TOXICOLOGICAL PROFILE FOR HYDRAZINES

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

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UPDATE STATEMENT

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

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance 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 that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1 . Green Border Review. Green Border review assures the consistency with ATSDR policy.

2 . Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

PEER REVIEW

A peer review panel was assembled for hydrazines. The panel consisted of the following members:

1. Dr. Emerich Fiala, Chief, Division of Biochemical Pharmacology, American Health Foundation, Valhalla, NY

2. Dr. Bela Toth, Professor, University of Nebraska Medical Center, Omaha, NE

3. Dr. Raghubir Sharma, Fred C. Davison Professor, University of Georgia, College of Veterinary Medicine, Athens, GA

These experts collectively have knowledge of hydrazines's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about hydrazines and to emphasize the human health effects that may result from exposure to these chemicals. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Hydrazines have been found in at least 8 of the 1,430 current or former NPL sites. However, the total number of NPL sites evaluated is not known. As more sites are evaluated, the number of sites at which hydrazines are found may increase. This information is important because exposure to hydrazines may cause harmful health effects and because these sites are potential or actual sources of human exposure to hydrazines.

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

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

1.1 WHAT ARE HYDRAZINES?

Hydrazines are chemical compounds that contain two nitrogen atoms joined by a single covalent bond. Three examples of hydrazines are

- hydrazine - also known as diamine, diamide, anhydrous hydrazine, and hydrazine base

- 1,1-dimethylhydrazine - also known as unsymmetrical dimethylhydrazine, dimazine, and by other names

- 1,2-dimethylhydrazine - also known as symmetrical dimethylhydrazine, hydrazomethane, and by other names

This document uses the term “hydrazines” to refer to hydrazine, l,l-dimethylhydrazine, and 1,2-dimethylhydrazine, collectively. These hydrazines are somewhat similar in chemical structure and reactivity. However, there are some clear differences in their production, uses, and adverse health effects. There are many other hydrazine compounds; however, these three hydrazines are discussed together in this document because they are of interest to the U.S. Department of Defense.

Hydrazines are manufactured from chemicals such as ammonia, dimethylamine, hydrogen peroxide, or sodium hypochlorite. A small amount of hydrazine occurs naturally in some plants. The amounts of hydrazine and l,l-dimethylhydrazine produced in the United States in the mid-1960s to mid-1980s have been reported to range from 15 million to 38 million pounds and from 9,900 to 99,000 pounds per year, respectively. 1,2-Dimethylhydrazine is a research chemical and the quantities produced are likely to be much less. We don’t know how much hydrazines is currently produced.

In their pure form, hydrazines are clear, colorless liquids, These liquids can evaporate in air. Hydrazines smell somewhat like ammonia. Most people can smell hydrazine or 1,1 -dimethylhydrazine when present at concentrations greater than 2-8 parts hydrazines per million parts of air (ppm). Hydrazines are highly reactive and easily catch fire.

Hydrazine has been used as fuel for many rockets and spacecraft, including the space shuttle. Hydrazine is used to treat boiler water to reduce corrosion, to reduce other chemicals, and to bring about or speed up chemical reactions. It is also used as a medicine and to make other medicines, farm chemicals, and plastic foams. 1,1-Dimethylhydrazine has been used as a rocket propellant and to make other chemicals. Other uses are also possible.
1,2 Dimethylhydrazine has no commercial uses but is used in labs to study colon cancer in experimental animals.

For more information about the chemical properties and uses of hydrazines, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO HYDRAZINES WHEN THEY ENTER THE ENVIRONMENT?

Hydrazines can be released to the environment from places that make, process, or use these chemicals. One of the primary ways hydrazine and 1,1-dimethylhydrazine enter the environment is from their use as rocket fuels. Accidental spills and leaks from storage and waste sites may add to environmental levels of hydrazines. Because 1,2-dimethylhydrazine is not used commercially and is produced only in small amounts, large releases to the environment are not expected.

Most of the hydrazines are released directly to the air where they are quickly destroyed by reactive molecules (small parts or bits) normally in air. Most of the hydrazines in air are gone within a few minutes or hours.

Smaller amounts of hydrazines are also released directly to surface water and soil: Lab studies show that some of the hydrazines released to soil and water can evaporate into the air. Hydrazines can also dissolve in water or bind to soil. The extent to which these processes occur depends on soil and water conditions. Hydrazines can move with water through soil as it flows underground. This is particularly true in sandy soils. In water and soil, some

microorganisms (tiny plants or animals) can break down hydrazines to form less toxic compounds. Most of the hydrazines in soil and water are gone within a few weeks.

Hydrazines may become concentrated in some fish living in contaminated water. However, most animals quickly digest and excrete hydrazines so high levels of these compounds are not expected to remain in their bodies.

For more information on what happens to hydrazines in the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO HYDRAZINES?

You may be exposed to significant amounts of hydrazines if you work in a place that makes, processes, or uses hydrazines, especially if you do not use proper protective equipment. People who live near these places, or near accidental spills or hazardous waste sites contaminated with hydrazines, may also be exposed. However, since hydrazines stay in air, water, and soil only briefly, most people are not exposed to them from these sources.

Small amounts of hydrazine and 1,1-dimethylhydrazine have been found in tobacco products. Therefore, people who chew tobacco, smoke cigarettes, or are exposed to cigarette smoke indirectly may be exposed to small amounts of these chemicals.

In the past, some people may have been exposed to 1,1-dimethylhydrazine in fruits sprayed with Alar, a growth enhancer. 1,1-Dimethylhydrazine is sometimes found where Alar is made or used. Because Alar is no longer used on food plants in the United States, people are no longer exposed to it from this source. However, Alar is still used on some nonfood plants. Therefore, some greenhouse workers who use Alar may be exposed to small amounts of 1, l-dimethylhydrazine.

Since 1,2-dimethylhydrazine is not used commercially, most people are not exposed to this chemical. It is used as a research chemical to produce colon cancer in lab animals. Therefore, lab workers who use 1,2-dimethylhydrazine for this purpose may be exposed to small amounts.

For more information about how you can be exposed to hydrazines, see Chapter 5.

1.4 HOW CAN HYDRAZINES ENTER AND LEAVE MY BODY?

Very little is known about how hydrazines enter and leave your body. Based on limited studies in animals, hydrazines are probably rapidly absorbed into your blood if you swallow them or if you get them on your skin. Based on their chemical and physical properties, hydrazines are also likely to be well absorbed if you breathe them into your lungs. Once they are in your blood, hydrazines are probably carried to all tissues of your body. Animal studies suggest that soon after you are exposed, the levels of hydrazines in your blood and tissues will fall rapidly. This is because your body changes hydrazines into other compounds called metabolites. Some of these metabolites (or compounds) can react with important molecules in your body and may harm you. Animal studies show that most metabolites and unchanged hydrazines leave your body in urine within 1 day. A small amount can also be found in the air you breathe out.

For more information about how hydrazines can enter and leave your body, see Chapter 2.

1.5 HOW CAN HYDRAZINES AFFECT MY HEALTH?

A small number of case studies of acute exposure in people suggest that your lungs, liver, kidney, and central nervous system may be injured if you breathe in hydrazine or 1,1-dimethylhydrazine or get them on your skin. Similar effects have been observed in animals.
Animal studies indicate that effects on the liver usually consist of fatty changes, but other effects have also been noted. Some animals developed convulsions, tremors, seizures, or

other effects on the nervous system after breathing hydrazines. Serious effects on the reproductive system were sometimes observed in animals. These effects included decreased sizes of the ovaries and testes and decreased sperm production. Some of these effects were seen in animals exposed to concentrations as low as 0.05-l ppm hydrazine or l,l-dimethylhydrazine in air for several months or more. Note that these concentrations are below those at which most people begin to smell hydrazines (2-8 ppm).

A few studies in people show that hydrazine and l,l-dimethylhydrazine affect your nervous system. If you swallow hydrazines, you may experience an upset stomach, vomiting, uncontrolled shaking, lethargy (sluggishness), coma, and neuritis (an inflammation of your nerves). These effects usually occur soon after exposure, but some may be delayed. Hydrazine has been used in the past to treat cancer patients. These effects occurred in some patients that swallowed 0.2-0.7 milligrams hydrazine per kilogram of their body weight per day (mg/kg/day) for 1 month or more. Vitamin B, has been given to people exposed to these chemicals to reduce nervous system effects. Effects on the nervous system have also been seen in animals exposed to hydrazine and l,l-dimethylhydrazine, but not to 1,2-dimethylhydrazine.

If you are exposed to hydrazines, you may have an increased cancer risk. The cancer-causing effects of hydrazines have not been well studied in people. However, many studies show that hydrazines can cause cancer in some animals after exposure to doses of 0.06-19 mg/kg/day through the mouth or exposure to concentrations of 0.05-5 ppm in the air. Tumors have been seen in many organs of animals exposed in this way but were found most often in the lungs, blood vessels, or colon. Some of the cancers caused by l,l-dimethylhydrazine may have been due to the presence of dimethylnitrosamine (a powerful carcinogen) as an impurity of this chemical. It is of particular concern that 1,2-dimethylhydrazine has caused colon cancer in lab animals following a single exposure.

Although it is hard to apply information from animal cancer studies directly to people, several government agencies have considered all the cancer evidence and developed the following conclusions:

- The Department of Health and Human Services (DHHS) has determined that hydrazine and 1,1-dimethylhydrazine may reasonably be anticipated to be carcinogens (cause cancer).

- The International Agency for Research on Cancer (IARC) has determined that hydrazine, 1,1 -dimethylhydrazine, and 1,2-dimethylhydrazine are possibly carcinogenic to humans (possibly cause cancer in humans).

- EPA has determined that hydrazine, l,l-dimethylhydrazine, and 1,2-dimethylhydrazine are probable human carcinogens (probably cause cancer in people).

- The American Conference of Governmental Industrial Hygienists (ACGIH) currently lists hydrazine and l,l-dimethylhydrazine as suspected human carcinogens, but has recently recommended that the listing of hydrazine be changed to that of animal carcinogen, not likely to cause cancer to people under normal exposure conditions.

For more information about how hydrazines can affect your health, see Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO HYDRAZINES?

If you are exposed to hydrazines, you can be tested for the presence of these chemicals or their metabolites in your blood, urine, or feces. These tests must be done soon after you are exposed (usually within 1 day). Exposure to some cancer drugs or other chemicals can produce hydrazines or their metabolites in your body. These tests cannot be used to tell how much you were exposed to or if you are going to be ill. These tests are not usually done in a

doctor's office but in special labs for testing. Because these tests require the use of expensive equipment and skilled technicians, their availability may be limited in some regions.

For more information about tests for exposure to hydrazines, see Chapters 2 and 6.

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

Several government regulatory agencies have taken action to protect people from excess exposure to hydrazines. EPA considers hydrazine and 1,1 -dimethylhydrazine to be hazardous air pollutants. The Occupational Safety and Health Administration (OSHA) limits the amount of hydrazine and l,l-dimethylhydrazine to 0.1 and 0.5 ppm, respectively, in workplace air for an S-hour workday and notes the potential for skin absorption in unprotected individuals. The National Institute of Occupational Safety and Health (NIOSH) recommends that the levels of hydrazine and l,l-dimethylhydrazine in workplace air not exceed 0.03 and 0.06 ppm, respectively, for a 2-hour period. The Food and Drug Administration (FDA) has ruled that hydrazine cannot be added to water for steam that will contact food. The EPA restricts the amount of hydrazines that may be released to the environment during burning or by disposal in landfills.

For more information regarding the regulations and guidelines for hydrazines, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

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

1. PUBLIC HEALTH STATEMENT

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
(404) 639-6000

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of hydrazines. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

The term “hydrazines” is a generic name used in this document to describe a group of three structurally related chemicals: hydrazine, l,l-dimethylhydrazine, and 1,2-dimethylhydrazine. These three hydrazines were selected for inclusion in this document because they have been detected at hazardous waste sites and are of concern to the Department of Defense. Numerous other hydrazine derivatives exist as well. For example, the reader is referred to the Toxicological Profile for 1 ,2-Diphenylhydrazine (ATSDR 1990) for information on this chemical.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are

those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of hydrazines are indicated in Tables 2-l and 2-2 and Figures 2-l and 2-2. Because cancer effects could occur at lower exposure levels, Figures 2-l and 2-2 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ($10m^{-4}$ to $10m^{-7}$), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for hydrazines. An MRL is defined as an estimate of daily human exposure-to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic

effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

In their pure form, hydrazines are fairly volatile liquids (see Section 3.2), and therefore inhalation exposures are of concern. Data regarding toxic effects in humans or animals after inhalation exposure to 1,2dimethylhydrazine are lacking. In one preliminary study, however, the toxicity of 1,2dimethylhydrazine vapors to rats was judged to be less than that of l, l-dimethylhydrazine but greater than that of hydrazine (Jacobson et al. 1955). More complete data are available from human and animal studies regarding the toxic effects of inhaled hydrazine and 1,1-dimethylhydrazine. These studies are discussed below.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to l, l-dimethylhydrazine.

A single case study was located which described the death of a male worker exposed to an undetermined concentration of hydrazine once a week for 6 months (Sotaniemi et al. 1971). Death was attributed to hydrazine exposure, resulting in severe lesions of the kidneys and lungs with complicating pneumonia.

A number of animal studies have reported deaths after inhalation exposure to hydrazines. For example, one out of three dogs died within 3 days of intermittent exposure to 25 ppm 1,1-dimethyl hydrazine (Rinehart et al. 1960). In another study involving a single 4-hour exposure of groups of 3 dogs to vapors of l,l-dimethylhydrazine at levels of 24, 52, or 111 ppm, all animals exposed to the two highest concentrations either died or were moribund within 24 hours, whereas the dogs receiving the lowest concentration showed no signs of adverse effects (Jacobson et al. 1955). During exposure at the two higher levels, the dogs experienced vomiting, convulsions, panting (respiratory distress), and diarrhea. One of the dogs exposed to 24 ppm suffered vomiting and convulsions during exposure but appeared to recover completely in the postexposure observation period. Two out of eight dogs exposed continuously to 1 ppm hydrazine progressively deteriorated and died after 16 weeks (Haun and Kinkead 1973).

A l-hour exposure to 80 ppm hydrazine did not cause any immediate deaths in rats, although one out of six died during the subsequent 14-day observation period (Cornstock et al. 1954). Twenty-two out of 40 mice died after continuous exposure to 1 ppm hydrazine for 6 months (Haun and Kinkead 1973). Death in these mice was attributed to the hepatotoxic effects of hydrazine. In contrast, mortality was not increased in rats or monkeys exposed to 1 ppm hydrazine, suggesting that mice may be more sensitive to the lethal effects of hydrazine than other species. Mortality was 32-33% in hamsters exposed intermittently to 0.25 ppm hydrazine for 1 year compared to 19% in controls (Vernot et al. 1985). Exposure to 5 ppm l,l-dimethylhydrazine for 6 months did not significantly affect the mortality rates in rats, mice, dogs, and hamsters (Haun et al. 1984).

The above studies indicate that exposure to relatively high concentrations of hydrazines in air can be lethal and suggest that hydrazine may be more toxic than l,l-dimethylhydrazine. In contrast, Jacobson et al. (1955) exposed mice, rats, and hamsters to substantially higher concentrations of hydrazine or 1,1-dimethylhydrazine vapors for 4 hours and found 1,1-dimethylhydrazine to be more toxic than hydrazine under these conditions. The LC_{50}s calculated by these authors for the 4-hour inhalation exposures were 570 and 252 ppm for hydrazine in rats and mice, respectively, and 252, 172, and 392 ppm for l,l-dimethylhydrazine in rats, mice, and hamsters, respectively. In these studies, rats were also exposed to vapors of 1,2-dimethylhydrazine for 4 hours, and based on a limited number of dose levels, an LC_{50} of 280-400 ppm was calculated. All LOAEL values from each reliable study for lethality are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The systemic effects observed after inhalation exposure are described below. No studies were located regarding dermal effects in humans or animals after inhalation exposure to hydrazines. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects after inhalation exposure to hydrazine and l,l-dimethylhydrazine are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. Acute accidental exposure to a mixture of hydrazine and l,l-dimethylhydrazine resulted in dyspnea and pulmonary edema in two men (Frierson 1965). A single case study reported pneumonia, tracheitis, and bronchitis in a man occupationally exposed to an undetermined concentration of hydrazine in air once a week for 6 months (Sotaniemi et al. 1971). These lesions were severe and were a contributing factor in this worker's death.

Respiratory effects have been observed in a number of animal studies. In dogs, alveolar hemorrhage, emphysema, and atelectasis were observed following intermittent exposure to 25 ppm l,l-dimethylhydrazine for 13 weeks (Rinehart et al. 1960). These effects were not observed in dogs exposed to 5 ppm for 26 weeks. Hyperplasia of the alveoli and lymphoid tissue of the lung was observed in rats and mice exposed to 0.05 ppm l,l-dimethylhydrazine for 6 months (Haun et al. 1984). A higher concentration (0.5 ppm) produced congestion and perivascular cuffing in the lungs of these mice. Intermittent exposure to 5 ppm hydrazine or l,l-dimethylhydrazine for 1 year produced inflammation, hyperplasia, and metaplasia of the upper respiratory tract epithelium in rats and mice (Haun et al. 1984; Vemot et al. 1985). No adverse effects were noted in the lungs of mice exposed intermittently to 1 ppm hydrazine. These data indicate that hydrazine and l,l-dimethylhydrazine can produce lung damage.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after inhalation exposure to l,l-dimethylhydrazine. Data regarding the adverse effects of hydrazine on the cardiovascular system in humans are limited to a single case study. Atria1 fibrillation, enlargement of the heart, and degeneration of heart muscle fibers were noted in a worker exposed to an undetermined concentration of hydrazine once a week for 6 months (Sotaniemi et al. 1971). It is uncertain whether these effects are directly attributable to hydrazine exposure.

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (NS)	4 hr				570 M (LC50)	Jacobson et al. 1955 H
2	Rat (NS)	4 hr				252 M (LC50)	Jacobson et al. 1955 11DMH
3	Mouse (NS)	4 hr				252 F (LC50)	Jacobson et al. 1955 H
4	Mouse (NS)	4 hr				172 F (LC50)	Jacobson et al. 1955 11DMH
5	Dog (Beagle)	4 hr				52 M (3/3 deaths)	Jacobson et al. 1955 11DMH
Neurological							
6	Dog (Beagle)	4 hr				24 M (convulsions)	Jacobson et al. 1955 11DMH

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
INTERMEDIATE EXPOSURE									
Death									
7	Mouse (CF-1)	2 wk (cont)						140 F (29/30 deaths)	Rinehart et al. 1960 11DMH
8	Mouse (CF-1)	5 wk (cont)						75 F (8/30 deaths)	Rinehart et al. 1960 11DMH
9	Mouse (ICR)	6 mo (cont)						1 F (22/40 deaths)	Haun and Kinkead 1973 H
10	Dog (Beagle)	3 d 6 hr/d						25 M (1/3 deaths)	Rinehart et al. 1960 11DMH
11	Dog (Beagle)	6 mo (cont)						1 M (2/8 deaths)	Haun and Kinkead 1973 H
Systemic									
12	Monkey (Rhesus)	6 mo 5 d/wk 6 hr/d	Hemato	5	F				Haun and Kinkead 1973 H
			Hepatic			1	F (slight to moderate fatty liver changes)		
			Derm	1	F	5	F (minimal eye irritation)		
			Bd Wt	5	F				

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
13	Monkey (Rhesus)	6 mo (cont)	Hemato	1	F				Haun and Kinkead 1973 H
			Hepatic			0.2	F (slight to moderate fatty liver changes)		
			Derm	0.2	F	1	F (minimal eye irritation)		
			Bd Wt	1	F				
14	Rat (F-344/ CrlBR)	6 mo 5 d/wk 6 hr/d	Resp			0.05	M (alveolar hyperplasia)		Haun et al. 1984 11DMH
			Hemato	5	M				
			Hepatic			0.05	M (fatty changes in the liver)		
15	Rat (Sprague-Dawley)	6 mo 5d/wk 6hr/d	Hemato	5	M				Haun and Kinkead 1973 H
			Bd Wt			1	M (unspecified decrease in body weight gain)		
16	Rat (Sprague-Dawley)	6 mo (cont)	Hemato	1	M				Haun and Kinkead 1973 H
			Bd Wt	0.2	M	1	M (unspecified decrease in body weight gain)		

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
17	Mouse (C57BL/6)	6 mo 5 d/wk 6 hr/d	Resp		0.05 F (lymphoid hyperplasia of the lung)		Haun et al. 1984 11DMH
					0.5 F (congestion and perivascular cuffing of the lung)		
			Hepatic		0.05[b] F (hyaline degeneration of the gall bladder)		
					0.5 F (congestion of the liver)		
			Bd Wt	5 F			
18	Mouse (ICR)	6 mo 5 d/wk 6 hr/d	Hepatic		1 F (moderate fatty liver changes)	5 F (severe fatty liver changes, cytoplasmic vacuolization)	Haun and Kinkead 1973 H
19	Mouse (ICR)	6 mo (cont)	Hepatic		0.2[c] F (moderate fatty liver changes)	1 F (severe fatty liver changes, cytoplasmic vacuolization)	Haun and Kinkead 1973 H
20	Hamster (Syrian Golden)	6 mo 5 d/wk 6 hr/d	Hemato	5 M			Haun et al. 1984 11DMH

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)	Reference Chemical Form
21	Dog (Beagle)	13-26 wk 5 d/wk 6 hr/d	Resp	5	M			25 M (alveolar hemorrhage, emphysema, and atelectasis)	Rinehart et al. 1960 11DMH
			Cardio	25	M				
			Gastro	25	M				
			Hemato			5	M (mild anemia)	25 M (anemia)	
			Hepatic	5	M	25	M (hemosiderosis)		
			Renal	25	M				
			Bd Wt			5	M (13% body weight loss)		
22	Dog (Beagle)	6 mo 5 d/wk 6 hr/d	Hemato	5	B				Haun et al. 1984 11DMH
			Hepatic	5	B				
			Bd Wt	5	B				
23	Dog (Beagle)	6 mo (cont)	Hemato	0.2	M	1	M (decreased hemoglobin, hematocrit, and red blood cell count)		Haun and Kinkead 1973 H
			Hepatic	0.2	M	1	M (fatty changes)		
			Bd Wt	0.2		1	M (unspecified decrease in body weight gain)		
Neurological									
24	Rat (Wistar)	6-7 wk (cont)						75 M (occasional tremors)	Rinehart et al. 1960 11DMH
25	Mouse (CF-1)	6-7 wk (cont)						75 F (occasional tremors)	Rinehart et al. 1960 11DMH

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
26	Dog (Beagle)	13-26 wk 5 d/wk 6 hr/d		5 M			Rinehart et al. 1960 11DMH
27	Dog (Beagle)	3 d 6 hr/d		5 M		25 M (depression, ataxia, salivation, emesis, and seizures after 3 days)	Rinehart et al. 1960 11DMH
28	Dog (Beagle)	6 mo (cont)		0.2 M		1 M (tonic convulsions)	Haun and Kinkead 1973 H
	Cancer						
29	Rat (F-344/ CrlBR)	6 mo 5 d/wk 6 hr/d				0.05 M (CEL: pancreatic islet cell adenoma, pituitary chromophobe adenoma, mononuclear cell leukemia)	Haun et al. 1984 11DMH
30	Mouse (C57BL/6)	6 mo 5 d/wk 6 hr/d				0.05 F (CEL: adenoma of the pituitary, hemangiosarcoma, and Kupffer cell sarcoma) 0.5 F (CEL: thyroid follicular cell carcinoma)	Haun et al. 1984 11DMH

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
CHRONIC EXPOSURE							
Death							
31	Hamster (Syrian Golden)	1 yr 5 d/wk 6 hr/d				0.25 M (increased mortality)	Vernot et al. 1985 H
Systemic							
32	Rat (Fischer-344)	1 yr 5 d/wk 6 hr/d	Resp	1 B	5 B (inflammation, hyperplasia, and metaplasia of the upper respiratory tract)		Vernot et al. 1985 H
			Hepatic	0.25 B	1 B (focal cellular change in females)		
33	Mouse (C57BL/6)	1 yr 5 d/wk 6 hr/d	Resp		5 F (inflammation, hyperplasia, metaplasia, and dysplasia of the nasal mucosa)		Haun et al. 1984 11DMH
			Hepatic		5 F (angiectasis in liver)		
			Bd Wt		5 F (15% decreased body weight gain)		

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)		LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
34	Mouse (C57BL/6)	1 yr 5 d/wk 6 hr/d	Resp	1	F					Vernot et al. 1985 H
			Resp	1	F					
			Gastro	1	F					
			Musc/skel	1	F					
			Hepatic	1	F					
			Renal	1	F					
			Derm	1	F					
35	Hamster (Syrian Golden)	1 yr 5 d/wk 6 hr/d	Hepatic			0.25	M (amyloidosis, hemosiderosis, and bile duct hyperplasia)			Vernot et al. 1985 H
			Renal			0.25	M (amyloidosis and mineralization)			
			Bd Wt			0.25	M (up to 14% loss of body weight)			
36	Dog (Beagle)	1 yr 5 d/wk 6 hr/d	Hepatic	0.25	B	1	M (focal areas of highly vacuolated cells, elevated serum glutamic oxaloacetic transaminase)			Vernot et al. 1985 H
Reproductive										
37	Rat (Fischer-344)	1 yr 5 d/wk 6 hr/d						5	B (atrophy of the ovaries and inflammation of the endometrium and uterine tube)	Vernot et al. 1985 H

TABLE 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
38	Hamster (Syrian Golden)	1 yr 5 d/wk 6 hr/d		0.25 M		1 M (senile testicular atrophy)	Vernot et al. 1985 H
	Cancer						
39	Rat (Fischer-344)	1 yr 5 d/wk 6 hr/d				1 M (CEL: nasal adenomatous polyps in males) 5 M (CEL: thyroid carcinoma in males)	Vernot et al. 1985 H
40	Mouse (C57BL/6)	1 yr 5 d/wk 6 hr/d				5 F (CEL: alveolar/ bronchiolar adenoma, hepatocellular adenoma, lymphoma, papilloma of the nose, osteoma, hemangioma)	Haun et al. 1984 11DMH
41	Hamster (Golden Syrian)	1 yr 5 d/wk 6 hr/d				5 M (CEL: nasal adenomatous polyp)	Vernot et al. 1985 H

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

[b]Used to derive an intermediate inhalation minimal risk level (MRL) of 2 X 10^{-4} ppm for 1,1-dimethylhydrazine; dose adjusted for intermittent exposure, converted to Human Equivalent Concentration (HEC), and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans following conversion to HEC and 10 for human variability).

[c]Used to derive an intermediate inhalation minimal risk level (MRL) of 4 X 10^{-3} ppm for hydrazine; converted to Human Equivalent Concentration (HEC), and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans following conversion to HEC, and 10 for human variability).

11DMH = 1,1-dimethylhydrazine; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; (cont) = continuous; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; H = hydrazine; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory; wk = week(s); yr = year(s).

Figure 2-1. Levels of Significant Exposure to Hydrazines - Inhalation

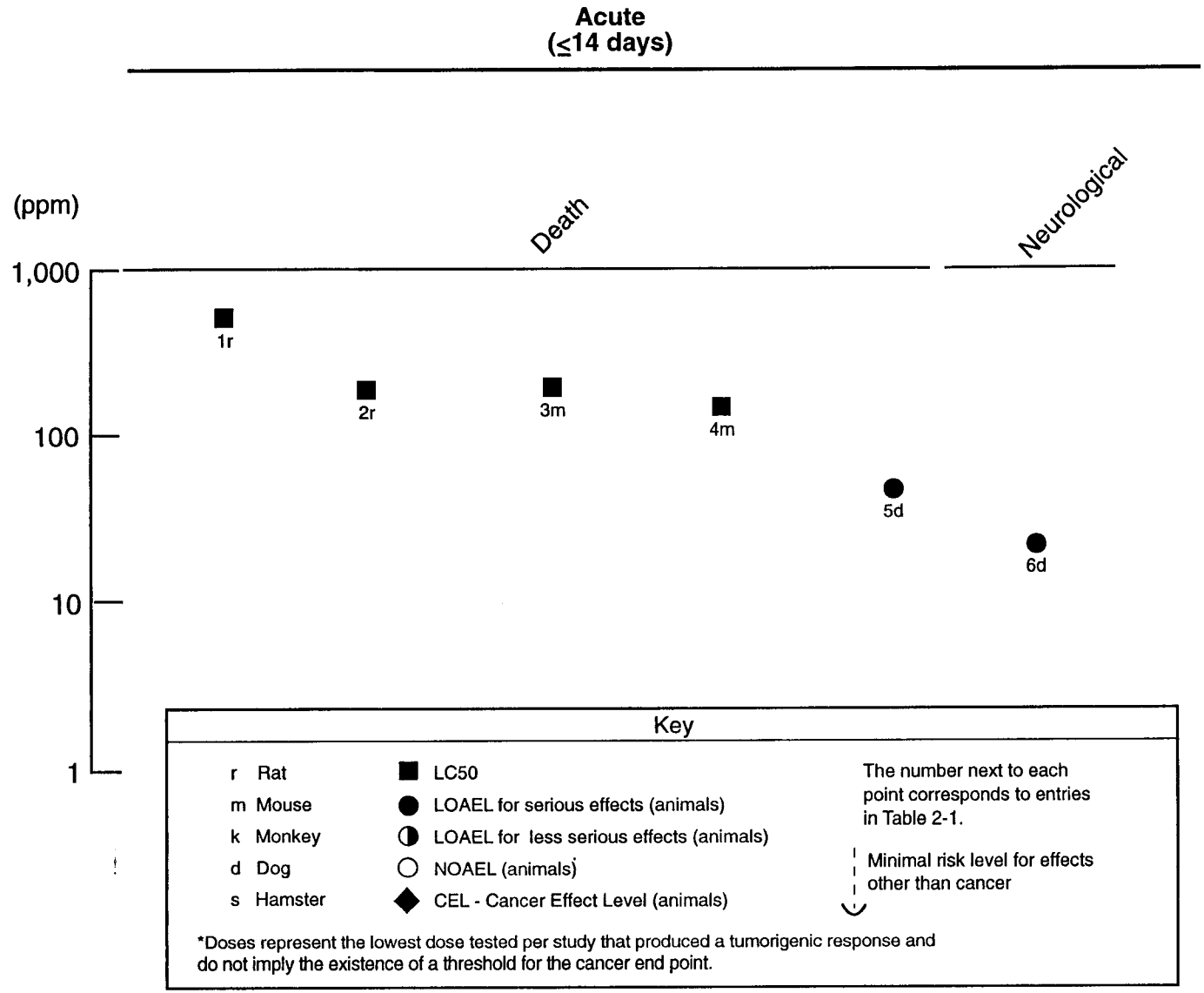


Figure 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

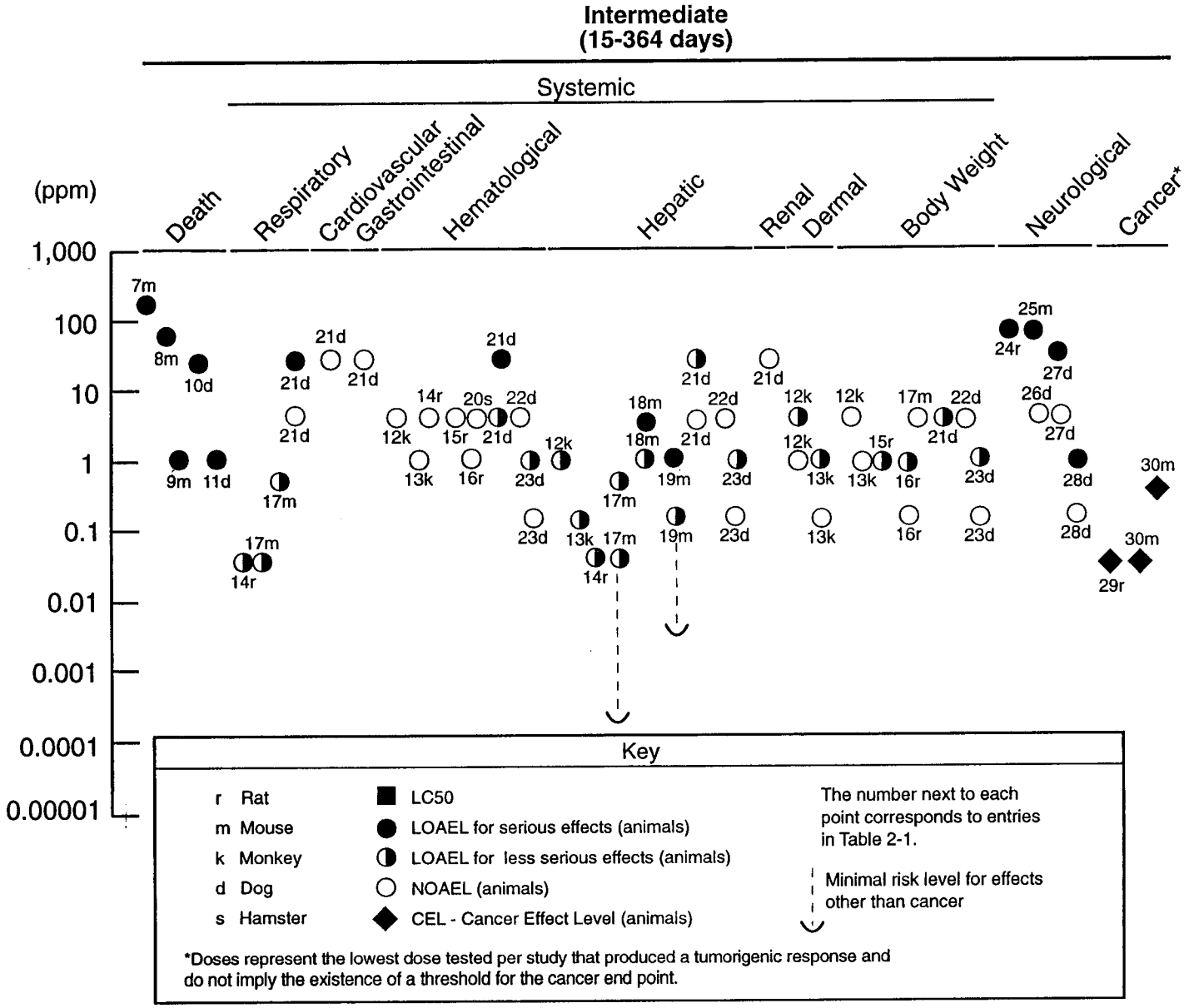


Figure 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)

