Nishie (1983) is the only adequately reported fetotoxicity study, 20 mg/kg is presented as a LOAEL for developmental effects in rats due to acute exposure to NDMA in Table 2-2 and Figure 2-2.

In another experiment conducted by Aleksandrov (1974), a single dose of 30 mg NDMA/kg was administered by gavage to rats on day 21 of gestation. Histological examination of the offspring at the time of natural death (•274 days after exposure) reportedly showed tumors in 5 of 20 animals. Although this is possibly a manifestation of transplacental carcinogenesis, evaluation of this finding is precluded by limitations including a lack of control data and inadequate reporting of tumor types.

Increased perinatal mortality (stillbirths and newborn deaths) occurred in mice as a consequence of maternal treatment with 0.02 mg NDMA/kg/day in the drinking water (Anderson et al. 1978). The mice were treated for 75 days prior to mating and throughout pregnancy and lactation. Histological examinations of the stillborn fetuses and dead neonates showed no abnormalities. The 0.02 mg/kg/day dose represents a LOAEL for developmental effects due to intermediate duration exposure (Table 2-2 and Figure 2-2).

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to NDMA.

There was no significant increase in time-to-conception in mice that were exposed to 0.02 mg NDMA/kg/day via drinking water for 75 days prior to mating (Anderson et al. 1978). Other reproductive indices were not evaluated.

2.2.2.7 Genotoxic Effects

Methylated DNA (7-methylguanine and O^6 -methylguanine) was detected in the liver of a victim of suspected NDMA poisoning (Herron and Shank 1980). Additional studies regarding genotoxic effects in humans following oral exposure to NDMA were not located.

Oral studies with rats indicate that the liver is sensitive to the genotoxic effects of NDMA. When administered by gavage at a dose of 5.2 mg/kg, NDMA induced damage in rat liver DNA as measured by increased alkaline elution (Brambilla et al. 1981). When administered to rats via diet at a dose of 2.5 mg/kg/day, NDMA induced DNA damage in the liver as measured by a slow sedimentation in alkaline sucrose gradients (Abanobi et al. 1979). The effect was first observed after 2 days of feeding, and became progressively worse during the next 8 weeks of feeding; no proportionate increases in damage occurred when the feedings were continued for 15 or 31 weeks. DNA synthesis and repair was detected in the liver of rats treated with single 10 or 50 mg/kg doses by gavage (Bermudez et al. 1982). Radiolabeled thymidine uptake during mouse testicular DNA synthesis was inhibited by a single gavage dose of 50 mg NDMA/kg (Friedman and Staub 1976).

Administration of NDMA to hamsters by gavage at doses of 50, 100, or 200 mg/kg on the 11th or 12th day of pregnancy caused micronucleus formation and chromosomal aberrations in the embryonic fibroblasts (Inui et al. 1979). NDMA did not induce significant increases in sister chromatid exchanges in bone marrow cells of Chinese hamsters following gavage administration of 12.5-400 mg/kg (Neal and Probst 1983).

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to NDMA.

The carcinogenicity of orally-administered NDMA has been demonstrated unequivocally in acute, intermediate and chronic duration studies with rats, mice, hamsters and mink. The liver and lungs are the primary targets for NDMA carcinogenesis but tumors of the kidneys and testes can also occur. Incidences of liver and lung tumors are generally very high (often 50-100%), but liver tumors appear to occur most frequently in rats and hamsters and lung tumors appear to occur most frequently in mice. The liver tumors are usually hemangiosarcomas and hepatocellular carcinomas, and lung tumors are usually adenomas and liver tumor metastases.

Low incidences of epithelial tumors (8.6%) and mesenchymal tumors (14.5%) developed in the kidneys of rats following treatment with 8 mg NDMA/kg/day for 6 days (McGiven and Ireton 1972, Ireton et al. 1972). Evaluation of these data is complicated by the lack of a control group. Daily diet treatment with 9.5 mg/kg for one week produced kidney and lung adenomas in mice (Terracini et al. 1966). No other acute duration oral carcinogenicity studies were found in the reviewed literature. The CEL from the mouse study is presented in the acute duration category in Table 2-2 and in Figure 2-2.

Numerous oral carcinogenicity studies of NDMA of intermediate duration have been conducted. Treatment durations were often in the range of 20-40 weeks, frequency of treatment ranged from once weekly to daily, and carcinogenicity was observed in all studies. Studies representing various treatment durations and various methods of oral treatment (drinking water, diet and gavage) for the lowest doses in different species are identified below.

Rats administered NDMA in the drinking water at doses of 0.3 mg/kg/day, 5 days/week for 30 weeks, developed malignant liver tumors (Keefer et al. 1973, Lijinsky and Reuber 1984). Lijinsky et al. (1987) observed high incidences of liver, lung and kidney tumors in rats that were treated by gavage with 6 mg NDMA/kg twice weekly for 30 weeks; controls were not used in this study. In an intermediate duration diet study with rats, daily treatment with a dose of 3.9 mg/kg for 40 weeks resulted in a 95% incidence of hepatic tumors (Magee and Barnes 1956). The CELs from these

intermediate duration studies with rats are recorded in Table 2-2 and plotted in Figure 2-2.

Liver, lung and/or kidney tumors developed in mice that were exposed to NDMA daily via drinking water at doses of 1.8 mg/kg for 49 days (Clapp and Toya 1970), 1.19 mg/kg for 38 weeks (Terracini et al. 1966) and 0.4 mg/kg for 224 days (Clapp and Toya 1970). Daily administration of NDMA via diet at doses of 13 mg/kg for 16-92 days (Otsuka and Kuwahara 1971), 5.26 mg/kg for 5 months (Takayama and Oota 1965) and 9.04 mg/kg for 10 months (Takayama and Oota 1965) also induced liver, lung and/or kidney tumors in mice. In the only intermediate duration gavage study with mice, twice weekly doses of 1 mg/kg for 50 weeks resulted in high (37-53%) incidences of malignant liver tumors (Griciute et al. 1981). The CELs from these intermediate duration studies with mice are recorded in Table 2-2 and plotted in Figure 2-2.

Hamsters that were treated with NDMA by gavage twice weekly with a dose of 5.4 mg/kg for 6.5 weeks, once weekly with a dose of 10.7 mg/kg for 4 weeks, or once weekly with a dose of 5.4 mg/kg for 20 weeks developed high (60-79%) incidences of liver tumors (Lijinsky et al. 1987). However, control groups were not included in the study of Lijinsky et al. (1987). Daily administration of 4 mg/kg in the drinking water to hamsters for 12 or 16 weeks resulted in high incidences of cholangiocellular adenocarcinomas (Ungar 1986). The CELs from these intermediate duration studies with hamsters are recorded in Table 2-2 and plotted in Figure 2-2. Hemangiomatous liver tumors occurred in 55% of deceased mink that received NDMA in the diet at an estimated dose of 0.18 mg/kg/day (Martin0 et al. 1988); limitations of this study, discussed in Section 2.2.2.1, include uncertainty regarding exposure duration and concentration, examination only of animals that died and use of historical controls. Due to the limitations of this study, it is inappropriate to present a CEL for mink due to intermediate duration exposure in Table 2-2 and Figure 2-2.

Chronic oral carcinogenicity studies of NDMA have been conducted with rats, mice and mink. Tumors at sites other than the liver and testis have not been associated with chronic treatment. *Terao et* al. (1978) observed a 47% increase in the incidence of testicular Leydig-cell tumors, but no tumors in the liver or other tissues, in rats that were treated with 0.5 mg/kg daily doses of NDMA in the diet for 54 weeks. Increased incidences of liver tumors, but not testicular interstitial cell tumors, occurred in rats that received 0.05 or 0.5 mg/kg/day doses of NDMA in the diet for 96 weeks (Arai et al. 1979). In this study, liver tumor incidences were generally higher in female rats than in male rats. Increased incidences of liver tumors also occurred in rats that were treated with NDMA in the diet for 96 weeks at a dose of 10.0 mg/kg/day (Ito et al. 1982); similar treatment with doses of 0.1 or 1.0 mg/kg/day did not produce increased incidences of liver tumors. It should be noted that Wistar rats were tested in both the Ito et al. (1982) and Arai et al. (1979) studies. The reason for the lack of liver tumors at doses below the relatively high 10 mg/kg/day dose in the Ito et al. (1979) study is not clear, but may be related to low susceptibility of

male rats. In a lifetime drinking water study, Peto et al. (1984) administered doses of 0.001-1.2 mg/kg/day to rats and observed that incidences of liver tumors were significantly increased at ≥0.02 mg/kg/day; median survival time at the lowest tumorigenic doses was in the range of 28-31 months. Crampton (1980) administered NDMA to rats in the drinking water at doses ranging from 0.002-1.5 mg/kg/day for life and observed increased liver tumor incidences at ≥0.008 mg/kg/day; median survival time at 0.008 mg/kg day was >900 days. The results reported by Crampton (1980) were preliminary and there is uncertainty regarding the dosages; ppm concentrations in water and mg/kg/day equivalency were reported, but the basis for the equivalency is not indicated and the conversion cannot be verified using standard methodology. Clapp and Toya (1970) administered NDMA to mice via drinking water at daily doses of 0.43 and 0.91 mg/kg/day for life and observed that incidences of lung tumors and liver hemangiosarcomas were significantly increased at both doses; mean survival time at the low and high doses were 12 and 17 months, respectively. Hemangiomatous liver tumors developed in mink exposed to 0.1 mg/kg/day NDMA in the diet for 321-607 days (Koppang and Rimeslatten 1976). The CELs for rats, mice and mink from these chronic studies, except the uncertain value from the Crampton (1980) study, are recorded in Table 2-2 and plotted in Figure 2-2.

The EPA (1988a) has derived and verified an oral slope factor (B_H) of 51 $(mg/kg/day)^{-1}$ for NDMA based on the liver tumor response in the Peto et al. (1984) study. Using this slope factor, the doses associated with upper bound lifetime cancer risk levels of 10^{-4} to 10^{-7} are calculated to be 1.96×10^{-6} to 1.96×10^{-9} mg/kg/day, respectively. The cancer risk levels are plotted in Figure 2-2.

2.2.3 Dennal Exposure

2.2.3.1 Death

No studies were located regarding lethality in humans or animals following dermal exposure to NDMA.

2.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans following dermal exposure to NDMA. Limited information was located regarding systemic effects in animals following dermal exposure; no animal studies provided information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic or renal effects.

Dermal/Ocular Effects. Small ulcerations and scarring of the skin were observed in hairless mice that were treated once weekly with topical doses of 33.3 mg NDMA/kg for 20 weeks (Iversen 1980). No studies were located regarding NDMA-related ocular effects in animals.

Other Systemic Effects. Barnes and Magee (1954) noted that daily application of 100 mg NDMA/kg to rats for 4 days had no effect on general condition.

No studies were located regarding the following effects in humans or animals following dermal exposure to NDMA:

2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans following dermal exposure to NDMA.
A low incidence of lung adenomas (13%), but no skin tumors, developed in hairless mice that were treated once weekly with 33.3 mg/kg topical doses of NDMA for 20 weeks (Iversen 1980). Lung and skin tumors were not observed in historical control groups. Although Iversen (1980) concluded that the lung cancers were related to the topical applications of NDMA, it should be noted that the mice were housed 8 to a cage and could have licked the NDMA off each other or inhaled the compound due to its volatility.

2.3 RELEVANCE TO PUBLIC HEALTH

Death. Oral LD_{50} values of 23 and 40 mg NDMA/kg have been reported for pregnant and nonpregnant rats, respectively (Nishie 1983, Druckrey 1967). Oral LD_{50}s have not been determined for NDMA in other species. LD_{50}s for single doses of NDMA administered by intraperitoneal injection have also been reported; these values are consistent with the oral LD_{50}s and include 26.5 mg/kg in rats (Barnes and Magee 1954), 42.7 mg/kg in rats (Heath 1962) and 19 mg/kg in mice (Friedman and Sanders 1976). Repeated oral exposure to NDMA resulted in decreased survival in rats, mice and all other species that have been tested. In general, doses ranging from approximately 0.1-5 mg/kg/day have produced death in animals after several days to several months of exposure. Variations in lethal doses appear to be attributable more to intraspecies differences than differences in frequency or method of oral treatment. With the exception of mink, there do not appear to be marked differences in sensitivity among the species that have been tested. Deaths resulting from a single exposure or repeated exposures for several days or several weeks are generally attributed to liver toxicity; deaths associated

with longer duration (e.g., 20-40 weeks) exposures are due to liver tumor development.

In general, lethal doses,of NDMA and causes of death are similar among animal species. Human fatalities due to ingestion or inhalation of NDMA were also attributed to liver toxicity but adequate dose information is not available.