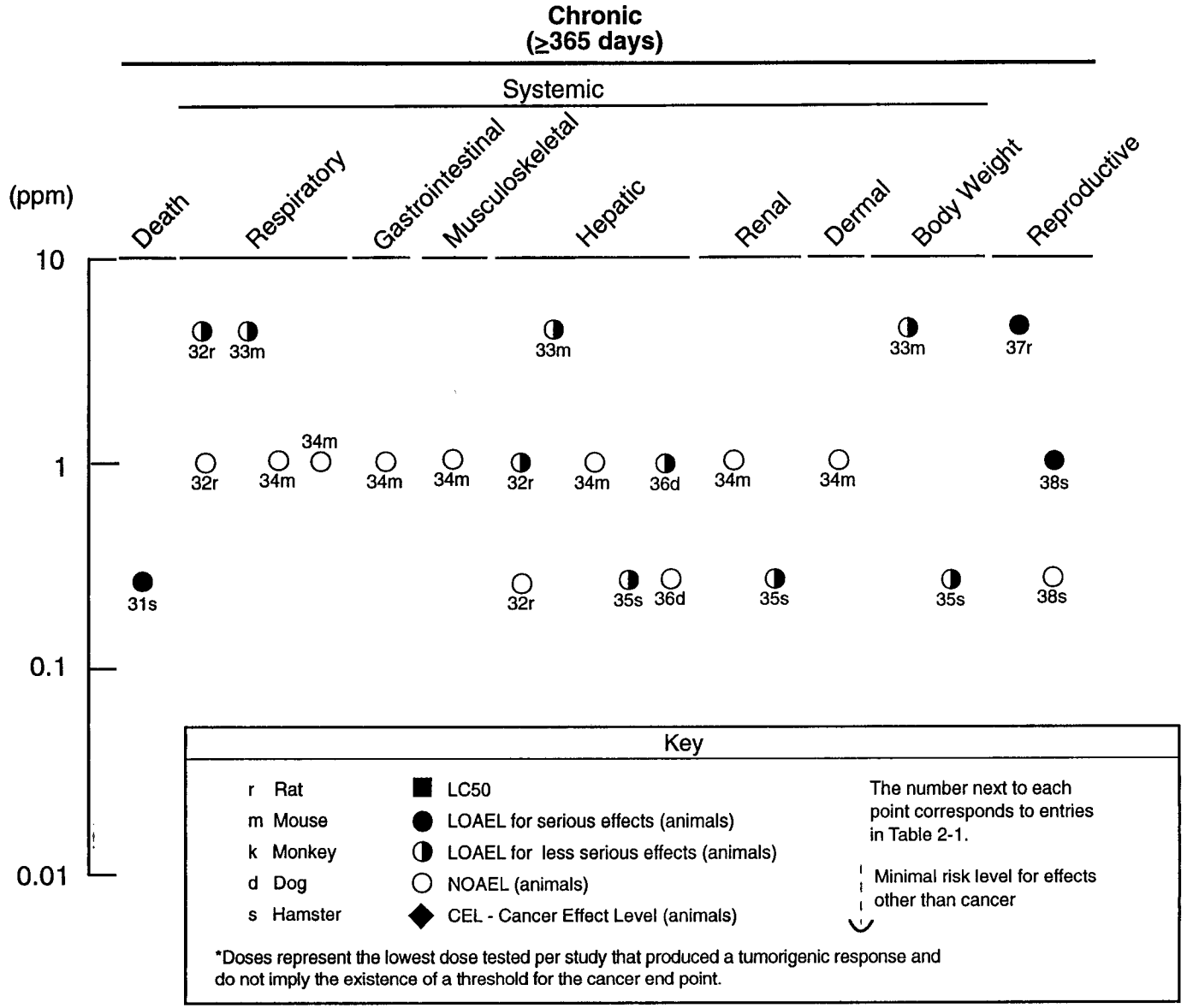
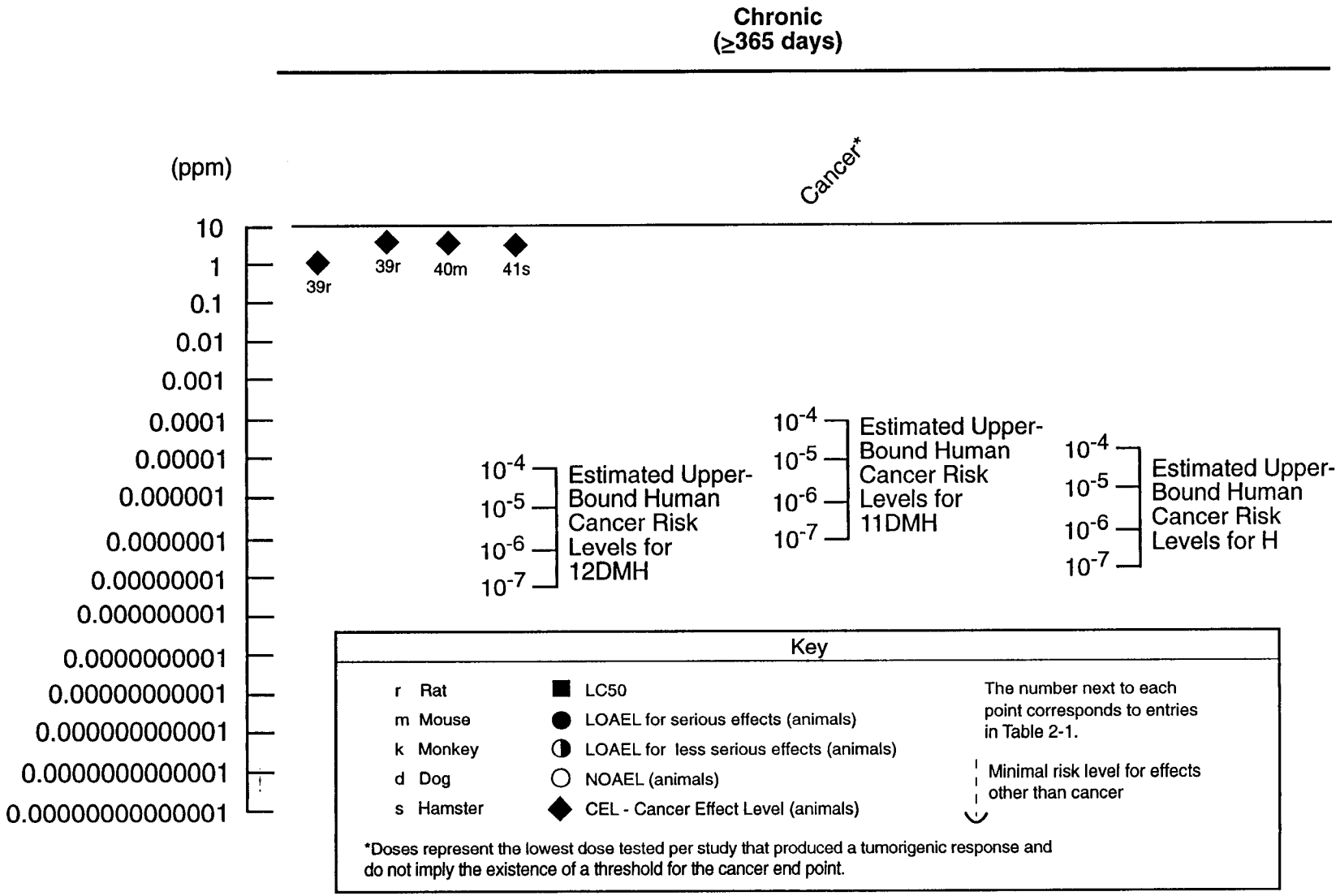


Figure 2-1. Levels of Significant Exposure to Hydrazines - Inhalation (continued)



No adverse effects were noted on the cardiovascular system of dogs exposed intermittently to 25 ppm 1,1-dimethylhydrazine for 13-26 weeks (Rinehart et al. 1960). In mice exposed to 0.05-5 ppm 1 ,l-dimethylhydrazine for 6 months to 1 year, the blood vessels were abnormally dilated (angiectasis) (Haun et al. 1984). However, no clinical or histopathological effects were noted on the cardiovascular system of mice exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al. 1985). The findings of the animal studies are inconsistent with the effects reported in the human case study and suggest that effects noted may not have been related to exposure. However, this is not certain.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to hydrazines.

No histopathological changes were observed in the gastrointestinal tract of dogs intermittently exposed to 25 ppm 1 ,l-dimethylhydrazine for 13-26 weeks (Rinehart et al. 1960) or in mice intermittently exposed to 1 ppm hydrazine for 1 year (Vernot et al. 1985). Although these data are limited, they suggest that the gastrointestinal system is not a primary target of the noncarcinogenic effects of hydrazine or 1,l -dimethylhydrazine.

Hematological Effects. No studies were located regarding the hematological effects in humans after inhalation exposure to hydrazines.

Mild anemia (17-26% decreases in red blood cell count, hemoglobin, and hematocrit) was observed in dogs intermittently exposed (5 days/week, 6 hours/day) to 5 ppm l,l-dimethylhydrazine for 24 weeks (Rinehart et al. 1960). Anemia was more pronounced (28-60% decreases in above described parameters) at a higher concentration (25 ppm) of l,l-dimethylhydrazine after 4 weeks of intermittent exposure. In dogs exposed continuously to 1 ppm hydrazine for 6 months, hemoglobin, hematocrit, and red blood cell count were all significantly reduced (approximately 25-30%) (Haun and Kinkead 1973). These effects were not observed in dogs exposed to 0.2 ppm hydrazine in this study. Hematological effects were not observed in rats, dogs, and hamsters exposed to 0.5 and3 ppm 1,1-dimethylhydrazine for 6 months (Haun et al. 1984). The lack of an anemic effect of purified l,ldimethylhydrazines in the dogs of this study is inconsistent with the observations made by Rinehart et al. (1960) in dogs exposed to the same concentration for a shorter duration. It is possible that impurities of the l,l-dimethylhydrazine (for example, dimethylnitrosamine) used by Rinehart et al. (1960) contributed to the anemic response. Alternatively, the anemic effects of hydrazine and

l,l-dimethylhydrazine may be related to their ability to react with pyridoxine (see Section 2.35); a deficiency of this vitamin results in anemia (NAS 1989).

No adverse effects were reported for a large number of hematological parameters in rats or monkeys exposed to 1 ppm hydrazine continuously for 6 months (Haun and Kinkead 1973). In dogs, the anemic effects of hydrazine in this study and l,l-dimethylhydrazine in the Rinehart et al. (1960) study appear to be fairly similar, and the data suggest that dogs may be particularly sensitive to the hematological effects of these compounds. However, some questions remain, considering the results with dogs seen by Haun et al. (1984), cited above. Rats (Haun and Kinkead 1973; Haun et al. 1984), monkeys (Haun and Kinkead 1973), and hamsters (Haun et al. 1984) appear to be relatively insensitive to the hematological effects of these compounds.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to hydrazines.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to 1,l -dimethylhydrazine. No musculoskeletal effects were observed in mice exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al. 1985).

Hepatic Effects. A single case study reported areas of focal necrosis and cell degeneration in the liver of a worker exposed to an undetermined concentration of hydrazine in air once a week for 6 months (Sotaniemi et al. 1971). Studies of workers exposed to l,l-dimethylhydrazine have reported changes indicative of a hepatic effect including elevated serum alanine aminotransferase activity, fatty degeneration, and a positive cephalin flocculation test (Petersen et al. 1970; Shook and Cowart 1957). Although the levels of hydrazine and l,l-dimethylhydrazine exposure were not determined, these studies indicate qualitatively that the liver is a target for both hydrazines.

In dogs exposed intermittently to 5 ppm l,l-dimethylhydrazine for 8.5 weeks, cytoplasmic degeneration of the liver was observed (Haun 1977). Hemosiderosis of the spleen was observed in dogs exposed intermittently to 5 ppm 1,1-dimethylhydrazine for 26 weeks, and the same effect was observed in the Kupffer cells of the liver after exposure to 25 ppm for 13 weeks (Rinehart et al. 1960). Dogs exposed to 5 ppm 1,1-dimethylhydrazine for 6 months showed transitory increases in serum glutamic pyruvic transaminase (SGPT) levels which returned to normal during the postexposure

recovery period (Haun et al. 1984). This study also found impaired liver function at the same dose level as measured by retention of injected bromosulphalein after a 6-month exposure to 1 ,l-dimethylhydrazine. Fatty changes were observed in the livers of mice, dogs, and monkeys exposed continuously to 0.2-l ppm hydrazine for 6 months (Haun and Kinkead 1973). The hepatotoxic effects of hydrazine were notably more severe in mice than in dogs or monkeys and were responsible for the increased mortality observed in this species. Based on a LOAEL of 0.2 ppm for liver effects in mice, an intermediate inhalation MRL of $4X10^{-3}$ ppm was calculated for hydrazine as described in footnote "c" in Table 2-l. Intermittent exposure to 0.25-l ppm hydrazine for 1 year resulted in a number of hepatic effects in rats, dogs, and hamsters including focal cellular change, vacuolated cells, elevated serum transaminases, amyloidosis, hemosiderosis, and bile duct hyperplasia (Vemot et al. 1985). The NOAEL values for hepatic effects range from 0.25 to 1 ppm for rats, mice, and dogs in this study. In addition, hamsters appeared to be the most sensitive species to hydrazineinduced hepatic effects, whereas mice appeared to be the most resistant.

In rats and mice, exposure to 0.05-5 ppm l,l-dimethylhydrazine for 6 months to 1 year produced fatty changes, angiectasis, hyaline degeneration of the gall bladder, and congestion in the liver (Haun et al. 1984). Based on a LOAEL of 0.05 ppm, an intermediate inhalation MRL of $2X10^{-4}$ ppm was calculated for 1, 1-dimethylhydrazine as described in footnote "b" in Table 2- 1.

Collectively, these data clearly indicate that the liver is a target for hydrazine and l,l-dimethylhydrazine toxicity. Furthermore, species differences are apparent in the sensitivity to hepatotoxicity. However, these data are inconsistent (mice were the most sensitive in one study but the most resistant in another) and suggest that strain differences in sensitivity may also exist in mice. It should be noted that dimethylnitrosamine, a potent liver toxin, occurs as a contaminant of technical grades of l,l-dimethylhydrazine and may contribute to the hepatotoxic effects observed in animals following exposure to this compound (Haun 1977). A single study reported hyaline degeneration of the gall bladder in mice exposed to 0.05 ppm l,l-dimethylhydrazine for 6 months (Haun et al. 1984).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to 1,1 -dimethylhydrazine. A single case study reported renal effects including tubular necrosis, hemorrhaging, inflammation, discoloration, and enlargement in a worker exposed to 0.07 mg/m^3 (0.05 ppm) hydrazine once a week for 6 months (Sotaniemi et al. 1971). These renal effects were severe and were a contributing factor in the death of this worker.

Renal effects were not observed in dogs exposed intermittently to 25 ppm l,l-dimethylhydrazine for 13-26 weeks (Rinehart et al. 1960). Mild renal effects including amyloidosis and mineralization were observed in hamsters exposed intermittently to 0.25 ppm hydrazine for 1 year (Vemot et al. 1985); however, no effects were noted in the kidneys of mice exposed intermittently to 1 ppm hydrazine for 1 year (Vemot et al. 1985). The findings of these animal studies are inconsistent with the severe effects observed in the human case study. However, more severe effects on the kidney have been observed in animals exposed to hydrazines by other routes (see Sections 2.2.2.2 and 2.4).

Ocular Effects. No studies were located regarding ocular effects in humans after inhalation exposure to l,l-dimethylhydrazine. A single case of a worker exposed to an undetermined concentration of hydrazine once a week for 6 months reported conjunctivitis (Sotaniemi et al. 1971). Since the conjunctivitis was repeatedly observed on each day the worker was exposed, continuing through to the following day, this effect is clearly related to hydrazine exposure.

No studies were located regarding ocular effects in animals after inhalation exposure to 1,l -dimethylhydrazine. Minimal irritation of the eyes was noted in monkeys during the first few weeks of exposure to 1 ppm hydrazine (Haun and Kinkead 1973). This effect was not observed in monkeys exposed to 0.2 ppm hydrazine (Haun and Kinkead 1973), or in mice exposed intermittently to 1 ppm hydrazine for 1 year (Vemot et al. 1985). Although these data are internally inconsistent, the data from monkeys are consistent with the human data which suggest that hydrazine acts as an irritant to the eyes.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to hydrazine or l,l-dimethylhydrazine.

Several studies in animals have reported decreased body weight gain. Male and female rats and male hamsters experienced significantly decreased body weight gains compared to controls during a lo-week period of exposure to 750 ppm hydrazine (1 hour/week) (Latendresse et al. 1995). Weight gains returned to normal during the subsequent recovery period. Body weight gain was reduced in rats and dogs exposed continuously to 1 ppm hydrazine for 6 months (Haun and Kinkead 1973), and in dogs exposed to 5 ppm l,l-dimethylhydrazine 6 hours/day, 5 days/week, for 26 weeks (Rinehart et al. 1960), or 5 ppm hydrazine for the same dosing regimen (Comstock et al. 1954). No effects in body weight gain were observed in several species exposed to concentrations of 0.2-1 ppm hydrazine or

5 ppm l,l-dimethylhydrazine for 6 months (Haun and Kinkead 1973; Haun et al. 1984). Chronic exposure to 0.25 ppm hydrazine caused a 14% loss of body weight in hamsters (Vernot et al. 1985). A similar decrease in body weight gain was noted in mice exposed to 5 ppm l,l-dimethylhydrazine for 1 year (Haun et al. 1984).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to hydrazines.

2.2.1.4 Neurological Effects

Data regarding the neurological effects of hydrazines in humans are limited to several case studies. Acute exposure to an undetermined concentration of a hydrazine/l,l-dimethylhydrazine mixture in air resulted in trembling, twitching, clonic movements, hyperactive reflexes, and weakness in two cases (Frierson 1965). Nausea, vomiting, and tremors were observed in a worker exposed to an undetermined levels of hydrazine in air once a week for 6 months (Sotaniemi et al. 1971). Difficulties in concentration, comprehension, memory, and task performance, as well as changes in mood status were noted in a water technician occupationally exposed to an undetermined concentration of hydrazine in air (Richter et al. 1992). Slow, gradual improvement was noted in the latter case after the subject was removed from exposure. Although limited, these studies suggest that inhalation exposure to hydrazine and l,l-dimethylhydrazine can adversely affect the central nervous system in humans.

In dogs exposed intermittently to 25 ppm l,l-dimethylhydrazine, depression, ataxia, salivation, emesis, and seizures were noted after 3 days (Rinehart et al. 1960). These effects were not observed in dogs exposed to 5 ppm for 26 weeks. Tonic convulsions were noted in one of eight dogs exposed continuously to 1 ppm hydrazine for 6 months but were not observed in any dogs exposed to 0.2 ppm (Haun and Kinkead 1973). Tremors were observed occasionally in rats and mice exposed continuously to 75 ppm l,l-dimethylhydrazine (Rinehart et al. 1960). These data confirm the observations from human studies and indicate that the central nervous system is a target for the toxicity of inhaled hydrazine or l,l-dimethylhydrazine. The highest NOAEL values and all LOAEL

values from each reliable study for neurological effects resulting from inhalation exposure to hydrazines are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to hydrazines.

Endometrial cysts were noted in female mice exposed to 0.05 ppm l,l-dimethylhydrazine for 6 months (Haun et al. 1984). The incidence of endometrial cysts were also elevated in female mice exposed to 5 ppm l,l-dimethylhydrazine for 1 year (Haun et al. 1984); however, this increase was not statistically significant. Furthermore, this type of lesion is common to aged female mice and therefore may not be related to treatment. In female rats exposed intermittently to 5 ppm hydrazine for 1 year, atrophy of the ovaries and inflammation of the endometrium and fallopian tube were noted (Vernot et al. 1985). Senile testicular atrophy was observed in male hamsters exposed to 1 ppm hydrazine for 1 year but not in hamsters exposed to 0.25 ppm hydrazine (Vernot et al. 1985). An absence of sperm production was observed in hamsters exposed to 5 ppm. The study authors noted that the changes observed in male hamsters are normally associated with aging and that exposure to hydrazine seemed to accelerate these changes. However, available studies suggest that hydrazine and l,l-dimethylhydrazine can produce serious reproductive effects. A complete assessment of the reproductive toxicity of hydrazines cannot be made since reproductive function was not determined in these studies. The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects resulting from inhalation exposure to hydrazines are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to hydrazines.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to hydrazines.

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A single epidemiological study reported no significant increase in cancer mortality in a group of men (n=427) occupationally exposed to an undetermined concentration of hydrazine in air (Wald et al. 1984). Although this study reported no evidence of a carcinogenic effect for hydrazine, the follow-up period was relatively short and only 49 deaths were observed. However, when the workers were observed for another 10 years, there was still no significant increase in cancer mortality (Morris et al. 1995).

Exposure to 0.05-0.5 ppm l,l-dimethylhydrazine for 6 months produced an increased incidence of leukemia and tumors of the pancreas, pituitary, blood vessels, liver, and thyroid in mice and/or rats (Haun et al. 1984). Tumors of the lung, liver, nasal cavity, bone, and blood vessels were observed in mice exposed to 5 ppm l,l-dimethylhydrazine for 1 year (Haun et al. 1984). A significantly increased incidence ($p \leq 0.05$) of nasal tumors and thyroid carcinomas was observed in male rats exposed intermittently to 1 and 5 ppm hydrazine, respectively, for 1 year (Vernot et al. 1985). Hamsters and rats exposed to 750 ppm hydrazine once for 1 hour, or 1 hour per week for 10 weeks, exhibited increased incidences of squamous metaplasia, hyperplasia, and neoplasia in the nose (Latendresse et al. 1995). Nasal tumors were also noted in hamsters and female rats intermittently exposed to 5 ppm hydrazine for 1 year (Vemot et al. 1985). Tumor incidence was not significantly increased in mice and dogs exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al. 1985). The studies suggest that hydrazine and l,l-dimethylhydrazine are carcinogenic by the inhalation route. All CEL values from each reliable study resulting from inhalation exposure to hydrazines are recorded in Table 2- 1 and plotted in Figure 2- 1.

The EPA has derived an inhalation unit risk of 0.0049 $(\mu g/m^3)^{-1}$ for hydrazine based on nasal cavity tumors, and an inhalation unit risk of 0.001 $(\mu g/m3)^{-1}$ for l,l-dimethylhydrazine based ontumor of the respiratory system (HEAST 1992; IRIS 1995). Although no studies were located regarding the carcinogenic effects of 1 ,2-dimethylhydrazine following inhalation exposures, EPA has derived an inhalation unit risk of 0.011 $(\mu g/m^3)^{-1}$ for 1,2-dimethylhydrazine (HEAST 1992), based on extrapolation of cancer data for oral exposures (see Section 2.2.2.8). The concentrations of hydrazine,

1, 1-dimethylhydrazine, and 1,2-dimethylhydrazine corresponding to excess cancer risks of 10^{-4} to 10^{-7}. are shown in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethal effects in humans after oral exposure to hydrazines.

Acute oral LD_{50} values of 11.7 and 27.1 mg/kg have been reported for 1 ,2-dimethylhydrazine in male and female mice, respectively (Visek et al. 1991). Mortality was 100% in mice given a single dose of 90 mg/kg 1,2-dimethylhydrazine (Visek et al. 1991) and in mice given 133 mg/kg/day hydrazine or 533 mg/kg/day l,l-dimethylhydrazine for 5 days (Roe et al. 1967). Death occurred in two of two dogs administered weekly doses of 60 mg/kg 1,2-dimethylhydrazine for 2 weeks (Wilson 1976). For intermediate exposures, doses of 2.3 and 4.9 mg/kg/day hydrazine for 15-25 weeks increased mortality in mice and hamsters, respectively (Biancifiori 1970). Exposure to 33 mg/kg/day l,l-dimethylhydrazine killed two of five mice exposed for 4-21 weeks (Roe et al. 1967). Mortality was 62.5-100% following intermediate-duration exposures to 1,2-dimethylhydrazine in rats given 13.6 mg/kg/day (Teague et al. 1981), guinea pigs given 60 mg/kg/day (Wilson 1976), dogs administered 15 mg/kg/day (Wilson 1976), pigs administered 60 mg/kg/day (Wilson 1976), and in mice given 4.5-5.1 mg/kg/day (Visek et al. 1991). Mortality in mice was 100% after chronic exposure to 0.95 mgfkg/day via the drinking water (Toth and Patil 1982). These data indicate that large doses of hydrazines are lethal by the oral route. Furthermore, male mice were 2-3 times more sensitive to the acutely lethal effects of 1,2-dimethylhydrazine than female mice (Visek et al. 1991), suggesting that there may be important sex differences. However, this was only observed in a single study. All LOAEL values from each reliable study for lethality are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

No studies were located regarding any systemic effects in humans after oral exposure to hydrazines. Also, no studies were located regarding the hematological effects in animals after oral exposure to hydrazines. The available studies regarding systemic effects in animals after oral exposure to hydrazines are described below. The highest NOAEL values and all LOAEL values for systemic

effects in animals resulting from oral exposure to hydrazines are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No adverse histological effects were observed in the lungs of mice exposed to 9.5 mg/kg/day hydrazine via the drinking water for 2 years (Steinhoff et al. 1990). No other studies were located regarding respiratory effects in animals ingesting hydrazines.

Cardiovascular Effects. Focal myocytolysis, fibrosis, and calcification of the heart were observed in mice receiving 1.6 mg/kg/day 1,2-dimethylhydrazine in the feed for 5 months (Visek et al. 1991). These effects were not observed in mice receiving 0.75 mg/kg/day. No adverse histological effects were observed in the hearts of mice receiving 9.5 mg/kg/day hydrazine in the drinking water for 2 years (Steinhoff et al. 1990). These data are too limited to make firm conclusions regarding the cardiovascular effects of hydrazines.

Gastrointestinal Effects. Although oral exposure to hydrazine has produced nausea in humans, this effect is probably due to effects on the central nervous system and is therefore discussed in Section 2.2.2.4.

Proliferative foci were noted in the colons of rats receiving two doses of 25 mg/kg 1,2-dimethylhydrazine within a 4-day period (Cademi et al. 1991). No adverse histological effects were observed in the gastrointestinal tracts of mice receiving 9.5 mg/kg/day hydrazine in the drinking water for 2 years (Steinhoff et al. 1990). These data are too limited to make firm conclusions regarding the gastrointestinal effects of hydrazines.

Musculoskeletal Effects. No adverse effects were observed in the muscle tissue of mice receiving 9.5 mg/kg/day hydrazine in the drinking water for 2 years (Steinhoff et al. 1990). No other studies were located regarding the effects of hydrazines on the musculoskeletal system.

Hepatic Effects. A number of studies in animals have reported effects on the liver after oral exposure to hydrazines. In rats and mice, relatively mild effects on the liver such as megamitochondria formation, increased lipogenesis, and fatty changes occurred following acute exposure to 49-650 mg/kg/day hydrazine (Marshall et al. 1983; Preece et al. 1992b; Wakabayashi et al. 1983). More notable effects, including degeneration, hemorrhage, and necrosis of the liver, were

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Mouse (B6C3F1)	Once (GW)				11.7 M (LD50) 27.1 F (LD50)	Visek et al. 1991 12DMH
2	Mouse (B6C3F1)	Once (GW)				90 B (100% mortality)	Visek et al. 1991 12DMH
3	Mouse (Swiss)	1 wk 5 x/wk (GW)				533 F (5/5 deaths)	Roe et al. 1967 11DMH
4	Mouse (Swiss)	1 wk 5 x/wk (GW)				133 F (5/5 deaths)	Roe et al. 1967 H
5	Dog (NS)	2 wk 1 x/wk (GW)				60 M (2/2 deaths)	Wilson 1976 12DMH
	Systemic						
6	Rat (Sprague-Dawley)	4 d 2 x (G)	Gastro		25 F (proliferative foci in colon)		Caderni et al. 1991 12DMH
7	Rat (Sprague-Dawley)	Once (GW)	Hepatic	27 M	81 M (fatty liver)		Preece et al. 1992a HS
8	Rat (Wistar)	Once (GW)	Hepatic		49 F (increased lipogenesis)		Marshall et al. 1983 HS

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
9	Dog (NS)	2 wk 1 x/wk (GW)	Hepatic			60 M (hepatic degeneration and hemorrhagic necrosis)	Wilson 1976 12DMH
			Bd Wt		60 M (unspecified decrease in weight loss)		
	Developmental						
10	Hamster (Syrian Golden)	Once Gd 12 (GW)		166 F			Schiller et al. 1979 H
11	Hamster (Syrian Golden)	Once Gd 12 (GW)		68 F			Schiller et al. 1979 12DMH
	Cancer						
12	Rat (Fischer)	Once (GW)				15.8 M (CEL: colonic epithelial polypoid tumors)	Schiller et al. 1980 12DMH
13	Rat (Sprague-Dawley)	Once (G)				30 M (CEL: colon adenocarcinomas)	Craven and DeRubertis 1992 12DMH
14	Rat (Sprague-Dawley)	Once (GW)				15.8 M (CEL: colonic adenocarcinomas or mucinous adenocarcinomas	Watanabe et al. 1985 12DMH
	INTERMEDIATE EXPOSURE						
	Death						
15	Rat (DA, HS, AS2)	10 wk 1 x/wk (GW)				13.6 B (100% mortality)	Teague et al. 1981 12DMH

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
16	Mouse (B6C3F1)	6 wk ad libitum (F)				5.1 M (100% mortality in males) 4.5 F (100% mortality in females)	Visek et al. 1991 12DMH
17	Mouse (CBA)	25 wk 150 x (GW)		1.1 B		2.3 B (38/50 deaths by 80 weeks)	Biancifiori 1970 HS
18	Mouse (Swiss)	4-21 wk 5 x/wk (GW)				33 F (2/5 deaths)	Roe et al. 1967 11DMH
19	Hamster (Syrian golden)	15-20 wk 60-100 x (GW)				4.9 B (32/35 deaths by week 50)	Biancifiori 1970 HS
20	Dog (NS)	4-10 wk 1 x/wk (GW)				15 M (9/10 deaths)	Wilson 1976 12DMH
21	Pig (Miniature)	10 wk 1 x/wk (GW)				60 M (5/8 deaths)	Wilson 1976 12DMH
22	Gn pig (Hartley)	7-10 wk 1 x/wk (GW)				60 M (5/6 deaths)	Wilson 1976 12DMH
	Systemic						
23	Rat (Fischer-344)	<10 mo ad libitum (W)	Hepatic			4.2 M (hepatic DNA alteration)	Bedell et al. 1982 12DMH
24	Rat (Sprague-Dawley)	9 wk 1 x/wk (GW)	Bd Wt	15 B	30 B (10% decrease in body weight gain)		Barbolt and Abraham 1980 12DMH

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
25	Mouse (B6C3F1)	5 mo ad libitum (F)	Cardio	0.75 M		1.6 M (myocytolysis, fibrosis, and calcification	Visek et al. 1991 12DMH
			Hepatic		0.75 [b] M (mild hepatitis)	1.6 M (hepatitis, centrilobular necrosis, and hepatocellular hypertrophy)	
			Renal	0.75 M		1.6 M (interstitial nephritis and pyelonephritis)	
26	Mouse (B6C3F1)	6 wk ad libitum (F)	Hepatic		1.4 B (decrease of 1.3% in relative liver weight)		Visek et al. 1991 12DMH
27	Mouse (CBA)	25 wk 150 x (GW)	Endocr		1.1 F (brown degeneration of the adrenals)		Biancifiori 1970 HS
28	Hamster (Golden)	15-20 wk 60-100 x (GW)	Hepatic			4.9 B (cirrhosis, cell proliferation, degenerative changes)	Biancifiori 1970 HS
			Endocr	5.3 B			
29	Dog (NS)	4-10 wk 1 x/wk (GW)	Hepatic			5 M (mild hepatic fibrosis, hemosiderosis, and ascites)	Wilson 1976 12DMH
						15 M (hepatic failure)	
30	Pig (Miniature)	10 wk 1 x/wk (GW)	Hepatic			30 M (focal megalocytosis and postfibrotic necrosis of the liver)	Wilson 1976 12DMH
31	Gn pig (Hartley)	7-10 wk 1 x/wk (GW)	Hepatic			30 M (hepatic necrosis and ascites)	Wilson 1976 12DMH
			Bd Wt			30 M (severe but unspecified decrease in body weight gain)	

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Immunological/Lymphoreticular						
32	Rat (Sprague-Dawley)	5 wk 1 x/wk (GW)		27.1 M			Locniskar et al. 1986 12DMH
	Neurological						
33	Human	1-47 d 3 x/d (C)			0.6 B (dizziness)		Spremulli et al. 1979 HS
34	Human	1-6 mo 3 x/d (C)				0.6 B (nausea, vomiting, dizziness, excitement, insomnia, and polyneuritic syndrome)	Gershanovich et al. 1981 HS
35	Human	30 d 3 x/d (C)			0.7 B (nausea, transient dizziness)		Chlebowski et al. 1984 HS
	Reproductive						
36	Mouse (CBA)	25 wk 150 x (GW)		9.3 B			Biancifiori 1970 HS
37	Hamster (Golden)	15-20 wk 60-100 x (GW)		5.3 B			Biancifiori 1970 HS
	Cancer						
38	Rat (DA, HS, AS2)	10 wk 1 x/wk (GW)				4.5 B (CEL: liver angiosarcoma, cholangioma, hepatocellular carcinoma, bowel adenocarcinoma) 13.6 B (CEL: ear canal papilloma)	Teague et al. 1981 12DMH

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
39	Rat (Fischer-344)	5 wk 1 x/wk (GO)				30 M	(CEL: adenomas and adenocarcinomas of the small intestine and colon)	Calvert et al. 1987 12DMH
40	Rat (Fischer-344)	<10 mo ad libitum (W)				4.2 M	(CEL: angiosarcoma of the liver and lung, hepatocellular carcinoma, renal adenoma and mesenchymal tumors)	Bedell et al. 1982 12DMH
41	Rat (NS)	11 wk 1 x/wk or 5 d/wk (G)				3 NS	(CEL: hemangioendo-theliomas of the liver)	Druckrey 1970 12DMH
						21 NS	(CEL: carcinomas of the colon, small intestine, and rectum)	
42	Rat (S-D, Lobund-Wistar, Buffalo)	10 wk 1 x/wk (GW)				30 B	(CEL: gastrointestinal adenocarcinomas)	Asano and Pollard 1978 12DMH
43	Rat (Sprague-Dawley)	4-8 wk 1 x/wk (GW)				30 M	(CEL: colon and squamous cell carcinoma of the ear)	Wilson 1976 12DMH
44	Rat (Sprague-Dawley)	5 wk 1 x/wk (GW)				27.1 M	(CEL: carcinomas of the colon and small intestine)	Locniskar et al. 1986 12DMH
45	Rat (Sprague-Dawley)	9 wk 1 x/wk (GW)				30 M	(CEL: gastrointestinal adenomas and adenocarcinomas)	Abraham et al. 1980 12DMH

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
46	Rat (Sprague-Dawley)	9 wk 1 x/wk (GW)					15	B (CEL: colon adenoma and adenocarcinoma)	Barbolt and Abraham 1980 12DMH
							30	B (CEL: duodenal adenocarcinoma)	
47	Rat (Wistar)	10 wk 1 x/wk (GW)					9	M (CEL: colorectal adenoma, adenocarcinoma, and signet ring cell carcinoma)	Thorup et al. 1992 12DMH
48	Mouse (A/J)	33-48 wk ad libitum (W)					0.46	M (CEL: lung adenomas and adenocarcinomas)	Yamamoto and Weisburger 1970 HS
49	Mouse (BALB/c)	24 wk 1 x/wk (GW)					30	F (CEL: angiosarcomas predominantly in the liver, adenomas and adenocarcinomas of the lungs and large intestines, and squamous cell carcinomas of the anus)	Izumi et al. 1979 12DMH
50	Mouse (Balb/c)	46 wk 1 x/d (GW)					9.3	F (CEL: pulmonary adenomas and adenocarcinomas)	Biancifiori and Ribacchi 1962 HS

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
51	Mouse (BALB/c)	10-48 wk ad libitum (W)				1.9 B (CEL: hemangiomas and hemangioendotheliomas predominantly in the liver, adenomas and adenocarcinomas of the lungs) 15.2 B (CEL: adenomas and adenocarcinomas of the large intestine and squamous cell carcinomas of the anus)	Izumi et al. 1979 12DMH
52	Mouse (CBA)	25 wk 150 x (GW)				2.3 B (CEL: hepatomas)	Biancifiori 1970 HS
53	Mouse (CBA)	36 wk 7 d/wk 1 x/d (GW)				9.2 B (CEL: lung adenomas adenocarcinomas, hepatomas)	Biancifiori et al. 1964 HS
54	Mouse (Swiss)	40 wk 5 x/wk (GW)				16.7 F (CEL: lung adenomas and adenocarcinomas)	Roe et al. 1967 H
55	Mouse (Swiss)	40 wk 5 x/wk (GW)				33 F (CEL: lung adenomas and adenocarcinomas)	Roe et al. 1967 11DMH
56	Mouse (Swiss, A, C17, ICRCxC3H)	4-11 mo 6 x/wk (G)				9 B (CEL: adenocarcinomas of the lungs and breast)	Bhide et al. 1976 HS
57	Gn pig (Hartley)	7-10 wk 1 x/wk (GW)				30 M (CEL: hepatomas and bile duct cell carcinomas)	Wilson 1976 12DMH

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
58	Mouse (Swiss)	Lifetime ad libitum (W)				0.95 B (100% mortality by week 70)	Toth and Patil 1982 12DMH
	Systemic						
59	Mouse (NMRI)	2 yr ad libitum (W)	Resp	9.5 B			Steinhoff et al. 1990 HH
			Cardio	9.5 B			
			Gastro	9.5 B			
			Musc/skel	9.5 B			
			Hepatic	9.5 B			
			Renal	9.5 B			
			Derm	9.5 B			
			Bd Wt	1.9 B	9.5 B (reduced body weight gain by 10%, and ruffled coats)		
	Cancer						
60	Rat (CBRI/SE)	68 wk 215 x (GW)				12 B (CEL: lung adenomas and carcinomas)	Biancifiori et al. 1966 HS
61	Mouse (Swiss)	55 wk 5 d/wk 1 x/d (GW)				9 B (CEL: lung tumors)	Maru and Bhide 1982 HS
62	Mouse (Swiss)	Lifetime ad libitum (W)				1.9 B (CEL: lung adenomas)	Toth 1972b H