Systemic Effects. Hepatotoxicity is the primary systemic effect of NDMA. Hepatotoxicity has been demonstrated in all animal species that have been tested, and has been observed in humans who were exposed to NDMA by ingestion or inhalation. The characteristic hemorrhagic necrosis caused by NDMA are particularly prevalent following exposure to acutely toxic single doses or repeated doses for short durations. Liver tumors are the predominant effect of longer duration exposures. The mechanism of NDMAinduced liver toxicity is not clearly understood but may be related to alkylation of cellular protein (Barnes and Magee 1954, Magee et al. 1976, Diaz Gomez et al. 1981, 1983, Martin0 et al. 1988).

Although the hepatotoxicity of NDMA has been established unequivocally in numerous acute, intermediate and chronic duration oral studies with animals, relatively few of the studies delineate dose-response relationships and appropriate information regarding thresholds for this effect is not available. As noted for lethality, reported hepatotoxic doses for all species occur in the same general range with variations attributable more to intraspecies differences than treatment schedule or method. Human fatalities due to oral and inhalation exposure to NDMA have been reported in which hemorrhagic, necrotic and cirrhotic alterations in the liver were observed, indicating that NDMA produces similar hepatic effects in humans and animals. Therefore it is reasonable to expect that NDMA also will be hepatotoxic in humans at sublethal doses.

Limited information is available regarding nonhepatic systemic effects of NDMA in humans. This information has been obtained from autopsies of victims accidentally exposed to NDYA vapors or poisoned after ingestion of NDMA. The effects can be described as a general bleeding tendency. Hemorrhages have been noticed in the gastrointestinal tract, heart, respiratory system and brain (Freund 1937; Kimbrough 1982). The mechanism by which NDMA could induce bleeding is not known, but the bleeding tendency could be a consequence of decreased formation of clotting factors resulting from liver damage, impairment of the clotting mechanism or decreased number or function of platelets. Jacobson et al. (1955), for example, showed that NDMA greatly increases prothrombin time in dogs exposed to NDMA by inhalation. It is also possible that hemorrhagic effects could be caused by effects of NDMA on tissues. Because of its irritant properties, it is not difficult to explain the occurrence of hemorrhages in tissues that have direct contact with NDMA (gastrointestinal bleeding after oral ingestion, or bleeding of the bronchi and trachea after inhalation). However, it remains unknown why gastrointestinal bleeding can occur following inhalation

exposure. An alternative explanation could be that NDMA has a direct effect on the blood vessels. In fact, Ungar (1984, 1986) showed that oral treatment of hamsters with NDMA induced fragmentation of elastic fibers in portal vessels as well as denudation of the portal endothelium. Furthermore, autopsy of a victim of acute NDMA poisoning showed that "the central hepatic veins had lost their endothelial'lining cells" (Kimbrough 1982).

There is a relative paucity of information for nonhepatic systemic effects in animals because the emphasis of most studies was on hepatotoxicity or cancer, for which the liver is the primary target organ. Nonhepatic systemic effects that have been reported include gastrointestinal hemorrhage and congestion of several organs (kidney, lung, heart, spleen) in rats and/or mink, but the prevalence of these effects cannot be determined because these sites were examined infrequently.

Immunological Effects. A single oral dose of NDMA near the oral LD_{50} did not reduce humoral immune response in rats, but a single intraperitoneal dose near the intraperitoneal LD_{50} reduced humoral immune response in mice (Waynforth and Magee 1974). A number of other recent studies have found that NDMA given by intraperitoneal injection alters humoral immunity and antibody-mediated host defense mechanisms (Kaminski et al. 1989; Thomas et al. 1985, Myers et al. 1986, 1987, Scherf and Schmahl 1975, Holsapple et al. 1983, 1984, 1985, Johnson et al. 1987a,b). Immunosuppression resulting from NDMA exposure is not believed to be a result of direct interaction between the reactive intermediaries of NDMA and splenic lymphocytes, thereby indicating a difference between the mechanisms of immunotoxicity and carcinogenicity/genotoxicity (Holsapple et al. 1984). In vivo studies have shown that NDMA modulates the cellular immune response by altering the production and/or maturation/differentiation of bone marrow stem cells into functional macrophages (Myers et al. 1986, 1987). In vitro tests identify the primary cell target of NDMA as the B-lymphocyte (Holsapple et al. 1984, 1985). Thus, it is likely that NDMA decreases the overall reactivity of both T- and B-lymphocytes. It is not known whether NDMA is likely to be immunosuppressive in humans.

Developmental Effects. NDMA was fetotoxic to rats at oral doses that were toxic to the mother. Limited data indicate that these doses were not teratogenic for the rats. Oral administration of NDMA to mice resulted in increased perinatal deaths without histological abnormalities. It is not known whether NDMA could cause developmental effects in humans, but it cou be a potential developmental toxicant at doses which are toxic to pregnant women.

Reproductive Effects. Mice that were exposed to NDMA in drinking water prior to mating and during pregnancy and lactation showed an increase in the frequency of perinatal death among their offspring. Based on these data, NDMA could be considered a potential human reproductive toxicant.

2. HEALTH EFFECTS

Genotoxic Effects. Several in vitro studies have examined genotoxic effects of NDMA in human cells. As indicated in Table 2-3, NDMA induced DNA repair and synthesis in human lymphoblasts, and sister chromatid exchange in human lymphocytes and fibroblasts.

Genotoxicity of NDMA has been demonstrated consistently in numerous in vitro studies with non-human systems. As indicated in Table 2-3, NDMA was mutagenic in bacteria (Salmonella tvnhimurium, Escherichia coli), yeast (Saccharomvces cerevisiae), and mammalian cells (Chinese hamster V79 and ovary cells and mouse lymphoma L5178Y cells). NDMA induced unscheduled DNA synthesis and DNA repair and synthesis in rat, mouse and hamster hepatocytes. Treatment-related DNA fragmentation occurred in rat and human hepatocytes. Chromosomal aberrations occurred in Chinese hamster primary lung cells, rat ascites hepatoma cells, and rat esophageal tumor cells. Sister chromatid exchanges occurred in Chinese hamster ovary cells, Chinese hamster primary lung cells, human lymphoblasts and fibroblasts, and rat esophageal tumor and ascites hepatoma cells.

In vivo studies (Table 2-4) have shown that NDMA methylates DNA, causes DNA fragmentation and induces DNA synthesis and repair in liver and other tissues of various species (e.g., rat, mouse, hamster, gerbil). NDMA induced chromosomal aberrations in hamster embryonic fibrolasts, sister chromatid exchanges in mouse bone marrow cells, and micronuclei in rat hepatocytes and rat and mouse bone marrow cells. The genotoxic effects indicated above occurred after inhalation, oral or intraperitoneal administration of NDMA. Sperm abnormalities were not seen in mice following intraperitoneal administration of NDMA. Sex linked recessive lethal mutations occurred in Drosophila melanogaster, which indicates potential heritable mutagenicity of NDMA.

The weight of evidence indicates that NDMA is genotoxic in mammalian cells. In vitro studies with human cells, as well as in vitro and in vivo studies with animals and microbes, support this conclusion. Given the type and weight of genotoxicity evidence, it is appropriate to predict that NDMA poses a genotoxic threat to humans.

Cancer. The oral carcinogenicity of NDMA has been demonstrated in numerous studies with various species of animals. Inhalation exposure to NDMA has been reported to be carcinogenic to rats and mice in two studies. The carcinogenicity of NDMA is also documented in numerous single and or weekly subcutaneous and intraperitoneal injection studies, and in studies in which NDMA was administered prenatally and to newborn animals. Many of the carcinogenicity studies of NDMA were conducted specifically to induce cancer for various purposes, such as investigations of structure-activity relationships and pathogenesis. Tumors in tissues other than the liver and respiratory system (e.g., kidney, testis) have not been observed often in many of the carcinogenicity studies; this appears to be attributable in part to limited examination of nonhepatic tissues.

TABLE 2-3. Genotoxicity of N-Nitrosodimethylamine In Vitro

Endpoint	Species (Test System)	Result		References
		With Activation	Without Activation	
Gene mutation	Salmonella typhimurium	+	+	Araki et al. 1984, *Bartsch et al. 1980, Langenbach et al. 1986,* DeFlora et al. 1984, Prival and Mitchell 1981, Ishidate and Yoshikawa 1980
	Escherichia coli	+	NT	Araki et al. 1984, DeFlora et al. 1984
	Saccharomyces cerevisae	+	NT	Jagannath et al. 1981, Frezza et al. 1983
	Chinese Hamster V79 and ovary cells	+	-	Kuroki et al. 1977, Adair and Carver 1983, O'Neill et al. 1982, Carver et al. 1981, Dickins et al. 1985, Bartsch et al. 1980, Katoh et al. 1982, Langenbach 1986, Hsie et al. 1978
	Mouse lymphoma L5178Y cells	+	-	Amacher and Paillet 1983, Clive et al. 1979
DNA fragmentation	Rat hepatocytes	NT	+	Bradley et al. 1982
	Human hepatocytes	NT	+	Martelli et al. 1985
Chromosomal aberrations	Chinese hamster lung cells	+	NT	Matsuoka et al. 1979, 1986, Ishidate and Yoshikawa 1980
	Rat ascites hepatoma (AH66B) and rat esophageal (R1, R3) tumor cells	NT	+	Ikeuchi and Sasaki 1981

TABLE 2-3 (continued)

Endpoint	Species (Test System)	Result: With Activation	Result: Without Activation	References
Sister-chromatid exchange	Rat esophageal tumor, ascites hepatoma	NT	+	Abe and Sasaki 1982, Ikeuchi and Sasaki 1981
	Human lymphocytes	+	-	Inoue et al. 1983, Madle et al. 1987,
	Human fibroblasts	+	NT	Tomkins et al. 1982
	Chinese hamster ovary cells	+	NT/-	Tomkins et al. 1982, Okinaka et al. 1981 Blazak et al. 1985
	Chinese hamster V79 cells	+	-	Madle et al. 1987, Sirianni and Huang 1987 Blazak et al. 1985
	Chinese hamster primary lung cells	+	-	Shimizu et al. 1984
DNA Damage	Rat hepatocytes	NT	+	Bermudez et al. 1982
DNA repair/ synthesis	Rat hepatocytes	+	+	Andrae and Schwarz 1981,
	Human lymphoblasts	+	NT	Andrae et al. 1979
	Mice hepatocytes	NT	+	McQueen et al. 1983
	Hamster hepatocytes	NT	+	McQueen et al. 1983
	Rat pancreatic cells	NT	-	Steinmetz and Mirsalis 1984

NT = Not tested

TABLE 2-4. Genotoxicity of N-Nitrosodimethylamine In Vivo

Endpoint	Species (Test System)	Result	References
DNA methylation	Rat, mouse, hamster and/or gerbil liver	+	O'Connor et al. 1982, Bamborschke et al. 1983, Pegg et al. 1981, Pegg and Hui 1978, Stumpf et al. 1979
	Human liver	+	Herron and Shank 1980
DNA fragmentation	Rat liver and kidney elution	+	Brambilla et al. 1981, Petzold and Swenberg 1978, Abanobi et al. 1979, Bermudez et al. 1982
	Mouse liver and kidney elution	+	Cesarone et al. 1982
DNA synthesis and repair	Fetal mouse kidney and liver	+	Bolognesi et al. 1988
	Mouse testes	+	Friedman and Staub 1976, Cesarone et al. 1979
	Rat liver	+	Bakke and Mirsalis 1984, Kornbrust and Dietz 1985, Doolittle et al. 1984
	Rat respiratory cells	+	Doolittle et al. 1984
	Rat spermatocytes	-	Doolittle et al. 1984
Sex-linked recessive lethal mutations	Drosophila melanogaster	+	Brodberg et al. 1987, Blount et al. 1985, Lee et al. 1983
Sperm abnormalities	Mouse	-	Wyrobek and Bruce 1975
Sister chromatid exchange	Chinese hamster bone marrow	+/-	Neal and Probst 1983
	Mouse bone marrow	+	Sharma et al. 1983, Bauknecht et al. 1977
Chromosome aberrations	Hamster embryonic fibroblasts	+	Inui et al. 1979
Micronucleus	Rat bone marrow	+/-	Trzos et al. 1978
	Rat hepatocytes	+	Mehta et al. 1987, Tates et al. 1980
	Mouse bone marrow	+	Odagiri et al. 1986, Bauknecht et al. 1977
	Hamster embryonic fibroblasts	+	Inui et al. 1983

2. HEALTH EFFECTS

There is increasing evidence, derived from in vitro and in vivo metabolic studies, indicating that the carcinogenic effects of NDMA are due to a metabolite rather than the compound itself (Singer 1979). NDMA is converted into an alkylating (methylating) agent after metabolism by microsomal mixed-function oxidases. This process occurs principally in the liver and to a lesser extent in kidney and lungs, and results in the methylation of cellular macromolecules such as DNA, RNA and other proteins. Methylation occurs at several positions in DNA including N^{-1}, N^{-3} or N^{-7} of deoxyadenosine; N^{-3}, N^{-7} or 0^{6} of deoxyguanosine; N^{-3} of deoxycytidine; and 0^{2} or 0^{4} of thymidine. Experimental evidence indicates that methylation at the 0^{6}-position of guanine may be responsible for the carcinogenic activity of nitrosamines in general, however, the carcinogenic potential of other methylated products cannot be ruled out. The methylation of DNA by NDMA has been studied extensively (e.g., Bamborschke et al. 1983, O'Connor et al. 1982, Pegg et al. 1981, Pegg and Hui 1978, Stumpf et al. 1979.).