TABLE 2-2 Levels of Significant Exposure to Hydrazines - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)		
63	Mouse (Swiss)	Lifetime ad libitum (W)				19	B	(CEL: angiosarcomas predominantly in the liver, hepatomas, adenomas and adenocarcinomas of the lungs, and adenomas of the kidneys)	Toth 1973a 11DMH
64	Mouse (Swiss)	Lifetime ad libitum (W)				0.059	B	(CEL: angiomas and angiosarcomas)	Toth and Patil 1982 12DMH
65	Mouse (Swiss, A, C17, ICRCxC3H)	13-18 mo 6 x/wk (G)				9	B	(CEL: adenocarcinomas of the lungs and breast)	Bhide et al. 1976 HS
66	Mouse (Swiss, C3H, AKR)	Lifetime ad libitum (W)				5.6	B	(CEL: lung adenomas and adenocarcinomas)	Toth 1969 HS
67	Hamster (Syrian Golden)	2 yr ad libitum (W)				8.3	M	(CEL: hepatocellular carcinoma, adrenal cortical adenoma)	Bosan et al. 1987 HS
68	Hamster (Syrian Golden)	Lifetime (W)				1.1	B	(CEL: angiosarcomas predominantly in the liver)	Toth 1972 12DMH

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

[b]Used to derive an intermediate oral miminimal risk level (MRL) of $8X10^{-4}$ mg/kg/d dose 1,2-dimethylhydrazine; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

11DMH = 1,1-dimethylhydrazine; 12DMH = 1,2-dimethylhydrazine; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm = dermal; Endocr = endocrine; (F) = feed; (G) = gavage (not specified); Gastro = gastrointestinal; GD = gestation day(s); Gn pig = guinea pig; (GO) = gavage (oil); (GW) = gavage (water); H = hydrazine; HS = hydrazine sulfate; HH = hydrazine hydrate; LD50 = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; mg/kg/d = milligram per kilogram per day; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s); x = times(s); yr = year(s)

Figure 2-2. Levels of Significant Exposure to Hydrazines - Oral

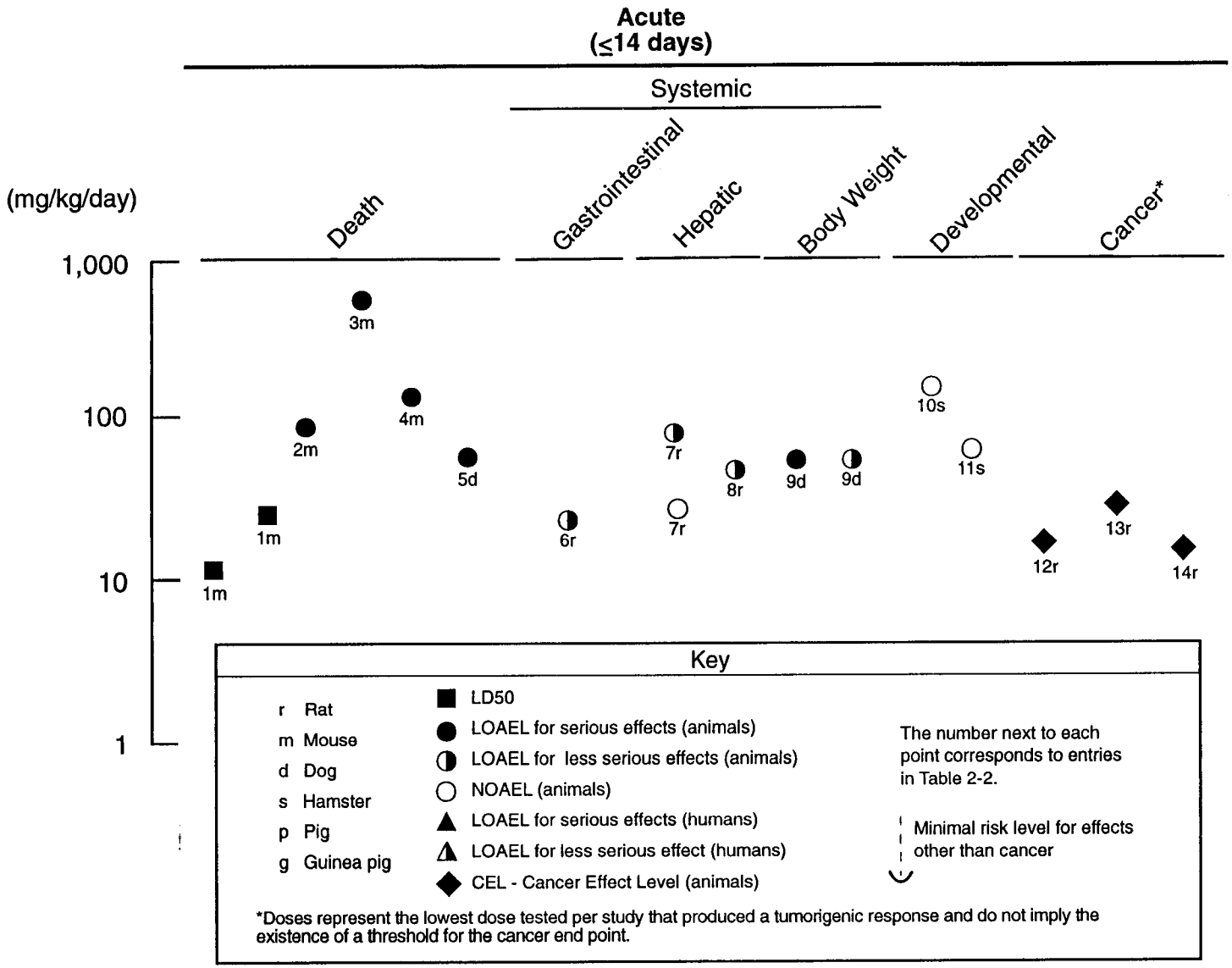


Figure 2-2. Levels of Significant Exposure to Hydrazines - Oral (continued)

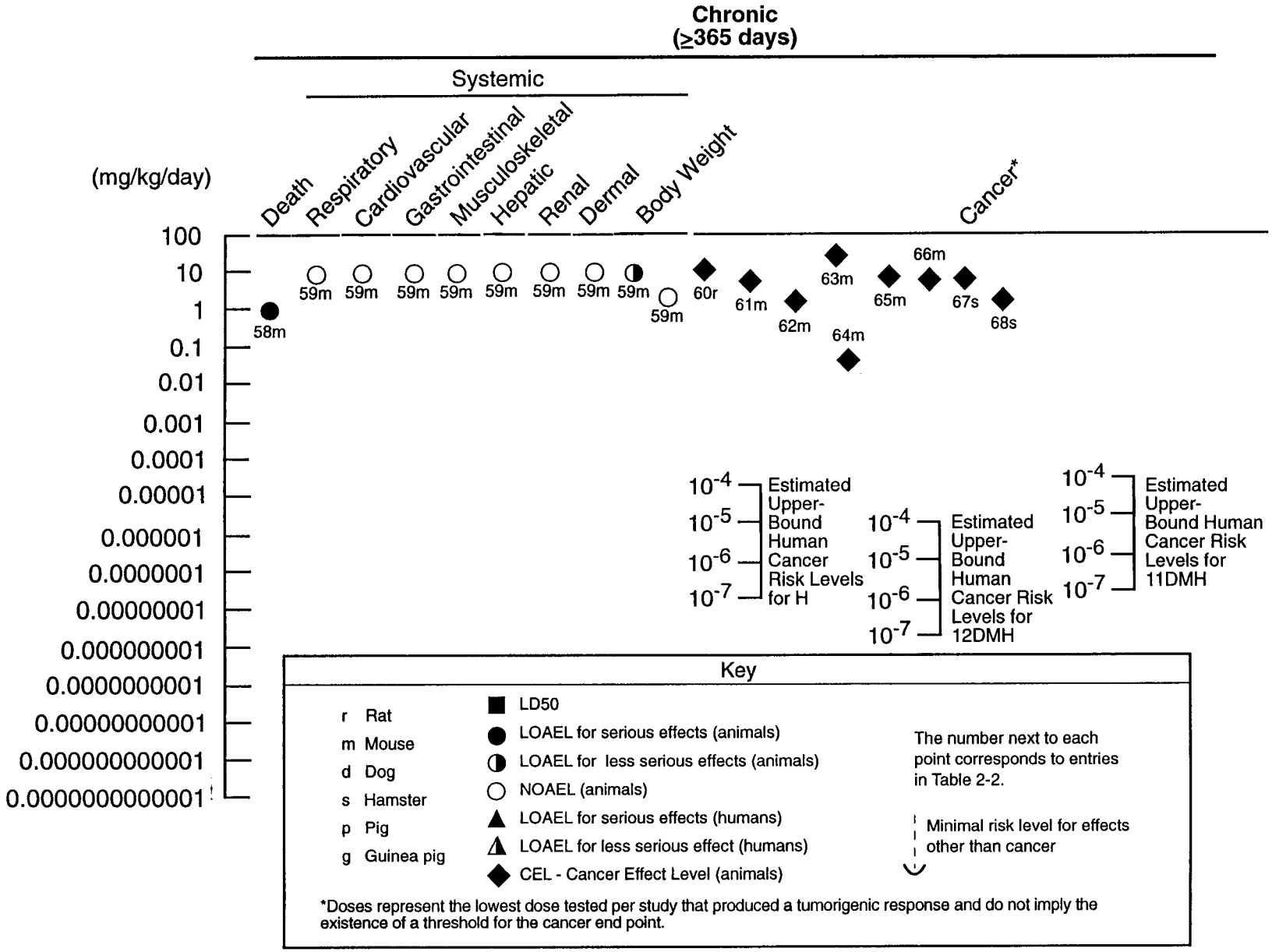
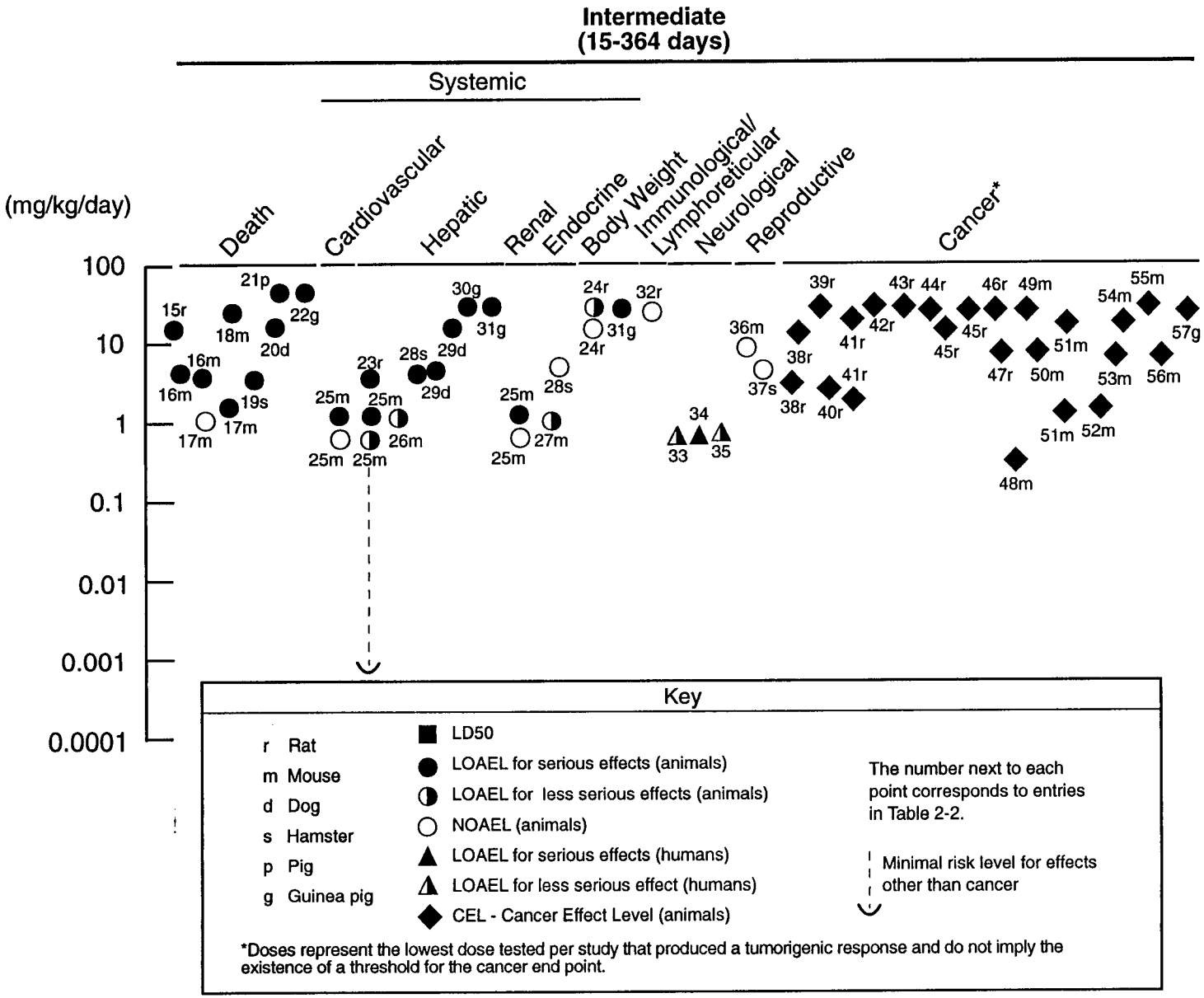


Figure 2-2. Levels of Significant Exposure to Hydrazines - Oral (continued)



observed in dogs administered weekly doses of 60 mg/kg 1,2-dimethylhydrazine for 2 weeks (Wilson 1976). Intermediate-duration exposure to 1,2-dimethylhydrazine produced liver damage (hemosiderosis, necrosis, hepatitis, fibrosis, ascites and/or failure) in rats receiving 4.2 mg/kg/day (Bedell et al. 1982), guinea pigs receiving 30 mg/kg/day or more (Wilson 1976), mice receiving 0.75 mg/kg/day or more (Visek et al. 1991), dogs receiving 5 mg/kg/day or more (Wilson 1976), and pigs receiving 30 mg/kg/day (Wilson 1976). Cirrhosis, reticuloendothelial cell proliferation, bile duct proliferation, and degenerative fibrous cells were observed in the livers of hamsters exposed to 4.9 mg/kg/day hydrazine for 15-20 weeks (Biancifiori 1970). No adverse effects were observed in the livers of mice receiving 9.5 mg/kg/day hydrazine for 2 years (Steinhoff et al. 1990). Collectively, these data indicate that hydrazine and 1,2-dimethylhydrazine are hepatotoxic by the oral route. Based on a LOAEL of 0.75 mg/kg/day for hepatic effects in mice (Visek et al. 1991), an intermediate oral MRL of $8X10^{-4}$ mg/kg/day was calculated for 1,2-dimethylhydrazine as described in footnote "b" in Table 2-2.

Renal Effects. Interstitial nephritis and pyelonephritis were observed in mice receiving 1.6 mg/kg/day 1,2-dimethylhydrazine in feed for 5 months (Visek et al. 1991). These effects were not observed in mice similarly exposed to 0.75 mg/kg/day 1,2-dimethylhydrazine. No adverse effects were noted in the kidneys of mice receiving 9.5 mg/kg/day hydrazine in the drinking water for 2 years (Steinhoff et al. 1990). These data are too limited to make firm conclusions but suggest that 1,2-dimethylhydrazine is toxic to the kidneys and hydrazine is not.

Endocrine Effects. Degeneration of the adrenals was noted in female mice exposed to 1.1 mg/kg/day or more hydrazine for 25 weeks (Biancifiori 1970). No adverse effects were noted in the thyroid of mice exposed to 9.3 mg/kg/day hydrazine for 25 weeks. Similarly, no effects were observed in the thyroid or adrenals of hamsters exposed to 5.3 mg/kg/day hydrazine for 15-20 weeks (Biancifiori 1970).

Dermal Effects. No adverse effects were observed in the skin of mice receiving 9.5 mg/kg/day hydrazine in their drinking water for 2 years (Steinhoff et al. 1990). No other studies were located regarding dermal effects in animals after oral exposure to hydrazines.

Ocular Effects. No adverse effects were observed in the eyes of mice receiving 9.5 mg/kg/day hydrazine in their drinking water for 2 years (Steinhoff et al. 1990). No other studies were located regarding ocular effects in animals after oral exposure to hydrazines.

Body Weight Effects. Body weight loss and decreased body weight gain were reported in animals exposed orally to 1,2-dimethylhydrazine and hydrazine. Weight loss was noted in dogs receiving 2 weekly doses of 60 mg/kg/day (Wilson 1976). Decreased body weight gains were reported for intermediate-duration exposure to 1,2-dimethylhydrazine for rats receiving 30 mg/kg/day (Barbolt and Abraham 1980), guinea pigs receiving 30 mg/kg/day (Wilson 1976), and in mice receiving 0.75 mg/kg/day or more (Visek et al. 1991). Decreased body weight gain was also noted in mice chronically exposed to 9.5 mg/kg/day hydrazine in the drinking water for 2 years (Steinhoff et al. 1990). No significant effect on body weight gain was noted in mice receiving 1.9 mg/kg/day. Decreases in body weight were often accompanied by decrements in food intake, organ weights, and altered physical appearance and therefore probably represent signs of general toxicity. In some cases, decreased body weight gain may be secondary to an underlying disease (e.g., cancer).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to hydrazines.

A single study in rats reported that splenic natural killer cell activity was not affected after exposure to 27.1 mg/kg/day 1,2-dimethylhydrazine once a week for 5 weeks (Locniskar et al. 1986). This NOAEL value is recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Ingestion of hydrazine (estimated between a mouthful and a cupful) resulted in several neurological effects including episodes of violent behavior, ataxia, coma, convulsions, hypesthesia of the hands, and paraesthesia of the arms and legs (Reid 1965). Confusion, lethargy, restlessness, paresthesia, and neurogenic atrophy were observed in a 24-year-old male who swallowed a mouthful of hydrazine (Harati and Niakan 1986). Hydrazine has been used as a chemotherapeutic agent in human cancer patients. Neurological side effects have been observed in some human cancer patients (450%) treated

with 0.2-0.7 mg/kg/day hydrazine as hydrazine sulfate for intermediate durations (Chlebowski et al. 1984; Gershanovich et al. 1976, 1981; Ochoa et al. 1975; Spremulli et al. 1979). For the most part, the neurological effects were relatively mild (lethargy, nausea, vomiting, dizziness, excitement, insomnia); however, two studies reported more serious effects (paresthesia, sensorimotor abnormalities, polyneuritis) (Gershanovich et al. 1976; Ochoa et al. 1975). The appearance of more serious effects in these two studies may be related to increased exposure duration. For example, Gershanovich et al. (1976, 1981) noted that polyneuritis developed only in patients receiving uninterrupted treatment with hydrazine for 2-6 months. The treatment duration used by Chlebowski et al. (1984) and Spremulli et al. (1979), which was less than 2 months in both studies, may have been sufficiently short enough to prevent the development of more serious neurological effects. Limitations in the findings of these studies lie in the fact that the test subjects were generally not healthy prior to hydrazine exposure. Therefore it is possible that some of the observed effects may be attributable to the underlying disease. However, collectively these studies strongly suggest that the central nervous systems is a target of hydrazine in humans after oral exposure. The highest NOAEL values and all LOAEL values for neurological effects resulting from oral exposure to hydrazines are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding neurological effects in animals after oral exposure to hydrazines.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to hydrazines. A single animal study reported no histopathological lesions in the ovaries of mice and hamsters exposed to 9.3 or 5.3 mg/kg/day hydrazine, respectively, for 15-25 weeks (Biancifiori 1970). However, the findings of this study are limited since reproductive function was not assessed. These NOAEL values for reproductive effects are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to hydrazines.

A single study in hamsters reported no evidence of developmental toxicity or teratogenicity following exposure to a single dose of 166 mg/kg hydrazine or 68 mg/kg 1,2-dimethylhydrazine on day 12 of gestation (Schiller et al. 1979). Although these data are limited, they suggest that fetal development is not adversely affected by hydrazine or 1,2-dimethylhydrazine. These NOAEL values for developmental effects resulting from oral exposure to hydrazines are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to hydrazines.

Alkylation of liver DNA was reported in rats acutely exposed to 30-90 mg/kg hydrazine for 1-3 days (Becker et al. 1981; Bosan et al. 1986). Micronuclei were observed in the bone marrow of mice exposed to a single oral dose of 10-50 mg/kg 1,2-dimethylhydrazine (Albanese et al. 1988; Ashby and Mirkova 1987). However, micronuclei were not observed in the bone marrow of rats after a single oral dose of 50-80 mg/kg 1,2-dimethylhydrazine (Ashby and Mirkova 1987). These data indicate that hydrazine and 1,2-dimethylhydrazine are genotoxic by the oral route. Furthermore, species differences may exist between rats and mice regarding their sensitivity to the genotoxic effects of 1,2-dimethylhydrazine.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to hydrazines.

Adenomas and adenocarcinomas of the colon have been observed in rats following a single oral exposure to 15.8-30 mg/kg 1,2-dimethylhydrazine (Craven and DeRubertis 1992; Schillm et al. 1980; Watanabe et al. 1985). Colon tumors are not common to rats and were not observed in the control animals of these studies.

Several tumor types have been observed in animals after intermediate-duration exposure to hydrazines. Exposure to 0.46-16.7 mg/kg/day hydrazine for 24-48 weeks produced a statistically significant

increase in the incidence of lung, liver, and breast tumors in mice (Bhide et al. 1976; Biancifiori 1970; Biancifiori and Ribacchi 1962; Biancifiori et al. 1964; Roe et al. 1967; Yamamoto and Weisburger 1970). A single study reported an increased incidence of lung tumors in mice after daily administration of 0.25 mg hydrazine or 0.5 1,1-dimethylhydrazine (0.8 or 1.7 mg/kg/day, respectively), 5 times per week for 40-50 or 50-60 weeks (Roe et al. 1967). A large number of studies have reported tumors in rodents after intermediate exposure to 1,2-dimethylhydrazine. Statistically significant increases were reported for tumor incidences of the blood vessels (Bedell et al. 1982; Dmckrey 1970; Izumi et al. 1979; Teague et al. 1981), liver (Bedell et al. 1982; Teague et al. 1981; Wilson 1976), lung (Izumi et al. 1979), kidney (Bedell et al. 1982), ear duct (Teague et al. 1981; Wilson 1976), and most notably the intestines, colon, and anus (Abraham et al. 1980; Asano and Pollard 1978; Barbolt and Abraham 1980; Calvert et al. 1987; Drnckrey 1970; Izumi et al. 1979; Locniskar et al. 1986; Teague et al. 1981; Thorup et al. 1992; Wilson 1976). Doses of 1,2-dimethylhydrazine resulting in increased tumor incidence ranged from 1.9 mg/kg/day to 30 mg/kg/day.

Chronic oral exposure to hydrazines has also resulted in statistically significant increases in the incidence of tumors in rodents. Exposure to 1.9-12 mg/kg/day hydrazine resulted in lung tumor formation in rats and mice (Biancifiori et al. 1966; Bhide et al. 1976; Maru and Bhide 1982; Toth 1969, 1972b). In hamsters, exposure to 8.3 mg/kg/day hydrazine produced an increased incidence of liver and kidney tumors (Bosan et al. 1987). The difference in target organ specificity for the carcinogenic effects of hydrazine may represent an important species difference between hamsters and other laboratory rodents. Several tumor types, including those of the blood vessels, lung, kidney, and liver were noted at elevated incidences in mice chronically exposed to 19 mg/kg/day l,l-dimethylhydrazine in the drinking water (Toth 1973a). Studies have reported a statistically significant increase in the incidence of blood vessel tumors in mice exposed to 0.059 mg/kg/day 1,2-dimethylhydrazine (Toth and Patil 1982) and in hamsters exposed to 1.1 mg/kg/day 1,2-dimethylhydrazine in the drinking water for life (Toth 1972c).

Collectively, these data indicate that hydrazines are carcinogenic by the oral route following acute, intermediate, or chronic exposure, and are capable of producing tumors in multiple tissue sites in several different animal species. Clearly, 1,2-dimethylhydrazine is the most potent carcinogen of the three hydrazines, since significant tumor incidences have been reported following single doses (Craven and DeRubertis 1992; Schiller et al. 1980; Watanabe et al. 1985) and at very low chronic doses (Toth and Patil 1982). Hydrazine and l,l-dimethylhydrazine are less potent carcinogens, producing tumors

primarily in the lungs (Bhide et al. 1976; Biancifiori et al. 1966; Maru and Bhide 1982; Roe et al. 1967). All CEL values from each reliable study resulting from oral exposure to hydrazines are recorded in Table 2-2 and plotted in Figure 2-2.

The EPA has derived oral slope factors of 30 $(mg/kg/day)^{-1}$ for hydrazine based on liver tumors, 2.6 $(mg/kg/day)^{-1}$ for1,1-dimethylhydrazine based on tumors of the cardiovascular system, and 37 $(mg/kg/day)^{-1}$ for 1,2-dimethylhydrazine based on tumors of the cardiovascular system (HEAST 1992; IRIS 1993). Doses of hydrazine, 1, 1-dimethylhydrazine, and 1,2-dimethylhydrazine corresponding to excess cancer risks of 10^{-4} to 10^{-7} are shown in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethal effects in humans after dermal exposure to hydrazines.

In rabbits and guinea pigs, the dermal LD_{50} values ranged from 93 to 190 mg/kg, 1,341 to 1,680 mg/kg, and 158 to 563 mg/kg for hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine, respectively (Rothberg and Cope 1956). One out of four dogs administered a single dermal dose of 300 mg/kg 1,1-dimethylhydrazine died 6 hours after exposure (Smith and Clark 1971). All dogs (three out of three) exposed to a single dermal dose of 1,800 mg/kg l,l-dimethylhydrazine died within 6 hours. In dogs exposed to hydrazine, two of three died following exposure to a single dermal dose of 96 mg/kg (Smith and Clark 1972). Additional deaths were noted in this study at higher dermal doses of hydrazine. These data indicate that acute dermal exposure to large doses of hydrazines can be lethal. These LOAEL values are recorded in Table 2-3. The lack of repeat dermal exposure studies in animals is probably due to the corrosiveness of hydrazines and their ability to induce dermal sensitization reactions.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to hydrazines. All LOAEL values for hematological, dermal, and ocular effects from each reliable study are recorded in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to Hydrazines - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE						
Death						
Dog (Mongrel)	Once				300 M (1/4 deaths)	Smith and Clark 1971 11DMH
Dog (Mongrel)	Once				96 M (2/3 deaths)	Smith and Clark 1972 H
Rabbit (Albino)	Once				467 NS (LD50)	Rothberg and Cope 1956 12DMH
Rabbit (Albino)	Once				1059 NS (LD50)	Rothberg and Cope 1956 11DMH
Rabbit (Albino)	Once				93 NS (LD50)	Rothberg and Cope 1956 H
Gn pig (NS)	Once				190 NS (LD50)	Rothberg and Cope 1956 H
Gn pig (NS)	Once				1327 NS (LD50)	Rothberg and Cope 1956 11DMH
Gn pig (NS)	Once				131 NS (LD50)	Rothberg and Cope 1956 12DMH

TABLE 2-3. Levels of Significant Exposure to Hydrazines - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
				Less Serious (mg/kg/day)		Serious (mg/kg/day)	
Systemic							
Dog (Mongrel)	Once	Derm		300 M	(slight irritation of the skin)		Smith and Clark 1971 11DMH
Dog (Mongrel)	Once	Derm		96 M	(discoloration and edema of the skin)		Smith and Clark 1972 H
Dog (NS)	Once	Hemato		300 NS	(decreased thromboplastin generation time)		Smith and Castaneda 1970 11DMH
		Ocular		300 NS	(corneal swelling)		

11DMH = 1,1-dimethylhydrazine; 12DMH = 1,2-dimethylhydrazine; Derm = dermal; Gn pig - guinea pig; H = hydrazine; Hemato = hematological; LD50 = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; mg/kg = milligram per kilogram; NOAEL = no-observed-adverse-effect level; NS = not specified.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to hydrazines.

Data in animals regarding hematological effects are limited to a single study. A decreased thromboplastin generation time was noted in dogs exposed to a single dose of 300 mg/kg l,l-dimethylhydrazine (Smith and Castaneda 1970). No other blood coagulation parameters were significantly affected.

Dermal Effects. Dermal exposure to hydrazine produces contact dermatitis. A number of studies have reported contact dermatitis in humans after dermal exposure to solutions containing 0.00005% to 1% hydrazine (Frost and Hjorth 1959; Hovding 1967; Suzuki and Ohkido 1979; Van Ketel 1964; Wrangsjo and Martensson 1986). These studies clearly indicate that hydrazine is a sensitizing agent.

Exposure to a single dermal dose of 93-190 mg/kg hydrazine resulted in discoloration of the exposed area in rabbits and guinea pigs (Rothberg and Cope 1956). Dermal discoloration and edema of the skin (application area) were observed in dogs dermally exposed to a single dose of 96 mg/kg hydrazine or more (Smith and Clark 1972). Discoloration was also observed in dogs after dermal exposure to a single dose of 300 mg/kg 1,1-dimethylhydrazine (Smith and Clark 1971).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to hydrazines. A single application of 3 μL of hydrazine, 1,1-dimethylhydrazine, or 1,2-dimethylhydrazine directly to the eyes produced conjunctivitis and erythema of the eyelids in rabbits (Rothberg and Cope 1956). Comeal damage was also noted in rabbits exposed to hydrazine but not in rabbits exposed to 1,1-dimethylhydrazine or 1,2-dimethylhydrazine. Dermal exposure to a single dose of 5 mmole/kg 1,1-dimethylhydrazine produced comeal swelling in dogs (Smith and Castaneda 1970). Although the ocular effects observed in this study may have resulted from hydrazine that was absorbed systemically, it is also possible that direct exposure of the eyes to hydrazine vapors was responsible for this effect. These data indicate that all three hydrazines can produce effects on the eyes.

2.2.3.3 Immunological and Lymphoreticular Effects

Data regarding the immunological or lymphoreticular effects of hydrazines in humans after dermal exposure are limited to a single case study. A female laboratory worker intermittently exposed to an undetermined amount of hydrazine developed a lupus erythematosus-like disease (Reidenberg et al. 1983). Symptoms included a photosensitive rash, fatigue, anthragias, and a breaking off of frontal hair. The subject also possessed antinuclear antibodies and antibody to DNA. A positive skin patch test response was obtained after a dermal challenge to hydrazine was administered. The study authors concluded that hydrazine can induce a lupus erythematosus-like disease in predisposed persons. In support of this view, a number of other hydrazine derivatives have been linked to the induction of lupus erythematosus in humans (Pereyo 1986). As discussed in Section 2.2.3.2, dermal exposure to hydrazine also produces allergic contact dermatitis in humans.

No data were located regarding the immunological or lymphoreticular effects in animals after dermal exposure to hydrazines.

2.2.3.4 Neurological Effects

Data regarding neurological effects in humans after dermal exposure to hydrazines are limited to two case studies. A man who suffered bums during an industrial hydrazine explosion became comatose 14 hours after the explosion (Kirklin et al. 1976). Rapid recovery from the coma was facilitated by pyridoxine treatment. Another man who suffered bums during an industrial 1,1-dimethylhydrazine explosion exhibited abnormal EEG readings and narcosis within 40 hours after exposure (Dhennin et al. 1988). Recovery from these symptoms was also facilitated by pyridoxine treatment.
Several months after the incident the latter worker developed polyneuritis. The findings from these studies are limited because the subjects were burn patients. The trauma from the bums may have played a role in some of the neurological effects observed. In addition, pyridoxine is also known to produce neurological effects at high doses, and may have been partially responsible for the delayed polyneuritis.

Mild convulsions were noted in 3 of 13 dogs receiving a single dermal dose of 300-1,800 mg/kg l,l-dimethylhydrazine (Smith and Clark 1971). Similarly, convulsions were noted in 3 of 25 dogs administered a single dermal dose of 96-480 mg/kg hydrazine (Smith and Clark 1972). The data from

animal studies support the findings of the human case studies which indicate that hydrazine and 1,1 -dimethylhydrazine adversely affect the central nervous system following large dermal exposures, No studies were located regarding the following effects in humans or animals after dermal exposure to hydrazines:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans or animals after dermal exposure to hydrazines.

2.3 TOXICOKINETICS

No data were located regarding the toxicokinetics of hydrazines in humans after inhalation, oral, or dermal exposure to hydrazines. Inhalation, oral, and dermal studies in animals indicate that hydrazines are rapidly absorbed into the blood. Animal studies also indicate that hydrazines readily distribute to tissues without preferential accumulation at any specific site. Hydrazines with a free amino group are able to react with endogenous alpha-keto acids and in so doing produce a variety of adverse health effects. *In vivo* and *in vitro* studies indicate that hydrazines are metabolized by several pathways, both enzymatic and nonenzymatic. Free radical and carbonium ion intermediates are produced during the metabolism of hydrazines and may also be involved in adverse health effects produced by exposure to hydrazines. Limited data from animal studies indicate that metabolites of hydrazines are excreted principally in the urine and expired air. Although the data are limited, animal studies appear to indicate that the toxicokinetics of hydrazines may vary among animal species.

2.3.1 Absorption

2.3.1 .l Inhalation Exposure

No studies were located regarding absorption in humans after inhalation exposure to hydrazines. A single animal study was located which investigated the absorption of hydrazine in the lungs. Groups of eight rats were exposed to concentrations of 10, 60, or 500 ppm hydrazine in a nose-only chamber for 1 hour (Llewellyn et al. 1986). Based on the levels of hydrazine and its metabolites excreted in the urine within 48 hours, the absorption of hydrazine was estimated to be at least 8.4-29.5%. However, because a large percentage of the dose may have been retained in the body or excreted by fecal or pulmonary routes, absorption in the lungs is probably significantly higher than 8.4-29.5%.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to hydrazines. It should be noted, however, that the drug isoniazid, which is used to treat tuberculosis, is metabolized to hydrazine, and thus patients administered isoniazid exhibit elevated levels of hydrazine in their blood plasma (Blair et al. 1985).

A single animal study was located which investigated the oral absorption of hydrazine. Groups of 15 rats were administered a single dose of hydrazine, ranging from 2.9 to 81 mg/kg (Preece et al. 1992a). Based on the levels of hydrazine and its metabolites excreted in the urine within 24 hours, at least 19-46% of the administered dose was absorbed. However, since the analytical method employed in this study cannot detect certain metabolites of hydrazine, and since 24 hours may have been too short a time period to collect all urinary metabolites, the absorption of hydrazine in the gastrointestinal tract is most likely higher than 19-46%. In a more detailed description of presumably the same study, Preece et al. (1992b) reported dose saturation effects with respect to urinary excretion and liver concentration of hydrazine. Both the ratio of plasma to liver hydrazine levels and the proportion of hydrazine and acetylhydrazine excreted in the urine declined with the dose. These authors also reported that evidence of fatty liver and reduction in liver and body weights occurred only at the highest dose examined (81 mg/kg).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to hydrazines. Two studies in dogs reported that hydrazine and 1,1-dimethylhydrazine were detected in the blood within 30 seconds of exposure to a single dermal dose (Smith and Clark 1971, 1972). In dogs exposed to a single dermal dose of 96-480 mg/kg hydrazine, maximum levels of hydrazine in the blood (approximately 70 μg/L) were detected 3 hours after exposure (Smith and Clark 1972). Similarly, in dogs exposed to a single dermal dose of 300-1,800 mg/kg 1,1-dimethylhydrazine, the highest levels of l,l-dimethylhydrazine (approximately 130 μg/mL) were detected 3 hours after exposure (Smith and Clark 1971). These data indicate that hydrazine and 1,1-dimethylhydrazine are rapidly absorbed from the skin into the blood. However, these studies do not provide enough information to estimate the extent to which hydrazine and 1,1-dimethylhydrazine are absorbed. The lack of repeat dermal exposure studies in animals is probably due to the corrosiveness of hydrazines and their ability to induce dermal sensitization reactions.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to hydrazines.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to hydrazines.

A single study in animals reported limited information on the distribution of hydrazine after oral exposure. Following a single oral dose of 2.9-81 mg/kg hydrazine, peak levels of hydrazine in the plasma and liver of rats were achieved within 30 minutes (Preece et al. 1992a). These levels ranged from approximately 0.0003 to 0.01 mg/mL in the plasma and from 0.0006 to 0.006 mg/kg in the liver. The levels of hydrazine in other tissues were not reported. In a more detailed description of presumably the same study, Preece et al. (1992b) found that there was a fivefold greater amount of

hydrazine in the liver than in blood plasma 24 hours after dosing. No acetylhydrazine was found at that time. The concentration of hydrazine in the liver (other organs were not examined) did not increase proportionately with the dose, suggesting saturation effects. Similarly, the urinary excretion was dose-dependent, with a greater portion of hydrazine and acetylhydrazine being excreted at lower doses than at higher doses.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to hydrazines.