The carcinogenic properties of NDMA, and nitrosamines in general, have been extensively studied. It is of considerable interest that, despite its ubiquitous distribution, NDMA induces tumors in a limited number of organs and tissues and that there are marked differences in this response among animal species. Differences in pharmacokinetics properties seem to play an important role in the carcinogenic action of NDMA (Pegg 1980, Lijinsky 1987). For example, the degree of hepatic extraction from the portal blood seems to determine whether tumors develop in extrahepatic sites. Therefore, large doses of NDMA tend to induce extrahepatic tumors (spill-over effect). In addition, metabolic activating systems and repair mechanisms may not operate at the same rates in different organs and different species. Route of administration also seems to be a factor in NDMA carcinogenesis since different responses are seen in a particular species when different routes of exposure are used. This suggests that rates of absorption can determine the site of tumor development.

Based on the unequivocal evidence of carcinogenicity in animals, it is reasonable to anticipate that NDMA will be carcinogenic in humans. It is important to recognize that this evidence also indicates that oral exposures of acute and intermediate duration are sufficient to induce cancer.

2.4 LEVELS IN HUMAN TISSUES AND FLUIDS ASSOCIATED WITH HEALTH EFFECTS

A considerable amount of DNA methylation in the liver of a suspected NDMA poisoning case was reported by Herron and Shank (1980). Based on studies in rats, in which the amount of DNA alkylation could be correlated with known amount of orally administered NDMA, the authors estimated that the victim had been exposed to a dose of 20 mg/kg or more of NDMA. No other studies were located regarding levels of NDMA or its metabolites in human tissues and fluids associated with effects. Several analytical methods have been developed to determine levels of NDMA in human tissues and fluids. These methods are described in Chapter 6.

2. HEALTH EFFECTS

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

Although data relating specific amounts of NDMA in the environment with levels in human tissues and/or health effects have not been reported, some qualitative information is available. This information, given below, has to be interpreted with caution since results were not always rigorously reported or evaluated, and endogenous formation of NDMA was not quantitated.

A high incidence of nasopharyngeal carcinoma was found in Tunisia (North Africa), Southern China and Greenland among populations who consume foods with a high content of volatile nitrosamines (Poirier et al. 1987). Lu et al. (1987) found a positive correlation between the amount of NDMA and other nitrosamines in the gastric juice of Chinese with a high incidence of esophageal carcinoma. Wild et al. (1987) observed a positive relationship between levels of 0^6-methyldeoxyguanosine (implicated in the initiating process of nitrosamine-induced cancer) and incidences of esophageal and stomach cancer in the province of Lin-xian, China. Yu and Henderson (1987) reported finding a high incidence of nasopharyngeal carcinoma in individuals from Hong Kong, who are known to consume from early in life considerable amounts of Cantonese-style salted fish, which has a high content of NDMA and other nitrosamines.

2.6 TOXICOKINETICS

2.6.1 Absorption

2.6.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption of NDMA following inhalation exposure of humans or animals to NDMA. However, it can be inferred that NDMA is absorbed from the air since it can be detected in the urine of rats (Klein and Schmezer 1984) and dogs (Raabe 1986) after inhalation exposure. Absorption is also indicated by reports of human deaths following inhalation of NDMA (see Section 2.2.1.1).

2.6.1.2 Oral Exposure

No studies were located regarding the absorption of NDMA following oral exposure of humans.

The absorption of NDMA from the gastrointestinal tract of animals is fast. Less than 2% of the labelled compound could be recovered from the gastrointestinal tract 15 minutes after oral administration of 14C-NDMA to rats (Diaz Gomez et al. 1977). Absorption seems to be independent of the dose administered (Diaz Gomez et al. 1972). In the rat, NDMA is absorbed much faster from the small intestine than from the stomach, in isolated preparations (Heading et al. 1974) and in vivo (Pegg and Perry 1981).

Ishiwata et al. (1977) reported that the disappearance curve of NDMA from isolated guinea pig stomach and small intestine follows first order kinetics.

2.6.1.3 Dermal Exposure

No studies were located regarding the absorption of NDMA following dermal exposure of humans.

Indirect evidence indicating that NDMA may be absorbed through the skin was found in a study published by Iversen (1980) in which topical application of NDMA induced lung adenomas in mice. The results from Iversen, however, should be interpreted with caution since the mice were housed 8 to a cage and could have licked the NDMA from each other and also could have inhaled this volatile compound.

2.6.2 Distribution

Unmetabolized NDMA was found to be evenly distributed among the main organs of mice and rats shortly after i.v. injection to animals in which the metabolism of NDMA had been inhibited (Magee 1956; Johansson and Tjalve 1978). Wishnok et al. (1978) reported a similar finding in rats following i.p. injections. Johnson et al. (1987a) reported that one hour after a dose of 6 mg ^{14}C-NDMA/kg was administered by intraperitoneal injection to mice, the liver contained two times as much radioactivity as the kidney, spleen and thymus.

2.6.2.1 Inhalation Exposure

No studies were located regarding the distribution of NDMA following inhalation exposure of humans or animals.

2.6.2.2 Oral Exposure

No studies were located regarding the distribution of NDMA following oral exposure of humans.

Daugherty and Clapp (1976) reported that 15 minutes after oral administration of ^{14}C-NDMA to mice, the relative amounts of radioactivity in the homogenates of heart, forestomach, esophagus, liver and lung were 1, 2, 3, 10 and 70, respectively. The differences could be attributed to different tissue affinity, transport and/or metabolism. Measurable amounts of NDMA were reported in blood, liver, kidney, lungs and brain of mice exposed to 5 mg NDMA/kg/day in drinking water.for up to 4 weeks (Anderson et al. 1986). NDMA has been detected in maternal blood, placenta, fetus and amniotic fluid of pregnant Syrian hamsters for up to 2 hours after a single subcutaneous dose of 12.5 mg/kg of the chemical (Althoff et al. 1977).

Liver and kidney DNA from 14-day-old rats became labelled after treating the nursing mothers with ^{14}C-NDMA by gavage (Diaz Gomez et al. 1986).

2.6.2.3 Dermal Exposure

No studies were located regarding the distribution of NDMA following dermal exposure of humans.

The study by Iversen (1980), in which lung adenomas were noticed in mice after skin application of NDMA, indicates that this chemical (or a metabolite) was distributed to the lungs.

2.6.3 Metabolism

Evidence from in vitro and in vivo studies with rodents indicates that NDMA is metabolized by hydroxylation of the a-carbon, followed by formation of formaldehyde, molecular nitrogen and a methylating agent, which is considered to be the carcinogenic form (Lotlikar et al. 1975; Czygan et al. 1973). Recent evidence suggests that a significant proportion of NDMA is metabolized via a denitrosation mechanism. The latter mechanism takes place in rats in vivo, as indicated by the urinary excretion of labelled methylamine after i.v. administration of ^{14}C-NDMA (Keefer *et* al. 1987), and in human liver microsomes (Yoo et al. 1988). The metabolism of NDMA is summarized in Figure 2-3.

Metabolism of NDMA varies among species (Prassana et al. 1985; Montesano et al. 1982). Age of the animal and route of administration can also influence the rate of metabolism of NDMA (Phillips et al. 1975). In addition, at varying doses, different forms of enzymes appear to be responsible for NDMA metabolism (Kroeger-Koepke and Michejda 1979; Lotlikar et al. 1978).

2.6.3.1 Inhalation Exposure

No studies were located regarding the metabolism of NDMA following inhalation exposure of humans or animals.

2.6.3.2 Oral Exposure

No studies were located regarding the metabolism of NDMA following oral exposure of humans.

Phillips et al. (1975) demonstrated that NDMA is metabolized at a lower rate when given orally to rats than when administered by parenteral routes.

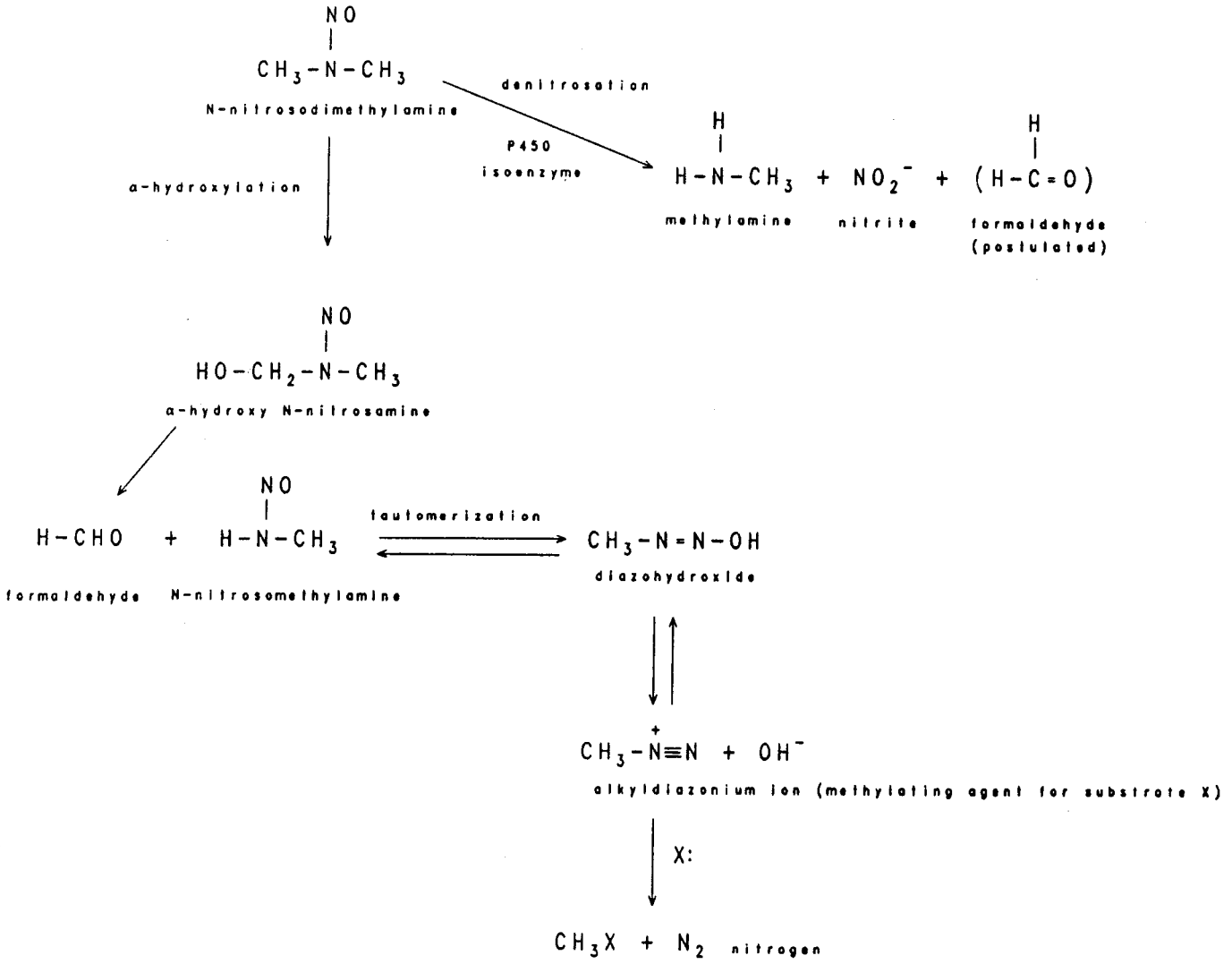

Figure 2-3. Metabolism of N-Nitrosodimethylamine

Source: Crygan et al. 1973; Keefer et al., 1987; Lotikar et al. 1975; Yoo et al. 1988

2.6.3.3 Dermal Exposure

No studies were located regarding the metabolism of NDMA following dermal exposure of humans or animals.

2.6.4 Excretion

Labelled $C0_2$ can be detected in the exhaled air 1 hour after i.p. administration of ^{14}C-NDMA to rats (Phillips et al. 1975). Hemminki (1982) administered labelled NDMA by intraperitoneal injection to rats and was able to detect three main radioactive fractions in the urine over a period of 5 days. Fraction I was composed of radioactive aminoacids, fraction II of allantoin and a metabolite of thiazolidine-4-carboxylic acid, and fraction III of 7-methylguanine.

2.6.4.1 Inhalation Exposure

Klein and Schmezer (1984) reported that 10-30% of NDMA is excreted by exhalation after exposing rats to the chemical during 10 minutes by endotracheal intubation. In beagle dogs, 23% of the administered radioactive label is exhaled in 30 minutes after a 3 hour inhalation exposure (Raabe 1986).