2.3.2.4 Other Routes of Exposure

No studies were located regarding distribution in humans after exposure to hydrazines.

In rats administered a single dose of 9.9 mg/kg hydrazine by subcutaneous injection, hydrazine was observed to rapidly distribute to tissues (Kaneo et al. 1984). Maximum tissue levels were observed within 30 minutes in the liver, lung, plasma, and particularly the kidney. Hydrazine was detected in the brain of rats at levels of 0.5-1 μg/g following intravenous injection of 5.1 mg/kg hydrazine (Matsuyama et al. 1983). The levels of hydrazine in various tissues in rats were reported to decrease with half-times ranging from 2.3 to 3.3 hours (Kaneo et al. 1984).

In a series of experiments, groups of rats, rabbits, cats, dogs, and monkeys were administered a single intraperitoneal dose of l,l-dimethylhydrazine ranging from 10 to 50 mg/kg (Back et al. 1963). The plasma levels of l,l-dimethylhydrazine in all species reached maximum values within 1 hour of the injection, accounting for up to 14.3% of the dose in dogs and 8.7% of the dose in cats. Plasma levels were not detectable in rats after 2-24 hours, indicating that 1,1-dimethylhydrazine was rapidly distributed to tissues or was excreted. Plasma levels in monkeys tended to drop off after1 hour and were not detectable after 24 hours. In a limited study, male rats were subcutaneously injected with 50 mg/kg 1,1-dimethylhydrazine or 100 mg/kg 1,2-dimethylhydrazine (Fiala and Kulakis 1981). Plasma levels of these two hydrazines decreased rapidly after exposure, with half-lives of approximately 1 hour for each chemical.

In rats administered a single dose of 0.78-80 mg/kg 1,1-dimethylhydrazine by intraperitoneal injection, approximately 71 .1% of the dose was retained in the body after 4 hours (Mitz et al. 1962), and approximately 7.1-38.7% of the dose was retained in the body after 53 hours (Dost et al. 1966). Low levels of 1,1-dimethylhydrazine (approximately 0.1-3.1% of the dose) were detected in tissues (brain, liver, kidney, heart, blood) of rats administered a single dose of 11-60 mg/kg 1,1-dimethylhydrazine by intraperitoneal injection (Mitz et al. 1962; Reed et al. 1963). Preferential accumulation of 1,1-dimethylhydrazine was not observed in any organ. Although higher concentrations of 1,1-dimethylhydrazine were detected in the liver and colon of rabbits within 2 hours after receiving a single intravenous or intraperitoneal dose (Back et al. 1963), this was not judged to be evidence of preferential accumulation by the study authors. The highest levels in these rabbits were detected in the liver (8.9%) and colon (11.6%) after 2 hours, whereas other tissue levels ranged from 0.02 to 4.18% of the dose.

These data indicate that hydrazines distribute rapidly to all tissues without preferential accumulation following injection of a single dose. Furthermore, tissue levels of hydrazine and 1,1-dimethylhydrazine tend to reach maximal values within 1 hour and are generally not detectable after 24 hours.

2.3.3 Metabolism

Several enzymatic and nonenzymatic pathways are involved in the metabolism of hydrazines. Humans with a slow acetylator genotype may accumulate more hydrazine in the plasma because of an impaired ability to metabolize and excrete the compound (Blair et al. 1985). Although the extent to which each pathway contributes to total metabolism may depend somewhat on the route of exposure (a first-pass metabolic effect for oral exposure, for example), the types of pathways involved and metabolites formed do not appear to be dependent on route. Therefore this section discusses the data without reference to route of exposure. While the metabolic pathways of hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are similar in some ways, there are some important differences. Therefore, data from *in vivo* and in vitro studies regarding the metabolism of hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are discussed separately below.

Hydrazine. In rats exposed to 10-500 ppm hydrazine for 1 hour, approximately 2-10% of the inhaled dose was excreted in the urine unchanged, 1.74% as acetyl hydrazine, and 4.5-11.4% as diacetyl

hydrazine (Llewellyn et al. 1986). In rats exposed to a single dose of 16-64 mg/kg hydrazine, approximately 20% was excreted in the urine as an unspecified hydrazine derivative, 30% was excreted in the urine unchanged, and 25% of the nitrogen in hydrazine was released in expired air as nitrogen gas (Springer et al. 1981). In rats administered a single dose of 2-81 mg/kg hydrazine, a small percentage of the dose (1-19%) was recovered in the urine as acetyl hydrazine and/or diacetyl hydrazine within 2448 hours of exposure (Kaneo et al. 1984; Llewellyn et al. 1986; Preece et al. 1992a). Following exposure to larger doses of 427 mg/kg hydrazine, a number of metabolites were excreted in the urine, including acetyl hydrazine, diacetyl hydrazine, pyruvate hydrazone, urea, and a cyclic compound (1,4,5,6-tetrahydro-6-oxo-3-pyridazine carboxylic acid, a product of the reaction between 2-oxoglutarate and hydrazine) (Preece et al. 1991). These data indicate that hydrazine undergoes acetylation and can react with cellular molecules *in vivo*.

Hydrazine is rapidly metabolized by rat liver microsomes *in vitro* (Timbrell et al. 1982). Oxygen, nicotinamide-adenine dinucleotide phosphate (NADPH), and active enzyme were required for maximal activity. Metabolism of hydrazine by rat liver hepatocytes was increased when rats were pretreated with cytochrome P-450 inducers (phenobarbital and rifampicin) and was decreased by the addition of cytochrome P-450 inhibitors (metyrapone and piperonyl butoxide) (Noda et al. 1987). Cytochrome P-450 inhibitors and inducers were also reported to increase and decrease hydrazine toxicity, respectively, indicating a relationship between metabolism and toxicity (Timbrell et al. 1982). Free radical formation was reported to occur when hydrazine was incubated with purified NADPHcytochrome P-450 reductase (Noda et al. 1988). This reaction required NADPH and oxygen, was stimulated by FAD, inhibited by superoxide dismutase, and was unaffected by carbon monoxide. Free radicals were also noted when hydrazine was metabolized in perfused rat livers (Sinha 1987). These free radicals included acetyl, hydroxyl, and hydrogen radicals, the type of which was dependent upon the addition of an activating system (horseradish peroxidase or copper ion) to the perfusate. The occurrence of an acetyl radical suggests that hydrazine is acetylated prior to radical formation. These data indicate that hydrazine is metabolized by cytochrome P-450 but that transformation via other enzyme systems (peroxidases) or nonenzymatic reactions (copper ion-mediated) may occur as well. The formation of free radicals during the metabolism of hydrazine may be important to the mechanism of action of hydrazine toxicity.

1,1-Dimethylhydrazine. In rats administered a single dose of 0.78-60 mg/kg 1,1-dimethylhydrazine, approximately 12-27% of the dose was detected in expired air as carbon dioxide (Dost et al. 1966;

Reed et al. 1963). Four hours after receiving a single dose of 40 mg/kg 1,1-dimethylhydrazine, less than 2% of the dose was released in expired air (Mitz et al. 1962). Approximately 3-10% and 20-25% of the dose was recovered in the urine as the glucose hydrazone of 1,1-dimethylhydrazine and an unidentified metabolite (Mitz et al. 1962). The study authors speculated that the unidentified metabolite was another hydrazone of 1,1-dimethylhydrazine. These data indicate that 1,1-dimethylhydrazine undergoes demethylation and can react with cellular molecules *in vivo*.

N-demethylation of 1,1-dimethylhydrazine by rat and hamster liver microsomes *in vitro* required the presence of NADPH and oxygen and was decreased by the addition of flavin-containing monooxygenase inhibitor (methimazole) but not by the addition of cytochrome P-450 inhibitors (Prough et al. 1981). 1,1-Dimethylhydrazine was also noted to be a good substrate for *N*-oxidation by amine oxidase (Prough 1973). In rat liver microsomes and S-9 fractions, both a nonenzymatic and an enzymatic component were identified for the metabolism of 1,1-dimethylhydrazine (Godoy et al. 1983). Formaldehyde was produced by both components, although the nonenzymatic component dominated the formation of a reactive protein-binding species. In contrast, rat liver slices metabolized 1,1-dimethylhydrazine to carbon dioxide and did not generate any reactive protein-binding species (Godoy et al. 1983), suggesting that *in vitro* metabolic studies may not be presenting an accurate picture of 1,1-dimethylhydrazine metabolism as it occurs *in vivo*. The formation of formaldehyde by rat colon microsomes was decreased by the addition of lipoxygenase and cyclooxygenase inhibitors (indomethacin and eicosatetranoic acid) and was stimulated by the addition of fatty acids, suggesting that lipoxygenase and cyclooxygenase may be involved in the colonic metabolism of 1,1-dimethylhydrazine (Craven et al. 1985).

Several studies have shown that the reactive binding species generated by 1,1-dimethylhydrazine metabolism may be free radical intermediates. Rat liver microsomes and rat hepatocytes are capable of metabolizing 1,1-dimethylhydrazine to form methyl radical intermediates (Albano et al. 1989; Tomasi et al. 1987). The formation of these radicals was inhibited by the addition of inhibitors of cytochrome P-450 (SKF 525A, metyrapone, and carbon monoxide) and inhibitors of the flavin-containing monooxygenase system (methimazole). The formation of free radicals could also be supported nonenzymatically by the presence of copper ion (Tomasi et al. 1987). These data indicate that at least two independent enzyme systems and one nonenzymatic pathway may be involved in the metabolism of 1,1-dimethylhydrazine.

1,2-Dimethylhydrazine. *In vivo* studies indicate that 1,2-dimethylhydrazine is metabolized to form azomethane, azoxymethane, methylazoxymethanol, ethane, and carbon dioxide. In rats administered a single dose of 20-200 mg/kg 1,2-dimethylhydrazine, approximately 4-24% and 14-23% of the dose was detected in expired air as carbon dioxide and azomethane, respectively (Fiala et al. 1976; Harbach and Swenberg 1981). Azoxymethane and methylazoxymethanol were detected in the urine of rats injected with 21 mg/kg 1,2-dimethylhydrazine (Fiala et al. 1977). It has been proposed that 1,2-dimethylhydrazine undergoes sequential oxidations to form azomethane, which in turn is metabolized to form azoxymethane and then methylazoxymethanol (Druckrey 1970). Ethane was detected in the expired air of rats exposed to a single dose of 9-91 mg/kg 1,2-dimethylhydrazine (Kang et al. 1988). The study authors proposed that ethane was formed by a dimerization of methyl radicals originating from 1 ,2-dimethylhydrazine metabolism. These data indicate that oxidation can occur at both the nitrogen and the carbon of 1,2-dimethylhydrazine *in vivo* and suggest that free radicals may be formed as well.

Human colon microsomes and human colon cancer cells were capable of generating formaldehyde from 1,2-dimethylhydrazine *in vitro* (Newaz et al. 1983). The formation of formaldehyde was decreased by the addition of cytochrome P-450 inhibitors and was increased by the pretreatment of cancer cells with cytochrome P-450 inducers. Interestingly, the study authors noted a gradient with respect to 1,2-dimethylhydrazine metabolism activity in the colon (ascending < transverse < descending). Other studies have reported that the greatest capacity to produce DNA-binding intermediates from 1,2-dimethylhydrazine is in the ascending colon of humans (Autrup et al. 1980a). Rat colon epithelial cells were found to metabolize 1,2-dimethylhydrazine to azoxymethane, methylazoxymethanol, and a reactive binding species (Glauert and Bennink 1983). In the hamster colon cells, surface columnar epithelial cells were found to metabolize 1,2-dimethylhydrazine 2-3 times as well as crypt cells (Sheth-Desai et al. 1987). In addition, metabolism was inhibited by an alcohol dehydrogenase inhibitor (pyrazole). In a rat liver perfusion study, the metabolites of 1,2-dimethylhydrazine were identified as azomethane, azoxymethane, and methylazoxymethanol (Wolter et al. 1984). Rat liver microsomes were found to metabolize 1,2-dimethylhydrayine to azomethane (N-N oxidation) and formaldehyde (C-N oxidation) (E&son and Prough 1986). These activities were increased in rats pretreated with cytochrome P-450 inducers (phenobarbital) indicating the involvement of this enzyme. Mitochondrial amine oxidase demonstrated considerable activity as well (Coomes and Prough 1983; Erikson and Prough 1986), although 1,2-dimethylhydrazine was not as good a substrate for this enzyme as was l,l-dimethylhydrazine (Prough 1973). Likewise,

1,2-dimethylhydrazine was not as good a substrate as 1,1-dimethylhydrazine for flavin-containing monooxygenase-mediated metabolism (Prough et al. 1981) or colonic cyclooxygenase and lipoxygenase (Craven et al. 1985). Since 1,2-dimethylhydrazine is a potent colon carcinogen while 1,1-dimethylhydrazine is not carcinogenic for the rodent colon, the significance of these findings is uncertain.

Reactive intermediates are formed during the metabolism of 1,2-dimethylhydrazine. *In vitro* studies indicate that methylazoxymethane can form a reactive species (probably a methyldiazonium ion) either spontaneously (Nagasawa and Shirota 1972) or enzymatically by alcohol dehydrogenase and/or cytochrome P-450 (Feinberg and Zedeck 1980; Sohn et al. 1991). Other *in vitro* studies suggest that free radicals are formed during the metabolism of 1,2-dimethylhydrazine. For example, as observed with 1,1-dimethylhydrazine, the formation of methyl free radicals from 1,2-dimethylhydrazine in rat liver microsomes and rat hepatocytes was inhibited by cytochrome P-450 inhibitors (SKF 525A, metyrapone, and carbon monoxide) (Albano et al. 1989; Tomasi et al. 1987). However, unlike 1,1-dimethylhydrazine, the formation of methyl radicals was not decreased by the addition of a flavin-containing monooxygenase inhibitor (methimazole), suggesting that this enzyme is not involved in the production of free radicals from 1,2-dimethylhydrazine. Carbon-centered radicals were observed when 1,2-dimethylhydrazine was metabolized by horseradish peroxidase (August0 et al. 1985; Netto et al. 1987). These data indicate differences exist between the enzyme systems involved in metabolism of 1,2-dimethylhydrazine and 1,1-dimethylhydrazine to reactive intermediates.

Reactive intermediates produced during the metabolism of 1,2-dimethylhydrazine are most likely responsible for DNA adducts observed *in vivo* (Becker et al. 1981; Netto et al. 1992; Pozharisski et al. 1975) and *in vitro* (Autrup et al. 1980a; Harris et al. 1977; Kumari et al. 1985). There is evidence for both the methyldiazonium and methyl radical as reactive species derived from 1,2-dimethylhydrazine, and it is clear that metabolism of the compound is required for its carcinogenicity. Inhibition of metabolism by disulfiram and other thiono sulfur compounds (Fiala et al. 1977) resulted in inhibition of DNA alkylation (Swenberg et al. 1979) and colon carcinogenicity (Wattenberg 1975):. Moreover, azoxymethane and methylazoxymethanol, two metabolites of 1,2-dimethylhydrazine, are also potent colon and liver carcinogens (Williams and Weisburger 1991).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans after inhalation exposure to hydrazines.

Forty-eight hours after a l-hour exposure to 10-500 ppm hydrazine, approximately 8.4-29.5% of the inhaled dose was excreted in the urine of rats (Llewellyn et al. 1986). Most of the recovered dose was excreted during the first 24 hours. Three metabolites were identified in the urine as unchanged hydrazine, acetyl hydrazine, and diacetyl hydrazine. No other studies were located regarding excretion in animals after inhalation exposure to hydrazine.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to hydrazines.

A single study was located that reported excretion in animals after oral exposure to hydrazine. Twenty-four hours after a single oral dose of 2.9-81 mg/kg hydrazine, approximately 19-46% of the dose was recovered in the urine of exposed rats (Preece et al. 1992a). Two metabolites were identified in the urine as unchanged hydrazine and acetyl hydrazine. Fecal excretion and release of the compound in expired air were not investigated in this study.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to hydrazines.
Data in animals regarding the excretion of hydrazines are limited to two studies. In dogs administered a single dermal dose of 300-1,800 mg/kg 1,1-dimethylhydrazine, levels of up to 600 μg/L 1,1-dimethylhydrazine were detected in the urine within 5 hours (Smith and Clark 1971). Similarly, in dogs administered a single dermal dose of 96-480 mg/kg hydrazine, levels of up to 70 μg/mL were detected in the urine within 3 hours (Smith and Clark 1972). However, neither of these studies examined fecal excretion nor did they provide sufficient information to estimate the fraction of the dose excreted in the urine.

2.3.4.4 Other Exposure

No studies were located regarding excretion in humans after other exposures to hydrazines.

The levels of hydrazine in the blood were reported to decrease in a biphasic manner in rats administered 16-64 mg/kg hydrazine via indwelling catheters, with half-times of 0.74 and 26.9 hours (Springer et al. 1981). In dogs administered a single dose of 16-64 mg/kg hydrazine via an indwelling cannula, approximately 25% and 50% of the dose was recovered within 48 hours in the expired air and urine, respectively (Springer et al. 1981). Forty-eight hours after receiving a single intravenous dose of 2-12 mg/kg hydrazine, rats excreted approximately 13.8-37.3% of the dose in the urine (Llewellyn et al. 1986). Approximately 29.2% of a single subcutaneous dose of 9.9 mg/kg hydrazine was excreted in the urine of rats after 48 hours (Kaneo et al. 1984). Although these data are limited by the lack of information on fecal excretion, they suggest that the majority of an absorbed dose of hydrazine is excreted in the urine but that a significant fraction of the dose may be released in expired air.

In rats administered a single dose of 0.78-80 mg/kg 1,1-dimethylhydrazine, approximately 18.9-76% of the carbon dose was recovered in the urine and 2-23% of the carbon dose was excreted in expired air within 4-53 hours (Dost et al. 1966; Mitz et al. 1962; Reed et al. 1963). Approximately 34.8-39.1% of the carbon dose was excreted in the urine within 5 hours in dogs intraperitoneally injected with 50 mg/kg 1,1-dimethylhydrazine (Back et al. 1963). Approximately 37.2-51.2% of the carbon dose was recovered in the urine within 6 hours in cats intraperitoneally injected with 10-50 mg/kg 1,1-dimethylhydrazine (Back et al. 1963). These studies typically employed a carbon radiolabel (^{14}C-1,1-dimethylhydrazine). This radiolabel can become separated from the rest of the molecule during the demethylation of 1,1-dimethylhydrazine; therefore, these studies may not accurately depict the metabolic fate of the nitrogen contained within the dose. In addition, fecal excretion of 1,1-dimethylhydrazine was not determined in these studies. Despite these limitations, these data suggest that the majority of the carbon from an absorbed dose of 1,1-dimethylhydrazine is excreted in the urine but that a significant fraction of the carbon dose may be released in expired air. In rats treated subcutaneously with 21 mg/kg ^{14}C-labelled 1,2-dimethylhydrazine, approximately 13-16% of the radioactivity was released in expired air as CO_2 within 24 hours, while 14-15% was expired as azomethane and 17% was released in urine (Fiala et al. 1977). A similar rat study found

that the levels of radiolabel in expired CO_2 and azomethane after 24 hours were 11% and 14%, respectively, when the dose was 21 mg/kg 1,2-dimethylhydrazine, and 4% and 23%, respectively, when the dose was 200 mg/kg (Fiala et al. 1976). Likewise, rats injected with 20 mg/kg 1,2-dimethylhydrazine expired about 22% of the radioactive dose as azomethane and about 16% as CO_2 after 12 hours (Harbach and Swenberg 1981). By quantitating the radioactivity released as azomethane, which contains both nitrogens from the 1,2-dimethylhydrazine, the metabolic fate of these nitrogens can be followed, in contrast to studies which only measure expired CO_2. Female mice injected with 15 mg/kg ^{14}C-labelled 1,2-dimethylhydrazine expired about 24% of the radioactivity as CO_2 within 24 hours, while 10% was excreted in the urine (Hawks and Magee 1974). This same study found that 0.9% of the radioactivity was excreted in the bile after a dose of 200 mg/kg. These data suggest that a significant fraction of the carbon dose of 1,2-dimethylhydrazine may be released in expired air and urine, whereas fecal excretion is relatively low.

2.4 MECHANISMS OF ACTION

Studies in animals indicate that hydrazines are rapidly absorbed through the skin (Smith and Clark 1971, 1972), and presumably in the lungs and gastrointestinal tract as well. Although the mechanism by which hydrazines are absorbed into the blood has not been studied, this most likely does not occur by passive diffusion because of the polar nature of these compounds.

A number of studies have investigated the mechanisms by which hydrazines produce adverse health effects. These data suggest there are at least two distinct mechanisms of action for hydrazines: one involving the direct binding of those hydrazines with a free amino group (hydrazine and 1,1-dimethylhydrazine) to key cellular molecules, and the other involving the generation of reactive species such as free radical intermediates or methyldiazonium ions as a result of metabolism. Studies which support the existence of these mechanisms are discussed below.

In vitro studies have shown that hydrazine reacts with alpha-keto acids to form hydrazoines compounds (O'Leary and Oikemus 1956). By binding to keto acids and forming hydrazones, hydrazine inhibited oxygen consumption with mitochondrial substrates *in vitro* (Fortney 1967). This mechanism may well account for the hyperlactemic and hypoglycemic effects of hydrazine observed in humans (Ochoa et al. 1975) and dogs *in vivo* (Fortney 1967). Hydrazine and 1,1-dimethylhydrazine can form hydrazones with vitamin B_6 derivatives (Comish 1969). By binding to vitamin B_6 derivatives, hydrazine and

1,1-dimethylhydrazine are able to inhibit reactions that require vitamin B_6 as a cofactor. These reactions include transamination reactions, decarboxylation and other transformations of amino acids, the metabolism of lipids and nucleic acids, and glycogen phosphorylation (NRC 1989). Deficiency of vitamin B_6 can produce convulsions, dermatitis, and anemia. These data suggest that the convulsions and anemia observed in animal studies are the result of the formation of hydrazone derivatives of vitamin B_6. In addition, some authors have proposed that a free amino group, as found in hydrazine and 1,1-dimethylhydrazine, is required for hydrazone formation (Comish 1969). This would explain why convulsions are associated with exposures to hydrazine and 1,1-dimethylhydrazine, and not 1 ,2-dimethylhydrazine. It should be noted that pyridoxine (one of the forms of vitamin B_6) is commonly used to treat humans exposed to hydrazine or 1,1-dimethylhydrazine.

A number of *in vitro* studies have reported the production of reactive intermediates during the metabolism of hydrazines (see Section 2.3.3). Evidence for the production of radicals including methyl, acetyl, hydroxyl, and hydrogen radicals has been observed during the metabolism of hydrazine (Ito et al. 1992; Noda et al. 1988; Runge-Morris et al. 1988; Sinha 1987), l,l-dimethylhydrazine (Albano et al. 1989; Tomasi et al. 1987), and 1,2-dimethylhydrazine (Albano et al. 1989; Augusto et al. 1985; Netto et al. 1987; Tomasi et al. 1987). Multiple pathways, both enzymatic and nonenzymatic, appear to be involved in free radical generation. Free radicals have been implicated in protein (hemoglobin) damage associated with hydrazine in human erythrocytes (Runge-Morris et al. 1988), suggesting that free radicals may be involved in the anemic effects of hydrazines observed in animals *in vivo* (Haun and Kinkead 1973; Rinehart et al. 1960). It has also been proposed that metabolism of 1,2-dimethylhydrazine yields a reactive, methyldiazonium ion (Feinberg and Zedeck 1980; Sohn et al. 1991). The production of reactive species during the metabolism of hydrazines may also explain their genotoxic effects, such as the formation of DNA and RNA adducts *in vivo* (Becker et al. 1981; Beranek et al. 1983; Bolognesi et al. 1988; Bosan et al. 1986; Netto et al. 1992; Pozharisski et al. 1975; Quintero-Ruiz et al. 1981). DNA and RNA adducts may well be responsible for gene mutations observed in a number of *in vitro* studies (DeFlora and Mugnoli 1981; Hawks and Magee 1974; Kang 1994; Kerklaan et al. 1983; Levi et al. 1986; Malaveille et al. 1983;Noda et al. 1986; Oravec et al. 1986; Parodi et al. 1981; Rogers and Back 1981; Sedgwick 1992; Wilpart et al. 1983) and may also serve as the initiating event for cancers induced by hydrazines *in vivo.*

2.5 RELEVANCE TO PUBLIC HEALTH

Data regarding the toxic effects of hydrazines in humans are limited to a few case studies of accidental exposure and chemotherapy trials in cancer patients. Studies consistently indicate that the central nervous system is the primary target for hydrazine and 1,1-dimethylhydrazine following inhalation, oral, and dermal exposures. In some cases, neurological effects were delayed, but most effects were observed either during exposure or soon after. Quantitative data on human exposures are available only for oral exposures of intermediate durations.

Studies in animals, which support the findings from human studies, report neurological effects following inhalation, dermal, and parenteral exposures to hydrazine and 1,1-dimethylhydrazine. Neurological effects do not appear to be of concern following exposure to 1,2-dimethylhydrazine. Effects on the liver have been consistently reported in animal studies following exposure to all three hydrazines. Limited studies in animals suggest that exposure to hydrazines by the inhalation, oral, and parenteral routes may cause reproductive and developmental effects. A number of species-, sex-, and strain-specific differences have been observed for sensitivity to the toxic effects of hydrazines. All three hydrazines are carcinogenic in animals following oral and inhalation exposures. 1,2-Dimethylhydrazine is a potent carcinogen in animals and can induce tumors following single oral or parenteral doses.

Data regarding the toxicokinetics of hydrazines are limited but suggest that in animals hydrazines are rapidly absorbed and distributed to all tissues and that metabolites are excreted largely in the urine or released in expired air. Limited data in humans suggest that people with a slow acetylator genotype do not clear hydrazine from the body as well as those who are fast acetylators and therefore may be more susceptible to the toxic effects of hydrazine.

Minimal Risk Levels for Hydrazines

Inhalation MRLs

- An MRL of $4X10^{-3}$ ppm has been derived for intermediate-duration inhalation exposure to hydrazine. This MRL is based on a LOAEL of 0.2 ppm for moderate fatty liver changes observed in female mice (Haun and Kinkead 1973). In this study, groups of 40 female ICR

mice were exposed for 6 months to either 0, 0.2, or 1 ppm hydrazine continuously, or to 0, 1, or 5 ppm intermittently (6 hours/day, 5 days/week). The study authors also investigated the effects of inhaled hydrazine in other species. In support of this MRL, fatty liver changes were also observed in dogs exposed to 1 ppm hydrazine for 6 months and in monkeys exposed to 0.2 ppm for 6 months.

- An MRL of $2x10^{-4}$ ppm has been derived for intermediate inhalation exposure to 1,1 -dimethylhydrazine. This MRL is based on a LOAEL of 0.05 ppm for hepatic effects (hyaline degeneration of the gall bladder) in female mice (Haun et al. 1984). In this study, female C57BL/6 mice were exposed for 6 months to 0, 0.05, 0.5, or 5 ppm l,l-dimethylhydrazine for 6 hours/day, 5 days/week. The MRL is supported by other studies in humans (Petersen et al. 1970; Shook and Cowart 1957), rats (Haun et al. 1984), and dogs (Haun 1977; Rinehart et al. 1960), which indicate that the liver is a target of 1,1-dimethylhydrazine after inhalation exposure.

No inhalation MRLs were derived for exposures to hydrazines for acute or chronic durations. Although data from animal studies indicate that inhalation exposures to hydrazines produce adverse effects on the liver and central nervous system following acute (Rinehart et al. 1960) and chronic exposures (Vemot et al. 1985), these studies do not define the threshold exposure level for these effects with confidence.

Oral MRLs

- An MRL of $8x10^{-4}$ mg/kg/day has been derived for intermediate oral exposure to 1,2-dimethylhydrazine. This MRL is based on a LOAEL of 0.75 mg/kg/day for mild hepatitis in mice (Visek et al. 1991). In this study, groups of 25 male mice were administered 0, 0.75, 1.6, or 2.7 mg/kg/day 1,2-dimethylhydrazine in the diet for 5 months. This MRL is supported by studies reporting LOAELs for hepatic effects ranging from 4.2-30 mg/kg/day 1,2-dimethylhydrazine in several other species, including rats (Bedell et al. 1992), guinea pigs (Wilson 1976), dogs (Wilson 1976), and pigs (Wilson 1976).

No oral MRLs were derived for exposures to hydrazine or for exposure to l,l-dimethylhydrazine for acute and chronic durations. Although data are available for neurological effects in humans after

intermediate-duration exposure to hydrazine (Chlebowski et al. 1984; Gershanovich et al. 1976, 1981; Ochoa et al. 1975; Spremulli et al. 1979), the effects levels were inconsistent among studies. Studies in animals have reported effects on the liver following acute-duration (Marshall et al. 1983; Wakabayashi et al. 1983; Wilson 1976) and intermediate-duration exposures (Biancifiori 1970). However, these data do not define the threshold dose for hepatic effects with confidence.

No acute-, intermediate-, or chronic-duration dermal MRLs were derived for hydrazines because of the lack of an appropriate methodology for the development of dermal MRLs.

Death. Data regarding the lethal effects of hydrazines in humans are limited to a single case study involving inhalation exposure to hydrazine. Death was reported in a male worker exposed to an undetermined concentration of hydrazine once a week for 6 months (Sotaniemi et al. 1971). Death in this case was due to lesions of the kidneys and lungs with complicating pneumonia. The effects on the kidneys and lungs, as well as effects in other tissues, were comparable to those observed in animals exposed to hydrazine. Therefore, death in this case is most likely attributed to hydrazine exposure.

A number of animal studies have reported acute lethality after exposure by most routes to hydrazines. For inhalation exposures, deaths were observed in dogs and mice after acute exposure to 25-140 ppm 1,1-dimethylhydrazine (Rinehart et al. 1960). No studies were located that examined lethality after acute-duration inhalation exposure to hydrazine or 1,2-dimethylhydrazine. For oral exposures, doses of 133 mg/kg hydrazine, 533 mg/kg/day 1,1-dimethylhydrazine, and 11.7-90 mg/kg 1,2-dimethylhydrazine caused deaths in mice and/or dogs (Roe et al. 1967; Visek et al. 1991; Wilson 1976). For dermal exposures, LD_{50} values ranging from 93 to 1,680 mg/kg were reported for all three hydrazines in rabbits and guinea pigs (Rothberg and Cope 1956). Deaths were noted in dogs after application of a single dose of 96 mg/kg hydrazine or 300 mg/kg 1,1-dimethylhydrazine (Smith and Clark 1971, 1972). A large number of studies have reported deaths in several animal species following injections of 8-400 mg/kg/day hydrazine (Bodansky 1923; Lee and Aleyassine 1970; O'Brien et al: 1964; Roberts and Simonsen 1966; Rothberg and Cope 1956; Wakebayashi et al. 1983), 71-125 mg/kg/day l,l-dimethylhydrazine (Back and Thomas 1962; Furst and Gustavson 1967; Geake et al. 1966; O'Brien et al. 1964; Rothberg and Cope 1956), and 44-60 mg/kg 1,2-dimethylhydrazine (Rothberg and Cope 1956; Wilson 1976). These doses are comparable to those producing death following oral exposure, suggesting that hydrazines are absorbed fairly well by the oral route. Limited information

from a single oral study suggests that male animals are more sensitive to the lethal effects of hydrazine than females (Visek et al. 1991).

A number of studies have reported increased mortality following exposure to hydrazines for intermediate durations. Following inhalation exposures, increased mortality was noted in mice and dogs exposed to 1 ppm hydrazine (Haun and Kinkead 1973), and in mice exposed to 75 ppm 1,1-dimethylhydrazine (Rinehart et al. 1960), but not in several species following intermediate exposure to 0.05-5 ppm l,l-dimethylhydrazine (Haun et al. 1984). Oral exposures of 2.3-4.9 mg/kg/day hydrazine (Biancifiori 1970), 33 mg/kg/day 1,1-dimethylhydrazine (Roe et al. 1967), and 4.5-60 mg/kg/day 1,2-dimethylhydrazine (Teague et al. 1981; Visek et al. 1991; Wilson 1976) caused deaths in a number of animal species. Increased mortality was observed in several animal species after injections of 20-21.8 mg/kg/day hydrazine (Bodansky 1923; Patrick and Back 1965), 30 mg/kg/day l,l-dimethylhydrazine (Comish and Hartung 1969), and 15-60 mg/kg/day 1,2-dimethylhydrazine (Wilson 1976).

Data regarding lethality effects in animals after chronic exposure to hydrazines are limited to two studies. Mortality was significantly increased in hamsters exposed to 0.25 ppm hydrazine in air for 1 year (Vernot et al. 1985), and in mice exposed to 0.95 mg/kg/day hydrazine via the drinking water (Toth and Patil 1982). These exposures are notably lower than those producing fatalities after acuteand intermediate-duration exposure to hydrazine.

Systemic Effects

Respiratory Effects. Pneumonia, tracheitis, and bronchitis were observed in a man occupationally exposed to an undetermined concentration of hydrazine in air once a week for 6 months (Sotaniemi et al. 1971). Dyspnea and pulmonary edema were observed in two men exposed to a mixture of hydrazine and 1,1-dimethylhydrazine (Frierson 1965). Hyperplasia was observed in the lungs of rats and mice exposed to 0.05 ppm 1,1-dimethylhydrazine for 6 months (Haun et al. 1984). Lung irritation and damage has been noted in dogs after intermediate-duration exposure to 25 ppm l,l-dimethylhydrazine but not 5 ppm l,l-dimethylhydrazine (Rinehart et al. 1960). Similarly, pulmonary effects were observed in rats chronically exposed to 5 ppm hydrazine but not in mice chronically exposed to 1 ppm hydrazine (Vernot et al. 1985). Effects on the nasal mucosa, including inflammation, hyperplasia, and dysplasia were noted in mice chronically exposed to 5 ppm 1,1-dimethylhydrazine

(Haun et al. 1984). Pulmonary edema, congestion, and pneumonia were observed in rats injected with 20 mg/kg/day hydrazine but not in rats injected with 10 mg/kg/day hydrazine (Patrick and Back 1965). No adverse effects were observed in the lungs of mice exposed to 9.5 mg/kg/day hydrazine via the drinking water for 2 years (Steinhoff et al. 1990). These data suggest that effects on the lungs and upper respiratory tract are of concern primarily following inhalation exposures to hydrazines.

Cardiovascular Effects. Data regarding the cardiovascular effects of hydrazines in humans are limited to a single case study involving inhalation exposure to hydrazine. Intermittent exposure of a worker to an undetermined concentration of hydrazine in air for 6 months produced atria1 fibrillation, enlargement of the heart, and degeneration of heart muscle fibers (Sotaniemi et al. 1971). The findings from animal studies have been inconsistent. No adverse effects were noted on the cardiovascular system of dogs exposed to 25 ppm l,l-dimethylhydrazine or mice exposed to 1 ppm hydrazine for intermediate and chronic durations (Rinehart et al. 1960; Vernot et al. 1985). Mice exposed to 0.05-5 ppm l,l-dimethylhydrazine for 6 months to 1 year had abnormally dilated blood vessels (angiectesis) (Haun et al. 1984). Focal myocytolysis, fibrosis, and calcification of the heart were noted in mice receiving 1.6 mg/kg/day 1,2-dimethylhydrazine in the feed for 5 months (Visek et al. 1991). Slight accumulation of fat was observed in the myocardium of monkeys receiving 5 mg/kg/day hydrazine by intraperitoneal injection for l-4 weeks (Patrick and Back 1965). Changes in blood pressure were noted in dogs following a single injection of 100 mg/kg 1,1-dimethylhydrazine (Back and Thomas 1962). Cardiovascular effects were not observed in mice receiving 0.75 mg/kg/day 1,2-dimethylhydrazine (Visek et al. 1991). No adverse effects were observed in the hearts of rats injected with 20 mg/kg/day hydrazine for 5 weeks (Patrick and Back 1965) or in mice receiving 9.5 mg/kg/day hydrazine in the drinking water for 2 years (Steinhoff et al. 1990). The findings of the animal studies, although inconsistent, suggest that the cardiovascular effects observed in the human case study are related to hydrazine exposure.

Gastrointestinal Effects. Oral exposure to hydrazine has produced nausea and vomiting in human cancer patients. These effects could be due to direct irritation of the gastrointestinal tract but could also be due to effects on the central nervous system. Studies in animals generally have not reported effects on the gastrointestinal system following intermediate and chronic inhalation exposures to 25 ppm l,l-dimethylhydrazine (Rinehart et al. 1960) or 1 ppm hydrazine (Vernot et al. 1985). Similarly, chronic oral exposure to 9.5 mg/kg/day hydrazine were without effect on the gastrointestinal system of mice (Steinhoff et al. 1990). Proliferation, dysplasia, and hyperplasia of the colon mucosa

have been observed in rats orally exposed to 25 mg/kg 1,2-dimethylhydrazine or injected with 15-20 mg/kg 1,2-dimethylhydrazine (Caderni et al. 1991; Decaens et al. 1989; Wargovich et al. 1983). These effects are most likely precursors of carcinogenic lesions induced by 1,2-dimethylhydrazine in this tissue site. Although these data suggest that the gastrointestinal system is not a primary target of the noncarcinogenic effects of hydrazines, this is not certain, particularly for 1,2-dimethylhydrazine.

Hematological Effects. No studies were located regarding hematological effects in humans after exposure to hydrazines. Studies in dogs indicate that inhalation exposure for intermediate durations to relatively high concentrations of hydrazine (1-5 ppm), but not 1,1-dimethylhydrazine, produces anemia (Haun and Kinkead 1973; Haun et al. 1984; Rinehart et al. 1960). Signs of anemia were not observed in dogs exposed to 0.2 ppm hydrazine. Hematological effects (decreased thromboplastin generation time) were also noted in dogs exposed to a single dermal dose of 5 mmol/kg 11-dimethylhydrazine (Smith and Castaneda 1970). However, hematological effects have not been observed in other species. For example, rats, hamsters, and monkeys exposed to 1 ppm hydrazine or 5 ppm 1,1-dimethylhydrazine for 6 months (Haun and Kinkead 1973; Haun et al. 1984) and rats and monkeys injected with 10-50 mg/kg/day 1,1-dimethylhydrazine (Cornish and Hartung 1969; Patrick and Back 1965) did not exhibit any hematological effects. These data suggest that dogs may be particularly sensitive to the hematological effects of hydrazines. Currently, it is not known if dogs are good animal models for the hematological effects of hydrazines in humans; therefore, it is uncertain if this effect is of concern to humans exposed to hydrazines.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after exposure to hydrazines. Data in animals are limited to a single study. No adverse effects were observed in the muscle tissue of mice chronically exposed to 9.5 mg/kg/day hydrazine (Steinhoff et al. 1990). These data are too limited to determine if effects on the musculoskeletal system are of concern for humans exposed to hydrazines.

Hepatic Effects. Areas of focal necrosis and cell degeneration were noted in the liver of a worker exposed to an undetermined concentration of hydrazine in air once a week for 6 months (Sotaniemi et al. 1971). These effects on the liver, however, were not contributing factors in the worker's death. Elevated serum alanine aminotransferase activity, fatty degeneration, and a positive cephalin flocculation test were seen in workers exposed to 1,1-dimethylhydrazine (Petersen et al. 1970; Shook and Cowart 1957). A large number of studies in animals were located regarding the hepatotoxic

effects of hydrazines. Multiple effects on the liver (hemosiderosis, degeneration, fatty changes, elevated serum enzymes, hyperplasia) have been observed in a number of species following inhalation exposure to 0.25-5 ppm hydrazine (Haun and Kinkead 1973; Vernot et al. 1985) or 0.05-25 ppm 1,1-dimethylhydrazine (Haun 1977; Haun et al. 1984; Rinehart et al. 1960). Hepatotoxic effects (fatty changes, degeneration, necrosis, hemosiderosis, hepatitis, fibrosis) were also observed in animals following oral exposure to 4.9-650 mg/kg/day hydrazine (Biancifiori 1970; Marshall et al. 1983; Preece et al. 1992a; Wakabayashi et al. 1983) and 0.75-60 mg/kg/day 1,2-dimethylhydrazine (Bedell et al. 1982; Visek et al. 1991; Wilson 1976). Similar effects were observed in animals receiving injections of 5-45 mgfkg/day hydrazine (Bodansky 1923; Patrick and Back 1965; Reinhardt et al. 1965b; Warren et al. 1984) or 3-333 mg/kg/day 1,2-dimethylhydrazine (Dixon et al. 1975; Pozharisski et al. 1976; Wilson 1976). Species differences in sensitivity were noted in individual studies, but these were not consistently observed across studies. Although data are lacking on the hepatic effects of 1,2-dimethylhydrazine by the inhalation route and 1,1-dimethylhydrazine by the oral route, these data clearly indicate that the liver is an important target organ and that hepatic effects are of potential concern for humans exposed to hydrazines.

Renal Effects. Data regarding the renal effects of hydrazines in humans are limited to a single case study. This study reported severe renal effects (tubular necrosis, hemorrhaging, inflammation, discoloration, enlargement) in a worker after exposure to an undetermined concentration of hydrazine (Sotaniemi et al. 1971). The renal effects were a significant factor in the worker's death. Renal effects have been observed in several animal studies. Following inhalation exposure to 0.25 ppm hydrazine, mild effects were noted in the kidneys of hamsters (Vernot et al. 1985). Similarly, signs of mild renal toxicity were observed in rats and dogs injected with 16-64 mg/kg/day hydrazine (Dominguez et al. 1962; Van Stee 1965) or 50 mg/kg/day 1,1-dimethylhydrazine (Comish and Hartung 1969). More severe effects (nephritis) were noted in the kidneys of mice orally exposed to 1.6 mg/kg/day 1,2-dimethylhydrazine (Visek et al. 1991) and in dogs and monkeys injected with 20-28 mg/kg/day hydrazine (Bodansky 1923; Patrick and Back 1965). However, no effects were observed in the kidneys of dogs exposed to 25 ppm l,l-dimethylhydrazine by the inhalation route (Rinehart et al. 1960), in mice exposed to 0.75 mg/kg/day 1,2-dimethylhydrazine or 9.5 mg/kg/day hydrazine by the oral route (Steinhoff et al. 1990; Visek et al. 1991), or in rats injected with 20 mg/kg/day hydrazine (Patrick and Back 1965). These animal studies support the findings of the human case study and suggest that the kidney is an important target organ, at least following exposure to high doses of hydrazines.

Endocrine Effects. Mice exposed to hydrazine for 25 weeks exhibited degeneration of the adrenals, but no adverse effects in the thyroid, while exposed hamsters exhibited no effects in either organ (Biancifiori 1970). Overall, there is little evidence that the endocrine system is a major target of hydrazines.

Dermal Effects. Contact dermatitis has been observed in humans after dermal exposure to dilute solutions containing hydrazine (Hovding 1967; Suzuki and Ohkido 1979; Wrangsjo and Martensson 1986). Dermal effects (discoloration, irritation) and ocular effects (cornea1 swelling) were also observed in dogs, rabbits, and guinea pigs after dermal exposure to hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine (Rothberg and Cope 1956; Smith and Castaneda 1970; Smith and Clark 1971, 1972). However, by the oral route, no effects were observed in the skin of mice exposed to 9.5 mg/kg/day hydrazine (Steinhoff et al. 1990). These data indicate that direct contact with hydrazines causes irritation of the skin.

Ocular Effects. Conjunctivitis was consistently observed in a worker repeatedly exposed to an undetermined concentration of hydrazine (Sotaniemi et al. 1971). Eye irritation was noted in monkeys exposed to 1 ppm hydrazine in air but not in monkeys exposed to 0.2 ppm hydrazine (Haun and Kinkead 1973). Thus direct contact with hydrazine may cause irritation of the eyes.

Body Weight Effects. A large number of studies in animals exposed orally or by injection to hydrazines have reported decreased body weight gain. For example, oral exposure to 0.75-60 mg/kg/day 1,2-dimethylhydrazine (Barbolt and Abraham 1980; Visek et al. 1991; Wilson 1976), 5 mg/kg/day 1,1-dimethylhydrazine (Haun et al. 1984), or 9.5 mg/kg/day hydrazine (Steinhoff et al. 1990) decreased body weight gain in a number of animal species. Similarly, injection of 5-10 mg/kg/day hydrazine (Patrick and Back 1965), 10 mg/kg/day 1,1-dimethylhydrazine (Patrick and Back 1965), or 60 mg/kg/day 1,2-dimethylhydrazine (Wilson 1976) decreased animal body weight gain. These decreases in body weight gain are most likely due, at least in part, to decreased food intake. The decreased food intake may be due to taste aversion in feed studies; however; the appearance of this effect in animals exposed by other routes suggests that appetite may be decreased. Alternatively, decreases in body weight gain may be secondary to an underlying disease (e.g., cancer).

Immunological and Lymphoreticular Effects. Very little information is available regarding immunological and lymphoreticular effects of hydrazines. Several studies in humans indicate that dermal exposure to hydrazine produces contact dermatitis (Hovding 1967; Suzuki and Ohkich 1979; Wrangsjo and Martensson 1986). In addition, there are some data from case studies in humans which suggest that exposure to hydrazine and other hydrazine derivatives can produce a lupus erythematosuslike disease (Pereyo 1986; Reidenberg et al. 1983). However, this possibility warrants further investigation before firm conclusions can be made.

A single study in animals reported no effect in the splenic natural killer cell activity in rats orally exposed to 27.1 mg/kg/day 1,2-dimethylhydrazine (Locniskar et al. 1986). However, in mice injected with 75 mg/kg/day 1,1-dimethylhydrazine, a decreased T helper cell count was observed (Frazier et al. 1991). *In vitro* studies have reported that l,l-dimethylhydrazine induces immunomodulation (enhancing some immune functions while diminishing others) in mouse lymphocytes and splenocytes (Bauer et al. 1990; Frazier et al. 1992). These data are limited, but suggest that humans exposed to hydrazines may be at risk of developing immunological effects.

Neurological Effects. Neurological effects have been noted in humans after inhalation, oral, and dermal exposure to hydrazines. For inhalation exposure, these effects included nausea, vomiting, tremors, and impairment of cognitive functions (Richter et al. 1992; Sotaniemi et al. 1971). Neurological symptoms of nausea, vomiting, dizziness, excitement, lethargy, and neuritis have been reported in some cancer patients treated orally with 0.2-0.7 mg/kg/day hydrazine (Chlebowski et al. 1984; Gershanovich et al. 1976, 1981; Ochoa et al. 1975; Spremulli et al. 1979). Dermal exposure to hydrazine or l,l-dimethylhydrazine as a result of an industrial explosion produced narcosis, coma, and polyneuritis in two workers (Dhennin et al. 1988; Kirklin et al. 1976). Neurological effects (depression, seizures, convulsions, tremors, lethargy, behavioral changes) have also been observed in a number of animal species following inhalation exposure to 1 ppm hydrazine (Haun and Kinkead 1973), and 25-75 ppm l,l-dimethylhydrazine (Rinehart et al. 1960). Effects on the central nervous system were also observed in dogs after dermal exposure to 96-480 mg/kg hydrazine (Smith and Clark 1972) or 300-1,800 mg/kg l,l-dimethylhydrazine (Smith and Clark 1971). Similar neurological effects were noted in animals after injection of 16-350 mg/kg/day hydrazine (Floyd 1980; Mizuno et al. 1989; Patrick and Back 1965) or 4-125 mg/kg/day l,l-dimethylhydrazine (Furst and Gustavson 1967; Geake et al. 1966; Goff et al. 1967, 1970; Minard and Mushahwar 1966; O'Brien et al. 1964; Reynolds et al. 1964; Segerbo 1979; Stern-ran and Fairchild 1967). The studies in humans and animals

convincingly demonstrate that the central nervous system is a target for persons exposed to hydrazine or l,l-dimethylhydrazine. However, based on the mechanism by which hydrazine and l,l-dimethylhydrazine affect the central nervous system, neurological effects do not appear to be of concern for humans exposed to 1 ,2-dimethylhydrazine.

Reproductive Effects. Data regarding the reproductive effects of hydrazines are limited to a few animal studies. Reproductive effects (ovarian and testicular atrophy, endometrial inflammation, aspermatogenesis) were observed in hamsters exposed to 1-5 ppm hydrazine by the inhalation route (Vemot et al. 1985). The incidence of endometrial cysts was significantly elevated in female mice exposed to 0.05 ppm 1,1-dimethylhydrazine (Haun et al. 1984). Sperm abnormalities and decreased caudal epididymal sperm counts were noted in mice injected with 8 mg/kg/day hydrazine or 12.5-68.8 mg/kg/day 1,1-dimethylhydrazine (Wyrobek and London 1973). These effects were not observed in hamsters exposed to 0.25 ppm hydrazine by the inhalation route (Vemot et al. 1985) or in mice and hamsters exposed to 5.3-9.5 mg/kg/day hydrazine by the oral route (Biancifiori 1970). No studies were located regarding the reproductive effects of 1,2-dimethylhydrazine. In addition, no studies were located which investigated effects of hydrazines on reproductive function. Despite the inconsistency of the findings from animal studies, the serious nature of the reproductive effects observed in the positive studies makes them one of concern for humans exposed to hydrazine.

Developmental Effects. Signs of developmental toxicity or teratogenicity were not observed in hamsters exposed to a single dose of 166 mg/kg hydrazine or 68 mg/kg 1,2-dimethylhydrazine on day 12 of gestation (Schiller et al. 1979). Likewise, Keller et al. (1984) examined the effects of 1,l -dimethylhydrazine (10-60 mg/kg/day) and 1 ,2-dimethylhydrazine (2-10 mg/kg/day) given intra peritoneally to pregnant rats on days 6-15 of gestation, and found no dose-related teratogenic effects. Embryotoxicity, manifested as reduced fetal weight, occurred only in the animals treated with the highest dose levels of either chemical. However, in another study increased prenatal and perinatal mortality was reported in rats injected with 8 mg/kg/day hydrazine during gestation days 11-21 (Lee and Aleyassine 1970). The data in animals are inconsistent between routes of exposure and are too limited to permit firm conclusions regarding the potential for developmental effects in humans exposed to hydrazines.

Genotoxic Effects. No studies were located regarding genotoxic effects in humans after exposure to hydrazines. Studies regarding the genotoxic effects in animals after oral or injection exposure to hydrazines are summarized in Table 2-4, while in vitro studies are presented in Table 2-5. These findings are discussed below.

Data from *in vivo* studies indicate that hydrazines are alkylating agents. The methylation of tissue DNA was reported in animals exposed orally to hydrazine (Becker et al. 1981; Bosan et al. 1986) or by injection to hydrazine (Bosan et al. 1986; Quintero-Ruiz et al. 1981) or 1,2-dimethylhydrazine (Beranek et al. 1983; Bolognesi et al. 1988; Hawks and Magee 1974; Netto et al. 1992; Pozharisski et al. 1975; Rogers and Pegg 1977). The mechanism by which adducts are formed may involve the generation of reactive species (methyldiazanium ions or methyl free radicals) (Albano et al. 1989; August0 et al. 1985; Feinberg and Zedeck 1980; Netto et al. 1987, 1992). The formation of methyl adducts with DNA bases *in vivo* may be one of the mechanisms by which hydrazines have produced DNA damage (Parodi et al. 1981), gene mutations (Jacoby et al. 1991; Winton et al. 1990; Zeilmaker et al. 1991; Zijlstra and Vogel 1988), micronuclei (Albanese et al. 1988; Ashby and Mirkova 1987), and sister chromatid exchange (Couch et al. 1986; Neft and Conner 1989). *In vivo* studies on the genotoxicity of hydrazines have largely reported positive results, although hydrazine did not induce unscheduled DNA synthesis in mouse sperm cells (Sotomayor et al. 1982). In addition, 1,2-dimethylhydrazine failed to induce micronuclei in rat bone marrow cells, even though this effect has been observed in mouse bone marrow cells (Albanese et al. 1988; Ashby and Mirkova 1987).

A large number of in vitro studies have reported genotoxic effects for all three hydrazines. Hydrazines produced methyl adducts in DNA from human cells (Au&up et al. 1980a; Harris et al. 1977; Kumari et al. 1985) and in free DNA (Bosan et al. 1986; Lambert and Shank 1988), but adducts were not noted in Chinese hamster V79 cells (Boffa and Bolognesi 1986). Gene mutations have been observed in human teratoma cells (Oravec et al. 1986), mouse lymphoma cells (Rogers and Back 1981), and in several strains of bacteria (DeFlora and Mugnoli 1981; Kerklaan et al. 1983; Levi et al. 1986; Malaveille et al. 1983; Noda et al. 1986; Parodi et al. 1981; Sedgwick 1992; Wilpart et al. 1983). Other genotoxic effects observed in mammalian cells exposed to hydrazines include sister chromatid exchange (MacRae and Stich 1979), transformation (Kumari et al. 1985), and unscheduled DNA synthesis (Mori et al. 1988). The administration of 25 or 50 mg/kg hydrazine subcutaneously to neonatal rats was necrogenic to the liver (Leakakos and Shank 1994). Liver DNA isolated from these animals was shown to have site-specific damage in that one or more *Mspl* sites were lost or blocked.

TABLE 2-4. Genotoxicity of Hydrazines *In Vivo*

Species (test system)	End point	Results	Reference	Form
Mammalian cells:				
Rat liver and colon	DNA alkylation	+	Netto et al. 1992	12DMH
Rat liver and colon	DNA alkylation	+	Hawks and Magee 1974	12DMH
Rat liver and colon	DNA alkylation	+	Netto et al. 1992	12DMH
Rat liver	DNA alkylation	+	Bosan et al. 1986	H
Rat liver, colon, and kidney	DNA alkylation	+	Rogers and Pegg 1977	12DMH
Rat liver, kidney and intestines	DNA alkylation	+	Pozharisski et al. 1975	12DMH
Rat liver	DNA alkylation	+	Becker et al. 1981	H
Rat liver	DNA alkylation	+	Beranek et al. 1983	12DMH
Mouse liver	DNA alkylation	+	Quintero-Ruiz et al. 1981	HS
Mouse liver and colon	DNA alkylation	+	Hawks and Magee 1974	12DMH
Rat liver and colon	RNA alkylation	+	Kang 1994	12DMH
Rat liver, kidney, and colon	DNA damage	+	Bolognesi et al. 1988	12DMH
Mouse liver and lung	DNA damage	+	Parodi et al 1981	11DMH
Mouse liver and lung	DNA damage	+	Parodi et al 1981	12DMH
Mouse liver and lung	DNA damage	+	Parodi et al 1981	HH
Mouse lung, liver, and kidney	Decreased DNA content	+	D'Souza and Bhide 1975	HS
Mouse intestine	Gene mutation	+	Winton et al. 1990	12DMH
Rat colon	Gene mutation	+	Jacoby et al. 1991	12DMH
Rat colon	Gene mutation	+	Jacoby et al. 1991	12DMH
Rat colon	Gene mutation	+	Llor et al. 1991	12DMH
Mouse colon	Inhibition of DNA repair	+	Koval 1984	12DMH
Rat bone marrow	Micronuclei	-	Albanese et al. 1988	12DMH
Mouse bone marrow	Micronuclei	+	Albanese et al. 1988	12DMH
Mouse bone marrow	Micronuclei	+	Ashby and Mirkova 1987	12DMH
Mouse colon	Sister chromatid exchange	+	Couch et al. 1986	12DMH
Mouse bone marrow, lung, liver, and kidney	Sister chromatid exchange	+	Neft and Conner 1989	12DMH
Mouse blood and spleen lymphocytes	Sister chromatid exchange	+	Neft and Conner 1989	12DMH
Mouse sperm	Unscheduled DNA synthesis	–	Sotomayor et al. 1982	H
Mouse sperm	Dominant lethal mutation	–	Brusick and Matheson 1976	11DMH

TABLE 2-4. Genotoxicity of Hydrazines *In Vivo* (continued)

Species (test system)	End point	Results	Reference	Form
Nonmammalian cells:				
Drosophila melanogaster	Gene mutation	–	Zijlstra and Vogel 1988	11DMH
Drosophila melanogaster	Gene mutation	--	Zijlstra and Vogel 1988	12DMH
Host-mediated assays:				
Mouse	Gene mutation (*Escherichia coli*)	+	Zeilmaker et al. 1991	12DMH

-- = negative result; + = positive result

11DMH = 1,1-dimethylhydrazine; 12DMH = 1,2-dimethylhydrazine; DNA = deoxyribonucleic acid; H = hydrazine; HH = hydrazine hydrate; HS = hydrazine sulfate

TABLE 2-5. Genotoxicity of Hydrazines *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Salmonella typhimurium	Gene mutation	+	+	Parodi et al 1981	HH
S. Typhimurium	Gene mutation	+	+	DeFlora and Mugnoli 1981	HH
S. Typhimurium	Gene mutation	+	+	Wilpart et al. 1983	12DMH
S. Typhimurium	Gene mutation	No data	–	Pence 1985	12DMH
S. Typhimurium	Gene mutation	+	+	Parodi et al 1981	12DMH
S. Typhimurium	Gene mutation	+	–	Malaveille et al. 1983	12DMH
S. Typhimurium	Gene mutation	+	–	Kerklaan et al. 1983	12DMH
S. Typhimurium	Gene mutation	+	+	DeFlora and Mugnoli 1981	12DMH
S. Typhimurium	Gene mutation	+	+	DeFlora and Mugnoli 1981	11DMH
S. Typhimurium	Gene mutation	+	+	Parodi et al 1981	11DMH
S. Typhimurium	Gene mutation	–	–	Brusick and Matheson 1976	11DMH
Saccharomyas cerevisiae	Gene mutation	–	–	Brusick and Matheson 1976	11DMH
Photobacterium leiognathi	Gene mutation	No data	+	Levi et al. 1986	H
Escherichia coli	Gene mutation	+	No data	Noda et al. 1986	H
E. coli	Gene mutation	No data	+	Sedgwick 1992	12DMH
E. coli	Gene mutation	No data	+	Sedgwick 1992	11DMH
E. coli	Gene mutation	–	–	Brusick and Matheson 1976	11DMH
Mammalian cells:					
Human colon	DNA alkylation	No data	+	Autrup et al. 1980a	12DMH
Human bronchi	DNA alkylation	+	No data	Harris et al. 1977	12DMH
Human fibroblasts	DNA alkylation	No data	+	Kumari et al. 1985	12DMH
Human fibroblasts	DNA alkylation	No data	+	Kumari et al. 1985	11DMH
Human teratoma	Gene mutation	+	No data	Oravec et al. 1986	12DMH
Human fibroblasts	Transformation	No data	+	Kumari et al. 1985	12DMH
Human fibroblasts	Transformation	No data	+	Kumari et al. 1985	11DMH
V79 Chinese hamster	DNA alkylation	+	–	Boffa and Bolognesi 1986	12DMH
Mouse lymphoma	Gene mutation	No data	+	Rogers and Back 1981	H
Mouse lymphoma	Gene mutation	No data	+	Rogers and Back 1981	12DMH
Mouse lymphoma	Gene mutation	No data	+	Rogers and Back 1981	11DMH
Mouse lymphoma	Gene mutation	+	+	Brusick and Matheson 1976	11DMH

TABLE 2-5. Genotoxicity of Hydrazines *In Vitro* (continued)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Chinese hamster ovary	Sister chromatid exchange	No data	+	MacRae and Stich 1979	H
Chinese hamster ovary	Sister chromatid exchange	+	+	MacRae and Stich 1979	12DMH
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Mori et al. 1988	HS
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Mori et al. 1988	HH
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Mori et al. 1988	12DMH
Rat hepatocytes	Unscheduled DNA synthesis	No data	+	Mori et al. 1988	12DMH
Human diploid W1-38	Unscheduled DNA synthesis	–	(+)	Brusick and Matheson 1976	11DMH
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Mori et al. 1988	11DMH
Noncellular assays:					
Calf thymus DNA	DNA alkylation	+	–	Bosan et al. 1986	H
Calf thymus DNA	DNA alkylation	+	–	Lambert and Shank 1988	H
Plasmid DNA	DNA damage	No data	+	Yamamoto and Kawanishi 1991	H
Plasmid DNA	DNA damage	No data	+	Kawanishi and Yamamoto 1991	11DMH
Plasmid DNA	DNA damage	No data	+	Kawanishi and Yamamoto 1991	12DMH

– = negative result; + = positive result; (+) = weakly positive result

11DMH = 1,1-dimethylhydrazine; 12DMH = 1,2-dimethylhydrazine; DNA = deoxyribonucleic acid; H = hydrazine; HH = hydrazine hydrate; HS = hydrazine sulfate

In vitro studies regarding the genotoxic effects of hydrazines have generally reported positive results, with and without metabolic activation. Taken together with the *in vivo* studies discussed above, these data clearly indicate that all three forms of hydrazine are genotoxic.

Cancer. No significant increase in cancer mortality was observed in a single epidemiology study of workers exposed to hydrazine (Morris et al. 1995; Wald et al. 1984), or in a U.S. Public Health Service survey of tuberculosis patients with isoniazid (Glassroth et al. 1977), which is metabolized to hydrazine. However, a large number of studies in animals have reported increased tumor incidence following inhalation, oral, and parenteral exposures to hydrazines. Following inhalation exposures to 5 ppm hydrazine, increased nasal and thyroid tumor incidences were reported in mice and hamsters (Vemot et al. 1985). Tumors of the lung, nasal passageways, bone, pancreas, pituitary, blood vessels, liver, and thyroid, and leukemia were observed at an increased incidence in mice or rats exposed to 0.05-5 ppm 1,1-dimethylhydrazine (Haun et al. 1984). It is possible that some of the carcinogenic effects of impure grades of l,l-dimethylhydrazine may be attributable to the presence of dimethylnitrosamine, a potent carcinogen, as a contaminant (Haun 1977).

Following oral exposures, doses of 0.46-16.7 mg/kg/day hydrazine increased the incidence of liver, kidney, breast, and particularly lung tumors in several animal species (Bhide et al. 1976; Biancifiori 1970; Biancifiori and Ribacchi 1962; Biancifiori et al. 1964, 1966; Bosan et al. 1987; Maru and Bhide 1982; Roe et al. 1967; Yamamoto and Weisburger 1970). Oral exposure to 33 mg/kg/day l,l-dimethylhydrazine increased the incidence of lung tumors in mice (Roe et al. 1967). Multiple tumor types, but most notably colon and blood vessel tumors, were induced in several animal species exposed to oral doses of 0.059-30 mg/kg/day 1,2-dimethylhydrazine (Abraham et al. 1980; Asano and Pollard 1978; Barbolt and Abraham 1980; Bedell et al. 1982; Calvert et al. 1987; Izumi et al. 1979; Locniskar et al. 1986; Teague et al. 1981; Thorup et al. 1992; Toth and Patil 1982; Wilson 1976). Colon tumors were also induced after single oral doses of 15.8-30 mg/kg 1,2-dimethylhydrazine (Craven and DeRubertis 1992; Schiller et al. 1980; Watanabe et al. 1985).

A large number of studies have reported the carcinogenic effects of 1,2-dimethylhydrazine by the injection route. These studies have reported an induction of tumor types similar to those reported for oral exposure following single injections of 15-143 mg/kg 1,2-dimethylhydrazine (Barnes et al. 1983; Decaens et al. 1989; Fujii and Komano 1989; Glauert and Weeks 1989; Karkare et al. 1991; Sunter and Senior 1983; Toth et al. 1976; Wargovich et al. 1983) and repeated injections of 3-40 mg/kg/day

(Andrianopoulos et al. 1990; Barsoum et al. 1992; Decaens et al. 1989; Druckrey 1970; Hagihara et al. 1980; James et al. 1983; Nelson et al. 1992; Pozharisski et al. 1976; Shirai et al. 1983; Vinas-Salas et al. 1992). Peripheral nerve sheath tumors were observed in hamsters injected with 32.5 mg/kg/day 1,1l-dimethylhydrazine (Ernst et al. 1987).

Several government departments and regulatory offices have evaluated the evidence regarding the carcinogenicity of hydrazines. The Department of Health and Human Services has determined that hydrazine and 1,1-dimetbylhydrazine are reasonably anticipated to be carcinogens (NTP 1994). The International Agency for Research on Cancer has determined that hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are probably carcinogenic to humans (Group 2B) (IARC 1987). The EPA has determined that hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are probable human carcinogens (Group B2) (HEAST 1992; IRIS 1995). The American Conference of Governmental Industrial Hygienists (ACGIH) currently lists hydrazine and 1,1-dimethylhydrazine as suspected human carcinogens (ACGIH 1994a). However, it has recently been recommended that the listing of hydrazine be changed to that of animal carcinogen, not likely to cause cancer in humans under normal exposure conditions (ACGIH 1994b).

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAUNRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAWNRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g.g high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance

(e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to hydrazines are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by hydrazines are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, "Populations That Are Unusually Susceptible."

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Hydrazines

Methods exist for measuring the levels of hydrazines and their metabolites in the plasma of humans (Blair et al. 1985) and in tissues, urine, and expired air of animals (Alvarez de Laviada et al. 1987; Back et al. 1963; Dost et al. 1966; Fiala and Kulakis 1981; Fiala et al. 1976; Harbach and Swenberg 1981; Kaneo et al. 1984; Kang et al. 1988; Matsuyama et al. 1983; Preece et al. 1991; Reed et al. 1963; Springer et al. 1981). These studies have employed calorimetric, chromatographic; and nuclear magnetic resonance techniques. Such methods require the use of expensive equipment and skilled technicians, which may limit the availability of facilities capable of monitoring exposure on a routine basis. The levels of hydrazines or their metabolites in tissues and excreta cannot presently be used to quantify past exposures. The detection of hydrazines and some of their metabolites (for example, azomethane and azoxymethane from 1,2-dimethylhydrazine) is a fairly specific biomarker of exposure.

However, hydrazine is a metabolite of drugs such as isoniazid and hydralazine (Blair et al. 1985). Therefore, care must be taken to ensure that exposure to these drugs has not occurred. Other metabolites of hydrazines (for example, carbon dioxide and nitrogen) are endogenous to the body, and therefore, cannot be used as specific biomarkers of exposure.

2.6.2 Biomarkers Used to Characterize Effects Caused by Hydrazines

Effects on the liver are associated with exposure to hydrazines in humans (Sotaniemi et al. 1971) and animals (Haun and Kinkead 1973; Rinehart et al. 1960; Vemot et al. 1985; Wilson 1976). Therefore, assessment of serum transaminase activities may be useful in revealing liver damage in people exposed to hydrazines. Neurological effects are often observed following exposure to hydrazine and 1,1-dimethylhydrazine in humans (Chlebowski et al. 1984; Gershanovich et al. 1976; Ochoa et al. 1975; Richter et al. 1992; Sotaniemi et al. 1971) and animals (Haun and Kinkead 1973; Rinehart et al. 1960). The mechanism by which hydrazine and l,l-dimethylhydrazine produce neurological effects involves binding to vitamin B_6 derivatives. Therefore, assessment of vitamin B_6 status either by direct measurement in the blood, tryptophan load tests, or measurements of vitamin B_6 -dependent activities in plasma or erythrocytes may serve to indicate if vitamin B6 status has been compromised by hydrazine or 1,1-dimethylhydrazine.

DNA adducts have been observed in animals exposed to hydrazines *in vivo* (Becker et al. 1991; Beranek et al. 1983; Bolognesi et al. 1988; Bosan et al. 1986; Netto et al. 1992; Pozharisski et al. 1975; Quintero-Ruiz et al. 1981; Rogers and Pegg 1977). RNA base adducts have also been observed in liver and colon after treatment of rats with 1,2-dimethylhydrazine (Hawks and Magee 1974; Kang 1994). However, these are somewhat difficult to detect and quantitate, and therefore, may not be useful as biomarkers of effect. An increased incidence of colon tumors is the most consistent effect observed following exposure to 1,2-dimethylhydrazine in animals (Abraham et al. 1980; Asano and Pollard 1978; Barbolt and Abraham 1980; Calvert et al. 1987; Izumi et al. 1979; Locniskar et al. 1986; Teague et al. 1981; Thorup et al. 1992; Wilson 1976). Simple tests for occult blood in the stools can be used as a preliminary screen for intestinal tumors. However, these types of effects can be caused by exposures to a large number of agents, and in no way are these biomarkers specific for the effects of hydrazines.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

No studies were located regarding interactions in humans or animals after exposure to hydrazine or 1,1-dimethylhydrazine. On the other hand, a large number of studies are available in animals regarding the interactions of various treatments on 1,2-dimethylhydrazine-induced colon cancer. For example, high-fat diets, high-cholesterol diets, potassium chloride, caffeine, vitamin C, iron, ethoxyquin, and colorectal surgery were all found to increase the incidence, multiplicity, or malignancy of 1,2-dimethylhydrazine-induced intestinal tumors (Balansky et al. 1992; Bansal et al. 1978; Cruse et al. 1982; Locniskar et al. 1986; Nelson et al. 1992; Shirai et al. 1985; Siegers et al. 1992), whereas aspirin, bran, pectin, calcium, vitamin D, vitamin E, carbon tetrachloride, carbon disulfide, sodium selenate, butylated hydroxytoluene, corn oil, and calcium chloride were all found to decrease the incidence of these tumors (Balansky et al. 1992; Barnes et al. 1983; Barsoum et al. 1992; Belleli et al. 1992; Culvert et al. 1987; Colacchio et al. 1989; Craven and DeRubertis 1992; Heitman et al. 1992; Shirai et al. 1985). Other studies have reported that bran, beta-carotene, butylated hydroxyanisole, propyl gallate, and stress had no significant effect on tumors of the colon induced by 1,2-dimethylhydrazine (Andrianopoulos et al. 1990; Barbolt and Abraham 1980; Colacchio et al. 1989; Shirai et al. 1985; Thorup et al. 1992). A number of mechanisms are possible for these interactions including but not limited to interference with the metabolism of 1,2-dimethylhydrazine (Fiala et al. 1977), action as a scavenger for free radicals produced during 1,2-dimethylhydrazine metabolism, and influences at the post-initiation stage of colon carcinogenesis.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hydrazines than will most persons exposed to the same level of hydrazines in the environment. Reasons include genetic makeup, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than

healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

Data from a single human study indicate that people with a slow acetylator genotype may be unusually susceptible to the effects of hydrazine. A pronounced accumulation of hydrazine was noted in the plasma of slow acetylator patients treated with isoniazid compared to those patients that were rapid acetylators (Blair et al. 1985). With 1,1-dimethylhydrazine, similar results may be observed. However, no information is available on humans for 1,1-dimethylhydrazine. Further investigation of this mechanism is warranted.

In animals, a number of studies have reported differences in susceptibility to the toxic effects of hydrazines with respect to species (Haun and Kinkead 1973; Rinehart et al. 1960; Vernot et al. 1985; Wilson 1976), strain (Asano and Pollard 1978; Bhide et al. 1976; Teague et al. 1981; Toth 1969), sex (Bhide et al. 1976; Biancifiori 1970; Teague et al. 1981; Visek et al. 1991), and age (Wakabayashi et al. 1983). Some of the differences in susceptibility may be related to differences in ability to metabolize hydrazines; however, many other differences still lack a satisfactory explanation.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

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

2.9.1 Reducing Peak Absorption Following Exposure

No data were located regarding methods for reducing absorption after inhalation exposure to hydrazines.

There are several methods by which the absorption of hydrazines can be reduced in the gastrointestinal tract. Induced emesis, gastric lavage, use of saline cathartics, or activated charcoal are all methods which are commonly used to decrease the gastrointestinal absorption of compounds such as hydrazines

(Bronstein and Currance 1988; Sittig 1991; Stutz and Janusz 1988). In general, these treatments are most effective when used within a few hours after oral exposure. In some cases, these treatments may be contraindicated. For example, some authors contend that emesis should not be induced (Bronstein and Currance 1988). In addition, emesis should not be induced in obtunded, comatose, or convulsing patients. Oils should not be used as a cathartic, since they may enhance the gastrointestinal absorption of hydrazines.

Following dermal or ocular exposures to hydrazines, there are several methods by which absorption can be reduced. All contaminated clothing should be removed, and contacted skin should be washed immediately with soap and water (Bronstein and Currance 1988; Haddad and Winchester 1990; Sittig 1991; Stutz and Janusz 1988). Eyes that have come in contact with hydrazines should be flushed with copious amounts of water. Contact lenses should be removed prior to flushing with water. Proparacaine hydrochloride may be used to assist eye irrigation (Bronstein and Currance 1988).