2.6.4.2 Oral Exposure

Spiegelhalder et al. (1982) reported that, in a 24 hour period, human volunteers excreted in the urine between 0.5 and 2.4% of an ingested dose of 12-30 pg of NDMA added to drinking fluids containing ethanol.

Unchanged NDMA was recovered in the urine and feces of rats up to 24 hours after a single oral dose of 50 mg (Magee 1956). Swann et al. (1984) did not detect labelled NDMA in the urine of rats after oral administration of 30 μg/Kg of ^{14}C-NDMA in water. Phillips et al. (1975 determined that after administration of a single oral dose of 5 mg of ^{14}C-NDMA to female rats the maximum rate of $^{14}C0_2$ production was 12.4% of the dose/hour, and that 48% of the dose could be recovered as $^{14}C0_2$ in the exhaled air in 7 hours and 5.7% as ^{14}C (total label) in a 24 hour urine sample.

2.6.4.3 Dermal Exposure

No studies were located regarding the excretion of NDMA following dermal exposure of humans or animals.

2.7 INTERACTIONS WITH OTHER CHEMICALS

NDMA is normally formed by bacteria in the human stomach and small intestine, but not in the large intestine (Archer et al 1982; Spiegelhalder and Preussmann 1985; Zeisel et al. 1988). Also, rats and guinea pigs have

been shown to make NDMA in their stomachs (Hashimoto et al. 1976; Omori et al. 1979). Small amounts of NDMA are formed in the saliva of humans; concentrations can vary from 4 to 10 pg/mL depending on pH and type of food in the mouth (Rao et al. 1982). NDMA formation in the saliva can be increased by chemicals such as chlorogenic acid, which is found in coffee, and decreased by a number of synthetic additives, as well as caffeic acid, tannic acid and ascorbic acid, which are found in coffee, tea, and citrus fruits, respectively.

Consumption of alcohol has been shown to have complicated effects on the toxicity of NDMA. Rats that received alcohol (ethanol or isopropanol) by gavage for 2 days before receiving NDMA had more liver damage with the alcohol than without it (Lorr et al. 1984; Maling et al. 1975). Increased levels of plasma glutamic pyruvate transaminase were monitored and used as a sign of liver damage. Another study showed that 4 weeks of ethanol pretreatment in rats worsened the effects on DNA repair that occurred following DNA alkylation induced by NDMA (Mufti et al. 1988). There is at least one other study in rats, however, that showed that 23 days of pretreatment with ethanol decreased the hepatotoxicity of NDMA (Gellert et al. 1980).

Other substances to which people are exposed have been shown to alter the toxic effects of NDMA in rats. Vitamin E and calcium channel blocking agents have been shown to decrease the hepatotoxicity associated with NDMA (Landon et al. 1986; Skaare and Nafstad 1978). Selenium increased the toxic effect of NDMA on the liver (Skaare and Nafstad 1978) and cadmium increased the carcinogenic effect of NDMA in the kidney (Wade et al. 1987). NDMA induced higher incidences of stomach cancer in rats fed diets low in zinc than in those fed normal diets (Ng et al. 1984). Rats fed diets low in copper developed more kidney tumors from NDMA than rats fed normal diets (Carlton and Price 1973). In contrast, rats given NDMA and cupric acetate had fewer tumors than rats given NDMA (Yamane et al. 1984). Although these data indicate that simultaneous administration of other chemicals may augment NDMA toxicity in animals, it not clear how these simultaneous exposures may occur in humans.

2.8 POPUIATIONS THAT ARE UNUSUALTaY SUSCEPTIBLE

People with chronic renal failure produce more NDMA in their small intestines due to increased levels of bacterial growth than normal people do (Lele et al. 1983). This increase in NDMA can be blocked by injections of ascorbic acid or antibiotics, but is potentiated by alcohol (Lele et al. 1987). People who consume alcohol may be unusually susceptible to NDMA for reasons discussed in Section 2.7.

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 NDMA 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-Nitrosodimethylamine

Information regarding health effects of NDMA in humans is limited to case reports of fatalities due to hepatotoxicity following ingestion or inhalation. Health effects of NDMA in animals have been investigated in numerous oral studies and several inhalation and dermal studies. As indicated in Figure 2-4, animal oral data are available for lethality, systemic toxicity, immunological effects, neurological effects, developmental effects, reproductive effects, genotoxic effects and cancer. These data indicate that hepatotoxicity and cancer are the most prominent NDMA-related effects.

2.9.2 Data Needs

Single Dose Exposure. Information on lethality in rats following single oral doses, including two LD^{50} values, are available. Information on hepatic effects in rats due to single oral exposures are also available. Additional single dose oral studies with rats would provide more information on thresholds for lethality and hepatotoxicity, and on nonhepatic effects. Studies on species other than the rat would provide data on interspecies differences. Single-exposure inhalation experiments provide limited information on lethality in rats, mice and dogs, and dermal/ocular effects in rats; additional studies could corroborate these data as well as provide NOAELs. Single application dermal studies would provide information on lethality and skin and eye irritation.

Repeated Dose Exposure. Numerous repeated dose studies of intermediate duration have been conducted with rats, mice and other species. These studies provide extensive information on doses and treatment schedules that are lethal and hepatotoxic but do not adequately identify thresholds for these effects, particularly in species that may be more sensitive (e.g., mink). Additional repeated dose oral studies designed to examine tissues other than the liver could provide useful information on nonhepatic systemic effects of NDMA. Oral studies conducted over periods longer than 20-30 weeks may not be necessary as sufficient evidence indicates that cancer will be the predominant effect. Repeated exposure inhalation studies could provide

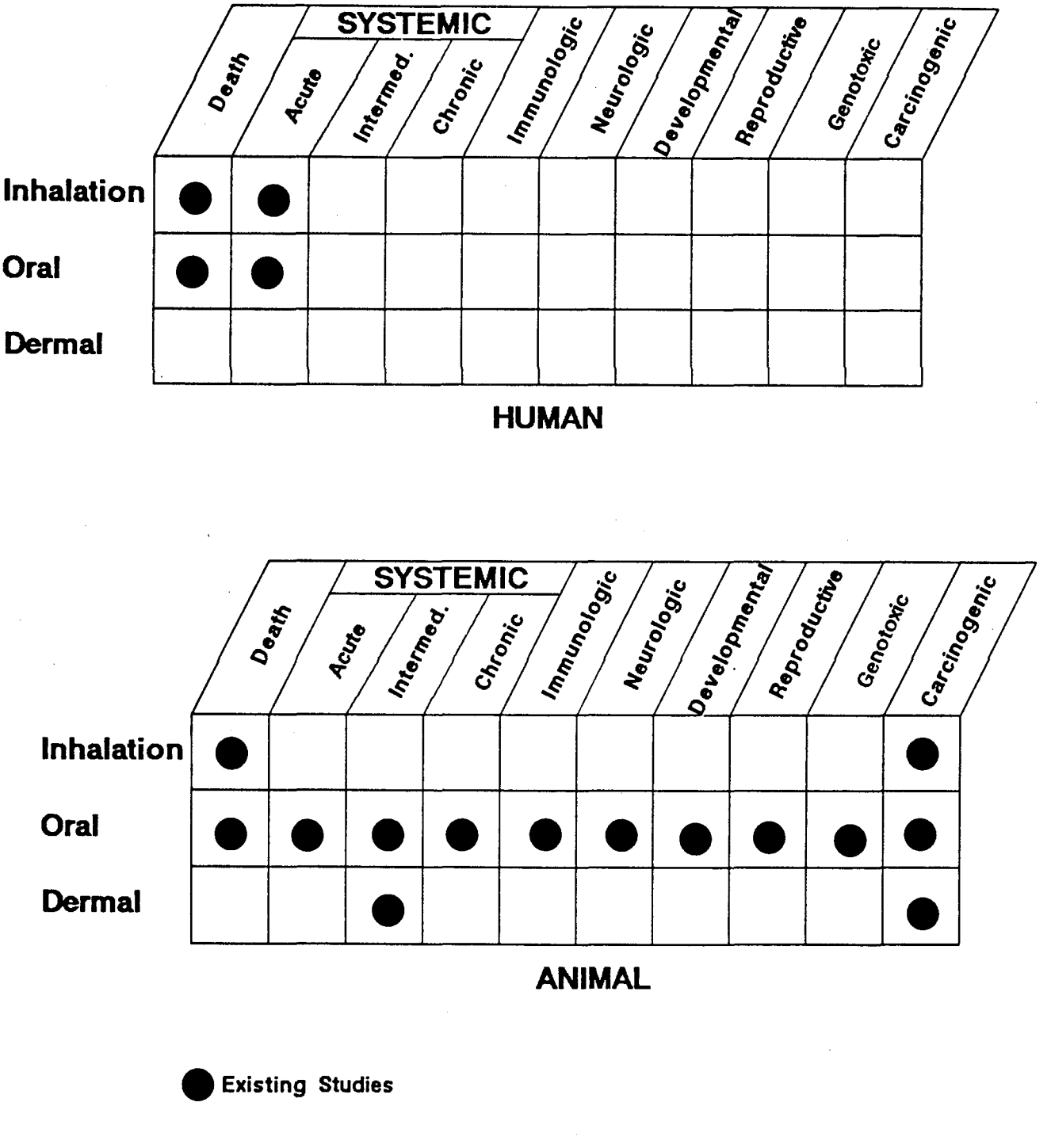

FIGURE 2-4. Existing Information on Health Effects of N-Nitrosodimethylamine

information on concentrations associated with lethality and systemic effects.

Chronic Exposure and Carcinogenicity. Chronic oral and inhalation studies of NDMA have been conducted with rats and mice. These studies indicate that the predomin&nt effect of chronic exposure to NDMA is cancer. As low doses of NDMA have been tested in chronic oral studies and it is established that intermediate duration exposure to NDMA is sufficient to induce cancer, additional chronic studies may not be needed.

Genotoxicity. The genotoxic potential of NDMA is established unequivocally. Only several studies, however, evaluated genotoxic effects in animals following oral or inhalation exposure to NDMA, and only several in vitro studies evaluated human cells. Additional studies, particularly assays with human cells and assays providing information on the potential for heritable mutations, would add to the data base on genotoxicity.

Reproductive Toxicity. Oral exposure to NDMA for 75 days prior to mating had no significant effect on time-to-conception in mice. Other reproductive indices or species have not been evaluated. 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 NDMA in animals, which may be related to possible reproductive effects in human.

Developmental Toxicity. Evidence indicates that NDMA is fetotoxic to rats and mice, but NOAELs have not been defined. Well-conducted developmental studies using several exposure levels and environmentally relevant routes of exposure could provide the dose-response information necessary to determine the threshold for fetotoxicity and to determine the possible relevance and risk for humans. Additional studies also could determine if NDMA is a transplacental carcinogen.

Immunotoxicity. Information regarding immunological effects of NDMA in humans is not available. Immunosuppression by NDMA has been demonstrated in a number of intraperitoneal injection studies, but not in an oral study, with mice. Specific immunotoxicity tests or a battery of immunotoxicity tests in which NDMA is administered by the oral route would provide a better assessment of possible immunotoxic effects. Sensitization tests in animals could provide information on whether an allergic response to NDMA is likely in humans. Additional studies also could determine if NDMA is a transplacental carcinogen.

Neurotoxicity. Dogs that were orally treated with NDMA reportedly experienced central nervous system depression, but it is likely that this effect is a consequence of liver damage rather than direct neurotoxicity. Additional information pertaining to neurotoxicity was not found.

Neurotoxicity tests in animals exposed to NDMA could provide additional information on possible neurotoxic effects.

Epidemiological and Human Dosimetry Studies. The only information available concerning effects of NDMA in humans comes from cases of acute poisoning and subsequent death. In these cases, hemorrhagic and necrotic alterations and cirrhosis of the liver were observed. On the other hand, effects in animals have been well documented (Section 2.2). Attempts have been made to measure occupational exposure to NDMA, in particular in the rubber industry. Unfortunately these attempts have failed because NDMA is metabolized almost completely to CO_2 and water. Excretion rates for NDMA measured in experimental animals are in the order of 0.02% of the ingested dose (Spiegelhalder 1984). Although unchanged NDMA is unlikely to be detected in the urine, it may be possible to measure urinary excretion of nonspecific DNA adducts (e.g., 7-methylguanine). As stated by Spiegelhalder (1984), limited information is available on airborne exposures of individual workers for the following reasons: 1) usually workers are exposed to a variety of chemicals and there is cross-contamination between jobs, 2) transfers from job to job involve different exposures, 3) increases in cancer incidences most likely result from exposures that occurred in the past, when no exposure data were available, and 4) no comprehensive study has been conducted so far. Epidemiology studies of individuals who live in areas where NDMA has been detected are necessary to obtain information on whether NDMA induces effects in humans similar to those seen in animals.