2.9.2 Reducing Body Burden

Elimination of hydrazines in the urine may be enhanced by forced diuresis and acidification of the urine (Haddad and Winchester 1990). Hemodialysis and peritoneal dialysis may also be helpful, but this has not been fully studied. Activated charcoal is sometimes administered in serial doses to minimize the enterohepatic recirculation of persistent chemicals. Data regarding the enterohepatic recirculation of hydrazines were not located. However, available data suggest that hydrazines are readily cleared from the body since the levels in various tissues in animals are usually not detectable after 24 hours. In addition, studies in rats indicate that only a small percentage of a dose of 1,2-dimethylhydrazine (0.4-0.9%) is excreted in the bile (Hawks and Magee 1974). Therefore, it is not likely that efforts to minimize enterohepatic recirculation of hydrazines would be of much use.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

There are at least two distinct mechanisms by which hydrazines produce adverse health effects. Methods for interfering with these mechanisms are discussed below. The first mechanism involves the reaction of hydrazine or 1,1-dimethylhydrazine with endogenous alpha-keto acids such as vitamin B, (pyridoxine). The formation of hydrazones of pyridoxine is the proposed mechanism by which hydrazine and 1,1-dimethylhydrazine produce neurological effects. Several studies have reported

successful treatment of neurological effects in humans exposed to hydrazine and 1,1-dimethylhydrazine with pyridoxine (Dhennin et al. 1988; Ellenhorn and Barceloux 1988; Haddad and Winchester 1990; Kirklin et al. 1976). In addition, several animal studies reported that pyridoxine diminished, and in some cases completely abolished, the lethal and neurological effects of hydrazine and 1,1-dimethylhydrazine (Geake et al. 1966; Lee and Aleyassine 1970; O'Brien et al. 1964; Segerbo 1979).

However, treatment with pyridoxine is not without risk. For example, some authors suggested that pyridoxine is also capable of producing neuropathy (Harati and Niakan 1986). This effect has been noted in humans exposed to hydrazines and treated with pyridoxine (Dhennin et al. 1988; Harati and Niakan 1986; Ochoa et al. 1975), but it is difficult to ascribe this effect to exposure to either hydrazines or pyridoxine alone. It is possible that the adverse effects of pyridoxine treatment may be associated with treatments using large doses. Evidence of a therapeutic window has been reported in animal studies (Geake et al. 1966). Studies in animals have also reported that the hydrazones of pyridoxine are more toxic than the corresponding hydrazine (Furst and Gustavson 1967). These data indicate that pyridoxine should be used with caution and that all potential risks and benefits should be considered prior to treatment. In any case, treatment with pyridoxine would not be expected to be beneficial for exposures to 1,2-dimethylhydrazine since this compound, unlike hydrazine and 1,1-dimethylhydrazine, does not form hydrazones.

The second mechanism by which hydrazines produce adverse health effects involves the generation of free radical intermediates. Free radicals have been detected during the metabolism of hydrazines in *vitro* (Albano et al. 1989; Augusto et al. 1985; Ito et al. 1992; Netto et al. 1987; Noda et al. 1988; Runge-Morris et al. 1988; Sinha 1987; Tomasi et al. 1987). Therefore, treatment with agents that act as free radical scavengers could offer a protective effect. *In vitro* studies have shown that glutathione is an effective scavenger of the free radicals produced from the metabolism of 1,1-dimethylhydrazine and 1,2-dimethylhydrazine (Tomasi et al. 1987). A number of animal studies have reported that aspirin, vitamin C, vitamin E, and butylated hydroxytoluene decreased the incidence, multiplicity, or malignancy of 1,2-dimethylhydrazine-induced intestinal tumors (Belleli et al. 1992; Colacchio et al. 1989; Cook and McNamara 1980; Craven and DeRubertis 1992; Shirai et al. 1985). It is possible that this protective effect may occur via inhibition of metabolic activation or a free radical scavenging mechanism, and if so, treatment would be most effective if administered relatively soon after exposure; however, the mechanism is not known conclusively and warrants further investigation.

Since reactive intermediates are produced as a result of the metabolism of hydrazines, the administration of inhibitors of the cytochrome P-450 or the flavin-containing monooxygenase system may offer some protective effect. For example, disulfiram, an inhibitor of cytochrome P45011E1 (Guengerich et al. 1991), decreased the oxidation of azomethane (a metabolite of 1,2-dimethylhydrazine) to azoxymethane, and the further oxidation of azoxymethane to methylazoxymethanol (Fiala et al. 1977). The inhibition of the activation pathway of 1,2-dimethylhydrazine by disulfiram resulted in decreased DNA methylation in the liver and colon of rats (Swenberg et al. 1979), and inhibition of l,2-dimethylhydrazine-induced colon carcinogenesis (Wattenberg 1975). Although disulfiram is a toxic compound which is known to inhibit other enzyme systems, it has been used in humans as an alcohol deterrent (Ellenhorn and Barceloux 1988). In cases of significant exposure to 1,2-dimethylhydrazine, the potential benefits of disulfiram in preventing colon cancer may outweigh the potential risk of adverse toxic effects.

2.10 ADEQUACY OF THE DATABASE

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

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

2.10.1 Existing Information on Health Effects of Hydrazines

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hydrazines are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of hydrazines. Each dot in the figure indicates that one or

more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

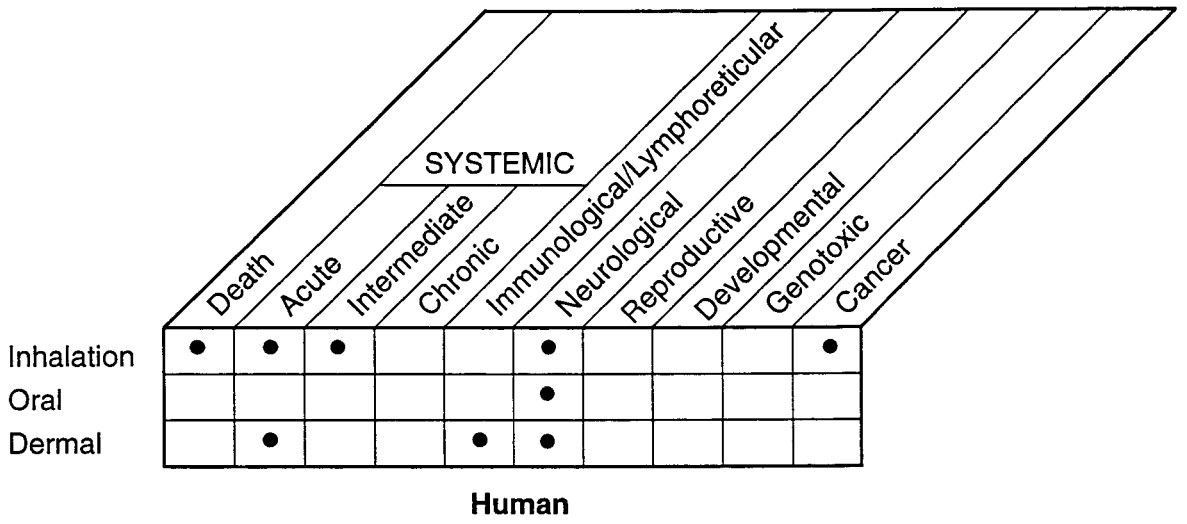
As shown in Figure 2-3, data are available in humans regarding lethal, neurological, and carcinogenic effects after inhalation exposure to hydrazines. Data are also available for the systemic effects observed in humans exposed to hydrazines by the inhalation route for intermediate durations. By the oral route, information is only available for the neurological effects in humans exposed to hydrazines. Acute systemic, immunological, and neurological effects have been reported in humans after dermal exposure to hydrazines.

Considerably more information on the health effects of hydrazines is available from animal studies. These are data for all effect categories from animal studies for oral exposure to hydrazines. The lethal, neurological, reproductive, carcinogenic, and systemic effects for all exposure durations are available from studies in animals exposed to hydrazines by the inhalation route. For dermal exposures to hydrazines, animal data are available regarding the lethal, neurological, and acute systemic effects.

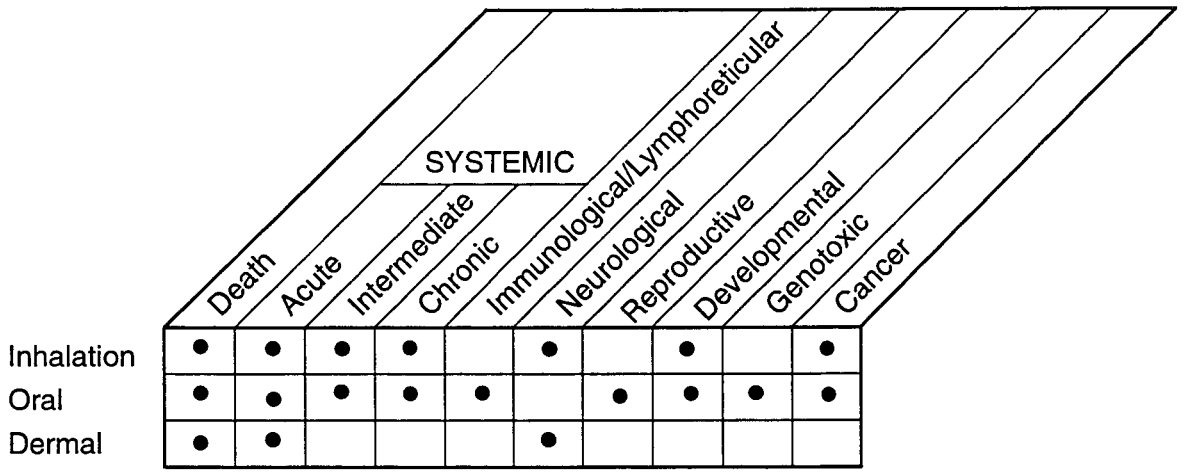
2.10.2 Identification of Data Needs

Acute-Duration Exposure. Data are available for the acute toxicity of hydrazine in humans after inhalation and dermal exposures, and in several animal species after oral and dermal exposures. Although a human case study suggests neurological effects are of concern following inhalation exposure to hydrazine (Frierson 1965), quantitative data are not available for the acute toxicity of hydrazine after inhalation exposure. Data from animal studies (rats, dogs) indicate that the liver is the primary target organ after oral exposures (Marshall et al. 1983; Preece et al. 1992a; Wakabayashi et al 1983), and that the skin is the most sensitive target in humans and animals (rabbits, guinea pigs, dogs) following dermal exposures (Hovding 1967; Suzuki and Ohkido 1979). These data do not sufficiently define the threshold dose for these effects and do not support the derivation of an MRL.

FIGURE 2-3. Existing Information on Health Effects of Hydrazines



Human



Animal

● Existing Studies

Data are available for the acute toxicity of 1,1-dimethylhydrazine after inhalation exposure in humans, and inhalation, oral, and dermal exposures in animals. A human case study suggests that neurological effects are of concern following acute inhalation exposure to 1,1-dimethylhydrazine (Frierson 1965). Data from a study in dogs indicate that the central nervous system is affected following inhalation of 1,1-dimethylhydrazine (Rinehart et al. 1960). This finding is supported by data in rats, mice, cats, and monkeys acutely exposed to 1,1-dimethylhydrazine by injection (Furst and Gustavson 1967; Furst et al. 1969; Geake et al. 1966; Goff et al. 1967, 1970; Minard and Mushahwar 1966; O'Brien et al. 1964; Reynolds et al. 1963, 1964; Segerbo 1979; Sterman and Fairchild 1967). Data regarding the effects of acute oral exposure to 1,1-dimethylhydrazine are limited to a lethality study in mice (Roe et al. 1967). Animal studies (rabbits, dogs) have reported hematological and ocular effects following dermal exposure to 1,1-dimethylhydrazine (Rothberg and Cope 1956; Smith and Castaneda 1970; Smith and Clark 1971). These studies do not define the threshold for effect with confidence, and do not support the derivation of an MRL.

Data are available for the acute toxicity of 1,2-dimethylhydrazine in animals after acute oral and dermal exposures. No human studies were located regarding the acute toxicity of 1,2-dimethylhydrazine. Two studies in rats and dogs were located which reported effects on the colon, liver, and body weight after oral exposure (Caderni et al. 1991; Wilson 1976). Studies in rabbits and guinea pigs indicate that acute dermal exposure to 1,2-dimethylhydrazine can produce irritation and death (Rothberg and Cope 1956). These studies do not define the effect level for 1,2-dimethylhydrazine with confidence and do not support the derivation of an MRL. Studies are also available on the carcinogenic effects of 1,2-dimethylhydrazine after acute oral exposure (Craven and DeRubertis 1992; Schiller et al. 1980; Watanabe et al. 1985). No animal studies were located regarding the effects of acute inhalation exposure to 1,2-dimethylhydrazine.

Additional animal studies to investigate the acute effects of hydrazines after inhalation, oral, and dermal exposures would better define the threshold dose for adverse health effects. Such studies would be useful in predicting adverse health effects in humans following acute exposures.

Intermediate-Duration Exposure. Data are available on the toxicity of hydrazine and 1,1-dimethylhydrazine in humans and several animal species after intermediate-duration exposure by the inhalation and oral routes. These studies reported effects on the central nervous system in humans following oral exposure (Chlebowski et al. 1984; Gershanovich et al. 1976, 1981; Ochoa et al. 1975)

and in animals (rats, mice, dogs) after inhalation exposure (Haun and Kinkead 1973), and effects on the liver in animals (mice, dogs, monkeys, rats) after inhalation exposure (Biancifiori 1970; Haun and Kinkead 1973; Haun et al. 1984; Rinehart et al. 1960). The data were sufficient to support the derivation of inhalation MRLs of $4x10^{-3}$ ppm for hydrazine and $2X10^{-4}$ ppm for 1,1-dimethylhydrazine based on hepatic effects. No data were located regarding the toxicity of hydrazine or l,l-dimethylhydrazine following dermal exposure for an intermediate duration. Studies are also available for the carcinogenic effects of hydrazine and 1,1-dimethylhydrazine after intermediate duration exposures (Haun et al. 1984; Roe et al. 1967).

No studies were located regarding the toxicity of 1,2-dimethylhydrazine in humans after intermediate duration exposure. Data on the toxicity of 1,2-dimethylhydrazine in animals after intermediateduration exposure are limited to those regarding the oral route. These studies have generally reported hepatic effects in rats, guinea pigs, mice, and pigs (Bedell et al. 1982; Visek et al. 1991; Wilson 1976), and support the derivation of an intermediate oral MRL of $8X10^{-4}$ mg/kg/day for 1,2-dimethylhydrazine. In addition, a large number of studies report the carcinogenic effects of 1,2-dimethylhydrazine after intermediate exposures (Izumi et al. 1979; Teague et al. 1981; Wilson 1976).

Additional studies in animals to investigate the effects of hydrazines after intermediate-duration inhalation, oral, and dermal exposures would better define the threshold dose for adverse health effects. Such studies would be useful in predicting adverse health effects in humans exposed for intermediate-durations to hydrazines.

Chronic-Duration Exposure and Cancer. Data are available on the toxicity of hydrazine and l,l-dimethylhydrazine in animals after chronic-duration exposure by the inhalation and oral routes. Effects on the liver, lung, and body weight gain are the most consistent findings observed in rats, mice, dogs, and hamsters (Haun et al. 1984; Steinhoff et al. 1990; Vernot et al. 1985). However, these studies do not define the threshold dose level for these effects with confidence, and therefore do not support the derivation of an MRL. Data regarding the noncarcinogenic effects of 1,2-dimethylhydrazine after chronic exposures are largely lacking. Additional studies which investigate the effects of hydrazines in animals after chronic inhalation, oral, and dermal exposures would help define the threshold dose for adverse health effects. Such studies would be useful in predicting adverse health effects in humans chronically exposed to hydrazines.

As discussed in the previous sections, hydrazines can cause cancer in animals following acute- or intermediate-duration exposure by the oral and inhalation route. In addition, several studies reported carcinogenic effects in a number of animal species exposed to hydrazine (Bhide et al. 1976; Bosan et al. 1987; Maru and Bhide 1982; Toth 1969, 1972b; Vernot et al. 1985), 1,1-dimethylhydrazine (Haun et al. 1984; Toth 1973a), and 1,2-dimethylhydrazine (Toth and Patil 1982), following chronic oral and inhalation exposures. These studies demonstrate that hydrazines are carcinogenic in animals following chronic oral and inhalation exposures. Epidemiological studies which investigate the carcinogenic effects in humans exposed occupationally or therapeutically to hydrazine would confirm whether or not the cancer effects observed in animal studies also occur in humans.

Genotoxicity. Data regarding the genotoxicity of hydrazines in humans are not available. A large number of studies are available that report the genotoxic effects of hydrazines in animals *in vivo* (Albanese et al. 1988; Ashby and Mirkova 1987; Becker et al. 1981; Beranek et al. 1983; Bolognesi et al. 1988; Bosan et al. 1986; Couch et al. 1986; Jacoby et al. 1991; Netto et al. 1992; Parodi et al. 1981; Pozharisski et al. 1975; Quintero-Ruiz et al. 1981; Winton et al. 1990; Zeilmaker et al. 1991; Zijlstra and Vogel 1988) and in a number of cell lines *in vitro* (Autrup et al. 1980a; Bosan et al. 1986; DeFlora and Mugnoli 1981; Harris et al. 1977; Kerklaan et al. 1983; Kumari et al. 1985; Lambert and Shank 1988; Levi et al. 1986; Malaveille et al. 1983; Noda et al. 1986; Oravec et al. 1986; Parodi et al. 1981; Rogers and Back 1981; Sedgwick 1992; Wilpart et al. 1983). These studies convincingly demonstrate that all three hydrazines are genotoxic. Additional genotoxicity studies in humans exposed to hydrazines, either occupationally or therapeutically would determine whether or not the effects observed in animals and in cells are also observed in humans.

Reproductive Toxicity. Data regarding the reproductive toxicity of hydrazines in humans are not available. Data regarding the reproductive effects of hydrazines are limited to a few animal studies regarding inhalation, oral, and parenteral exposure to hydrazine (Biancifiori 1970; Vernot et al. 1985; Wyrobek and London 1973) and inhalation exposure to 1,1-dimethylhydrazine (Haun et al. 1984). The serious nature of the effects caused by the inhalation of hydrazines suggests they may be of concern in humans similarly exposed. Studies that investigate the reproductive effects of 1,2-dimethylhydrazine, hydrazine, and 1,1-dimethylhydrazine, particularly those which also evaluate reproductive function over several generations, would be valuable in determining if the reproductive system is adversely affected in humans exposed to hydrazines.

Developmental Toxicity. Data regarding the developmental toxicity of hydrazines in humans are not available. Data regarding the developmental effects of hydrazines in animals are limited to a study which reported increased fetal and neonatal mortality following exposure to hydrazine by the parenteral route (Lee and Aleyassine 1970). No apparent developmental effects were seen after oral exposure of pregnant hamsters to 1,2-dimethylhydrazine dihydrochloride (Schiller et al. 1979). Studies that investigate the developmental effects of 1,1-dimethylhydrazine for any exposure route, as well as studies that better define the dose-response relationship for the developmental effects of hydrazine and 1,2-dimethylhydrazine for any exposure route, would be useful in determining whether developmental effects are of concern in humans exposed to hydrazines.

Immunotoxicity. The data regarding the immunological effects of hydrazines are limited. There is some suggestive evidence from human studies that exposure to hydrazine and other hydrazine derivatives can produce a lupus erythematosus-like disease (Pereyo 1986; Reidenberg et al. 1983). Data in animals reported immunological effects in mice with parenteral exposure to 1,1-dimethylhydrazine (Frazier et al. 1991) but not in rats with oral exposure to 1,2-dimethylhydrazine (Locniskar et al. 1986). In vitro studies suggest 1,1-dimethylhydrazine produces immunomodulatory effects (Bauer et al. 1990; Frazier et al. 1992). Additional case studies in humans and studies in animals which better define the dose-response relationship for the immunological effects of all three hydrazines would help determine if these effects are of concern to humans exposed to hydrazines.

Neurotoxicity. Data are available for the neurological effects of hydrazines in humans following inhalation, oral, and dermal exposures to hydrazine (Chlebowski et al. 1984; Gershanovich et al. 1976, 1981; Haun and Kinkead 1973; Ochoa et al. 1975; Richter et al. 1992; Sotaniemi et al. 1971; Spremulli et al. 1979) and 1,1-dimethylhydrazine (Dhennin et al. 1988; Kirklin et al. 1976; Rinehart et al. 1960). Effects on the central nervous system were also observed in animals following dermal and parenteral exposures to hydrazine (Floyd 1980; Mizuno et al. 1989; Patrick and Back 1965; Smith and Clark 1972) and 1,1-dimethylhydrazine (Furst and Gustavson 1967; Geake et al. 1966; Goff et al. 1970; Minard and Mushahwar 1966; O'Brien et al. 1964; Reynolds et al. 1964; Segerbo 1979; Smith and Clark 1971). Although these studies convincingly demonstrate that the central nervous system is a primary target of hydrazine and 1,1-dimethylhydrazine, these data do not define the threshold dose and more fully characterize neurological effects with confidence. Additional studies which better define the threshold dose for the neurological effects of hydrazine and l,l-dimethylhydrazine would be useful in determining the risk of neurological effects in humans exposed to these hydrazines. Preliminary

neurological screening studies on 1,2-dimethylhydrazine in animals may determine if neurological effects are of concern for humans exposed to this chemical.

Epidemiological and Human Dosimetry Studies. Only one epidemiological study was located regarding the effects of hydrazine. This study showed no significant increase in cancer mortality in 427 hydrazine workers (Wald et al. 1984). However, the number of deaths examined was relatively small and the follow-up period may not have been sufficient for detecting a weak carcinogenic effect. Additional epidemiological studies investigating the neurological, hepatic, renal, and carcinogenic effects of hydrazines, particularly studies which also provide quantitative information on exposure, would be valuable in estimating the risk of adverse health effects in persons exposed to hydrazines in the workplace or therapeutically.

Biomarkers of Exposure and Effect

Exposure. Methods are available for determining the levels of hydrazine in the plasma of humans (Blair et al. 1985), and the levels of all three hydrazines and their metabolites and in tissues, urine, and expired air of animals (Alvarez de Laviada et al. 1987; Back et al. 1963; Dost et al. 1966; Fiala et al. 1976; Harbach and Swenberg 1981; Kaneo et al. 1984; Kang et al. 1988; Matsuyama et al. 1983; Preece et al. 1991; Reed et al. 1963; Springer et al. 1981). The detection of hydrazines and some of their metabolites (for example, the metabolites of 1,2-dimethylhydrazine-azoxymethane and methylazoxymethanol) are fairly specific for exposures to hydrazines. However, it should be kept in mind that treatment with certain drugs such as isoniazid or hydralazine can result in the presence of hydrazine in human plasma (Blair et al. 1985); therefore, care should be taken to ensure subjects have not been exposed to these drugs. Other metabolites of hydrazines (for example, carbon dioxide and nitrogen) are endogenous to the body, and therefore, cannot be used as specific biomarkers of exposure. Studies which investigate the quantitative relationship between exposure intensity, time since exposure, and the levels of hydrazines or their unique metabolites detected in biological samples, particularly in the urine, would be useful for estimating human exposures to hydrazines: Studies that identify biomarkers of exposure that are specific to 1,1-dimethylhydrazine and hydrazine could lead to the development of a reliable method for estimating recent exposures to hydrazines.

Effect. Exposure to hydrazine and 1,1-dimethylhydrazine is associated with the development of neurological and hepatic effects in humans (Chlebowski et al. 1984; Gershanovich et al. 1976; Ochoa

et al. 1975; Richter et al. 1992; Sotaniemi et al. 1971) and animals (Haun and Kinkead 1973; Rinehart et al. 1960; Vernot et al. 1985; Wilson 1976). Studies which investigate if serum transaminase levels or vitamin B_6 status could be used to predict effects of hydrazines could be useful, if they are coupled with confirmed exposures to hydrazines. The carcinogenic effects of hydrazines have also been amply demonstrated in animal studies (Abraham et al. 1980; Asano and Pollard 1978; Barbolt and Abraham 1980; Calvert et al. 1987; Izumi et al. 1979; Locniskar et al. 1986; Teague et al. 1981; Thorup et al. 1992; Wilson 1976). Studies which investigate if tests for occult blood in stools could be used to predict intestinal tumors induced by 1,2 dimethylhydrazine could be useful. However, the etiology of colon cancer is multifactional and may not be related to exposures to 1,2-dimethylhydrazine. Studies which identify biomarkers of effect that are specific to exposures to hydrazines could lead to the development of a reliable method for predicting past exposures to hydrazines.

Absorption, Distribution, Metabolism, and Excretion. Data regarding the toxicokinetics of hydrazines are limited to in vitro metabolic assays (Albano et al. 1989; August0 et al. 1985; Coomes and Prough 1983; Craven et al. 1985; Erikson and Prough 1986; Glauert and Bennink 1983; Godoy et al. 1983; Netto et al. 1987; Newaz et al. 1983; Noda et al. 1987, 1988; Prough 1973; Prough et al. 1981; Sheth-Desai et al. 1987; Sinha 1987; Timbre11 et al. 1982; Tomasi et al. 1987; Wolter et al. 1984) and *in vivo* studies in rats exposed via inhalation (Llewellyn et al. 1986), rats exposed orally (Preece et al. 1992b), dogs exposed dermally (Smith and Clark 1971, 1972), and in several species exposed by parenteral routes (Back et al. 1963; Dost et al. 1966; Fiala et al. 1976; Harbach and Swenberg 1981; Kaneo et al. 1984; Mitz et al. 1962; Reed et al. 1963; Springer et al. 1981). These studies invariably employed a single radiolabel (either 14C or i5N), and therefore, in the case of l,l-dimethylhydrazine and 1,2-dimethylhydrazine, the metabolic fate data (expressed as a carbon or nitrogen dose) were often incomplete. Studies which investigate the toxicokinetics of hydrazines for all routes and durations, particularly those which employ both a carbon and nitrogen label, would enhance the current understanding of the metabolic fate of hydrazines in humans exposed at hazardous waste sites.

Comparative Toxicokinetics. Studies in humans (Dhennin et al. 1988; Kirklin et al. 1976; Sotaniemi et al. 1971) and several animal species (Biancifiori 1970; Haun and Kinkead 1973; Marshall et al. 1983; Rinehart et al. 1960; Vernot et al. 1985; Wakabayashi et al. 1983) indicate that the liver and central nervous system are the primary target organs affected following oral, inhalation, and dermal exposures to hydrazine and 1,1-dimethylhydrazine. Studies in several animal species indicate

that the intestinal tract and liver are the primary target organs affected following oral exposure to 1,2 dimethylhydrazine (Bedell et al. 1992; Wilson et al. 1976). Data regarding the toxicokinetics of hydrazines are lacking in humans and are limited in animals. These data are not sufficient to conclude which animal species is best for modeling human exposures. Similarly, these data do not reveal the basis of species differences in the toxicokinetics or pharmacodynamics of hydrazines which may underlie the species differences in toxicity. For example, dogs appear to be particularly sensitive to the hematological effects of hydrazine and 1,1-dimethylhydrazine (Haun and Kinkead 1973; Haun et al. 1984; Rinehart et al. 1960; Smith and Castaneda 1970). Additional studies which investigate the toxicokinetics in multiple species, including humans or human tissues, would be useful in developing an appropriate animal model for humans exposed to hydrazines at hazardous waste sites.

Methods for Reducing Toxic Effects. General methods exist for reducing the absorption of chemicals from the eyes, skin, and gastrointestinal tract (Bronstein and Currance 1988; Sittig 1991; Stutz and Janusz 1988). However, none of these methods are specific for exposures to hydrazines. No data were located for reducing body burden after exposure to hydrazines. Pyridoxine, which interferes with the mechanism of action of hydrazine and 1,1-dimethylhydrazine, is often administered to humans exposed to these hydrazines (Dhennin et al. 1988; Kirklin et al. 1976). However, exposure to pyridoxine may also be associated with adverse health effects. Additional studies that investigate the threshold dose for adverse effects of pyridoxine, and studies that investigate alternative agents that interfere with the mechanism of action of hydrazines could lead to a safer method of treatment. Inhibitors of metabolic activation (Fiala et al. 1977) and free radical scavengers may also be useful in interfering with the mechanism of action of hydrazines (Belleli et al. 1992; Colacchio et al. 1989; Cook and McNamara 1980; Craven and DeRubertis 1992; Shirai et al. 1985; Tomasi et al. 1987). Additional studies that investigate the effects of metabolic inhibitors and various free radical scavengers in humans occupationally exposed to hydrazines and in animals could lead to other methods of interfering with the mechanism of action of hydrazines.

2.10.3 On-going Studies

A number of researchers are continuing to investigate the toxicity and toxicokinetics of 1,2-dimethylhydrazine. Table 2-6 summarizes studies sponsored by agencies of the U.S. federal government.

TABLE 2-6. On-going Studies on the Health Effects of Hydrazines*

Investigator	Affiliation	Research description	Sponsor
Brasitus, TA	University of Chicago	Colonic epithelial cell plasma membranes in rats treated with 1,2-dimethylhydrazine	NIH, NCI
Goldman, P	Harvard School of Public Health	Metabolism of 1,2-dimethylhydrazine by rat intestinal bacteria	NIH, NCI
Kazarinoff, MN	Cornell University	Induction of ornithine decarboxylase by 1,2-dimethylhydrazine	USDA
McGarrity, TJ	Milton S Hershey Medical Center	Cellular changes in 1,2-dimethylhydrazine-induced colon tumors in the rat	NIH, NCI
Pretlow, TP	Case Western Reserve University	Colonic putative preneoplastic foci in rats by metabolite, azoxymethane	NIH, NCI
Shank, RC	University of California	Environmental hydrazines and methylation of DNA in rats and hamsters	NIH, NIEHS
Strobel, HW	University of Texas Medical School	Identification of cytochrome P-450 isozymes involved in the metabolism of 1,2-dimethylhydrazine	NIH, NCI

*Source: CRISP (1993)

NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institute of Health; USDA = U.S. Department of Agriculture

3. CHEMICAL AND PHYSICAL INFORMATION

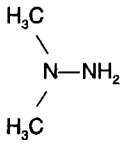
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of hydrazines is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical properties of hydrazines is located in Table 3-2.

TABLE 3-1. Chemical Identity of Hydrazines

Characteristic	Hydrazine	1,1-Dimethylhydrazine	1,2-Dimethylhydrazine	References
Synonym(s)	Diamine; diamide; anhydrous hydrazine; hydrazine base	Hydrazine, 1,1-dimethyl; DMH; unsymmetrical dimethylhydrazine; UDMH; dimazine; and others	Hydrazine, 1,2-dimethyl; DMH; symmetrical dimethylhydrazine; SDMH; hydrazomethane; and others	HSDB 1993
Registered trade name(s)	Levoxin®; SCAV-OX; Zerox; Oxytreat 35	No data	No data	HSDB 1993; WHO 1987
Chemical formula	H_4N_2	$C_2H_8N_2$	$C_2H_8N_2$	HSDB 1993
Chemical structure	H_2N-NH_2		$CH_3 - NH - NH - CH_3$	IARC 1974
Identification numbers:				
CAS registry	302-01-2	57-14-7	540-73-8	HSDB 1993
NIOSH RTECS	MU7175000	MV2450000	MV2625000	HSDB 1993
EPA hazardous waste	U133	U098	U099	HSDB 1993
OHM/TADS	No data	No data	No data	
DOT/UN/NA/IMCO shipping	UN2029, UN2030 IMCO 3.1 IMCO 8.2 NA 9188	UN1163 IMCO 3.2	UN2382 IMCO 3.1	HSDB 1993
HSDB	544	528	4039	HSDB 1993
NCI	No data	No data	No data	

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

TABLE 3-2. Physical and Chemical Properties of Hydrazines

Property	Hydrazine	1,1-Dimethylhydrazine	1,2-Dimethylhydrazine	Reference
Molecular weight	32.05	60.10	60.10	HSDB 1993
Color	Colorless	Colorless	Colorless	HSDB 1993
Physical state	Liquid	Liquid	Liquid	HSDB 1993
Melting point	2°C	-58°C	-9°C	HSDB 1993
Boiling point	113.5°C	63.9°C	81°C	WHO 1987
Density	1.0036 g/mL at 25°C	0.7914 g/mL at 25°C	0.8274 g/mL at 20°C	HSDB 1993; WHO 1987
Odor	Ammoniacal, pungent, fishy	Ammoniacal, fishy	Ammoniacal	HSDB 1993; WHO 1987
Odor threshold:				
Water	160 mg/L	No data	No data	Amoore and Hautala 1983
Air	3–4 mg/m^3	12–20 mg/m^3	No data	Ruth 1986
Solubility:				
Water	Miscible	Miscible	Miscible	Budavari et al. 1989; HSDB 1993
Organic solvent(s)	Miscible with alcohol, insoluble in chloroform and ether	Miscible with alcohol, ether, dimethyl formamide and hydrocarbons	Miscible with alcohol, ether, dimethyl formamide and hydrocarbons	ACGIH 1991a, 1991b; Budavari et al. 1989
Partition coefficients:				
Log K_{ow}	-3.08 -1.07	No data	No data	Radding et al. 1977; Poitrast et al. 1988
Log K_{oc}	No data	No data	No data	
Vapor pressure	10.4-16 mmHg at 20°C	157 mmHg at 25°C	68 mmHg at 24°C	HSDB 1993; Verschueren 1983;
Henry's law constant	No data	No data	No data	WHO 1987
Autoignition temperature	No data	249°C	No data	
Flashpoint	38°C (open cup)	-15°C (closed cup)	<23°C (closed cup)	HSDB 1993; WHO 1987
Flammability limits	1.8–100%	No data	No data	WHO 1987
Conversion factors	1 ppm = 1.31 mg/m^3 1 mg/m^3 = 0.76 ppm	1 ppm = 2.5 mg/m^3 1 mg/m^3 = 0.407 ppm	1 ppm = 2.5 mg/m^3 1 mg/m^3 = 0.407 ppm	HSDB 1993; Verschueren 1983; WHO 1987
Explosive limits	4.7–100%	2–95%	No data	ACGIH 1991a, 1991b

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

For most uses, hydrazine is produced as hydrazine hydrate in a formulation with water. The hydrate may be produced commercially by three methods: the Raschig process, the ketazine process, and the peroxide process. The Raschig process, the original commercial production process for hydrazine, involves oxidation of ammonia to chloramine with sodium hypochlorite, then further reaction of the chloramine with excess ammonia and sodium hydroxide to produce an aqueous solution of hydrazine with sodium chloride as a by-product. Fractional distillation of the product yields hydrazine hydrate solutions. Currently, most hydrazine is produced by the ketazine process, which is a variation of the Raschig process. Ammonia is oxidized by chlorine or chloramine in the presence of an aliphatic ketone, usually acetone. The resulting ketazine is then hydrolyzed to hydrazine. In the peroxide process, hydrogen peroxide is used to oxidize ammonia in the presence of a ketone. Anhydrous hydrazine is the formulation used in rocket fuels and is produced by dehydration of the hydrate by azeotropic distillation with aniline as an auxiliary fluid (Budavari et al. 1989; IARC 1974; Schmidt 1988; WHO 1987).

1,1-Dimethylhydrazine is currently prepared commercially by a modified Raschig process: reacting dimethylamine with the chloramine produced from ammonia and sodium hypochlorite. Formerly, it was prepared by the reduction of dimethylnitrosamine or by the reductive catalytic alkylation of carboxylic acid hydrazides with formaldehyde and hydrogen, followed by basic hydrolysis (Budavari e al. 1989; EPA 1984a, 1992b; IARC 1974; Schmidt 1988). 1,2-Dimethylhydrazine may be prepared from dibenzoylhydrazine or by electrosynthesis from nitromethane (Budavari et al. 1989).

The two current chemical producers of hydrazine in the United States are the Olin Corporation in Lake Charles, Louisiana, and Miles Inc. in Baytown, Texas. The chemical was also produced by Fairmount Chemical Company, Inc., Newark, New Jersey, as recently as 1987. 1,1-Dimethylhydrazine is produced by Olin and Uniroyal Chemical Company, Inc., Geismar, Louisiana. Estimates of past production (based on anhydrous hydrazine, although most production was of the hydrate) indicate that U.S. production volume was about 7,000 metric tons (15 million pounds) per year in the mid-1960s and increased to 17,000 metric tons (37 million pounds) per year in the mid-1970s. Production

capacity in the United States was estimated at 17,240 metric tons (38 million pounds) in 1979 and about 14,000 metric tons (30 million pounds) in 1984, the most recent year for which information was located. 1,1-Dimethylhydrazine production volume was estimated to be at least 45 metric tons (99,000 pounds) in 1977 and more than 4.5 metric tons (9,900 pounds) in 1982 (HSDB 1995; Schmidt 1988; SRI 1987, 1988, 1992; WHO 1987). Information on current production volume is not publicly available for either hydrazine or 1,1-dimethylhydrazine (EPA 1991d).