Biomarkers of Disease. Since acute NDMA poisoning in humans caused severe liver disease, sensitive clinical biochemistry liver function tests might detect early hepatic damage from toxic exposure to NDMA. Recently, Wild et al. (1987), using a radioimmunoassay, were able to detect elevated levels of the promutagenic lesion O^6 -methyldeoxyguanosine in DNA of esophageal cells from individuals with high incidence of esophageal and stomach cancer. These individuals were found to consume foods with a relatively high content of nitrosamines.

Disease Registries. The only known health effects of NDMA on humans are those obtained from acute poisoning cases, in which postmortem examination revealed severe liver damage. If disease states attributed to exposure to NDMA could be identified by epidemiological studies, the number of individuals affected, the exposure levels involved, and the factors associated with identifying the disease in a given population, such as, the vicinity to hazardous waste sites or industrial plants, could be determined.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of NDMA from environmental media. Since NDMA has been detected in ambient air, water and soil (ppb levels), it is important to determine if NDMA can be absorbed by humans from environmental samples. It must be noted that NDMA has been found in trace amounts in some foods and beverages and that endogenous formation of NDMA has been found to occur from the nitrosation of amines in the gastrointestinal tract. An

understanding of the bioavailability of NDMA from environmental media may be obtained by studying the biological fluids of individuals exposed in the workplace or through the ingestion of NDMA-containing foods and beverages. The limited information available regarding absorption parameters of NDMA in experimental animals indicates that NDMA is rapidly absorbed from the gastrointestinal tract; therefore, one can assume that if water or soil contaminated with NDMA are ingested, NDMA will be readily absorbed.

Food Chain Bioaccumulation. No studies were available concerning food chain bioaccumulation of NDMA from environmental sources. NDMA has been detected in samples of cooked fish and meat. However, occurrence of NDMA in these samples is not the result of bioaccumulation but is the result of formation during preservation and/or cooking (Scanlan 1983). Estimation techniques have been used to determine that NDMA would not bioaccumulate in lipids of fish (see Section 5.3.1). Based on this limited amount of information, it is speculated that human exposure to NDMA through diet is not the result of food chain bioaccumulation. Monitoring for the accumulation of NDMA in organisms from several trophic levels could be used to support this conclusion.

Absorption, Distribution, Metabolism, Excretion. Examination of Section 2.6 clearly indicates that oral administration of NDMA has been the preferred route for studying its absorption, distribution, metabolism and excretion. This is not surprising since oral administration is easier to monitor when compared to other routes. The oral route seems to be the most pertinent to study since humans are most likely to be exposed to nitrosamines orally. Toxicokinetic data with regard to dermal and inhalation exposure of NDMA are clearly lacking. Furthermore, dermal and inhalation exposures may lead to different metabolic pathways and patterns of distribution and excretion, which could account for differences in the degree of toxicity exhibited by different routes of exposure. The metabolism of NDMA in isolated microsomal preparations seems to be well understood, but studies with cultured human cells could provide additional useful information. However, exploration of the denitrosation mechanism as an alternative to a-hydroxylation requires more attention. Determination of the urinary excretion of NDMA in control human volunteers and in individuals known to consume foods with high contents of nitrosamines could provide information concerning absorption and excretion of the xenobiotic.

Comparative Toxicokinetics. No studies were located regarding comparative toxicokinetics of NDMA in vivo. In vivo studies are available indicating differences in hepatic 0^6 -methylguanine repair activity among rodent species (O'Connor et al. 1982). A report by Prasanna et al. (1985) indicates that the in vitro metabolism of NDMA by liver microsomes from hamsters, rats and chickens is qualitatively similar, but with different rates. Montesano et al. (1982) showed that liver slices from humans have a metabolic capacity to activate NDMA similar to that found in rats and slightly lower than that found in liver slices from hamsters. Differences among species in the toxic responses to a chemical can be attributed to

differences in the toxicokinetic parameters. This seems to be particularly true for N-nitrosamines in general (Lijinsky 1987). The fact that a number of factors (animal species, route of exposure, dosing schedule) appear to determine the organ-specificity and the severity of the effect of NDMA indicates that caution must be exercised when assuming possible effects in humans. Although little information is available regarding the toxicokinetics of NDMA in humans, analysis of NDMA in the urine of individuals accidentally exposed to the chemical or of individuals consuming foods with a relatively high content of NDMA could provide quantitative information on absorption and excretion.

2.9.3 On-going Studies

Two studies regarding the immunotoxicity of NDMA are known to be ongoing (Federal Research In Progress, 1988). One is investigating the immunosuppressive activity of subchronic and chronic administration of NDMA, specifically the in vitro antibody response of NDMA treated spleen cell suspensions to a number of mutagens. This research is being performed by Holsapple at Virginia Commonwealth University. A second study, performed by Schook at the University of Illinois, is attempting to identify molecular mechanisms for the immunosuppressive effects of NDMA.

In research being conducted by Anderson at the Division of Cancer Etiology, National Cancer Institute, NDMA is being examined for its ability to cause neurogenic tumors in mice by transplacental exposure.

In studies sponsored by NIEHS, Faustman at the Univerity of Washington is evaluating NDMA and other related N-nitroso compounds for their in vitro developmental toxicity (Faustman 1989).

A number of ongoing studies are investigating the metabolism of NDMA (Federal Research in Progress, 1988). These include N-nitroso compound detoxification by Jensen at Temple University, Philadelphia, PA, formation and metabolism of nitrosamines in pigs by Magee at Temple University, metabolism and genotoxicity of nitrosamines in rats by Rogan at the University of Nebraska, Omaha, NE, and enzymology of nitrosamine metabolism in rats, mice and rabbits in a NCI-sponsored study by Yang at the University of Medicine and Dentistry, Newark, NJ. Other studies sponsored by NCI are being conducted to find means of shifting the balance of the metabolic pathway towards increasing inactivation and characterizing the possible role of α-nitrosamino radicals in the metabolism of NDMA (written communication, Keefer 1989).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENITY

Data pertaining to the chemical identity of NDMA are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of NDMA are presented in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of N-Nitrosodimethylamine

	Value	Reference
Chemical name	Methanamine, N-methyl-N-nitroso	CAS 1988
Synonyms	N-nitrosodimethylamine; dimethylnitrosamine; DMNA; DMN; NDMA	CAS 1988
Trade name(s)	ND	
Chemical Formula	C2 H6 N2 O	SANSS 1988
Chemical Structure	$(CH_3)_2N$-N=O	SANSS 1988
Identification Numbers:		
CAS Registry	62-75-9	CAS 1988
NIOSH RTECS	IQ0525000	RTECS 1988
EPA Hazardous Waste	P082	RTECS 1988
OHM-TADS	7217418	OHM-TADS 1988
DOT/UN/NA/IMCO	ND	
HSBD	1667	HSDB 1988
NCI	ND	

ND = No Data
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

TABLE 3-2. Physical and Chemical Properties of N-Nitrosodimethylamine

Property	Value	Reference
Molecular weight	74.08	Weast 1983
Color	yellow	IARC 1978
Physical State	liquid	IARC 1978
Melting point	-25°C (estimated) -50°C (estimated)	Lyman 1985 EPA 1986
Boiling point	154°C	Weast 1983
Specific gravity, 20/4°C	1.0059	Weast 1983
Odor	No distinct odor	Frank and Berry 1981
Odor threshold	Not available	
Solubility		
Water	Miscible	Mirvish et al. 1976
Organic solvents	Soluble in alcohol, ether, other organic solvents	Weast 1983, IARC 1978
Partition coefficient		
Log octanol/water	-0.57	Hansch and Leo 1985
Log Koc	1.07 (estimated using Equation 4-8)	Lyman 1982
Vapor pressure	2.7 mm Hg (20°C)	Klein 1982
Henry's Law constant		
at 37°C	1.99×10^{-6} atm-m^3/mol	Mirvish et al. 1976
at 20°C	2.63×10^{-7} atm-m^3/mol (estimated using vapor pressure and water solubility data)	

TABLE 3-2 (continued)

Property	Value	Reference
Autoignition temperature, °C	ND	
Flashpoint, open cup	ND	
Flammability limits in air	ND	
Conversion factors		
ppm (v/v) to mg/m^3 in air (20°C)	ppm (v/v) x 3.08 = mg/m^3	
mg/m^3 to ppm (v/v) in air (20°C)	mg/m^3 x 0.325 = ppm (v/v)	

ND = no data

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

NDMA is not produced for commercial use in the United States (HSDB 1988). The public portion of the U.S. EPA TSCA Production File indicates that during 1977, the Ames Laboratories in Milford, CT and Columbia Organics in Columbia, SC both prepared small research quantities of this chemical. Eastman-Kodak in Rochester, NY and Teledyne McCormick Selph, an importer, supplied no NDMA during 1977, although both had the capability to produce/import this compound and had done so in the past (EPA 1977). Small research quantities of this chemical presently are available from Sigma Chemical Co. and Aldrich Chemical Co. NDMA can be prepared by reaction of nitrous acid with dimethylamine or by addition of acetic acid and sodium

4.2 IMPORT

Data pertaining to the import of NDMA into the U.S. were not located in the available literature.

4.3 USE

NDMA is prepared in laboratory-scale quantities solely for use as a research chemical (HSDB 1988). NDMA was formerly used (prior to April 1, 1976) as an intermediate in the production of l,l-dimethylhydrazine, a storable liquid rocket fuel, which was believed to have contained up to 0.1% NDMA as an impurity (IARC 1978). NDMA has also been used or has been proposed for use as an antioxidant, additive for lubricants, and as a softener for copolymers (Windholz 1983). NDMA has also been used as a solvent and rubber accelerator (Hawley 1981).

4.4 DISPOSAL

Combustion in an incinerator equipped with an afterburner and NOx scrubber is the recommended method for disposing NDMA. Liquid wastes should be neutralized, if necessary, filtered to remove solids, and then put into closed polyethylene containers for transport. All equipment should be thoroughly rinsed with solvent, which should be added to the liquid waste for incineration. Great care should be practiced to insure that there is no contamination on the outside of the solvent container. If possible, solid waste should also be incinerated. If this is not possible, the nitrosamine should be extracted from the waste and the extract should be handled as a liquid waste. Any rags, papers or other materials which are contaminated during the disposal process should be incinerated. Contaminated solid materials should be enclosed in sealed plastic bags that are labeled cancer suspect agent, with the name and amount of carcinogen. Bags should be stored in well-ventilated areas until they are incinerated (HSDB 1988). Nitrosamine residues generated in laboratory research or accidental spills

in research laboratories should be diluted to a concentration of less than 10 μg/L and then reduced to innocuous amines, ammonia, or alcohols by aluminum-nickel alloy powder and aqueous alkali. This method of disposal is applicable to a variety of media (water, mineral oil, olive oil, dimethylsulfoxide, solutions of agar gel), but is not recommended for use in solutions of acetone or dichloromethane because reactions are slow and incomplete. After the reduced reaction mixture is filtered, the liquid can be disposed of by pouring it over a sufficient amount of absorbent material to convert it to a solid waste for incineration. The filtercake is discarded with non-burnable solid wastes (HSDB 1988). Other methods of destruction of NDMA in laboratory wastes (e.g., using hydrobromic acid or potassium permanganate/sulfuric acid) are described by IARC (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 NDMA 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.

4.5.1 Data Needs

Production, Use, Release, and Disposal. Uses, methods of synthesis, and methods of disposal for NDMA are described in the literature and there does not appear to be a need for further information on these topics. Lack of information pertaining to the import of this compound is not surprising since this compound has no commercial applications. Data regarding the amount of NDMA released to air, water, and soil would be useful in order to establish potential sources of exposure and levels of exposure from environmental media. In particular, information releases from hazardous waste landfills and industries in which this compound is inadvertently formed may help 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.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

NDMA is not an industrially or commercially important chemical; nevertheless, it can be released into the environment from a wide variety of manmade sources. This is due to the inadvertent formation of NDMA in industrial situations when alkylamines, mainly dimethylamine and trimethylamine, come in contact and react with nitrogen oxides, nitrous acid, or nitrite salts, or when trans-nitrosation via nitro or nitroso compounds occurs. Thus, potential exists for release into the environment from industries such as tanneries, pesticide manufacturing plants, rubber and tire manufacturers, alkylamine manufacture/use sites, fish processing industries, foundries and dye manufacturers. At this time, NDMA has been found in at least 1 out of 1177 hazardous waste sites on the National Priorities List (NPL) in the United States (VIEW Database 1989). Nitrosation reaction may also result in the formation of NDMA in the environment. In air, NDMA may form as a product of the nighttime reaction of dimethylamine with NOx. In water and soil, NDMA forms by the reaction of widely-occurring primary, secondary or tertiary amines in the presence of nitrite.

In the ambient atmosphere, NDMA should be rapidly degraded upon exposure to sunlight. The half-life for direct photolysis of NDMA vapor is on the order of 5 to 30 minutes. In surface water exposed to sunlight, NDMA would also be subject to photolysis. On soil surfaces, NDMA would be subject to removal by photolysis and volatilization. The volatilization half-life of NDMA from soil surfaces under field conditions has been found to be 1 to 2 hours. In subsurface soil and in water beyond the penetration of sunlight, NDMA would be susceptible to slow microbial decomposition under both aerobic and anaerobic conditions. In aerobic subsurface soil, the half-life of NDMA has been found to be about 50 to 55 days. Degradation has been found to proceed slightly faster under aerobic conditions than under anaerobic conditions.

NDMA has been detected in ambient air, water and soil; however, monitoring data are rather scant. Low levels of NDMA (measurable in terms of ppb) are commonly found in the air of car interiors, food, malt beverages (beer, whiskey), toiletry and cosmetic products, rubber baby bottle nipples and pacifiers, tobacco products and tobacco smoke, pesticides used in agriculture, hospitals, and homes, and sewage sludge.

The general population is exposed to NDMA from a variety of different sources. Primary sources of exposure include: chewing tobacco, tobacco smoke, foods [beer, liquor, cured meats (particularly bacon), fish, cheeses, and other food items], cosmetics and toiletry articles, interior air of cars, various household commodities such as detergents and home-and-garden pesticides, and formation in the upper gastrointestinal tract during digestion of secondary amine-containing foods. Infants may also be exposed

to NDMA from the use of rubber baby bottle nipples and pacifiers which may contain very low amounts of NDMA, from ingestion of contaminated infant formula, and from breast milk from some nursing mothers. Very low levels of NDMA have been found in breast milk. Occupational settings in which there is potential for exposure to NDMA include, but are not limited to: leather tanneries, rubber and tire industries, rocket fuel industries, dye manufacturers, soap, detergent and surfactant industries, foundries (coremaking), fish-processing industries (fish-meal production), pesticide manufacturers, warehouse and sale rooms (especially for rubber products), and research laboratories where NDMA is synthesized/studied.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

NDMA may occasionally be emitted into the atmosphere from sites of manufacture/use of dimethylamine and other sites at which NDMA is inadvertently formed, i.e. tanneries, pesticide manufacturing plants, rubber and tire industries, etc. NDMA may also form in nighttime air as the result of the atmospheric reaction of dimethylamine with NOx (Cohen and Bachman 1978, Fine et al. 1976a, Fine et al. 1976b, Hanst et al. 1977).

5.2.2 Water

NDMA may be released in waste streams from facilities at which NDMA was inadvertently formed during manufacturing processes. This would include such facilities as amine manufacturing plants, tanneries, rubber and tire industries, fish processing industries, foundries, rocket fuel industries, dye manufacturers, soap, detergent, and surfactant industries, and pesticide manufacturers (Cohen and Bachman 1978). In addition to industrial sources, NDMA may form in aqueous systems, sewage and soil as the result of either biological, chemical or photochemical processes. Biological formation occurs via the reaction of a secondary or tertiary amine with nitrite. The nitrite can arise in the environment from the microbial transformation of ammonia or nitrate or through manmade production. Chemical formation of nitrosamines occurs optimally under acidic conditions and may occur from the reaction of primary, secondary or tertiary amines with nitrite (Ayanaba and Alexander 1974; Mills and Alexander 1976). Formation of NDMA by photochemical transformation of dimethylamine in the presence of nitrite has been found to occur more readily under alkaline conditions than under acidic or neutral conditions (Ohta et al. 1982). Nitrosamine precursors are widespread throughout the environment, occurring in plants, fish, algae, urine, and feces and are formed in the environment as pesticide degradation products (Ayanaba and Alexander 1974, Greene et al. 1981, Neurath et al. 1977, Windholz 1983). The Contract Laboratory Program statistical data base reports that NDMA has been detected in groundwater samples at one out of 1177 hazardous waste site on the National Priorities List (NPL). This site is Martin Marietta (Denver Aerospace) in Waterton, CO (VIEW Database 1989):

5. POTENTIAL FOR HUMAN EXPOSURE

No data are available regarding contamination of drinking water, irrigation water, sewers, or storm drains in the vicinity of NPL sites.

5.2.3 Soil

NDMA may be released into the environment as the result of land application of sewage sludge containing this compound or as the result of land application of certain pesticides contaminated with this compound. NDMA may also form in soils under conditions which favor nitrosation of nitrosamine precursors (Mills and Alexander 1976, Pancholy 1978). There is rio data pertaining to the detection of NDMA in soil samples collected at or in the vicinity of NPL sites.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Organic compounds in the atmosphere having vapor pressures greater than 10^{-4} mm Hg are expected to exist almost entirely in the vapor phase (Eisenreich et al. 1981). The esgimated vapor pressure of NDMA [2.7 mm Hg at 20°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 Kow data [log Kow = -0.57 (see Table 3-2)], a bioconcentration factor of 0.2 and a soil adsorption coefficient (Koc) of 12 have been estimated for NDMA (Bysshe 1982, Hansch and Leo 1985, Lyman 1982). These values, as well as the complete water solubility of NDMA, indicate that bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments in water would not be important environmental fate processes. The low value of the Henry's Law Constant for NDMA [2.63×10^{-7} atm-m^3/mol at 20°C (see Table 3-2)] suggests that volatilization would be a relatively insignificant fate process in water (Thomas 1982).

NDMA is expected to be highly mobile in soil and it has the potential to leach into groundwater supplies (Dean-Raymond and Alexander 1976, Greene et al. 1981, Swann et al. 1983). If NDMA were released to soil surfaces, as might be the case during application of contaminated pesticides, a substantial proportion of the nitrosamine would volatilize. The volatilization half-life from soil surfaces under field conditions is estimated to be on the order of l-2 hours (Oliver 1979). If NDMA were incorporated into subsurface soil, far less of the nitrosamine would enter the atmosphere by volatilization and the rate of volatilization would be greatly reduced. Under these circumstances volatilization would be of minor importance (Oliver 1979).

5.3.2 Transformation and Degradation

5.3.2.1 Air

In the atmosphere, NDMA vapor would rapidly degrade by direct photolysis to form dimethylnitramine. Based on experimental data, the photolytic half-life of NDMA vapor exposed to sunlight has been determined to be about 5 to 30 minutes (Hanst et al. 1977, Tuazon et al. 1984). Reaction of NDMA with photochemically-generated hydroxyl radicals or ozone molecules in the atmosphere would be too slow to be environmentally . significant (Atkinson and Carter 1984, Tuazon et al. 1984).

5.3.2.2 Water

Limited available data suggest that NDMA would be subject to slow photolysis in natural waters exposed to sunlight (Polo and Chow 1976; Callahan et al. 1979). In unlit waters, it appears that NDMA would be rather persistent, eventually degrading as the result of microbial transformation (Kaplan and Kaplan 1985, Kobayashi and Tchan 1978, Tate and Alexander 1975). There is evidence which suggests that formaldehyde and methylamine may form as biodegradation products of NDMA (Kaplan and Kaplan 1985). Insufficient data are available to predict the rate at which NDMA would degrade in water. NDMA is not expected to chemically react under the conditions found in natural waters (Callahan et al. 1979, O.liver et al. 1979).

5.3.2.3 Soil

It appears that microbial degradation would be an important removal process for NDMA in subsurface soil. Oliver et al. (1979) amended Metapeake loam with 10 ppm NDMA at 23°C and observed a half-life of 50 days (Oliver et al. 1979). Loss of NDMA was attributed to volatilization and biodegradation. Tate and Alexander (1975) amended silt loam with 22.5 ppm NDMA at 30°C and observed a lag of approximately 30 days before slow disappearance from soil commenced; 50% loss occurred after about 55 days incubation and 60% loss occurred after about 70 days incubation. As part of the same study, 40% loss was observed in 2 days in soil amended with 50 ppm NDMA and 44% loss was observed in 5 days in soil amended with 250 ppm NDMA. These initial losses were followed by very little or no loss over the next 3 weeks. Initial, rapid loss of NDMA was attributed to volatilization and slow, gradual loss of NDMA was attributed to biodegradation. Mallik and Tesfai (1981) incubated NDMA at 4, 25 and 37°C and found that at all three temperatures, about 20-30% of added NDMA disappeared in the first 20 days of incubation, but little loss was noted thereafter; even after 30 days of incubation, over 50% of the NDMA was retained. The rate of disappearance of NDMA was found to be slightly higher in sandy loam soil than in either clay or silt loam soil. The rate of loss was also found to be slightly higher in aerobic soil at field capacity compared to super saturated (anaerobic) soil. After a 30-day incubation period, 60% of added NDMA remained in soil at

field capacity and 70% of added NDMA remained in super saturated soil. Available data on the degradation of NDMA 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

When it was used as a rocket fuel intermediate, NDMA was identified in ambient air on-site and in the vicinity of factories which were manufacturing rocket fuel (Fine et al. 1977b; Gordon 1978). At a plant in Baltimore, MD, which was manufacturing unsymmetrical dimethylh drazine rocket fuel, the average concentration on-site was 11,600 ng/m^3, and in neighboring residential communities it was 1,070 ng/m^3, with levels ranging between 30 to 100 ng/m^3 in the downtown area (Fine et al. 1977b). As a result of these findings, the use of NDMA was discontinued at this plant (Shapley 1976). During December 1975, NDMA was found in air samples collected in Belle, WV near a factory which was manufacturing dimethylamine. The highest level found (980 ng/m^3) was collected during a temporary weather inversion (Fine et al. 1976b). NDMA has also been measured in ambient air in urban areas with no known point sources of nitrosamines: Baltimore, MD several miles upwind of the rocket fuel plant (0.02-0.1 μg/m^3); the Cross Bronx Expressway in New York City (0.8 μg/m^3); and Philadelphia, PA (0.025 ppb) (Fine et al. 1976b, Shapley 1976).

Occurrence of volatile nitrosamines in air has been associated with tire and rubber products, leather tanneries, and automotive upholstery, and, as a result, measurable levels of the nitrosamines have been found in certain confined areas, e.g. automobile interiors. Concentrations of NDMA in interior air of automobiles have been found to vary widely due to differences in age of the car, design and decor. Levels of NDMA in interior air of new cars were found to range from <0.02 to 0.83 μg/m^3 (Dropkin 1985, Rounbehler et al. 1980).

5.4.2 Water

Data from the EPA STORET Water Quality data base indicate that NDMA is not a common contaminant of surface waters in the United States (EPA 1988b). During the time when NDMA was being used as a chemical intermediate at a rocket fuel manufacturing plant in Baltimore, MD, concentrations up to 940 ng/L were found in adjacent surface waters. Mud puddles adjacent to the facility contained 0.20-9.0 mg/kg (moist basis) of NDMA (Fine et al. 1977b). Information found in STORET also reveals that NDMA is infrequently found in groundwater samples. STORET gross analysis data input from 1980 to 1988 indicate that NDMA was positively identified in 0.9% of 2308 groundwater samples collected in the United States. The average concentration of positive samples was 12.4 μg/L (EPA,l988b). NDMA also has been detected at a concentration of 10 μg/L in groundwater samples at one of 1177 hazardous waste sites on the National Priorities List (NPL). This site is Martin

Marietta (Denver Aerospace) in Waterton, Co (VIEW 1989, VIAR 1987). NDMA was reportedly found in tap water from Philadelphia, PA at levels of 0.003-0.006 μg/L (Kimoto et al. 1981). The authors of this study concluded that NDMA did not form in the resin used to accumulate the nitrosamines, but that it may have formed from the reaction of low concentrations of nitrite, an oxidizing agent (possibly chlorine) and secondary amines present in the water sample. NDMA has been found in deionized laboratory water at levels ranging from 0.03-0.34 μg/L (Fiddler et al. 1977, Gough et al. 1977). Anion exchanger resins were identified as the source of NDMA found in the water samples. There have been reports of NDMA occurring infrequently in wastewater samples collected from various locations situated throughout the United States. When present, levels of NDMA are generally in the low μg/L range (maximum reported concentration 2.7 μg/L) (Cohen and Bachman 1978, Ellis et al. 1982, EPA 1988b, Fine et al. 1977b).

5.4.3 Soil

NDMA has been found in soil at l-8 μg/kg (dry basis) in Belle and Charleston, WV, New Jersey and New York City (Fine et al. 1977c). It is speculated that occurrence of NDMA in soil may have arisen from (a) absorption of NDMA in air, (b) absorption of dimethylamine from air and its subsequent N-nitrosation, or (c) from pesticide application.