Tables 4-l and 4-2 list information on U.S. companies that reported the manufacture and use of hydrazine and 1,1-dimethylhydrazine, respectively, in 1993 (TRI93 1995). The data listed in the Toxics Release Inventory (TRI) should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

4.2 IMPORT/EXPORT

There is some indication that hydrazine was imported into the United States from Japan during the 1970s (IARC 1974), but no data were located on past or current U.S. import or export quantities of hydrazine or 1,1-dimethylhydrazine.

4.3 USE

Hydrazine (anhydrous or as the hydrate) has numerous commercial uses. The principal current use for hydrazine is as an intermediate in the production of agricultural chemicals such as maleic hydrazide. It is also used as an intermediate in the manufacture of chemical blowing agents which are used in the production of plastics such as vinyl flooring and automotive foam cushioning, as a corrosion inhibitor and water treatment agent, as a rocket propellant, and, to a lesser extent, as a reducing agent, in nuclear fuel reprocessing, as a polymerization catalyst, as a scavenger for gases, and several other uses. It has also been used as a medication for sickle cell disease and cancer.

From the late 1950s through the 1960s the primary use of hydrazine was as a rocket propellant. In 1964, 73% of the hydrazine consumed in the United States was used for this purpose. By 1982, other commercial uses dominated the market; 40% of the hydrazine consumed was used in agricultural

Table 4-1. Facilities That Manufacture or Process Hydrazine

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
OCCIDENTAL CHEMICAL CORP.	MUSCLE SHOALS, AL	10,000-99,999	As a chemical processing aid
HALL CHEMICAL CO.	ARAB, AL	10,000-99,999	As a chemical processing aid
OLIN CORP.	MCINTOSH, AL	10,000-99,999	In repackaging only
GREAT LAKES CHEMICAL CORP.	EL DORADO, AR	10,000-99,999	As a chemical processing aid
GREAT LAKES CHEMICAL CORP.	EL DORADO, AR	10,000-99,999	As a formulation component
NA	AZ	100-999	Ancillary uses
DEEPWATER IODIDES INC.	CARSON, CA	10,000-99,999	As a reactant
AEROJET SACRAMENTO OPS.	SACRAMENTO, CA	100,000-999,999	Ancillary uses
HERCULES INC.	BRUNSWICK, GA	10,000-99,999	As a reactant
AMOCO	WOOD RIVER, IL	10,000-99,999	As a reactant
3M	IL	10,000-99,999	As a reactant
SUNDSTRAND AEROSPACE	ROCKFORD, IL	1,000-9,999	Ancillary uses
ALLIED-SIGNAL INC.	PITTSBURG, KS	10,000-99,999	As a reactant
VANDERBILT CHEMICAL CORP.	MURRAY, KY	10,000-99,999	As a reactant
UNIROYAL CHEMICAL CO. INC.	GEISMAR, LA	100,000-999,999	As a reactant
OLIN CORP.	WESTLAKE, LA	100,000-999,999	Produce; For sale/distribution; Ancillary uses
SHELL OIL PRODS.	NORCO, LA	1,000-9,999	As a chemical processing aid
NA	MA	100-999	As a reactant
ZENECA RESINS	WILMINGTON, MA	1,000-9,999	As a reactant
BF GOODRICH	LEOMINSTER, MA	1,000-9,999	As a reactant
BAYER CORP.	KANSAS CITY, MO	100,000-999,999	As a reactant
FAIRMOUNT CHEMICAL CO. INC.	NEWARK, NJ	10,000-99,999	As a reactant
JOHNSON MATTHEY INC.	WEST DEPTFORD, NJ	1,000-9,999	As a chemical processing aid
DEGUSSA CORP.	SOUTH PLAINFIELD, NJ	10,000-99,999	As a reactant; As a chemical processing aid
E. I. DU PONT DE NEMOURS & CO.	NJ	10,000-99,999	As a chemical processing aid
PROCTER & GAMBLE	NORWICH, NY	10,000-99,999	As a reactant
OLIN CORP.	ROCHESTER, NY	10,000-99,999	As a reactant; As a formulation component
HALL CHEMICAL CO.	WICKLIFFE, OH	1,000-9,999	As a chemical processing aid
LUBRIZOL CORP.	PAINESVILLE, OH	10,000-99,999	As a reactant
BF GOODRICH	AVON LAKE, OH	10,000-99,999	As a reactant

Table 4-1. Facilities That Manufacture or Process Hydrazine (continued)

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
DOWELL SCHLUMBERGER INC.	TULSA, OK	10,000-99,999	As a reactant
BILCHEM LTD.	PONCE, PR	10,000-99,999	As a reactant
GREAT LAKES CHEMICAL CORP.	NEWPORT, TN	10,000-99,999	As a chemical processing aid
NA	TN	10,000-99,999	As a reactant
DREXEL CHEMICAL CO.	MEMPHIS, TN	10,000-99,999	As a reactant
MILES INC.	BAYTOWN, TX	1,000,000-9,999,999	Produce; For sale/distribution
PHELPS DODGE CORP.	TX	1,000-9,999	As a reactant
LUBRIZOL CORP.	PASADENA, TX	10,000-99,999	As a reactant
HOECHST-CELANESE CHEMICAL GROU	TX	1,000-9,999	Ancillary uses
SHELL OIL CO.	DEER PARK, TX	10,000-99,999	Ancillary uses
ASHLAND CHEMICAL CO.	HOUSTON, TX	100,000-999,999	Import; For sale/distribution; As a formulation component; As a product component; In repackaging only
MOBIL OIL BEAUMONT REFINERY	BEAUMONT, TX	10,000-99,999	As a manufacturing aid
MERCK & CO. INC.	ELKTON, VA	10,000-99,999	As a reactant
SPECIALTYCHEM PRODS. CORP.	MARINETTE, WI	10,000-99,999	As a reactant
BAYER CORP.	NEW MARTINSVILLE, WV	100,000-999,999	As a reactant

Source: TRI93 1995

[a] Post office state abbreviations used

NA = not available

Table 4-2. Facilities That Manufacture or Process 1,1-Dimethylhydrazine

Facility	Location [a]	Range of maximum amounts on site in pounds	Activities and uses
OLIN CORP.	AL	10,000-99,999	In repackaging only
AEROJET SACRAMENTO OPS.	SACRAMENTO, CA	100,000-999,999	Ancillary uses
UNIROYAL CHEMICAL CO. INC.	GEISMAR, LA	100,000-999,999	Import; For on-site use/processing; As a reactant
OLIN CORP.	WESTLAKE, LA	100,000-999,999	Produce; For sale/distribution

Source: TRI93 1995

[a] Post office state abbreviations used

chemicals, about 33% for blowing agents, 15% as a corrosion inhibitor in boiler water and only 5% as an aerospace propellant (Budavari et al. 1989; Fajen and McCammon 1988; HSDB 1995; Schmidt 1988; WHO 1987).

1,1-Dimethylhydrazine is used mainly as a component of jet and rocket fuels. Other uses include an adsorbent for acid gases, a stabilizer for plant growth regulators, an intermediate for organic chemical synthesis, and in photography. 1,2-Dimethylhydrazine is used only as a research chemical and has no known commercial uses (ACGIH 1991a; Budavari et al. 1989; HSDB 1995).

4.4 DISPOSAL

Hydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and wastes containing these chemicals are classified as hazardous wastes by EPA. Generators of waste containing these contaminants must conform to EPA regulations for treatment, storage, and disposal (see Chapter 7). Liquid injection or fluidized bed incineration methods are acceptable disposal methods for these wastes. Oxidation of spills of hydrazine fuels with sodium or calcium hypochlorite or hydrogen peroxide prior to disposal has been recommended. However, incomplete reaction of 1,1-dimethylhydrazine with hypochlorite leads to formation of several by-products, including carcinogenic *N*-nitrosoalkylamines. Ozonation of wastewater containing hydrazine fuels has been shown to reduce concentrations of the fuels, their associated impurities, and oxidation products to environmentally acceptable levels. Biodegradation is also an acceptable treatment for wastewaters containing hydrazine wastes (Brubaker 1988; EPA 1991a; HSDB 1995; Jody et al. 1988; WHO 1987).

According to the TRI, about 106,000 pounds of hydrazine and 3,000 pounds of l,l-dimethylhydrazine were transferred to landfills and/or treatment/disposal facilities in 1993 (see Section 5.2) (TRI93 1995). Of this quantity, about 1,400 pounds of hydrazine were discharged to publicly owned treatment works.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Hydrazine and 1,1-dimethylhydrazine are industrial chemicals that enter the environment primarily by emissions from their use as aerospace fuels and from industrial facilities that manufacture, process, or use these chemicals. Treatment and disposal of wastes containing these chemicals also contribute to environmental concentrations. These chemicals may volatilize to the atmosphere from other media and may sorb to soils. These chemicals degrade rapidly in most environmental media. Oxidation is the dominant fate process, but biodegradation occurs in both water and soil at low contaminant concentrations. The half-lives in air range from less than 10 minutes to several hours, depending on ozone and hydroxyl radical concentrations. Half-lives in other media range up to several weeks, under various environmental conditions. Bioconcentration does occur, but biomagnification through the food chain is unlikely.

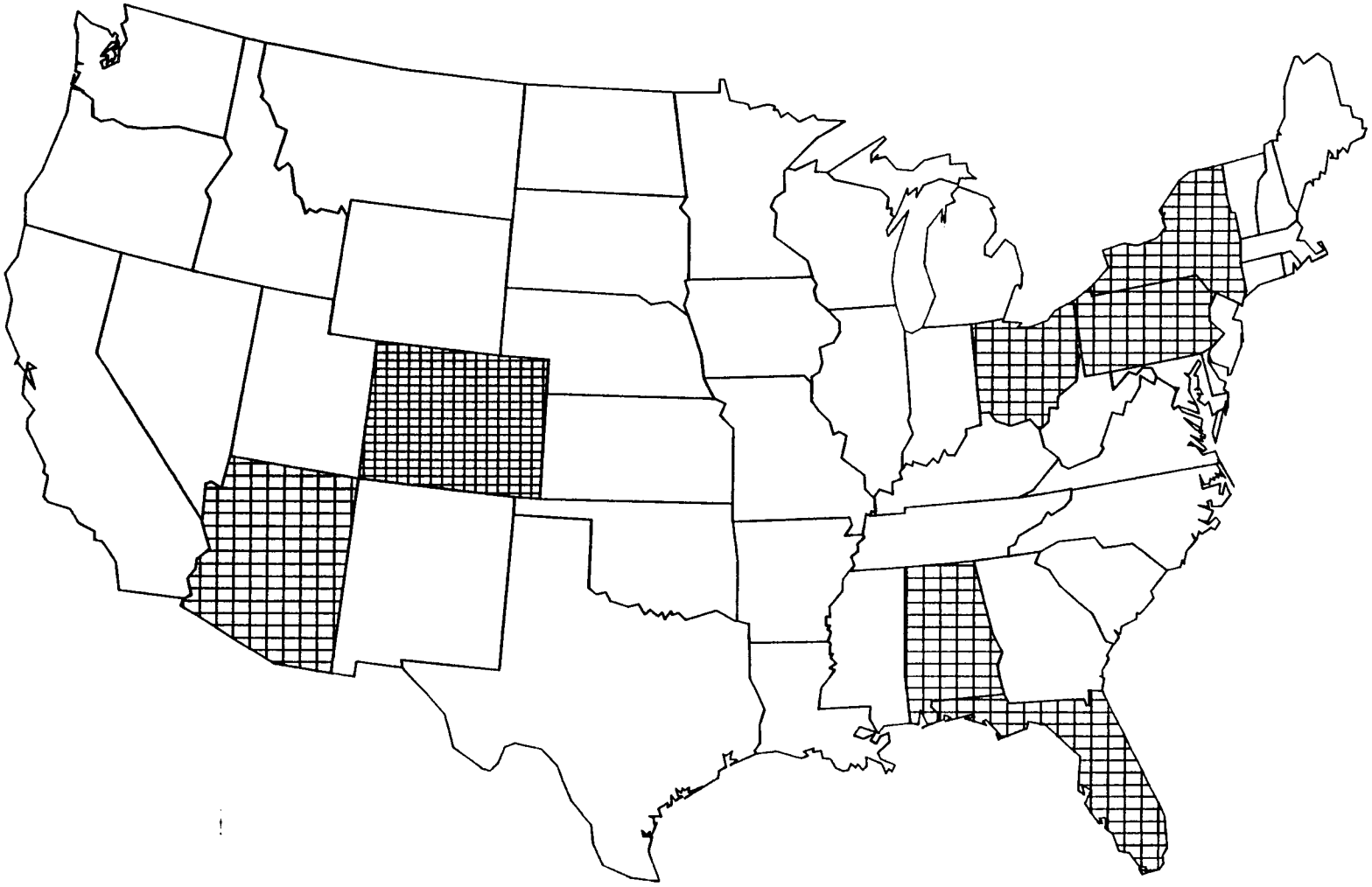
Human exposure to hydrazine and 1,1-dimethylhydrazine is mainly in the workplace or in the vicinity of aerospace or industrial facilities or hazardous waste sites where contamination has been detected. These chemicals have not been detected in ambient air, water, or soil. Humans may also be exposed to small amounts of these chemicals by using tobacco products.

Hydrazine has been found in at least 4 of the 1,430 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1996). 1,1 -Dimethylhydrazine and 1,2-dimethylhydrazine have been identified in at least 3 and 1 of these sites, respectively. However, the number of sites evaluated for these chemicals is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

Hydrazine occurs naturally as a product of nitrogen fixation by some algae and in tobacco and tobacco smoke (IARC 1974). However, the major environmental sources of hydrazine are anthropogenic. There are no known natural sources of dimethylhydrazines. The estimated total annual environmental release of hydrazine and 1,1-dimethylhydrazine from manufacture and processing reported to the

FIGURE 5-1. FREQUENCY OF NPL SITES WITH HYDRAZINES CONTAMINATION *



*Derived from HazDat 1995

TRI were about 30,000 and 4,000 pounds, respectively, in 1988 (EPA 1991d). However, more recent data reported to the TRI indicate that environmental releases from manufacture and use of these chemicals total about 17,000 and 200 pounds, respectively (TRI93 1995). 1,1-Dimethylhydrazine may also be released to the environment from the application of daminozide (Alar®), a growth enhancer which contains about 0.005% 1,1-dimethylhydrazine as a contaminant to nonfood plants (EPA 1992c).

5.2.1 Air

The major sources of hydrazine releases to air are expected to be from its use as an aerospace propellant and boiler water treatment agent (HSDB 1995). However, hydrazine released as a boiler water treatment agent is present only briefly since it would oxidize rapidly in water (HSDB 1995). Burning of rocket fuels containing hydrazine and/or 1,1-dimethylhydrazine reportedly produces exhaust gases containing trace amounts of unchanged fuel (IARC 1974). Emissions are also expected from the production and processing of hydrazine (EPA 1991d; WHO 1987). It has been estimated, based on data from Germany, that 0.06-0.08 kg of hydrazine are emitted to the air for every metric ton produced, and an additional 0.02-0.03 kg are emitted for every metric ton subjected to handling and further processing (WHO 1987). On this basis, assuming production volume of about 14,000 metric tons (30 million pounds) (see Section 4.1) and handling or processing of the product, emissions to the air may range from 1,100 to 1,500 kg (500-680 pounds) annually. Atmospheric releases of hydrazine may also occur from tobacco smoking (see Section 5.4.4) and from hazardous waste sites at which this chemical has been detected (HSDB 1995; WHO 1987).

Release of 1,1 dimethylhydrazine to the atmosphere is expected to occur primarily from its use as an aerospace propellant (HSDB 1995). Release of this chemical and 1,2-dimethylhydrazine may also occur from hazardous waste sites at which they have been detected.

As shown in Tables 5-1 and 5-2, an estimated total of 16,452 pounds of hydrazine and 194 pounds of 1,1-dimethylhydrazine, amounting to about 95% and 100% of the total environmental releases, respectively, were discharged to the air from manufacturing and processing facilities in the United States in 1993 (TRI93 1995). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hydrazine

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
AL	MUSCLE SHOALS	OCCIDENTAL CHEMICAL CORP.	75	33			108		
AL	ARAB	HALL CHEMICAL CO.	250				250		
AL	MCINTOSH	OLIN CORP.	6				6		
AR	EL DORADO	GREAT LAKES CHEMICAL CORP.	24				24		
AR	EL DORADO	GREAT LAKES CHEMICAL CORP.	18				18		
AZ	NA	NA							
CA	CARSON	DEEPWATER IODIDES INC.	5				5		
CA	SACRAMENTO	AEROJET SACRAMENTO OPS.	9				9		2,874
GA	BRUNSWICK	HERCULES INC.	30				30		
IL	WOOD RIVER	AMOCO	19				19	1,400	
IL	NA	3M							
IL	ROCKFORD	SUNDSTRAND AEROSPACE	500				500		
KS	PITTSBURG	ALLIED-SIGNAL INC.	15				15		
KY	MURRAY	VANDERBILT CHEMICAL CORP.	1				1		
LA	GEISMAR	UNIROYAL CHEMICAL CO. INC.	222				222		
LA	WESTLAKE	OLIN CORP.	690				690		2,802
LA	NORCO	SHELL OIL PRODS.	933				933		4,500
MA	NA	NA							
MA	WILMINGTON	ZENECA RESINS	1				1		491

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hydrazine (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
MA	LEOMINSTER	BF GOODRICH	332				332		
MO	KANSAS CITY	BAYER CORP.	439	1			440		
NJ	NEWARK	FAIRMOUNT CHEMICAL CO. INC.	2,500				2,500		
NJ	WEST DEPTFORD	JOHNSON MATTHEY INC.	5				5		
NJ	SOUTH PLAINFIELD	DEGUSSA CORP.	1,360				1,360		
NJ	NA	E. I. DU PONT DE NEMOURS & CO.							
NY	NORWICH	PROCTER & GAMBLE	130				130		
NY	ROCHESTER	OLIN CORP.	161				161	3	
OH	WICKLIFFE	HALL CHEMICAL CO.	5				5		
OH	PAINESVILLE	LUBRIZOL CORP.	50				50		
OH	AVON LAKE	BF GOODRICH	3				3		
OK	TULSA	DOWELL SCHLUMBERGER INC.	5				5		
PR	PONCE	BILCHEM LTD.	255				255		
TN	NEWPORT	GREAT LAKES CHEMICAL CORP.	1				1		
TN	NA	NA							
TN	MEMPHIS	DREXEL CHEMICAL CO.	10		5		15	5	
TX	BAYTOWN	MILES INC.	500	750			1,250		92,000
TX	NA	PHELPS DODGE CORP.							
TX	PASADENA	LUBRIZOL CORP.	6,131				6,131		3,617
TX	NA	HOECHST-CELANESE CHEMICAL GROUP							
TX	DEER PARK	SHELL OIL CO.	914				914		

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Hydrazine (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
TX	HOUSTON	ASHLAND CHEMICAL CO.	31				31		27
TX	BEAUMONT	MOBIL OIL BEAUMONT REFINERY	14				14		
VA	ELKTON	MERCK & CO. INC.	50				50		
WI	MARINETTE	SPECIALTYCHEM PRODS. CORP.	1				1		
WV	NEW MARTINSVILLE	BAYER CORP.	757				757		
		Totals	16,452	784	5		17,241	1,408	106,311

Source: TRI93 1995

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

NA = not available; POTW = publicly owned treatment works

Table 5-2. Releases to the Environment from Facilities That Manufacture or Process 1,1-Dimethylhydrazine

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
AL	NA	OLIN CORP.							
CA	SACRAMENTO	AEROJET SACRAMENTO OPS.	65				65		2,851
LA	GEISMAR	UNIROYAL CHEMICAL CO. INC.	104				104		
LA	WESTLAKE	OLIN CORP.	25				25		74
		Totals	194				194		2,925

Source: TRI93 1995

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

NA = not available; POTW = publicly owned treatment works

5.2.2 Water

Releases of hydrazine and 1,1-dimethylhydrazine to water may occur during production, processing, use, or disposal of the chemical. Hydrazine was detected at a concentration of 0.01 μg/L in effluent from one industrial facility (EPA 1984b). However, since these chemicals are rapidly oxidized in water (see Section 5.3.2.2), the unreacted compounds are not likely to persist in detectable concentrations.

As shown in Tables 5-l and 5-2, an estimated total of 784 pounds of hydrazine amounting to about 4.5% of the total environmental releases and no 1,1-dimethylhydrazine were discharged to surface water from manufacturing and processing facilities in the United States in 1993 (TRI93 1995). An additional 423 pounds of hydrazine (1% of the total) were discharged by underground injection. The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2.3 Soil

No data were located documenting release of hydrazine or dimethylhydrazines to soil. However, releases to soil may occur from spills and leakage of underground storage tanks during the use of hydrazine and 1,1-dimethylhydrazine as rocket propellants (Street and Moliner 1988). Deposition from air is not expected to be significant (see Section 5.3.1). Hydrazine and dimethylhydrazines may be released to soil from hazardous waste sites at which these chemicals have been detected. 1,1-Dimethylhydrazine may also be released to soil from the application of daminozide (Alar®) as a growth enhancer on nonfood plants. The use of this chemical on food products was voluntarily cancelled in 1989 by the manufacturer (Uniroyal Chemical Company) (EPA 1992c). Daminozide contains about 0.005% 1,1-dimethylhydrazine as an impurity and about 0.012% of a daminozide solution that hydrolyzes to 1,1-dimethylhydrazine after 24 hours (EPA 1992c). No data were located on the amount of daminozide used annually, but it is estimated that, in 1989, 90% of potted chrysanthemums and 40-50% of 65 million square feet of bedding plants were treated with this chemical.

As shown in Tables 5-l and 5-2, 5 pounds of hydrazine (<0.1% of the total environmental release) and no 1,1-dimethylhydrazine were reported discharged to land from manufacturing and processing facilities in the United States in 1993 (TRI93 1995). The data listed in the TRI should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Hydrazine or dimethylhydrazines released to water or soil may volatilize into air or sorb onto soil. These chemicals have low vapor pressures and are miscible in water (see Table 3-2). Therefore, volatilization is not expected to be an important removal process. Reported evaporation rates from aqueous solutions under laboratory conditions were 0.49 mg/cm^2 minute for hydrazine and 13 mg/cm^2 minute for 1,1-dimethylhydrazine (EPA 1984a). The significance of these values to environmental conditions is unknown. Data from other studies indicate that volatilization of these chemicals from water increases with higher concentrations of the chemical and in the presence of sunlight (due to increased temperature of the hydrazine pool). Based on air dispersion modeling, volatilization of hydrazine from surface soil following a spill is expected to be sufficient (16-100 mg/cm^2 hour) to generate a short-term ambient air concentration of 4 mg/m^3 up to 2 km downwind of the spill under worst-case meteorological conditions (MacNaughton et al. 1981). Degradation of hydrazine would likely reduce the concentration within several hours (see Section 5.3.2.1).

Atmospheric transport of hydrazine or dimethylhydrazines may occur, but transport will be limited by the high reactivity of the chemicals in the atmosphere (see Section 5.3.2.1). No data were located on deposition of hydrazine or dimethylhydrazines from air to water or soil, but deposition would also be limited by their high reactivity.

Hydrazine undergoes complex interactions with soils, including both reversible physical-sorption and irreversible chemisorption to colloids (Mansell et al. 1988). In a study on the adsorption and leaching characteristics of hydrazine fuels, no adsorption of 1,1-dimethylhydrazine was observed on sand, with almost 100% of the chemical leaching with water (Braun and Zirrolli 1983). In three other soils, adsorption ranged from 26% to 80%. No correlation between adsorption and soil organic content or pH was observed. The mechanisms of attenuation in soil materials were not reported. However,

reported results of additional hydrazine adsorption studies with clays and soils indicate that adsorption may be correlated with soil organic matter and clay content and is highly dependent on pH; hydrazine appears to be adsorbed by different mechanisms under acidic and alkaline conditions (Moliner and Street 1989b).

In a study of hydrazine in aqueous systems, the chemical was reported to be absorbed by guppies from a 0.5 μg/L solution (Slonim and Gisclard 1976). After 96 hours, the hydrazine concentration in fish was 144 μg/g, indicating a moderate tendency to bioconcentrate. However, the bioconcentration of hydrazine and dimethylhydrazines is not expected to be important in aquatic systems because of the rapid degradation of these chemicals in water (see Section 5.3.2.2) as well as their low octanol-water partition coefficients.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Hydrazine and dimethylhydrazines degrade rapidly in air through reactions with ozone, hydroxyl (OH) radicals, and nitrogen dioxide (WHO 1987). The reaction of hydrazine and 1,1-dimethylhydrazine with ozone is probably the major fate of these chemicals in the atmosphere. The reaction rate constant for hydrazine, derived from its decay rate in the presence of excess ozone, was about $3X10^{-17}$ cm^3 $molecule^{-1}s^{-1}$ and for 1,1-dimethylhydrazine the rate was greater than $1X10^{-15}$ cm^3 $molecule^{-1}s^{-1}$ (Atkinson and Carter 1984). Major reaction products were hydrogen peroxide for the hydrazine reaction and dimethylnitrosamine (about 60%) for the 1,1-dimethylhydrazine reaction. Estimated atmospheric half-lives ranged from less than 10 minutes for hydrazine during an ozone pollution episode to less than 2 hours under usual conditions, with a half-life about one-tenth that time for 1,1-dimethylhydrazine (Tuazon et al. 1981). Reported results of additional studies indicate a reaction rate constant for hydrazine of $2.5x10^{-l6}$ cm3 $molecule^{-1}s^{-1}$, resulting in an estimated half-life of less than 1 minute (Stone 1989). -.

The reported measured rate constant for reaction of hydrazine with atmospheric hydroxyl (OH) radicals producing ammonia and nitrogen gas was $6.1x10^{-11}cm^3$ $molecule^{-1}s^{-1}$ (Harris et al. 1979). The rate constant for 1,1-dimethylhydrazine was not measured since the chemical decomposed rapidly in the test system, but the value was estimated at $5X10^{-11}$ cm3 $molecule^{-1}s^{-1}$. Assuming an average OH radical

concentration of about 10^6 molecule/cm^3, the tropospheric half-lives of both chemicals due to reaction with OH were estimated to be about 3 hours. The half-lives are expected to range from less than 1 hour in polluted urban air to 3-6 hours in less polluted atmospheres (Tuazon et al. 1981).

Hydrazine and 1,1-dimethylhydrazine react rapidly with nitrogen oxides in both the light and dark, with a half-life of about 2 hours for hydrazine and less than 10 minutes for 1,1-dimethylhydrazine (Pitts et al. 1980).

Hydrazine and 1,1-dimethylhydrazine may also be removed from the atmosphere by autoxidation. In a dark reaction chamber, the approximate half-lives of hydrazine ranged from 1.8 to 5 hours, with the lower value measured at higher humidity. Reported values for 1,1 dimethylhydrazine under similar conditions were 5.9-9 hours. Surface interactions are important in controlling the rates of these reactions (Stone 1989).

Although data were not located for 1,2-dimethylhydrazine, this chemical is expected to be degraded in the atmosphere by undergoing the same reactions as hydrazine and 1,1-dimethylhydrazine, although the rate and extent of degradation may be different.

5.3.2.2 Water

Hydrazine and 1,1-dimethylhydrazine degrade in aqueous systems, but the rate of degradation is dependent on specific aquatic environmental factors, including pH, hardness, temperature, oxygen concentration, and the presence of organic matter and metal ions (Moliner and Street 1989a; Slonim and Gisclard 1976; WHO 1987). Oxidation and biodegradation are the primary removal mechanisms. Reaction of hydrazine with dissolved oxygen is catalyzed by metal ions, particularly copper (EPA 1984a). The reaction rate is strongly influenced by pH; degradation proceeds more rapidly in alkaline solutions. Hydrazine is rapidly removed from polluted waters, with less than one-third of the original concentration remaining in dirty river water after 2 hours (Slonim and Gisclard 1976). More than 90% of the hydrazine added to pond or chlorinated, filtered county water disappeared after 1 day. However, chlorinated, filtered, and softened city water contained almost the original amount of hydrazine after 4 days. Organic matter in the water and hardness were reported to be the major factors in the differing rates of degradation.

The primary reaction pathway for hydrazine degradation in water produces nitrogen gas and water (Moliner and Street 1989a). In oxygen-deficient waters or in the presence of metal ions which serve as catalysts, ammonia may also be produced.

The reaction of 1,1-dimethylhydrazine with dissolved oxygen in water may proceed by a process catalyzed by copper ions or by an uncatalyzed reaction (Banerjee et al. 1984). The products include dimethylnitrosamine, formaldehyde, dimethylamine, and other related chemicals. Dimethylnitrosamine did not form in dilute solutions, which might be encountered in ambient waters, but was reported in concentrated solutions, which could be present in the vicinity of spills (EPA 1984a). The reported half-life of 1,1-dimethylhydrazine in ponds and seawaters ranged from 10 to 14 days, presumably because of reaction with oxygen and other free radicals (EPA 1984a).

Biodegradation may be a significant removal process at low hydrazine concentrations in ambient waters, but at higher concentrations the chemical is toxic to microorganisms. In the presence of bacterial cells, more than 90% of the hydrazine was degraded in six water samples containing 11 μg/mL of the chemical within 2 hours (Ou and Street 1987b). Lower degradation rates were reported with increasing hydrazine concentrations. No degradation was reported for incubation of these waters without bacteria. Additional studies indicate that hydrazine and 1,1-dimethylhydrazine are toxic to bacterial populations. Concentrations of hydrazine and 1,1-dimethylhydrazine that reduced bacterial metabolism by 50% ranged from 14.6 to 145 mg/L and from 19.2 to 9,060 mg/L, respectively (Kane and Williamson 1983). Thus, biological treatment would not be useful for spills of these chemicals into the aquatic environment.

5.3.2.3 Sediment and Soil

Hydrazine appears to degrade more rapidly in soil than in water, with oxidation and biodegradation as the main removal processes. Hydrazine applied to nonsterile Arredondo soil (fine sand) at concentrations of 10, 100, and 500 μg/g was completely degraded in 1.5 hours, 1 day, and 8 days, respectively (Ou and Street 1987a). In this study, comparison to degradation rates in sterile soils indicated that autoxidation appeared to be the major factor contributing to disappearance of the chemical, but the study authors attributed about 20% of removal to biodegradation. Several heterotrophic soil bacteria were reported to degrade hydrazine, indicating that microbial degradation may contribute to removal of the chemical from soil (Ou 1987).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

No monitoring data were located for hydrazine or dimethylhydrazines in ambient air. Since these chemicals are readily degraded in the atmosphere (see Section 5.3.2.1), they are not expected to be present measurable levels, except in the vicinity of production or processing facilities or spills.

5.4.2 Water

No monitoring data were located for hydrazine or dimethylhydrazines in ambient water. Since these chemicals are readily degraded in aquatic systems (see Section 5.3.2.2), they are not expected to be present at measurable levels, except in the vicinity of production or processing facilities, spills, or possibly, hazardous waste sites.

5.4.3 Sediment and Soil

No data were located documenting hydrazine or dimethylhydrazine concentrations in ambient soil or sediments. Since these chemicals are readily degraded in soil (see Section 5.3.2.3), they are not expected to be present at measurable levels, except in the vicinity of production or processing facilities, spills, or hazardous waste sites.

5.4.4 Other Environmental Media

Hydrazine and 1,1-dimethylhydrazine have been detected in tobacco. 1,1-Dimethylhydrazine was reported at concentrations ranging from not detected to 147 ng/g in various types of tobacco in the United States (Schmeltz et al. 1977). Mainstream smoke from blended U.S. cigarettes contained an average of 31.5 ng of hydrazine per cigarette (Liu et al. 1974). Sidestream smoke may have higher hydrazine concentrations. The authors reported 94.2 ng of hydrazine in sidestream smoke from one cigarette. Although hydrazine may be an impurity in maleic hydrazide, a pesticide formerly used on tobacco plants, reports on studies of tobacco from both treated and untreated plants indicate that the application of maleic hydrazide is not the major source of hydrazine in tobacco. It has been suggested

that these chemicals may be produced in tobacco by bacterial or enzymatic processes which occur during curing (Schmeltz et al. 1977).

1,1-Dimethylhydrazine has been detected in several food products because of its presence as an impurity (about 0.005%) in daminozide (Alar)®, a plant growth enhancer. 1,1-Dimethylhydrazine was detected in several processed fruits at maximum levels ranging from 0.007 to 0.60 ppm (Saxton et al. 1989). The fruits had been treated with, and contained residues of, daminozide. It appears that during thermal processing, some of the daminozide degrades to 1,1-dimethylhydrazine, adding to the quantity of 1,1-dimethylhydrazine already present. However, daminozide is no longer used on food plants in the United States since its registered uses for food products were voluntarily cancelled in 1989 (EPA 1992c). Therefore, 1,1-dimethylhydrazine is no longer expected to be present in foods prepared from food plants grown in the United States.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to hydrazine and dimethylhydrazines is expected to be extremely low (WHO 1987). Because of the high reactivity of these chemicals, they are unlikely to remain in environmental media for extended periods. These chemicals have not been detected in ambient air, water, or soil.

Occupational exposures to hydrazine and 1,1-dimethylhydrazine may occur in facilities that manufacture, process, transport, or use these chemicals. The National Institute for Occupational Safety and Health (NIOSH) conducted a National Occupational Exposure Survey (NOES) during 1981-1983 and estimated that 59,675 and 2,197 workers were potentially exposed to hydrazine and 1,1-dimethylhydrazine, respectively, at that time (EPA 1991d). Since most hydrazine production processes involve closed systems, the potential for exposure is generally low (Fajen and McCammon 1988). The greatest potential for exposure probably occurs during process stream sampling, with measured time-weighted average (TWA) concentrations ranging from 0.04 to 0.27 ppm and excursions up to 0.91 ppm. Workplace breathing zone air levels of hydrazine and l,l-dimethylhydrazine ranged from 0.22 to 1.98 ppm and from 0.23 to 4.61 ppm, respectively, in a rocket propellant plant (Cook et al. 1979). Workers in facilities where exposure to these chemicals is possible are required to wear protective respirators. Analysis of samples from within the respirators indicated that these chemicals

are not usually present at detectable levels. Thus, routine exposure to these levels is not expected, but respirator failures and other accidental exposures may occur.

Occupational exposures may also occur to military and civilian personnel during the use of these chemicals as aerospace propellants. Exposure to workers may occur during loading or unloading of propellants, transfer operations, or testing of spacecraft components that use hydrazine fuels (Fajen and McCammon 1988). Although full-body supplied-air suits are usually worn during these operations, spills and other accidents may lead to short-term, high-level exposures, rather than longer-term, lowlevel exposures.

Exposure may also result from the use of hydrazine as an oxygen scavenger in boiler systems (Fajen and McCammon 1988). Long-term concentrations in areas where hydrazine was added to the boiler systems were generally below 0.1 ppm, but short-term concentrations ranged up to 0.23 ppm. In addition, those individuals who work as daminozide applicators in greenhouses may be exposed to 1,1-dimethylhydrazine (EPA 1992c).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potential exposures to hydrazines above ambient levels include those exposed occupationally (see Section 5.5), such as during the manufacture or agricultural application of hydrazines, people living or working near military or aerospace installations using these chemicals as fuels, or people living near hazardous waste sites where these chemicals have been detected. Others who may be exposed to these chemicals at above ambient levels include individuals who chew or smoke tobacco and those exposed to sidestream smoke (see Section 5.4.4). Furthermore, hydrazine is a metabolite of several drugs (e.g., hydralazine, isoniazid), and it has been suggested that individuals taking these drugs may be exposed to hydrazine, based on the detection of hydrazine in the urine of patients taking hydralazine (Timbrell and Harland 1979) and the blood plasma of patients taking isoniazid (Blair et al. 1985).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether

adequate information on the health effects of hydrazines is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of hydrazines.

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

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of hydrazine and dimethylhydrazines are sufficiently well characterized to allow estimation of their environmental fate (see Table 3-2) (HSDB 1993; IARC 1975; Verschueren 1983). On this basis, it does not appear that further research in this area is required.

Production, Import/Export, Use, Release, and Disposal. Hydrazine is produced at one facility and 1,1-dimethylhydrazine is produced at two locations (SRI 1992). However, production volume and import and export information are not available. This information would be useful in assessing potential exposure to workers and the general population. Since 1,2-dimethylhydrazine is produced only in gram quantities for research, additional information is not required.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The environmental fate of hydrazine and 1,1-dimethylhydrazine has been well defined (Atkinson and Carter 1984; EPA 1984a; Moliner and Street 1989a, 1989b; Ou and Street 1987a, 1987b; Stone 1989; WHO 1987). These chemicals are highly reactive and degrade readily in environmental media. Thus, they are not likely to be present in air or water and it is not likely that exposure to the general population is of concern. Nevertheless, because these chemicals may migrate to groundwater, additional studies might be useful to assess the potential for transport of these chemicals from hazardous waste sites and their fate in closed water systems such as groundwater.