5.4.4 Other Media

N-Nitrosamines are formed in foods by the reaction of secondary and tertiary amines with a nitrosating agent, usually nitrous anhydride, which forms from nitrite in acidic, aqueous solution. NDMA is the most common volatile amine found in food. Food constituents and the physical make-up of the food can affect the extent of nitrosamine formation. Ascorbic acid and sulfur dioxide have been used to inhibit the formation of nitrosamines. NDMA has been found in some processed foods as a result of direct-fire drying; it forms from the nitrosation of amines in drying food by oxides of nitrogen in drying air (Scanlan 1983). Trace levels (usually less than 1 ppb) of NDMA have been found in a variety of foods; however, not all samples of a particular type of food contain detectable levels of NDMA. Table 5-l lists the levels of NDMA which have been found in food. NDMA may also occur in human breast milk. In a study of 51 samples of breast milk collected from 13 nursing women, NDMA concentrations greater than 0.2 ppb were found in 23.5% of the samples, and the maximum concentration detected was 1.1 ppb (Lakritz and Pensabene 1984). During this study, it was determined that eating a meal containing bacon did not result in increased NDMA levels in milk, although eating a meal containing bacon and a vegetable high in nitrate occasionally resulted in higher levels of NDMA in breast milk. NDMA has been found to occur in a variety of toiletry and cosmetic products, including shampoos, hair conditioners, color toners, shower gels, bath cremes and oils, children's shampoos, children's bath and health care products, and face tonics, cleansers, and masks. In a study of 145

TABLE 5-1. Detection of N-Nitrosodimethylamine in Food[a]

Food Item	Concentration (μg/kg)
Vegetable oils and margarines	0.22-1.01
Apple cider distillates	1-10[b]
Dried cheeses (parmesan, romano, and American)	0.2-0.3
Soy-containing foods	0.1-0.6
Non-fat dry milk	0.17-4.47
Milk	0.05-0.60
Infant formula	1
Dried legumes	0.2-0.8
Malt vinegar	0.4
Cereal products	0.3-4.2
Cooked fish	0.1-4.2
Chinese seafood	0.1-131.5
Meat	0.1-7.4
Fried bacon	1-44

[a]Sources: Canas et al. 1986, Fazio and Havery 1982, Fiddler et al. 1981, Goff and Fine 1979, Huang et al. 1981, Lakritz and Pensabene 1981, Lawrence and Weber 1984, Sen and Seaman 1981b, Sen et al. 1984, Sen et al. 1985a, Song and Hu 1988, Weston 1984

[b] μg/L

products, 50 samples (34.5%) contained NDMA, with a maximum concentration of 24 μg/kg occurring in a sample of shampoo (Spiegelhalder and Preussman 1984).

The U.S. Food and Drug Administration (FDA) established an action level, effective January 1, 1984, of 60 ppb total N-nitrosamines in rubber nipples as measured by a dichloromethane extraction procedure (Thompson et al. 1986). This means that the Consumer Product Safety Commission can take action against any company which introduces baby bottle or pacifier nipples into interstate commerce containing greater than 60 ppb total N-nitrosamines. Compliance testing of infant pacifiers entered into commerce after January 1, 1984 and sold in the U.S. revealed that total N-nitrosamine levels ranged from not detectable to 36.9 ppb, and that NDMA levels ranged from not detectable to 3.55 ppb, with infrequent occurrence of NDMA (Billedeau et al. 1986). This compares well with levels found in pacifiers entered into commerce prior to January 1, 1984, when total N-nitrosamine levels as high as 332 ppb and NDMA levels as high as 6.78 ppb were detected using the same analytical procedure (Billedeau et al. 1986). It should be noted that several companies have discontinued supplying rubber nipples since January 1984, because they could not meet the compliance level.

Most malt beverages, regardless of origin, contain NDMA. This includes many domestic and foreign beers and most brands of whiskey (Havery et al. 1981, Hotchkiss et al. 1981, Scanlan et al. 1980, Sen and Seaman 198lC). It is generally accepted that the nitrosamine is formed in malt during the direct-drying phase of its processing (Fazio and Havery 1982). At one time, it was estimated that 64% by weight, of the dietary intake of NDMA of the West German male population could be attributed to the consumption of beer (Hotchkiss et al. 1981, Spiegelhalder et al. 1979). As a result of these findings, the U.S. Food and Drug Administration established an action level of 5 ppb for NDMA in malt beverages sold in the United States (Hotchkiss et al. 1981). Compliance testing of domestic (United States) and imported beers by the FDA showed that domestic beers (180 samples) contained NDMA levels ranging from not detectable to 9 ppb, with the average level being less than 1 ppb (1% contained greater than 5 ppb), and that imported beers (80 samples) contained levels ranging from not detectable to 13 ppb, with an average level of 1 ppb (5% contained greater than 5 ppb) (Havery et al. 1981). These results compared favorably with levels found during a market survey carried out prior to establishment of the action level, when 81% of domestic beers contained greater than or equal to 1 ppb and 17% contained greater than 5 ppb (Hotchkiss et al. 1981). Compliance survey data indicate that levels of NDMA in scotch whiskey (44 samples) ranged from not detectable to 2 ppb, with an average of less than 1 ppb (Havery et al. 1981).

NDMA is commonly found in commercially-available tobacco products in the United States. Results of one study showed that chewing tobaccos purchased in the United States contained NDMA at levels ranging from <0.2 to

85.1 ppb (Brunnemann et al. 1985). NDMA also occurs in mainstream and sidestream smoke from cigarettes and other tobacco products, with higher levels occurring in sidestream smoke than in mainstream smoke (Brunnemann et al. 1983, Chamberlain and Arrendale 1982, McCormick et al. 1973). Sidestream smoke from commercially-available tobacco products purchased in the United States were found to contain NDMA at the following levels: nonfiltered cigarette, 680 rig/cigarette; filtered cigarette, 736 rig/cigarette; and small cigar, 1700 rig/cigarette. The ratio of NDMA in sidestream smoke to NDMA in mainstream smoke in the non-filtered cigarette, filtered cigarette and small cigar was found to be 52:1, 139:1, and 41:1, respectively (Hoffman et al. 1987).

NDMA has been found to occur in various technical and commercial pesticides used in agriculture, hospitals and homes as the result of (a) formation during the manufacturing process, (b) formation during storage, and (c) contamination of amines used in the manufacturing process (Bontoyan et al. 1979). Herbicides in which NDMA has been found include the amine salt formulations of 2,4-D, dicamba, MCPA, MCPP,and 2,3,6-trichlorobenzoic acid. Levels ranging from 0.05 to 640 ppm have been detected inthese herbicides (Bontoyan et al. 1979, Cohen et al. 1978, Hindle et al. 1987, Ross et al. 1977).

NDMA is a common constituent of municipal sewage sludge (Brewer et al. 1980, Mumma et al. 1984). NDMA was detected in dried sludges from 14 out of 15 cities geographically located throughout the U.S. at levels ranging from 0.6-45 ppb (Mumma et al. 1984). Occurrence of NDMA in sewage sludge appears to be the result of biological and chemical transformation of alkylamines in the presence of nitrite (Ayanaba and Alexander 1974, Mills and Alexander 1976, Pancholy 1978).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

N-Nitrosamine precursors can be found in a large variety of man-made and natural products. Such products include agricultural chemicals, tobacco, detergents, rust inhibitors, rubber additives, solvents, drugs, plastics, leather tanning, textiles, and cosmetics. Considering the widespread occurrence of these products and the common occurrence of nitrogen oxides in industry, there is a fairly high likelihood that N-nitrosamines are found in these products or in industrial setting in which these products are used and/or produced (Fajen 1980). Occupational settings in which there is potential for exposure to NDMA include, but are not limited to: leather tanneries, rubber and tire industries, rocket fuel industries, dye manufacturers, soap, detergent and surfactant industries, foundries (core-making), fish-processing industries (fish-meal production), pesticide manufacturers, and warehouse and sale rooms (especially for rubber products) (Spiegelhalder 1984). When present in workroom air, NDMA levels are typically less than 1 ppb (Fajen et al. 1982). Exposure may result from inhalation or dermal contact. Results of a NIOSH survey carried out between

1981 and 1983 indicate that 747 workers are potentially exposed to NDMA in occupational settings (NIOSH 1988).

Laboratory workers handling NDMA could potentially be exposed to the nitrosamine as a result of diffusion through rubber gloves. Walker et al. (1978) showed that rubber gloves worn in research laboratories do not provide complete protection from dermal exposure to NDMA, because 11.8% of the NDMA contained in a dichloromethane solution was found to diffuse through latex surgical gloves into saline solution, over a period of 20 minutes. Dichloromethane is a common solvent for NDMA.

General population exposure to NDMA results from a number of different sources, primarily chewing tobacco, tobacco smoke, foods (beer, cured meats, fish, cheeses, and other food items), cosmetic products, interior air of cars, and various household commodities. Exposure to NDMA may also result from its in vivo formation during digestion in the upper gastrointestinal tract of secondary amine-containing foods or drugs, especially those containing dimethylamine (Groenen et al. 1980, Magee et al. 1976, Sakai et al. 1984). Infants may be exposed to NDMA from baby bottle nipples and pacifiers which may contain small amounts of NDMA, from ingestion of contaminated infant formulas, and from breast milk from some nursing mothers. Very low levels of NDMA have been found in breast milk. Based on older estimates of dietary intake in Germany, the Netherlands, and England and on recent data pertaining to occurrence of NDMA in various foods in the U.S., it appears that the average adult dietary intake of NDMA in the U.S. is less than 1 μg per day (Preussmann 1984). Insufficient data are available to predict the average daily intake of NDMA from other sources of exposure.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

It appears that those segments of the general population with potentially high exposure to NDMA from exogenous sources would include tobacco smokers and nonsmokers who come in contact with tobacco smoke for extended periods of time, snuff dippers, people who are occupationally exposed, and people who consume large quantities of food known to contain NDMA, beer or whiskey. .

5.7 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 NDMA 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 among environmental media. Many physical and chemical properties are available for NDMA; however, measured values for Koc and Henry's Law Constant at ambient temperature are not available. Methods for estimating these properties appear to provide relatively close estimates of Koc and Henry's Law Constant. Nevertheless, measured values at environmentally significant temperatures would assist in accurately predicting the fate of this compound in the environment.

Environmental Fate. Sufficient data are available to develop ***a*** general understanding of the environmental fate of NDMA. Kinetic data regarding photolysis in water and on soil surfaces, biodegradation in water under aerobic and anaerobic conditions, and biodegradation in soil under anaerobic conditions are lacking. Natural water grab sample biodegradation studies and soil metabolism studies carried out in the dark under aerobic and anaerobic conditions would be useful in establishing the persistence of NDMA in the environment. Photolysis studies carried out under simulated environmental conditions in water and soil would be useful in establishing the rate of photolytic degradation, the significance of this process as a removal mechanism, and the products of this reaction in these media.

Exposure Levels in Environmental Media. Limited data suggest that NDMA may be found in urban air, but recent comprehensive monitoring data pertaining to the detection of NDMA in ambient air are needed to establish this fact. Occurrence of NDMA in air has been associated with rubber products, leather products, and cigarette smoke and measurable levels of NDMA have been found in car interiors. This information, combined with the fact that NDMA has been found in ambient air at various urban locations, suggests that detectable levels of NDMA exist in the interior air of homes, offices, etc. Studies pertaining to the monitoring of NDMA in indoor air are needed to confirm this supposition.

Exposure Levels in Humans. Although numerous studies are available concerning the detection of NDMA in various foods, a market basket study is needed to provide a reliable estimate of the average daily dietary intake of NDMA. Available monitoring data on NDMA need to be evaluated, and estimates of the amount of exposure from each source need to be developed. These data would be useful in establishing the relative importance of each source of intake to overall human exposure and for predicting typical levels of exposure to NDMA.

5. POTENTIAL FOR HUMAN EXPOSURE

Exposure Registries. Since NDMA occurs most commonly in occupational settings as a result of its inadvertent formation, it would be difficult to develop a reliable estimate of occupational exposure to this compound. Nevertheless, NIOSH has established a registry for occupational exposure to NDMA. It would be difficult to develop a registry for environmental exposure to NDMA since such exposure can occur from a wide variety of sources and level of exposure can vary markedly depending upon an individual's lifestyle. There is no registry available for environmental exposure to this compound.

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 NDMA in environmental media, environmental fate of NDMA, or general population or occupational exposure to NDMA.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL MATERIALS

Methods used for the quantification of NDMA in biological samples are given in Table 6-1. Two problems encountered in the analysis of NDMA are poor recovery of the compound due to its high volatility and the artifactual formation of this compound during sample storage and treatment (Fine 1982). Since nitroso compounds are formed in acid solution, keeping the solution alkaline during storage and treatment may reduce artifact formation (Kosaka et al. 1984). Other authors have used ascorbic acid to inhibit in vitro formation of nitrosamines and have used morpholine to measure the extent of in vitro nitrosation during storage and handling (Dunn et al. 1986).

The method that has most selectivity for the quantification of this compound is thermal energy analyzer (TEA). A few investigators have oxidized this compound with pentafluoroperoxybenzoic acid to achieve higher sensitivity with electron capture detector (ECD).than with TEA (Kimoto et al. 1984). However, ECD detectors have less selectivity than TEA and will require more sample clean up. The confirmation of NDMA in a sample is usually done by mass spectrometry (MS). Samples containing small amounts of NDMA cannot be detected by MS in the presence of large background impurities (as in samples treated for TEA analysis). Photolysis at 366 nm affords an alternative means for validating the presence of this compound identified by TEA (Cooper et al. 1987). A method for the analysis of total N-nitroso compounds in gastric juice is also available (Pignatelli et al, 1987).

6.2 ENVIRONMENTAL SAMPLES

Methods for quantifying NDMA in environmental samples are summarized in Table 6-2. As with the biological samples, in situ artifact formation must be avoided in order to get accurate results from the analysis of environmental samples (Fisher et al. 1977; Fine et al. 1977a). The three quantification methods that give satisfactory sensitivity for NDMA are alkali flame ionization detector (in the nitrogen mode) (AFID), Hall electrolytic conductivity detector (HECD) in the reductive mode and TEA. The advantages and disadvantages of these detectors have been evaluated (Rhoades et al. 1980; Usero et al. 1987). Of the three detectors, the TEA detector has the highest sensitivity and selectivity. Because of its higher selectivity, the TEA detector cannot be versatile enough for multipollutant analysis. Mass spectrometric detector can be used not only for confirmation of the presence of NDMA in a sample, but for quantification as well (Eichelberger et al, 1983; Webb et al, 1979). When used in combination with a high resolution GC column, this method has the ability to quantify a large number of pollutants in a sample. The use of selected ion monitoring (SIM) may increase the sensitivity by orders of magnitude. The SIM method does not provide the full mass spectra necessary for the identification of unexpected compounds, however (Bellar et al. 1979). A method for the

TABLE 6-1. Analytical Methods for Determining N-Nitrosodimethylamine in Biological Samples

Sample Matrix	Sample Preparation	Analytical Method	Detection	Accuracy Limit	Reference
Whole blood	Distill alkaline solution, extract distillate in solvent and concentrate.	GC-TEA	0.1 µg/L	95%	Lakritz et al. 1980
Blood, liver, kidney, brain	Sample with added sulfamic acid and antifoaming agent, subjected to simultaneous distillation and extraction, extract concentrated.	GC-TEA	<1 ppb	93-97% at 2.3-4.2 ppb	Pylypiw et al. 1985; Pylypiw 1987
Blood	Sample mixed with ascorbic acid and morpholine, subjected to distillation in alkaline solution, distillate extracted with solvent and concentrated.	GC-TEA	8 pg or 0.05 µg/kg (for 20 g sample)	93%	Dunn et al. 1986
	Alkaline sample dialyzed with solvent, dialyzates separated and concentrated.	HRGC-MS	3-4 pg	60-70%	Kosaka et al. 1984
	Vacuum distillation in mineral oil, extracted with solvent and concentrated.	GC-TEA	0.1 µg/L	NG	Gough et al. 1983
Brain, liver, kidney, pancreas	Sample mixed with ammonium sulfamate, homogenized and distilled under vacuum, extracted with solvent, derivatized with pertrifluoroacetic acid, cleaned by column chromatography and concentrated.	GC-TEA and GC-ECD	NG	54.7%	Cooper et al. 1987
Urine	Sample buffered at pH 10 extracted with solvent, solvent concentrated.	GC-HRMS	5 ng/L	99-103% at 10-80 ng/L	Garland et al. 1986

NG = Not given; GC = gas chromatography; TEA = thermal energy analyses; HRGC = high resolution gas chromatography; MS = mass spectrometry; ECD = electron capture detector; HRMS = high resolution mass spectrometry

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

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Ambient air	Sample collected in impinger containing KOH, extracted in solvent and concentrated.	GC-MS	10 pg	NG	Fisher et al. 1977
	Sample sorbed on Tenax, thermally desorbed.	Cryofocusing HRGC-MS	0.5 ppt (for 150 L air)	90-110%	Sawicki et al. 1977
	Collected in Tenax, thermally desorbed and trapped in a cryogenically cooled trap and dissolved in solvent and concentrated.	HRGC-MS	0.3 pg	NG	Webb et al. 1979
	Collected in ambient or cold KOH trap, extracted in solvent and concentrated.	GC-TEA	1 ng/m	43.6%	Fine et al. 1977a,b
Water, wastewater	Sample extracted with solvent, column chromatographic clean-up, concentration.	GC-NPD or GC-reductive HECD or GC-TEA (EPA Method 607)	0.15 µg/L	32% at 0.8 µg/L	EPA 1982
	Extract with solvent at pH 7, concentrate extract.	Cryofocusing HRGC-MS (EPA Method 625.1)	1-10 µg/L	42% at 100 µg/L	Eichelberger et al. 1983
Water	Extract with solvent, concentrate extract.	GC-TEA	2 ng/L	68%	Fine et al. 1977a,b
Water, wastewater	Extracted with solvent, column chromatographic clean-up if required, concentration of extract.	GC-AFID GC-TEA GC-reduction HECD	NG	32% (AFID) 42% (TEA) 43% (HECD)	Rhoades et al. 1980
Soil	Extracted with water, water extracted with solvent and concentrated.	GC-TEA	NG	NG	Fine et al. 1977b
Minced fish and surimi	sample eluted with solvent, cleaned by column chromatography and concentrated	GC-TEA	0.2 ppb	77-97% at 10 ppb	Pensabene and Fiddler 1988

TABLE 6-2 (continued)

Sample Matrix	Sample Preparation	Analytical Method	Detection Limit	Accuracy	Reference
Meat, vegetable	Vacuum distill ground sample, extract distillate with solvent, clean up by column chromatography, derivatize with peroxytrifluoroacetic acid and column chromatographic clean up and concentrate.	GC-ECD	0.2 ppb (for 250 g sample)	<78%	Telling 1972
Malt, beer, milk powder, cured meat	Clean sample by dry column/elution or mineral oil distillation method, clean up further by column chromatography, oxidize with pentafluoroperoxybenzoic acid, clean up by column chromatography and concentrate.	GC-TEA or GC-ECD	<1 ppb	NG	Kimoto et al. 1984
Malt beverages	Clean sample by celite column chromatography, concentrate methylene chloride eluate.	GC-TEA	NG	90%	Hotchkiss et al. 1981
Beer	Sample treated with sulfamic acid, distillation under basic condition, extraction with solvent and concentration.	GC-TEA	0.1 ppb	78-112% at 0.08-4 ppb	Sen and Seaman 1981a
Fried bacon	Clean sample by acidic celite column	GC-TEA	NG	101% at 10 ppb	Pensabene et al. 1982

GC = Gas chromatography; MS = mass spectrometry; HRGC = High resolution gas chromatography; TEA = thermal energy analyzer; NPD = nitrogen-phosphorus detector; HECD = Hall electrolytic conductivity detector; AFID = alkali flame ionization detector; ECD = electron capture detector; NG = not given

analysis of apparent total N-nitroso compounds in beer is also available (Massey et al. 1987).

6.3 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCIA, 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 NDMA 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.

6.3.1 Data Needs

Methods for Determining Parent Compounds and Metabolites in Biological Materials. NDMA is equally distributed in the cellular elements of the blood and in the plasma and serum (Lakritz et al. 1980). Therefore, it is advantageous to analyze whole blood for the quantification of NDMA. Because NDMA is metabolized almost quantitatively in humans (Spiegelhalder 1984), determination of this compound in human urine needs an extremely sensitive technique (Garland et al. 1986). The urinary excretion of NDMA has been correlated with the concentration of NO_2 in air, suggesting that ambient air may play a role in the exposure of people to nitrosoamines (Garland et al. 1986). There is a paucity of data on the analytical methods for the determination of N-nitrosodimethylamine in human urine.

No metabolite of NDMA from human exposure to this compound has yet been identified (see Subsection 2.6.3). A metabolite identified in laboratory animal has been discussed in Subsection 2.6.3. 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.

Methods for Biomarkers of Exposure Recently, a radioimmunoassay was used to detect elevated levels of the promutagenic lesion 06-methyldeoxyguanosine in DNA cells from individuals with high incidence of cancer who consumed foods with a high nitrosamine content (Wild et al, 1987). Although no correlation has been established between the DNA-adduct

and the level of NDMA in consumed foods, the DNA-adduct has the potential to be used as a biomarker for exposure to NDMA.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The levels of this compound in 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-nitrosodimethylamine. 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. Such studies correlating the levels of this compound in any environmental medium with the levels in any human tissue or body fluid are not available.

Although the products of biotic and abiotic processes of this compound in the environment are known, no systematic study is available that measured the concentrations of its reaction products in the environment. In instances where the products of an environmental reaction are more toxic than the parent compound, it is important that the level of the reaction products in the environment be known. N-nitrosodimethylamine is not likely to form more toxic products as a result of environmental reactions (see Subsection 5.3.2). The analytical methods for the determination of the levels of environmental reaction products of N-nitrosodimethylamine are available.

6.3.2 On-going Studies

No ongoing studies are in progress for the improvement of the analytical method for NDMA in biological samples. Studies are currently conducted by J. Conboy and J. Hotchkiss at Cornell University, Ithaca, NY and by D. Havery at FDA, Washington, DC, for the development of analytical methods for this compound in environmental samples.

7. REGULATIONS AND ADVISORIES

The International Register of Potentially Toxic Chemicals (IRPTC 1988) lists regulations imposed by 13 countries for NDMA for occupational exposure, packing, storing and transport, disposal, and warns of its probable human carcinogenicity and its high level of toxicity by ingestion or inhalation.

NDMA is regulated by effluent guidelines under the Clean Water Act for the following industrial point sources: electroplating, steam electric power generation, asbestos products manufacturing, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, and carbon black manufacturing (EPA 1988a).

Additional national and state regulations and guidelines pertinent to human exposure to NDMA are summarized in Table 7-l.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to N-Nitrosodimethylamine

Agency	Description	Value	Reference
	INTERNATIONAL		
WHO	Cancer Classification	Group 2A[a]	IARC 1987a
	NATIONAL		
Regulations			
EPA OERR	Reportable Quantity (Proposed 1987)	10 lbs	EPA 1988a
EPA	Extremely Hazardous Substance Emergency Planning and Release Notification requirements:		EPA 1987 40 CFR 300 and 355
	Reportable Quantity	1 lb	
	Threshold Planning Quantity	1,000 lbs	
OSHA	Cancer Designation	Cancer - suspect agent	29 CFR 1910.1016 (7/1/88)
Guidelines			
a. Air	q_1* (inhalation)	51/mg/kg/day	EPA 1988a
b. Water			
EPA OWRS	Ambient Water Quality Criteria for the following lifetime increased cancer risk levels:		EPA 1980 45 FR 79318 (11/28/80)
	(With exposure to water, fish and shellfish) 10^{-5}	14.0 ng/L	
	10^{-6}	1.4 ng/L	
	10^{-7}	0.14 ng/L	
	(With exposure to fish and shellfish only) 10^{-5}	160,000 ng/L	
	10^{-6}	16,000 ng/L	
	10^{-7}	1,600 ng/L	
c. Food			
FDA	Action Level for NDMA in barley malt	10 ppb	Fed. Reg.1981 46 FR 39218
d. Other			
EPA	q_1* (oral)	51/mg/kg/day	EPA 1988a
EPA	Cancer Classification	Group B2[a]	EPA 1988a
ACGIH	Cancer Classification	Category A2[b]	ACGIH 1989

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (continued)

Agency	Description	Value	Reference
		STATE	
State	Acceptable Ambient Air Concentrations		
Kansas		0.0018 $\mu g/m^3$ (annual avg)	NATICH 1987
North Carolina		0.0000 $\mu g/m^3$ (24 hr avg)	NATICH 1987
Pennsylvania-Philadelphia		0.0004 ppb (1 yr avg)	NATICH 1987
Virginia		3.0000 $\mu g/m^3$ (24 hr avg)	NATICH 1987
Kentucky		BACT[c]	State of Kentucky 1986
State	Acceptable Drinking Water Concentrations		
Kansas		0.0014 µg/L	FSTRAC 1988
Minnesota		0.014 µg/L	FSTRAC 1988

[a]Probable human carcinogen.
[b]Suspected human carcinogen. It is noted for NDMA that exposure by the cutaneous route can potentially contribute to overall exposure.
[c]Best available control technology. Use of the best available technology to produce the maximum reduction in emissions at a specific emission site is required.

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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 (Kd) -- 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 populaton 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.

9. GLOSSARY

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(LO) (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

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

Lethal Dose(LO) (LD_{LO})-- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose(50) (LD_{50}) -- 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.

LT_{50} (lethal time) -- A calculated period of time within which a specific ccncentration 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.

9. GLOSSARY

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.

q1* -- 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/m^3 for air).

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

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 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.

9. GLOSSARY

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-nitrosodimethylamine. The panel consisted of the following members: Dr. Russell Cattley, Department of Microbiology, Pathology and Parasitology, College of Veterinary Medicine, North Carolina State University; Dr. Elaine Faustman, Department of Environmental Health, University of Washington; Dr. James Felton, Molecular Biology Section, Lawrence Livermore National Laboratory, University of California; Dr. Freddy Homburger, Bio-Research Consultants, Inc; and Dr. Raymond Smith, Department of Pathology and Microbiology, University of Nebraska Medical Center. These experts collectively have knowledge of N-nitrosodimethylamine'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.

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