Bioavailability from Environmental Media. Hydrazine is known to be absorbed following inhalation (Llewellyn et al. 1986), oral (dissolved in water) (Preece et al. 1992a), and dermal (Smith and Clark 1971, 1972) exposures. Little is known about the absorption of 1,1-dimethylhydrazine and 1,2-dimethylhydrazine, but based on their chemical properties, the absorption is most likely similar to that of hydrazine. No information was located on the bioavailability of hydrazine or dimethylhydrazines from environmental media. This information would be helpful in evaluating the impact of environmental exposures on human health.

Food Chain Bioaccumulation. Hydrazine in water may bioconcentrate in aquatic organisms to a moderate degree (Slonim and Gisclard 1976), but because of its high reactivity, the chemical is rapidly degraded in aquatic systems. This property, as well as the low octanol-water partition coefficient of hydrazine, makes food chain bioaccumulation unlikely.

Exposure Levels in Environmental Media. Hydrazine and dimethylhydrazines have not been detected in ambient air, water, or soil, since they are highly reactive and degrade readily in environmental media. Hydrazine and l,l-dimethylhydrazine have been detected in workplace air and in tobacco (Cook et al. 1979; Schmeltz et al. 1977). Since these chemicals are highly reactive and exposure of the general population is not expected to be of concern, monitoring of ambient environmental media does not appear to be required. However, monitoring of workplace air would help to determine potential sources and magnitude of exposure.

Exposure Levels in Humans. Hydrazine and dimethylhydrazines have not been detected in human tissues as a result of exposure to these chemicals from environmental media. Hydrazine has been detected in the urine of individuals taking medication (hydralazine) which may metabolize to hydrazine (Timbrell and Harland 1979). Since hydrazine and dimethylhydrazines are rapidly

metabolized *in vivo,* it is unlikely that any free chemical would be present in biological tissues within a few days after environmental exposure. Studies that investigate the levels of hydrazines in humans within the first few days after exposure, along with their relationship to exposure levels, would be useful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for hydrazines were located. These substances are not currently in a subregistry of the National Exposure Registry. These substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances.

5.7.2 On-going Studies

No information was located regarding on-going studies on the environmental fate or exposure levels of hydrazine or dimethylhydrazines.

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL MATERIALS

Spectrophotometric methods, high-performance liquid chromatography (HPLC), and gas chromatography (GC) may be used to detect and measure hydrazine and dimethylhydrazines in biological materials (Alvarez de Laviada et al. 1987; Amlathe and Gupta 1988; Fiala and Kulakis 1981; Preece et al. 1992a; Reynolds and Thomas 1965; Timbrell and Hat-laud 1979). The spectrophotometer measures the absorbance of light at a particular wavelength, thereby identifying and quantifying a compound that absorbs at that wavelength. The chromatograph separates complex mixtures of organics and allows individual compounds to be identified and quantified by a detector. An electrochemical detector (ED), in the case of HPLC, and a nitrogen phosphorus detector (NPD) or flame ionization detector (FID), in the case of GC, may be used to identify hydrazine or dimethylhydrazine or their derivatives. When unequivocal identification is required, a mass spectrometer (MS) coupled to the GC column may be employed.

Prior to GC or spectrophotometric analysis, hydrazine and dimethylhydrazines must be separated from the biological sample matrix and derivatives of the compounds must be prepared. Separation is usually effected by precipitation of residual protein with acid and extraction of interfering lipids with methylene chloride (Alvarez de Laviada et al. 1987; Preece et al. 1992a; Reynolds and Thomas 1965; Timbrell and Harland 1979). Hydrazine and 1,1-dimethylhydrazine, but not 1,2-dimethylhydrazine,

may then be derivatized with an aldehyde such as pentafluorobenzaldehyde or *p*-dimethylaminobenzaldehyde. 1,2-Dimethylhydrazine, which has no free-NH_2 group, cannot be derivatized in this way but may be quantified by chromatographic methods that do not require derivatization (Fiala and Kulakis 1981). Details of selected analytical methods for hydrazine and dimethylhydrazines in biological samples are summarized in Table 6-l.

Accurate analysis of hydrazine and dimethylhydrazines in biological samples is complicated by the tendency of these chemicals to autoxidize during storage (Preece et al. 1992a). Thus, derivatization should be completed as rapidly as possible, before autoxidation can occur.

6.2 ENVIRONMENTAL SAMPLES

Determination of hydrazine and dimethylhydrazines in air, water, soil, food, and tobacco is also carried out by spectrophotometry, GC, or HPLC analysis (Amlathe and Gupta 1988; ASTM 1991b; Holtzclaw et al. 1984; Leasure and Miller 1988; Liu et al. 1974; NIOSH 1977a, 1977b, 1984; Rutschmann and Buser 1991; Schmeltz et al. 1977; Wright 1987). Several representative methods for quantifying these chemicals in each of these media are summarized in Table 6-2. EPA-validated methods are not available for analysis of hydrazine or dimethylhydrazines in any environmental medium. Two EPA methods (8250 and 8270) are recommended for analysis of 1,1-dimethylhydrazine in wastes (EPA 1990e). However, these methods do not list 1,1-dimethylhydrazine as an analyte (EPA 1990c, 1990d) and do not appear to be suitable methods for analysis of this compound since 1,1-dimethylhydrazine is likely to degrade during the GC analysis unless it has been derivatized.

Separation of hydrazine and dimethylhydrazines from environmental samples is by acid extraction when necessary. Air samples are usually collected in a bubbler with acid or on an acid-coated silica gel (NIOSH 1977a, 1977b, 1984). When GC is employed, detection may be by electron capture detector (ECD), FID, nitrogen-specific detector (NSD), thermionic ionization detector (TID), and/or MS as described above (Section 6.1).

Accurate determination of hydrazine and dimethylhydrazines in environmental samples is also complicated by the susceptibility of these chemicals to oxidization. Air samples must be analyzed immediately after collection (Cook et al. 1979). Degradation of hydrazine in aqueous samples can be prevented by acidification with sulfuric acid (WHO 1987).

TABLE 6-1. Analytical Methods for Determining Hydrazine, 1,1-Dimethylhydrazine, and 1,2-Dimethylhydrazine in Biological Samples[a]

Sample matrix	Preparation method	Analytical metod	Sample detection limit	Percent recovery	Reference
Urine	Precipitate residual protein with hydrochloric acid and ammonium sulfate; extract interfering lipids with methylene chloride; derivatize aqueous fraction with pentafluoro-benzaldehyde; extract with ethyl acetate.	GC/NPD	8 μmol[b]	79±14	Preece et al. 1992
Urine	Extract with methylene chloride; discard extract; derivatize aqueous fraction with p-chlorobenzaldehyde; extract with methylene chloride; dry and dissolve in ethyl acetate.	GC/NPD	0.05 μg/mL	No data	Timbrell and Harland 1979
Urine	Deproteinate with trichloroacetic acid; derivatize with vanillin in ethanol; acidify with sulfuric acid.	Spectrophotometry	0.065 μg/mL	99.4–100	Amlathe and Gupta 1988
Urine[c]	Dilute with deionized water.	Ion-exchange HPLC/ECD	8 ng[b]/sample	No data	Fiala and Kulakis 1981
Plasma Liver Tissue	Precipitate residual protein with hydrochloric acid and ammonium sulfate; extract interfering lipids with methylene chloride; derivatize aqueous fraction with pentafluoro-benzaldehyde; extract with chloroform.	GC/MS	≈20 nmol/mL[b]	103±9	Preece et al. 1992

TABLE 6-1. Analytical Methods for Determining Hydrazine, 1,1-Dimethylhydrazine, and 1,2-Dimethylhydrazine in Biological Samples *(continued)*

Sample matrix	Preparation method	Analytical metod	Sample detection limit	Percent recovery	Reference
Plasma[c]	None	Ion-exchange HPLC/ED	8 ng[b]/sample	No data	Fiala and Kulakis 1981
Serum Liver/brain tissue	Acidify; derivatize with p-dimethyl-aminobenzaldehyde in ethanol.	Spectrophotometry	0.025 µg[b]/sample	No data	Alvarez de Laviada et al. 1987
Serum	Treat with trichloroacetic acid; centrifuge; derivatize supernatant with p-dimethylaminobenzaldehyde in ethanol.	Spectrophotometry	0.05 µg/mL[b]	No data	Reynolds and Thomas 1965

[a] Applicable to hydrazine only unless otherwise noted.
[b] Lowest detected amount.
[c] Method applicable to 1,1-dimethylhydrazine and 1,2-dimethylhydrazine as well as hydrazine.

ED = electrochemical detector; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectroscopy; NPD = nitrogen-phosphorus detector.

TABLE 6-2. Analytical Methods for Determining Hydrazine, 1,1-Dimethylhydrazine, and 1,2-Dimethylhydrazine in Environmental Samples[a]

Sample matrix	Preparation method	Analytical metod	Sample detection limit	Percent recovery	Reference
Air	Collect in bubbler with hydrochloric acid; neutralize with sodium hydroxide; derivatize with p-dimethylaminobenz-aldehyde; dilute with glacial acetic acid.	Spectrophotometry	0.9 µg/sample	No data	NIOSH 1984
Air[b]	Adsorb on sulfuric acid-coated silica gel; elute with water; derivatize with 2-furaldehyde; extract with ethyl acetate	GC/FID	0.002 mg/m^3 [c] (hydrazine) 0.04 mg/m^3 [c] (1,1-dimethyl-hydrazine)	No data	NIOSH 1977b
Air[d]	Collect in bubbler with hydrochloric acid; derivatize with phosphomolybdic acid	Spectrophotometry	0.02 mg/m^3	No data	NIOSH 1977a
Air[b]	Collect in a microimpinger containing acetone and glacial acetic acid to trap and derivatize in one step	GC/NSD	4 ppb (5 µg/m^3)	97–104	Holtzclaw et al. 1984
Water	Acidify with hydrochloric acid; derivatize with p-dimethylamino-benzaldehyde	Spectrophotometry	5 µg/L	97.5–100.3	ASTM 1991b
Water	Derivatize with vanillin in ethanol; acidify with sulfuric acid	Spectrophotometry	0.065 ppm	99.2–100.4	Amlathe and Gupta 1988

TABLE 6-2. Analytical Methods for Determining Hydrazine, 1,1-Dimethylhydrazine, and 1,2-Dimethylhydrazine in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical metod	Sample detection limit	Percent recovery	Reference
Soil[b]	Extract with sulfuric acid; derivatize with 2,4-pentanedione	GC/TID	0.1 ppm (hydrazine) 0.5 ppm (1,1-dimethyl-hydrazine)	98–100 (hydrazine) 94–101 (1,1-dimethyl-hydrazine)	Leasure and Miller 1988
Food[d]	Extract with L-ascorbic acid; derivatize with 2-nitrobenzaldehyde; cleanup on alumina column	GC/ECD	10 ppb	72–122	Wright 1987
Food[d]	Derivatize with pentafluorobenzoyl chloride; extract with methylene chloride	GC/MS	0.01 ppm	24–100	Rutschmann and Buser 1991
Tobacco/ tobacco smoke	Derivatize with pentafluorobenzaldehyde; enrich the resulting decafluorobenz-aldehyde azine by thin layer chromatrography; extract with ether	GC/ECD	0.1 ng/cigarette	No data	Liu et al. 1974

[a] Applicable to hydrazine only unless otherwise noted.
[b] Applicable to hydrazine and 1,1-dimethylhydrazine.
[c] Lower limit of range.
[d] Applicable to 1,1-dimethylhydrazine only.

ECD = electron capture detection; FID = flame ionization detector; GC = gas chromatography; MS = mass spectroscopy; NSD = nitrogen specific detector; TID = thermionic ionization detector

6.3 ADEQUACY OF THE DATABASE

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

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for determining the levels of hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine in biological samples, including urine, plasma, serum, liver tissue, and brain tissue (Alvarez de Laviada et al. 1987; Amlathe and Gupta 1988; Fiala and Kulakis 1981; Preece et al. 1992a; Reynolds and Thomas 1965; Timbrell and Harland 1979). These methods generally employ standard chromatographic and spectrophotometric procedures with detection limits ranging from 0.02 to 0.065 μg/rnL, and therefore, most likely are sufficiently sensitive to measure levels at which biological effects occur following recent exposures. The limited data available indicate that these methods are accurate and reliable if analyses are performed rapidly, before autoxidation can occur. The background levels of hydrazines in biological samples in the general population have not been determined; if hydrazines are-present at all, they are most likely present at levels below current detection limits. The detection limits for current methods are sufficiently sensitive to detect levels at which effects occur. Since hydrazines can occur in the body following exposure to drugs such as isoniazid and hydralazine (Timbre11 and Harland 1979), and many of the metabolites of hydrazines are ubiquitous or may occur following exposure to other chemicals, measures should be taken to ensure exposure to these confounding chemicals has not

occurred. Other metabolites such as azomethane, azoxymethane, and methylazoxymethanol are unique to exposure to 1 ,2 dimethylhydrazine. Studies which identify specific biomarkers for past exposure to hydrazines, in conjunction with the development of accurate and reliable methods for detecting such biomarkers, would be useful in estimating exposure to hydrazines at hazardous waste sites.

The effects of hydrazines have been fairly well characterized in humans and animals, and include neurological, hepatic, and carcinogenic effects (Chlebowski et al. 1984; Gershanovich et al. 1976; Haun and Kinkead 1973; Rinehart et al. 1960; Thorup et al. 1992; Wilson 1976). Methods exist for measuring serum transaminase levels, vitamin B_6 status, and occult blood in stool samples, all of which may serve as biomarkers of effect for hydrazines. Although these methods are fairly accurate and reliable, none of them are specific for effects of hydrazines. Studies which identify biomarkers of effect that are specific to hydrazines, in conjunction with the development of accurate and reliable methods for detecting such biomarkers, would be useful in determining if individuals have been exposed to predicting recent exposures to hydrazines at hazardous waste sites.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods are available to detect and quantify hydrazine and dimethylhydrazines in air, water, soil, food, and tobacco (Amlathe and Gupta 1988; ASTM 1991b; Holtzclaw et al. 1984; Leasure and Miller 1988; Liu et al. 1974; NIOSH 1977a, 1977b, 1984; Rutschmann and Buser 1991; Wright 1987). Air is the medium of most concern for human exposure to this chemical. Exposure may also occur from water, especially in the vicinity of hazardous waste sites or industrial sources. The existing analytical methods can provide determinations for these chemicals at levels sufficiently low to meet regulatory requirements (NIOSH 1977a, 1977b, 1984). Assuming that an adequate quantity of air is passed through the collector (for example: a volume of at least 41 m^3 is required to detect a level equivalent to the intermediate inhalation MRL of $2x10^{-4}$ ppm for 1,1-dimethylhydrazine, assuming a detection limit of 0.9 μg/sample), current methods are sufficiently sensitive to measure levels near the MRL value for 1,1-dimethylhydrazine. However, their tendency to degrade and their chemical reactivity limit the accuracy of analyses of thesechemicals in all media. Improved methods of extraction and analysis that minimize these reactions would enhance recovery of these chemicals from environmental samples and provide a better estimate of environmental levels, especially in drinking water and soil at hazardous waste sites.

In addition, methods are available to measure degradation products of hydrazine and dimethylhydrazines (see Section 5.3.2) in environmental samples and can be used to determine the environmental impact of these chemicals.

6.3.2 On-going Studies

On-going studies to improve analytical methods for hydrazine and dimethylhydrazines includes continuing research to improve HPLC columns and EDs. In addition, the Naval Research Laboratory has been investigating pattern recognition techniques using microsensors capable of measuring hydrazine in air at ppb concentrations (Anon 1987). These improvements are designed to overcome sampling problems and increase sensitivity and reliability of the analyses.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, numerous regulations and advisories have been established for hydrazines by various international, national and state agencies. Major regulations and advisories pertaining to hydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are summarized in Tables 7-1, 7-2, and 7-3, respectively.

ATSDR has derived an intermediate-duration inhalation MRL of $4x10^{-3}$ ppm for hydrazine, as described in Appendix A. The MRL is based on a LOAEL of 0.2 ppm for fatty liver changes in female mice (Haun and Kinkead 1973). The LOAEL was adjusted for intermittent exposure (6 hours/day, 5 days/week), converted to a Human Equivalent Concentration (HEC), and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

ATSDR has derived an intermediate-duration inhalation MRL of $2x10^{-4}$ ppm for 1,1-dimethylhydrazine, as described in Appendix A. The MRL is based on a LOAEL of 0.05 ppm for hepatic effects (hyaline degeneration of the gall bladder in female mice) (Haun et al. 1984). The LOAEL was adjusted for intermittent exposure (6 hours/day, 5 days/week), converted to an HEC, and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

ATSDR has derived an intermediate-duration oral MRL of $8X10^{-4}$ mg/kg/day for 1,2-dimethylhydrazine, as described in Appendix A. The MRL is based on a LOAEL of 0.75 mg/kg/day for mild hepatitis in male mice (Visek et al. 1991). The LOAEL was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

TABLE 7-1. Regulations and Guidelines Applicable to Hydrazine

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2B[a]	IARC 1994
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	Hazardous Air Pollutant	Yes	Public Law 101-549 Section 112
	High-risk Pollutant (proposed)	Yes	EPA 1991c
	List of Regulated Substances and Threshold for Accidental Release Prevention - Proposed	5,000 pounds	EPA 1993
OSHA	PEL TWA	0.1 ppm (0.1 mg/m^3), skin[b]	NIOSH 1994
b. Food:			
FDA	Boiler water additive-limits for steam that will contact food	0	21 CFR 173.310
c. Other:			
EPA OERR	Reportable quantity	1 pound	EPA 1989 (40 CFR 302.4)
	Extremely Hazardous Substance TPQ	1,000 pounds	EPA 1987 (40 CFR 355)
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980 (40 CFR 261)
	Land Disposal Restrictions	Yes	EPA 1990b, 1991a (40 CFR 268)
	Burning of Hazardous Waste in Boilers and Industrial Furnaces-Residue Concentration Limit	1x10^{-4} mg/kg	EPA 1991b
EPA OTS	Toxic Chemical Release Reporting Rule	Yes	EPA 1988b (40 CFR 372)
	Priority Testing List (Section 4E)	Yes	EPA 1991d
Guidelines:			
a. Air:			
ACGIH	TLV TWA	Suspected human carcinogen, 0.1 ppm (0.13 mg/m^3), skin	ACGIH 1994a
	Proposed TLV TWA	Animal carcinogen, 0.01 ppm (0.013 mg/m^3), skin	

TABLE 7-1. Regulations and Guidelines Applicable to Hydrazine *(continued)*

Agency	Description	Information	References
NIOSH	REL Ceiling (120 minutes)	Potential occupational carcinogen 0.03 ppm (0.04 mg/m^3)	NIOSH 1994
b. Other:			
EPA	Carcinogenic Classification	Group B2[c]	IRIS 1995
	Cancer slope factor (q_1*)		
	q_1* (oral)	3.0 (mg/kg-day)$^{-1}$	
	q_1* (inhalation)	1.7x10^1 (mg/kg-day)$^{-1}$	
DHHS	Carcinogenic Classification	May reasonably be anticipated to be a carcinogen	NTP 1994
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1995
Connecticut		1.0 µg/m^3 (8 hour)	
Florida		1.0 x 10^{-3} mg/m^3 (8 hour)	
		3.1 x 10^{-2} µg/m^3 (24 hour)	
		1.3 x 10^{-1} µg/m^3 (8 hour)	
		3.4 x 10^{-4} µg/m^3 (1 year)	
Kansas		2.0 x 10^{-4} µg/m^3 (1 year)	
Louisiana		2.0 x 10^{-2} µg/m^3 (1 year)	
Maine		2.0 x 10^{-4} µg/m^3 (1 year)	
Massachusetts		7.0 x 10^{-3} µg/m^3 (24 hour)	
		2.0 x 10^{-3} µg/m^3 (anuual)	
Michigan		2.0 x 10^{-4} µg/m^3 (1 year)	
Nevada		2.0 x 10^{-3} mg/m^3 (8 hour)	
New York		3.3 x 10^{-1} µg/m^3 (1 year)	
North Carolina		6.0 x 10^{-4} mg/m^3 (24 hour)	
North Dakota		0 (best available control technology)	
Oklahoma		3.93 x 10^{-1} µg/m^3 (24 hour)	
Pennsylvania		2.4 x 10^{-1} µg/m^3 (1 year)	
		2.4 x 10^{-1} ppb (1 year)	
Rhode Island		3.0 x 10^{-4} µg/m^3 (annual)	
South Carolina		5.0 x 10^{-1} µg/m^3 (24 hour)	

TABLE 7-1. Regulations and Guidelines Applicable to Hydrazine *(continued)*

Agency	Description	Information	References
Texas		1.3×10^{-1} µg/m^3 (30 minute) 1.3×10^{-2} µg/m^3 (annual)	
Virginia		1.3 µg/m^3 (24 hour)	

[a] Group 2B: Possible human carcinogen
[b] Due to a Federal court decision, not enforceable as of March 22, 1993 (Hanson 1993).
[c] Group B2: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; DHHS = Department of Health and Human Services; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OAQPS = Office of Air Quality Planning and Standards; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

TABLE 7-2. Regulations and Guidelines Applicable to 1,1-Dimethylhydrazine

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2B[a]	IARC 1994
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	Hazardous Air Pollutant	Yes	Public Law 101-549
	List of Regulated Substances and Threshold for Accidental Release Prevention - Proposed	5,000 pounds	EPA 1993
	NESHAP for Source Categories: Organic HAPs from Synthetic Organic Chemical Manufacturing Industry - Proposed	Yes	EPA 1992a
OSHA	Skin PEL TWA	.5 ppm (1 mg/m^3)	NIOSH 1994
b. Other:			
EPA OERR	Reportable quantity	10 pounds	EPA 1989 (40 CFR 302.4)
	Extremely Hazardous Substance TPQ	1,000 pounds	EPA 1987 (40 CFR 355)
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980 (40 CFR 261)
	Land Disposal Restrictions	Yes	EPA 1990b EPA 1991a EPA 1992b (40 CFR 268)
EPA OTS	Toxic Chemical Release Reporting Rule	Yes	EPA 1988b (40 CFR 372)
	Priority Testing List (Section 4E)	Yes	EPA 1991d
Guidelines:			
a. Air:			
ACGIH	TLV TWA	Suspected human carcinogen, 0.5 ppm (1.2 mg/m^3), skin	ACGIH 1994a
	Proposed TLV TWA	Animal carcinogen, 0.01 ppm (0.25 mg/m^3) skin	

TABLE 7-2. Regulations and Guidelines Applicable to 1,1-Dimethylhydrazine *(continued)*

Agency	Description	Information	References
NIOSH	REL Ceiling (120 minutes)	Potential occupational carcinogen 0.06 ppm (0.15 mg/m^3)	NIOSH 1994
b. Other:			
EPA	Carcinogenic Classification	Group B2[c]	HEAST 1992
	Cancer slope factor (q_1*)		
	q_1* (oral)	2.6 (mg/kg-day)$^{-1}$	
	q_1* (inhalation)	3.5 (mg/kg-day)$^{-1}$	
DHHS	Carcinogenic Classification	May reasonably be anticipated to be a carcinogen	NTP 1994
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1995
Connecticut		11 µg/m^3 (8 hour)	
Florida		1.0 x 10^{-2} mg/m^3 (8 hour) 6.0 x 10^{-2} µg/m^3 (24 hour) 2.5 x 10^{-1} µg/m^3 (8 hour)	
Nevada		2.4 x 10^{-2} mg/m^3 (8 hour)	
New York		3.3 µg/m^3 (1 year)	
North Dakota		0 (best available control technology)	
Oklahoma		1.5 µg/m^3 (24 hour)	
Pennsylvania		2.4 µg/m^3 (1 year) 1.2 ppb (1 year)	
South Carolina		5.0 µg/m^3 (24 hour)	
Texas		2.5 x 10^{-1} µg/m^3 (30 minute) 2.5 x 10^{-2} µg/m^3 (annual)	
Virginia		12 µg/m^3 (24 hour)	
Washington		3.3 µg/m^3 (24 hour)	

[a] Group 2B: Possible human carcinogen
[b] Due to a Federal court decision, not enforceable as of March 22, 1993 (Hanson 1993).
[c] Group B2: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; DHHS = Department of Health and Human Services; HAP = Hazardous Air Pollutants; IARC = International Agency for Research on Cancer; NESHAP = National Emission Standards for Hazardous Air Pollutants; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OAQPS = Office of Air Quality Planning and Standards; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average.

TABLE 7-3. Regulations and Guidelines Applicable to 1,2-Dimethylhydrazine

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2B[a]	IARC 1994
NATIONAL			
Regulations:			
a. Other:			
EPA OERR	Reportable quantity	1 pound	EPA 1989 (40 CFR 302.4)
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1980 (40 CFR 261)
	Land Disposal Restrictions	Yes	EPA 1990b EPA 1991a (40 CFR 268)
EPA OTS	Toxic Chemical Release Reporting Rule - Proposed	Yes	EPA 1992d (40 CFR 372)
Guidelines:			
a. Other:			
EPA	Carcinogenic Classification	Group B2[b]	HEAST 1992
	Cancer slope factor (q_1*)		
	q_1* (oral)	3.7×10^1 (mg/kg-day)$^{-1}$	
	q_1* (inhalation)	3.7×10^1 (mg/kg-day)$^{-1}$	
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		NATICH 1991
South Carolina		5.0 µg/m^3 (24 hour)	

[a] Group 2B: Possible human carcinogen
[b] Group B2: Probable human carcinogen

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

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9. GLOSSARY

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

Adsorption Coeffkient (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 period.

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

Carcinogen -- A chemical capable of inducing cancer.

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

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

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

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

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

Lethal Concentratioq($_{50}$) (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 defied 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.

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

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

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

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

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

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

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

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

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

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ 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 (I) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

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

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

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

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

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

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

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the US. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

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

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: Hydrazine
CAS Number: 302-01-2
Date: September 5, 1996
Profile Status: Draft 3
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 19
Species: mouse

Minimal Risk Level: 4×10^{-3} ppm [ ] mg/kg/day [X] ppm

Reference: Haun and Kinkead 1973

Experimental design:(human study details or strain, number of animals per exposure/control groups, sex, dose administration details): 40 female ICR mice per group, exposed by inhalation to 0, 0.2, or 1.0 ppm continuously for 6 months.

Effects noted in study and corresponding doses: Moderate to severe fatty liver changes were seen at both exposure levels.

Calculations:
$LOAEL_{(HEC)} = LOAEL \times [(V_A/BW)_A \div (V_A/BW)_H]$
$LOAEL_{(HEC)} = LOAEL \times [(V_A/BW)_A \div (V_A/BW)_H]$
$LOAEL_{(HEC)} = 0.2 \text{ ppm} \times [(0.043 \text{ m}^3/\text{day} \div 0.026 \text{ kg}) \div (20 \text{ m}^3/\text{day} \div 70 \text{ kg})]$
$LOAEL_{(HEC)} = 1.154 \text{ ppm}$

$MRL = LOAEL_{(HEC)} \div \text{Uncertainty Factor}$
$MRL = 1.154 \text{ ppm} \div 300$
$MRL = 4 \times 10^{-3} \text{ ppm}$

Dose and endpoint used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans following conversion to HEC
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: V_A mouse = 0.043 m^3/day, BW = 0.026 kg

V_A human = 20 m^3/day, BW = 70 kg

Other additional studies or pertinent information which lend support to this MRL: The authors (Haun and Kinkead 1973) also investigated the effects of inhaled hydrazine in other species. Fatty liver changes were also observed in dogs exposed to 1 ppm hydrazine for 6 months and in monkeys exposed to 0.2 ppm for 6 months.

Agency Contact (Chemical Manager): Hugh Hansen

Agency Review Date: 1° review:_____
2° review:_____

Chemical Name: 1,1 -Dimethylhydrazine
CAS Number: 57-14-7
Date: September 5, 1996
Profile Status: Draft 3
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 17
Species: mouse

Minimal Risk Level: 2×10^{-4} [ ] mg/kg/day [X] ppm

Reference: Haun et al. 1984

Experimental design:(human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 400 female C57BL/6 mice per group, exposed by inhalation to 0, 0.05, 0.5, or 5 ppm for 6 months, 5 days per week, 6 hours per day.

Effects noted in study and corresponding doses: Hyaline degeneration in the gallbladder was significantly increased in the 0.05, 0.5, and 5 ppm groups compared to controls. Thus, the LOAEL is set at 0.05 ppm.
Calculations:

$LOAEL_{(HEC)} = LOAEL(ADJ) \times [(VA/BW)A \div (V_A/B\ W)_H]$
$LOAEL_{(HEC)} = (0.05 \text{ ppm} \times 6 \text{ hr}/24 \text{ hr} \times 5 \text{ d}/7 \text{ d}) \times [(V_A/BW)_A + (V_A/BW)_H]$
$LOAEL_{(HEC)} = 0.0089 \text{ ppm} \times [(0.043 \text{ m}^3/\text{day} \div 0.026 \text{ kg}) \div 20 \text{ m}^3/\text{day} + 70 \text{ kg})]$
$LOAEL_{(HEC)} = 0.05 \text{ ppm}$

$MRL = LOAEL_{(HEC)} \div \text{Uncertainty Factor}$
$MRL = 0.05 \text{ ppm} + 300$
$MRL = 2 \times 10^{-4} \text{ ppm}$

Dose and endpoint used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans following conversion to HEC
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: V_A mouse = 0.043 m^3/day, BW = 0.026 kg
V_A human = 20 m^3/day, BW = 70 kg

APPENDIX A

Other additional studies or pertinent information which lend support to this MRL: Studies of workers exposed to 1,1-dimethylhydrazine have reported changes indicative of a hepatic effect (elevated serum alanine aminotransferase activity, positive cephalin flocculation test) (Petersen et al. 1970; Shook and Cowart 1957). Angiectasis was observed in the livers of all exposed mice. Hepatic congestion was noted in mice exposed to 0.5 or 5 ppm 1,1-dimethylhydrazine (Haun et al. 1984). No NOAEL was identified.

Agency Contact (Chemical Manager): Hugh Hansen

Agency Review Date: 1° review:_____
2°review:_____

Chemical Name: 1,2-Dimethylhydrazine
CAS Number: 540-73-8
Date: September 5, 1996
Profile Status: Draft 3
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 25
Species: mouse

Minimal Risk Level: 8×10^{-4} [X] mg/kg/day [ ] ppm

Reference: Visek et al. 199 1

Experimental design:(human study details or strain, number of animals per exposure/control groups, sex, dose administration details): 25 male mice per group, exposed to 0, 0.75, 1.6, or 2.7 mg/kg/day in the diet for 5 months. Although 2 diet preparations were administered (one containing 10% protein, the other containing 40% protein), the doses of 1,2-dimethylhydrazine were judged not to differ significantly between the two groups.

Effects noted in study and corresponding doses: Mild hepatitis and small decreases in body weight gain and relative organ weights were observed in mice exposed to the lowest dose (0.75 mg/kg/day). These effects were more severe in animals exposed to higher doses. For example, doses of 1.6 mg/kg/day produced frank toxic hepatitis, as characterized by lobular disorganization, hepatocellular hypertrophy, and centrilobular necrosis. Portal fibrosis and bile duct hyperplasia, two effects noted in only a few animals exposed to 1.6 mg/kg/day, were more frequently observed in animals receiving the highest dose (2.7 mg/kg/day).
Calculations:

MRL = LOAEL ÷ Uncertainty Factor
MRL = 0.75 mg/kg/day ÷1000
MRL = 8×10^{s4} mg/kg/day

Dose and endpoint used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: 0.058 mg/day (daily food intake provided by authors) ÷ 0.035 kg (body weight provided by authors) x 0.45 (molecular weight adjustment for use of dihydrochloride salt) = 0.75 mg/kg/day.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: N/A

Other additional studies or pertinent information which lend support to this MRL: Hepatic effects (hepatotoxicity, necrosis, fibrosis, hemosiderosis, ascites, cirrhosis, degeneration) have been observed in rats (Bedell et al. 1982), guinea pigs (Wilson 1976), dogs (Wilson 1976), and pigs (Wilson 1976) subchronically exposed to 4.2-30 mg/kg/day 1,2-dimethylhydrazine by the oral route.

Agency Contact (Chemical Manager): Hugh Hansen

Agency Review Date: 1° review:_____
2°review:_____

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 1 S), rats were exposed to 1 ,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

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

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 1% NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_l*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

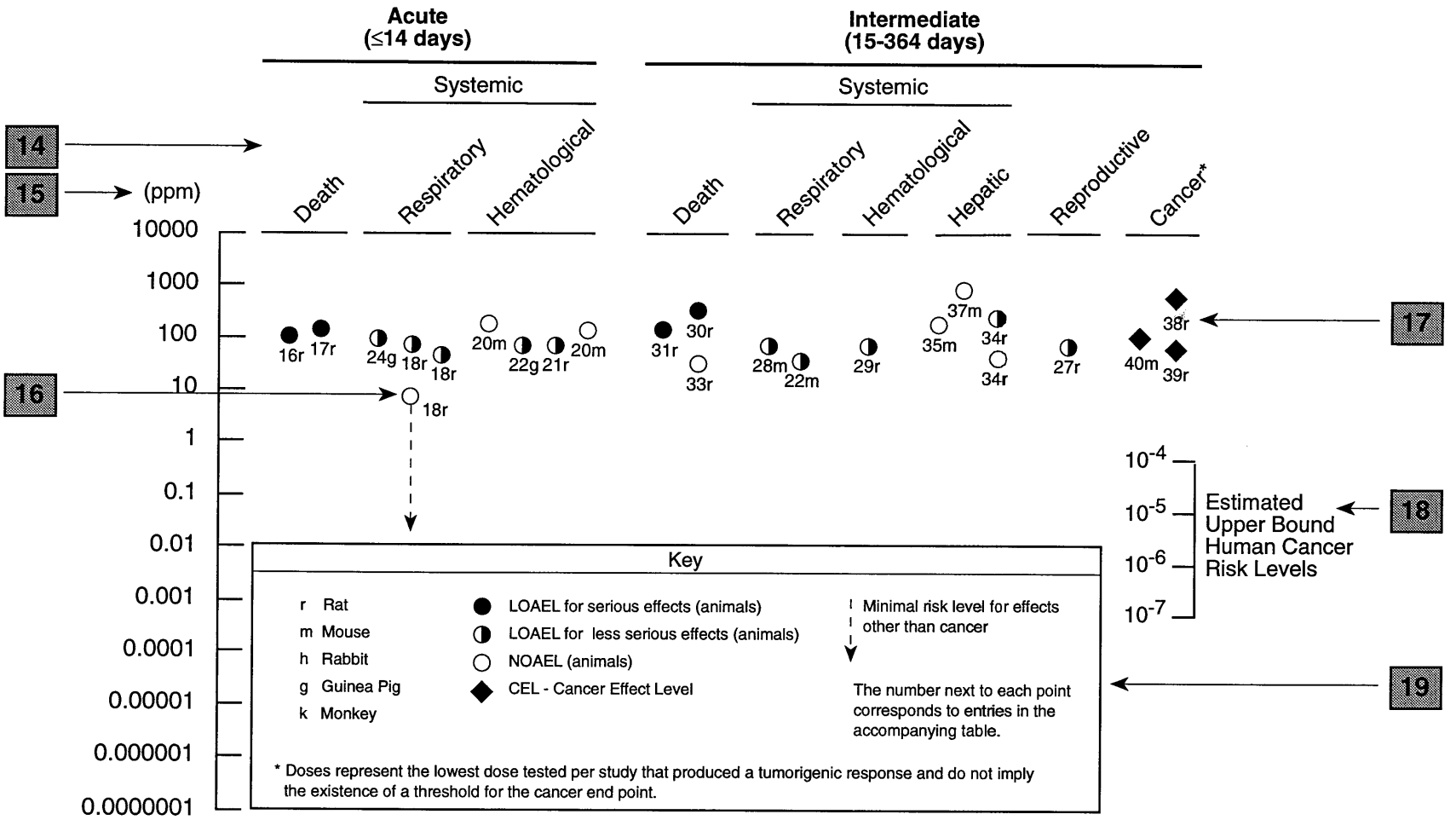
[a] The number corresponds to entries in Figure 2-1.

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

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

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2 . What effects observed in animals are likely to be of concern to humans?

3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observedadverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio

kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NCE	normochromatic erythrocytes
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PCE	polychromatic erythrocytes
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million

ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram