

TOXICOLOGICAL PROFILE FOR
1,2-DIPHENYLHYDRAZINE

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

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The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

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

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

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

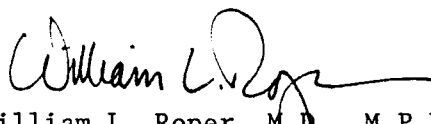
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological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

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

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

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



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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,2-diphenylhydrazine and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1177 sites on its National Priorities List (NPL). 1,2-Diphenylhydrazine has been found at 7 of these sites. However, we do not know how many of 1177 NPL sites have been evaluated for 1,2-diphenylhydrazine. As EPA evaluates more sites, the number of sites at which 1,2-diphenylhydrazine is found may change. The information is important for you because 1,2-diphenylhydrazine may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,2-diphenylhydrazine.

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

If you are exposed to a hazardous substance such as 1,2-diphenylhydrazine, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 1,2-DIPHENYLHYDRAZINE?

1,2-Diphenylhydrazine is a white solid. It dissolves only slightly in water and does not change into a gas unless it is heated to very high temperatures. It sticks to soil and can be carried into the air along with windblown dust. Once in water or exposed to air it is changed into other chemicals within minutes. These chemicals include the toxic chemicals azobenzene and benzidine. More information about these two chemicals can be found in the ATSDR Toxicological Profile on Benzidine or by contacting the Agency for Toxic Substances and Disease Registry (see Section 1.8).

1,2-diphenylhydrazine is used to make fabric dyes in other countries, and to make certain medicines. There are no other major manmade or natural sources of 1,2-diphenylhydrazine. More information on these subjects can be found in Chapters 3, 4, and 5.

1.2 HOW MIGHT I BE EXPOSED TO 1,2-DIPHENYLHYDRAZINE?

1,2-Diphenylhydrazine does not dissolve in water easily and reacts quickly when present in water. Therefore, it is extremely unlikely that you

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would be exposed to it by drinking water. Also, 1,2-diphenylhydrazine does not change to a gas at normal outside temperatures. Therefore, it is extremely unlikely that you would be exposed to it by breathing air even if you live near a hazardous waste site. Because 1,2-diphenylhydrazine may stick to soil, it is possible that you could breathe in dust coated with 1,2-diphenylhydrazine if you entered a hazardous waste site in which it had been recently spilled on the ground. It is also possible that children playing at this hazardous waste site could be exposed by eating dirt or smearing dirt on their skin. It would have to be a site in which the 1,2-diphenylhydrazine was recently spilled on the ground, since once exposed to air, 1,2-diphenylhydrazine changes into other substances within minutes. You also could be exposed to 1,2-diphenylhydrazine if you work in an industry in which it is used. For example, while working, you could be exposed to dust containing 1,2-diphenylhydrazine when it is moved from one place to another. It has not been found in food or in air or natural soils. If 1,2-diphenylhydrazine exists at all in lakes or streams, it is probably at levels that are less than 1 part 1,2-diphenylhydrazine in 1,000,000 parts water (ppm). More information on how you could be exposed to 1,2-diphenylhydrazine can be found in Chapter 5.

1.3 HOW CAN 1,2-DIPHENYLHYDRAZINE ENTER AND LEAVE MY BODY?

If you were to breathe in dust coated with 1,2-diphenylhydrazine you would probably breathe out most of it within a few minutes; however, some of it might enter your body. Also, if you were to eat dust or dirt coated with 1,2-diphenylhydrazine, some of it might enter your body. However, we do not know how much or how long it would take for the 1,2-diphenylhydrazine that you breathe in or eat to enter your body. It is not known if 1,2-diphenylhydrazine would enter your body if you were to spill it on your skin or if you were to get dirt coated with it on your skin. Some, maybe most of 1,2-diphenylhydrazine that enters your body leaves your body in the urine. It is not known how long it takes for 1,2-diphenylhydrazine to leave the body in the urine. Additional information on how 1,2-diphenylhydrazine can enter and leave your body is presented in Chapter 2.

1.4 HOW CAN 1,2-DIPHENYLHYDRAZINE AFFECT MY HEALTH?

It is not known if 1,2-diphenylhydrazine would affect your health if you were to breathe it in or eat it. The health effects of 1,2-diphenylhydrazine in humans have not been studied. Animals die if they swallow large amounts of 1,2-diphenylhydrazine, and develop liver disease if they eat small amounts of 1,2-diphenylhydrazine for more than a year. Therefore, it is possible that if you were to eat large amounts of 1,2-diphenylhydrazine for a long time you might experience liver damage or die. It is not known whether 1,2-diphenylhydrazine would harm you if you were to spill it on your skin. It is not known if 1,2-diphenylhydrazine causes birth defects or affects fertility. It is not known if 1,2-diphenylhydrazine causes cancer in humans; however, it has been shown to cause cancer in rats and mice that have eaten it in food for most of their

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lifetime. Additional information on the health effects of 1,2-diphenylhydrazine is presented in Chapter 2.

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

Tables 1-1, 1-2, 1-3, and 1-4 show how little we know about the levels of 1,2-diphenylhydrazine that might affect your health. As is shown in Table 1-4, animals that ate food containing 1,2-diphenylhydrazine for a long time developed lung inflammation, stomach damage, and liver damage, and some died. Although the levels of exposure that cause harmful effects in humans are not known, as discussed in Section 1.2, 1,2-diphenylhydrazine is not likely to be found in food, and you are not even likely to be exposed to levels of concern if you live near a hazardous waste site. Additional information on levels of exposure associated with effects can be found in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,2-DIPHENYLHYDRAZINE?

There is no test to determine if you have been exposed to 1,2-diphenylhydrazine. More information about tests for exposure and effects can be found in Chapters 2 and 6.

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

A guideline to protect human health, by limiting exposure to 1,2-diphenylhydrazine in water, has been issued by the federal government. The U.S. Environmental Protection Agency (EPA) has made recommendations to limit the concentration of 1,2-diphenylhydrazine in natural waters, such as lakes and streams. The EPA has developed regulations to limit the release of 1,2-diphenylhydrazine by industries. Any release of 1 pound or more of 1,2-diphenylhydrazine must be reported to EPA.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

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

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in the recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

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TABLE 1-1. Human Health Effects from Breathing 1,2-Diphenylhydrazine*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of humans to air containing specific levels of 1,2-diphenylhydrazine are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term exposure of humans to air containing specific levels of 1,2-diphenylhydrazine are not known.

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

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TABLE 1-2. Animal Health Effects from Breathing 1,2-Diphenylhydrazine

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of animals to air containing specific levels of 1,2-diphenylhydrazine are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Air</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term exposure of animals to air containing specific levels of 1,2-diphenylhydrazine are not known.

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TABLE 1-3. Human Health Effects from Eating or Drinking
1,2-Diphenylhydrazine*

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of humans to food containing specific levels of 1,2-diphenylhydrazine are not known.
<u>Levels in Water</u>		The health effects resulting from short-term exposure of humans to water containing specific levels of 1,2-diphenylhydrazine are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from long-term exposure of humans to food containing specific levels of 1,2-diphenylhydrazine are not known.
<u>Levels in Water</u>		The health effects resulting from long-term exposure of humans to water containing specific levels of 1,2-diphenylhydrazine are not known.

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

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**TABLE 1-4. Animal Health Effects from Eating or Drinking
1,2-Diphenylhydrazine**

Short-term Exposure (less than or equal to 14 days)		
<u>Levels in Food</u>	<u>Length of Exposure</u>	<u>Description of Effects</u>
		The health effects resulting from short-term exposure of animals to food containing specific levels of 1,2-diphenylhydrazine are not known.
<u>Levels in Water</u>		The health effects resulting from short-term exposure of animals to water containing specific levels of 1,2-diphenylhydrazine are not known.
Long-term Exposure (greater than 14 days)		
<u>Levels in Food (ppm)</u>	<u>Length of Exposure</u>	<u>Description of Effects*</u>
40	78 weeks	Inflammation of lungs in rats.
100	78 weeks	Death and liver damage in rats.
300	78 weeks	Stomach damage in rats.
400	78 weeks	Liver damage and death in mice.
<u>Levels in Water</u>		The health effects resulting from long-term exposure of animals to water containing specific levels of 1,2-diphenylhydrazine are not known.

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (minimal risk levels, MRLs) are of interest to health professionals and citizens alike. For certain chemicals, levels of exposure associated with carcinogenic effects may be indicated in the figures. These levels reflect the actual doses associated with the tumor incidences reported in the studies cited.

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Because cancer effects could occur at lower exposure levels, the figures also show estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to 1,2-diphenylhydrazine:

2.2.1.1 Death

2.2.1.2 Systemic Effects

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

2.2.1.8 Cancer

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans following oral exposure to 1,2-diphenylhydrazine. Limited information is available regarding the lethality of orally-administered 1,2-diphenylhydrazine in animals. This consists of an incompletely documented acute LD50 of 959 mg/kg in rats (Marhold et al. 1968), an unreliable acute lethal dose of

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1213 mg/kg/day in mice (Schafer and Bowles 1985), lethal doses for intermediate duration exposure (4 weeks) of 54 mg/kg/day in rats and 390 mg/kg/day in mice (NTP 1983), and nonlethal and lethal doses for chronic exposure in rats (2 and 5 mg/kg/day, respectively) and mice (10 and 52 mg/kg/day, respectively) (NTP 1983). The animal lethality data are discussed below and summarized in Table 2-1.

A single-dose LD₅₀ of 959 mg/kg was determined for rats treated by gavage with 1,2-diphenylhydrazine in water suspension (Marhold et al. 1968). Apparently, this value was determined using conventional methodology but the duration of observation was not reported and it was not indicated if treatment with undegraded compound was assured. Degradation could be an issue because 1,2-diphenylhydrazine degrades rapidly in water (Chapter 5). The cause(s) of mortality in the rats was not reported. The 959 mg/kg LD₅₀ is recorded in Table 2-1 and plotted in Figure 2-1.

In another study, the average amount of 1,2-diphenylhydrazine consumed by wild deer mice over a 3-day period without killing more than 50% of the mice was determined to be 1213 mg/kg/day (Schafer and Bowles 1985). The validity of this finding is uncertain; however, as the dose was estimated from consumption of seeds treated with only one concentration of chemical, only five mice were treated, and the actual number of deaths was not reported. Because of these limitations, the 1213 mg/kg/day dose is not a reliable effect level for lethality due to acute duration exposure.

Small groups (five) of rats or mice of each sex were administered various concentrations of 1,2-diphenylhydrazine in the diet for 4 weeks, followed by 2 weeks without treatment (NCI 1978). Estimated doses ranged from 3.5-210 mg/kg/day (eight dose levels) in male rats and 0.04-2600 mg/kg/day (nine dose levels) in female rats. Deaths occurred in 2 of 5 male rats at 54 mg/kg/day and in all rats of both sexes at higher doses. Although small numbers of rats were tested at each dose, it can be assumed that the mortality at 54 mg/kg/day was related to treatment because of death at higher doses. The 54 mg/kg/day dose, therefore, is a LOAEL value for lethality in rats due to intermediate duration exposure (Table 2-1, Figure 2-1). In mice, estimated doses ranged from 9.1-550 mg/kg/day (eight dose levels) in males and 0.39-6700 mg/kg/day (nine dose levels) in females. Deaths occurred in 1 of 5 male mice at 390 mg/kg/day, 2 of 5 male mice at 550 mg/kg/day, 4 of 5 male mice at 950 mg/kg/day, and in all female mice at 6700 mg/kg/day. Using the reasoning used for the rat LOAEL, the 390 mg/kg/day dose can be considered a LOAEL for lethality in mice for intermediate duration of exposure (Table 2-1, Figure 2-1). Because of uncertainty related to the small size of the groups, the doses below the rat and mouse LOAELs are not reliable NOAELs for lethality. The cause(s) of the mortality in these studies was not indicated.

Rats and mice were fed diets that contained 1,2-diphenylhydrazine for 78 weeks, followed by 28-30 weeks (rats) or 17-18 weeks (mice) without treatment (NCI 1978). Estimated doses for the rats were 4 and 15 mg/kg/day

TABLE 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect)		Reference
						Less Serious (mg/kg/d)	Serious (mg/kg/d)	
ACUTE EXPOSURE								
Death								
1	Rat	(G)	1 d				959 (LD ₅₀)	Marhold et al. 1968
INTERMEDIATE EXPOSURE								
Death								
2	Rat	(F)	4 wk				54	NCI 1978
3	Mouse	(F)	4 wk				390	NCI 1978
Systemic								
4	Rat	(F)	288 d	Other	19			Marhold et al. 1968
5	Rat	(F)	4 wk	Other	2600			NCI 1978
6	Mouse	(F)	4 wk	Gastro Other	 6700		390 (intestinal hemorrhage)	NCI 1978
CHRONIC EXPOSURE								
Death								
7	Rat	(F)	78 wk		2		5 ^a (increased mortality)	NCI 1978
8	Mouse	(F)	78 wk		10		52 ^b (increased mortality)	NCI 1978

TABLE 2-1 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect)		Reference
						Less Serious (mg/kg/d)	Serious (mg/kg/d)	
Systemic								
9	Rat	(F)	78 wk	Resp		2 ^c	(interstitial inflammation of lung)	NCI 1978
				Gastro	5	15 ^d	(hyperkeratosis, acanthosis)	
				Hepatic	4	5 ^a	(fatty degeneration)	
				Other	5	15	(decreased weight gain)	
10	Mouse	(F)	78 wk	Other	10	52	(decreased body weight)	NCI 1978
				Hepatic	10	52 ^b	(coagulative necrosis)	
				Resp	52			
				Gastro	52			
Cancer								
11	Rat	(F)	78 wk				4 (hepatocellular carcinoma)	NCI 1978
12	Mouse	(F)	78 wk				52 (hepatocellular carcinoma)	NCI 1978

^aConverted to an equivalent concentration of 100 ppm in food for presentation in Table 1-4.

^bConverted to an equivalent concentration of 400 ppm in food for presentation in Table 1-4.

^cConverted to an equivalent concentration of 40 ppm in food for presentation in Table 1-4.

^dConverted to an equivalent concentration of 300 ppm in food for presentation in Table 1-4.

d = day; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Resp = respiratory; wk = week.

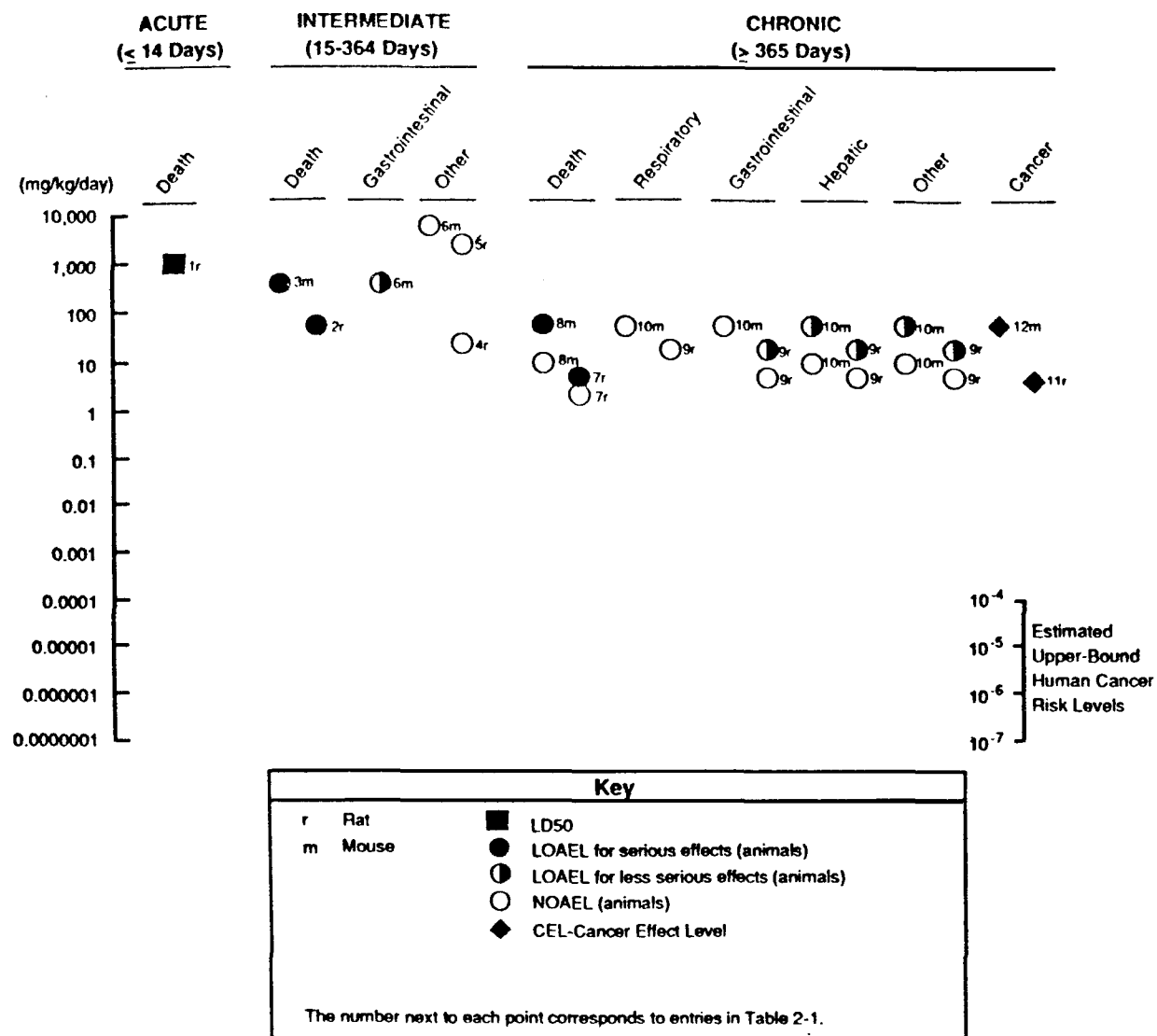


FIGURE 2-1. Levels of Significant Exposure to 1,2-Diphenylhydrazine-Oral

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in males, and 2 and 5 mg/kg/day in females. Mortality was increased significantly only in the high-dose female rats, indicating that 5 mg/kg/day is a LOAEL for decreased survival due to chronic exposure (Table 2-1, Figure 2-1). These data suggest that female rats are more sensitive than male rats. Because females appear to be the more sensitive sex and it is not known if 4 mg/kg/day (the NOAEL in males that is below the 5 mg/kg/day LOAEL in females) is lethal in females, the 2 mg/kg/day dose in females is the most reliable NOAEL for lethality in this species. Estimated doses for the mice were 10 and 52 mg/kg/day in males and 5.2 and 52 mg/kg/day in females. Mortality was increased significantly in both the high-dose male and female mice, indicating that the 52 mg/kg/day dose is the LOAEL and 10 mg/kg/day is the highest NOAEL for lethality in mice due to chronic exposure (Table 2-1, Figure 2-1). The cause(s) of the mortality in the rats or mice was not indicated.

2.2.2.2 Systemic Effects

No studies were located regarding cardiovascular, hematological, musculoskeletal, renal, or dermal/ocular systemic effects in humans or animals following oral exposure to 1,2-diphenylhydrazine.

Respiratory Effects. No studies were located regarding respiratory effects of 1,2-diphenylhydrazine in humans. One animal study, discussed below, indicates that chronic oral administration of 1,2-diphenylhydrazine produced interstitial inflammation of the lungs in rats (NCI 1978).

Evaluation of the incidence data for nonneoplastic lesions in the NCI (1978) chronic oral study shows that there were statistically increased incidences of interstitial inflammation in the lungs of male rats. These rats were treated with 1,2-diphenylhydrazine in the diet at doses of 4 or mg/kg/day for 78 weeks. Increased incidences of this lesion were also observed in female rats treated similarly with a dose of 2 mg/kg/day, but not in mice treated similarly with doses of 5.2 mg/kg/day (females), 10 w/k/day (males), or 52 mg/kg/day (males and females). The highest NOAEL value in mice and the LOAEL in rats for respiratory effects due to chronic exposure are recorded in Table 2-1 and plotted in Figure 2-1.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects of 1,2-diphenylhydrazine in humans. As discussed below, gastrointestinal effects were observed in an intermediate duration study with mice (intestinal hemorrhage) (NCI 1978) and a chronic study with rats (stomach hyperkeratosis and acanthosis) (NCI 1978).

NCI (1978) concluded from pathological examinations of mice that died in a 4-week diet study of 1,2-diphenylhydrazine that, "Intestinal hemorrhage was the single gross abnormality consistently observed in these mice." The severity of the hemorrhage was not described. As indicated in Section 2.2.2.1, deaths occurred in mice at doses 390 mg/kg/day or more but not 280 mg/kg/day or less. Intestinal hemorrhage was not observed in rats that

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died from similar treatment with doses as high as 2600 mg/kg/day. Based on these data, the 390 mg/kg/day dose can be considered a LOAEL for gastrointestinal effects in mice due to intermediate duration exposure (Table 2-1, Figure 2-1). As histological examinations were not conducted on any of the animals, reliable NOAELs for gastrointestinal effects due to intermediate exposure in either species cannot be identified.

Evaluation of the incidence data for nonneoplastic lesions in the NCI (1978) chronic oral study shows that there were statistically increased incidences of stomach hyperkeratosis and acanthosis in the high dose male rats. These rats were treated with 1,2-diphenylhydrazine in the diet at a dose of 15 mg/kg/day for 78 weeks. Increased incidences of these lesions were not observed in male rats treated with 4 mg/kg/day, female rats treated similarly with doses of 2 or 5 mg/kg/day, or mice treated similarly with doses of 5.2 mg/kg/day (females), 10 mg/kg/day (males), or 52 mg/kg/day (males or females). Due to the prevalence of the hyperkeratosis (21% versus 4% in controls) and acanthosis (36% versus 4% in controls), appearance of these lesions due to dietary treatment (they are more commonly associated with gavage treatment), and occurrence of gross intestinal hemorrhage in mice treated with higher doses of 1,2-diphenylhydrazine in the 4-week NCI (1978) study, the effects are considered to be adverse. The 15 mg/kg/day dose therefore is a LOAEL for gastrointestinal effects in rats due to chronic duration exposure (Table 2-1, Figure 2-1). The highest doses not producing gastrointestinal histologic alterations in the rats (5 mg/kg/day) and mice (52 mg/kg/day) are NOAELs for gastrointestinal effects due to chronic exposure (Table 2-1, Figure 2-1).

Hepatic Effects. No studies were located regarding hepatic effects of 1,2-diphenylhydrazine in humans. Chronic oral administration of 1,2-diphenylhydrazine produced degenerative alterations in the liver of rats (fatty metamorphosis) and mice (coagulative necrosis) (NCI 1978).

Evaluation of the incidence data for nonneoplastic lesions in the NCI (1978) chronic oral study shows that there was a statistically increased incidence of fatty metamorphosis of the liver in the high-dose male rats (20% versus 0% in controls). These rats were treated with 1,2-diphenylhydrazine in the diet at a dose of 15 mg/kg/day for 78 weeks. Fatty metamorphosis was also observed in 20% of the high dose (5 mg/kg/day) female rats. Although the increased incidence in the high dose female rats was not statistically significant when compared with the incidence (12%) in the matched control group, the incidence was statistically significant when compared with the incidence (4%) in the control group for the low dose group of females. Female mice treated similarly with 52 mg/kg/day had a statistically increased incidence of coagulative necrosis of the liver (13% versus 0% in controls). High incidences of focal necrosis were seen in low dose female rats, the high dose control male and female mice, the low dose treated male and female mice, and the high dose treated male mice. The incidence in the low dose female rats was significantly increased above the matching control group, but not above the control group for the high dose

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treated group. A similar effect was not seen in the high dose female rats. The high incidence of focal necrosis in the high dose control groups makes meaningful interpretation of the toxicological significance of this particular lesion difficult. Nevertheless, because of the severity and prevalence of the liver lesions taken together and the fact that hepatic neoplasms were observed in this study, the liver is a major target organ of 1,2-diphenylhydrazine in both species. The highest NOAEL value and all reliable LOAEL values for hepatic effects in both species for chronic exposure are recorded in Table 2-1 and plotted in Figure 2-1.

Other Systemic Effects. No studies were located regarding other systemic effects of 1,2-diphenylhydrazine in humans. Decreased body weight gain and/or weight loss was observed in chronic oral studies with rats and mice (NCI 1978). As discussed below, these effects may be a consequence of other toxic effects or cancer.

Initial and final body weights were not significantly different in rats treated with 19 mg/kg/day in the diet for 288 days (Marhold et al. 1968). Other endpoints of systemic toxicity were not reported in this study. Body weights were not depressed consistently in rats and mice treated with 1,2-diphenylhydrazine in the diet at doses as high as 2600 mg/kg/day (rats) or 6700 mg/kg/day (mice) for 4 weeks, followed by 2 weeks without treatment (NCI 1978). These NOAELs for rats and mice are presented in Table 2-1 and Figure 2-1 as other systemic effects for intermediate duration exposure.

Male rats treated with 1,2-diphenylhydrazine in the diet at a dose of 15 mg/kg/day for 78 weeks had approximately 10-15% decreased body weight gain (NCI 1978). NCI/NTP usually considers effects on body weight of this magnitude to be significant. Treatment-related effects on body weight were not apparent in male or female rats treated similarly with doses of 2-5 mg/kg/day. With the exception of respiratory, gastrointestinal, and hepatic alterations at 15 mg/kg/day (discussed previously), comprehensive histological examinations of the rats did not show treatment-related nonneoplastic lesions. Although food consumption data were not reported, the decreased weight gain is probably secondary to toxic or neoplastic effects and should be considered an adverse effect. The doses of 15 mg/kg/day and 5 mg/kg/day therefore are the LOAEL and highest NOAEL, respectively, for other systemic effects in rats due to chronic duration exposure (Table 2-1, Figure 2-1).

Male and female mice treated with 1,2-diphenylhydrazine in the diet at a dose of 52 mg/kg/day for 78 weeks had decreased weight gain and subsequent weight loss (approximately 30% at termination of the study) (NCI 1978). Treatment-related effects on body weight were not apparent in mice treated similarly with 5.2 mg/kg/day (females) or 10 mg/kg/day (males). Except for hepatic alterations at 52 mg/kg/day (discussed previously), comprehensive histological examinations of the mice showed no treatment-related nonneoplastic lesions. As body weight loss is an adverse effect, the 52 mg/kg/day dose is a LOAEL for other systemic effects in mice due to

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chronic duration exposure (Table 2-1, Figure 2-1). The highest NOAEL for other systemic effects in mice is 10 mg/kg/day (Table 2-1, Figure 2-1).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to 1,2-diphenylhydrazine.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 1,2-diphenylhydrazine.

Clinical signs and histological examinations of the brain were unremarkable in rats and mice treated with 1,2-diphenylhydrazine in the diet at doses of 15 and 52 mg/kg/day, respectively, for 78 weeks (NCI 1978). These data provide an inadequate basis for evaluating possible neurotoxicity, as behavioral or neurological evaluations were not conducted.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to 1,2-diphenylhydrazine.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,2-diphenylhydrazine.

Histological examinations of the seminal vesicle, testes, prostate, uterus, ovaries, and mammary gland were unremarkable in rats and mice treated with 1,2-diphenylhydrazine in the diet at doses as high as 15 and 52 mg/kg/day, respectively, for 78 weeks (NCI 1978). These data provide an insufficient basis for evaluating reproductive toxicity, as reproductive function was not evaluated.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to 1,2-diphenylhydrazine.

Sex-linked recessive lethal mutations were not produced in *Drosophila* fed ethanol solution containing 50 ppm 1,2-diphenylhydrazine for 3 days (Yoon et al. 1985). No oral genotoxicity studies of 1,2-diphenylhydrazine in mammals were located.

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2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans after oral exposure to 1,2-diphenylhydrazine. As discussed below, chronic oral administration of 1,2-diphenylhydrazine was carcinogenic in rats and female mice (NCI 1978).

Treatment-related neoplasms occurred in rats and mice that were treated with low or high doses of 1,2-diphenylhydrazine in the diet for 78 weeks, followed by untreated observation periods of 28 or 30 weeks (rats) and 17 or 18 weeks (mice) (NCI 1978). Male rats had statistically significant increased incidences of hepatocellular carcinomas or neoplastic nodules in the liver due to treatment with 4 mg/kg/day and 15 mg/kg/day, and squamous-cell carcinomas of the Zymbal's gland and adrenal pheochromocytomas resulted from treatment with 15 mg/kg/day. Incidences of liver neoplastic nodules and mammary gland adenocarcinomas were increased significantly in female rats treated with 5 mg/kg/day, but not 2 mg/kg/day. A significantly increased incidence of hepatocellular carcinoma occurred in female mice treated with 52 mg/kg/day, but not 5.2 mg/kg/day. Doses of 10.4 or 52 mg/kg/day were not neoplastic for male mice.

Tumors were not observed in male rats treated with 19 mg/kg/day doses of 1,2-diphenylhydrazine in the diet for life (mean survival time = 288 days) (Marhold et al. 1968). The significance of this finding is uncertain because the type and scope of pathological examination were not reported. Pliss (1974) reported increased numbers of tumors of the liver, Zymbal's gland, mammary gland and other sites in rats that were treated with 1,2-diphenylhydrazine in the diet at an estimated dose of 85 mg/kg/day, 5 days/week for 588 days (Pliss 1974). These findings are inconclusive, however, because of lack of control data and other report inadequacies.

The lowest Cancer-Effect-Levels (CELs) in the NCI (1978) bioassay are the doses that caused hepatocellular carcinoma in rats (4 mg/kg/day) and mice (52 mg/kg/day) (Table 2-1, Figure 2-1). Using the dose-response data for the hepatocellular carcinoma in rats, EPA (1980, 198Sa) derived and verified an oral slope factor (q_1^*) of 8.0×10^{-1} (mg/kg/day)⁻¹ for 1,2-diphenylhydrazine. Using this slope factor, the doses associated with upper-bound lifetime cancer risk levels of 10^{-4} to 10^{-7} are calculated to be 1.3×10^{-4} to 1.3×10^{-7} mg/kg/day, respectively (Figure 2-1).

2.2.3 Dermal Exposure

No studies were located regarding the following health effects in human or animals after dermal exposure to 1,2-diphenylhydrazine.

2.2.3.1 Death

2.2.3.2 Systemic Effects

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2.2.3.3 Immunological Effects

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects of 1,2-diphenylhydrazine in humans. As discussed below, inconclusive data for carcinogenicity of dermally-applied 1,2-diphenylhydrazine in mice are available.

Dermal application of an estimated 1,2-diphenylhydrazine dose of 63 mg/kg/day I three times a week for 442 days, caused a 22.2% incidence of tumors in mice (Pliss 1974). Tumors occurred in the lung, liver, and other tissues, and the tumor incidence in control mice was 17%. The significance of these findings cannot be determined, as incidences of specific tumors in the control group were not reported.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption in humans or animals after inhalation exposure to 1,2-diphenylhydrazine. Pulmonary absorption of 1,2-diphenylhydrazine by rats is suggested by detection of an unidentified metabolite in the urine following intratracheal administration of 1,2-diphenylhydrazine in water suspension and dimethyl sulfoxide (DMSO) (Dutkiewicz and Szymanska 1973). It is not known, however, if any of the dose was ingested.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to 1,2-diphenylhydrazine. Specific information regarding absorption in animals following oral exposure to 1,2-diphenylhydrazine was not located. Gastrointestinal absorption of 1,2-diphenylhydrazine by rodents is indicated by the occurrence of parent compound and metabolites in the urine following oral treatment (Section 2.3.3) and systemic effects in oral carcinogenicity and toxicity studies (Section 2.2).

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2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after exposure to 1,2-diphenylhydrazine. The inadequately reported dermal carcinogenicity study of 1,2-diphenylhydrazine summarized in Section 2.2.3.8 cannot be used to infer dermal absorption of 1,2-diphenylhydrazine because the effects are inconclusive.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to 1,2-diphenylhydrazine.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals after oral exposure to 1,2-diphenylhydrazine.

2.3.2.3 Dermal Exposure

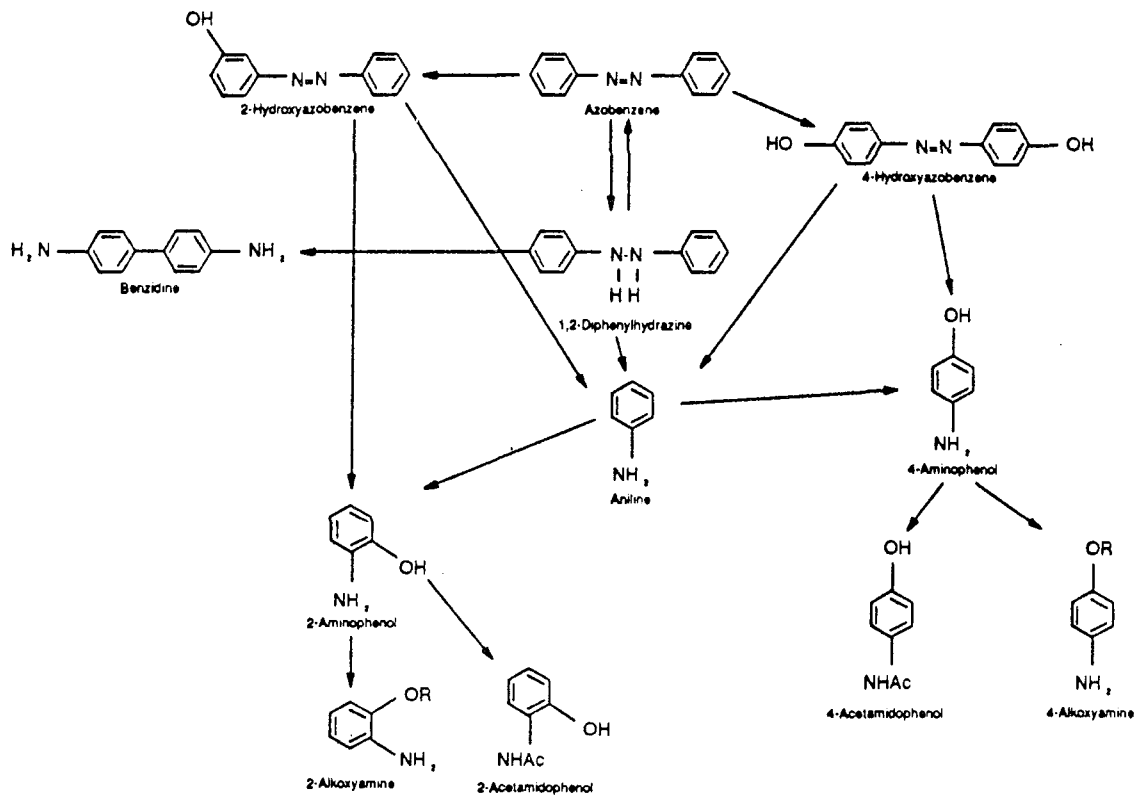
No studies were located regarding distribution in humans or animals after dermal exposure to 1,2-diphenylhydrazine.

2.3.3 Metabolism

Limited information is available on the metabolism of 1,2-diphenylhydrazine. In the only study involving 1,2-diphenylhydrazine as the parent compound, urine of rats was analyzed for metabolites following single oral, intraperitoneal, intravenous, and intratracheal doses of 1,2-diphenylhydrazine (Dutkiewicz and Szymanska 1973). Unchanged 1,2-diphenylhydrazine was detected following treatment by all routes, and aniline and benzidine were identified following the oral and intraperitoneal treatments. Other metabolites included two unspecified hydroxy derivatives of benzidine (oral route), 2- and 4- aminophenol (intraperitoneal route), and unidentified compounds (oral, intravenous, and intratracheal routes). Amounts of compounds excreted were not quantitated. Two of the known metabolites, aniline and benzidine, may contribute to the toxicity and/or carcinogenicity of 1,2-diphenylhydrazine. The validity of the findings of this study is uncertain, however, as the analytical methodology (thin-layer chromatography) may have produced degradation products that were identified as unchanged 1,2-diphenylhydrazine or metabolites (see Section 6.1).

The metabolites identified by Dutkiewicz and Szymanska (1973) are consistent with a metabolic scheme proposed by Williams (1959) (Figure 2-2), which is based on data for azobenzene and aniline. As summarized by NRC (1981), aniline is oxidized by hydroxylation of a ring carbon to form 2-or

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Source: Williams 1959.

FIGURE 2-2. Metabolic Scheme of 1,2-Diphenylhydrazine

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4-aminophenol or of the nitrogen to form phenylhydroxylamine, and then is conjugated to glucuronic or sulfuric acid. An oral study of azobenzene with conventional and germ-free rats (Macholz et al. 1985) showed that metabolism of 1,2-diphenylhydrazine to aniline resulted from the reductional and hydrolytic capability of gut flora. In vitro metabolism of 1,2-diphenylhydrazine to aniline by rat intestinal microorganisms has been demonstrated (Bolton and Griffiths 1978).

Benzidine is formed readily from 1,2-diphenylhydrazine by acid rearrangement. It has been suggested that benzidine may be produced from 1,2-diphenylhydrazine by acidity in the stomach (IARC 1972).

2.3.4 Excretion

2.3.4-1 Inhalation Exposure

No studies were located regarding excretion in humans or animals after inhalation exposure to 1,2-diphenylhydrazine. The presence of an unidentified metabolite in the urine of rats following intratracheal administration of 1,2-diphenylhydrazine in water and DMSO suspensions (Dutkiewicz and Szymanska 1973) suggests that urinary excretion could occur following inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans after oral exposure to 1,2-diphenylhydrazine. The identification of unchanged 1,2-diphenylhydrazine and metabolites in the urine following oral dosing of rats with 1,2-diphenylhydrazine (Dutkiewicz and Szymanska 1973) indicates that some urinary excretion occurs.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to 1,2-diphenylhydrazine.

2.4 RELEVANCE TO PUBLIC HEALTH

Death. Information regarding death in humans following exposure to 1,2-diphenylhydrazine by any route was not found. Some information is available on lethality of orally-administered 1,2-diphenylhydrazine in animals. This information, consisting of a gavage LD₅₀ value in rats (Marhold et al. 1968) and an unreliable 3-day dietary lethal dose in mice (Schafer and Bowles 1985), indicates that single or several oral doses of about 1000 mg/kg/day may be lethal for rodents. Based on these data, 1,2-diphenylhydrazine does not appear to be highly acutely toxic to humans by the oral route.

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Intermediate (4-week) and chronic (78-week) duration diet studies with rats found that 1,2-diphenylhydrazine produced death at doses as low as 54 and 15 mg/kg/day, respectively (NCI 1978). These doses are substantially lower than those associated with acute lethality. These data suggest that prolonged ingestion of these doses of 1,2-diphenylhydrazine may be lethal for humans. However, as discussed in the introduction to Section 2.8.2, prolonged environmental exposure to 1,2-diphenylhydrazine is unlikely.

Systemic Effects. No information regarding systemic effects in humans following exposure to 1,2-diphenylhydrazine by any route was found. Very limited information is available for systemic effects of 1,2-diphenylhydrazine in animals.

NCI (1978) observed a variety of nonneoplastic lesions in rats and mice exposed to 1,2-diphenylhydrazine in the diet for 78 weeks, concluding that "...none appeared to be compound-related." Evaluation of the incidence data for nonneoplastic lesions, however, shows that there were statistically significant increased incidences of lung interstitial inflammation and liver fatty metamorphosis in treated male and female rats, stomach hyperkeratosis and acanthosis in treated male rats, and liver coagulative necrosis in treated female mice. Nonneoplastic liver lesions, hepatocellular carcinomas and/or neoplastic liver nodules in orally-treated rats and mice indicate that the liver is a target of 1,2-diphenylhydrazine toxicity. Gross pathological examinations conducted in the 4-week NCI (1978) diet study showed intestinal hemorrhages in mice that died. A local irritative effect of 1,2-diphenylhydrazine is suggested by the occurrence of the stomach hyperkeratosis/acanthosis in rats and intestinal hemorrhage in mice. Since hydrazine and some hydrazine derivatives are hepatotoxic and local irritants (Reinhardt and Brittelli 1981), it is possible that 1,2-diphenylhydrazine could cause similar effects in humans.

Intravenous injection of an 18.4 mg/kg dose of 1,2-diphenylhydrazine did not cause methemoglobinemia in rats, although methemoglobin was formed by an equimolar dose of aniline (Pfordte 1973). Information on methemoglobinemia in animals following treatment with 1,2-diphenylhydrazine by other routes was not located. As aniline and other aromatic amino metabolites of 1,2-diphenylhydrazine (e.g., aminophenols) are methemoglobin-forming compounds by either oral or inhalation routes of exposure (Beard and Noe 1981), it is possible that 1,2-diphenylhydrazine may cause methemoglobinemia in humans. However, this would occur only if sufficient aniline were formed rapidly enough to exceed the capacity of methemoglobin reductase to reduce methemoglobin.

Immunological Effects. No studies were located regarding immunological effects of 1,2-diphenylhydrazine in humans or animals by any route of exposure. This lack of data precludes speculation on possible immunotoxicity of 1,2-diphenylhydrazine in humans.

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Neurological Effects. No studies were located regarding neurological effects of 1,2-diphenylhydrazine in humans by any route of exposure. Rats and mice that were treated with lethal doses of 1,2-diphenylhydrazine in a chronic (78-week) diet study did not show symptoms of toxicity or histological alterations in the brain (NCI 1978), but no behavioral or neurological evaluations were conducted. The insufficiency of these data precludes making any conclusions regarding neurotoxicity of 1,2-diphenylhydrazine in humans.

Developmental Effects. No studies were located regarding developmental effects of 1,2-diphenylhydrazine in humans or animals by any route of exposure. This lack of data precludes speculation on possible developmental toxicity of 1,2-diphenylhydrazine in humans.

Reproductive Effects. No studies were located regarding reproductive effects of 1,2-diphenylhydrazine in humans by any route of exposure. Rats and mice that were treated with lethal doses of 1,2-diphenylhydrazine in a chronic (78-week) diet study did not show histological alterations in reproductive organs (NCI 1978), but reproductive function was not evaluated. The insufficiency of these data precludes making any conclusions regarding reproductive toxicity of 1,2-diphenylhydrazine in humans.

Genotoxic Effects. No studies were located regarding the genotoxicity of 1,2-diphenylhydrazine in humans by any route of exposure. A limited number of assays have been conducted using bacteria, mammalian cell and whole animal systems. As indicated in Table 2-2, 1,2-diphenylhydrazine was mutagenic in Salmonella typhimurium, but not in Escherichia coli, and produced chromosome aberrations and sister chromatid exchanges in Chinese hamster cells. An exogenous metabolic activation system was necessary for expression of the aforementioned effects. In in vivo studies (Table 2-3), 1,2-diphenylhydrazine inhibited testicular DNA synthesis in mice when administered as a single 100 mg/kg intraperitoneal injection, but did not cause sex-linked recessive lethal mutations in Drosophila when administered in the feed or by injection.

Although only limited data are available, the weight of evidence indicates that 1,2-diphenylhydrazine is genotoxic in animals. In particular, positive results were obtained in all assays with mammalian systems. Overall, the available evidence suggests that 1,2-diphenylhydrazine may cause chromosomal damage or other genotoxic effects in humans.

Cancer. Information regarding the carcinogenicity of 1,2-diphenylhydrazine in humans by any route of exposure was not located. In animals, significantly increased incidences of hepatocellular carcinomas, neoplastic liver nodules, mammary adenocarcinomas, Zymbal's gland carcinomas and adrenal pheochromocytomas occurred in rats and/or mice treated with 1,2-diphenylhydrazine in the diet for 78 weeks (NCI 1978). Other carcinogenicity studies of 1,2-diphenylhydrazine, involving diet treatment

TABLE 2-2. Genotoxicity of 1,2-Diphenylhydrazine In Vitro

End Point	Species (Test System)	Result		Reference
		With Activation	Without Activation	
Prokaryotic organisms:				
Gene mutation	<u>Salmonella typhimurium</u> / plate incorporation	(+)	-	Dunkel et al. 1985
	<u>S. typhimurium</u> / plate incorporation	+	-	Haworth et al. 1983
	<u>Escherichia coli</u> WP2uvrA	-	-	Dunkel et al. 1985
Eukaryotic organisms:				
Chromosome aberrations	Chinese hamster ovary cells	+	?	Galloway et al. 1987
Sister chromatid exchange	Chinese hamster ovary cells	+	-	Galloway et al. 1987

+ = positive; (+) = weakly positive; - = negative; ? = inconclusive.

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TABLE 2-3. Genotoxicity of 1,2-Diphenylhydrazine In Vivo

End Point	Species (Test System)	Result	Reference
Sex-linked recessive lethal mutation	<u>Drosophila melanogaster</u> / feeding	-	Yoon et al. 1985
	<u>D. melanogaster</u> /injection	-	Yoon et al. 1985
DNA damage	Mouse/inhibition of testicular DNA synthesis/ intraperitoneal injection	+	Seiler 1977

- = negative; + = positive.

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in rats (Pliss 1974; Marhold et al. 1978), dermal treatment in mice (Pliss 1974), and subcutaneous or intraperitoneal injection in rats and mice (Spitz et al. 1950; Genin et al. 1975; Pliss 1974; Shabad and Genin 1975; Kurlyandskiy et al. 1976; Maronpot et al. 1986), are inconclusive due to inadequate reporting and other limitations. Although inconclusive, most of these studies reported tumors at sites that are generally consistent with sites of tumors in the NCI (1978) bioassay (e.g., liver, mammary gland, adrenal gland, and Zymbal's gland).

The NCI (1978) bioassay, which demonstrated carcinogenicity in two species, provides sufficient evidence of carcinogenicity of 1,2-diphenylhydrazine in animals. Biotransformation products of 1,2-diphenylhydrazine include aniline and benzidine, which are known carcinogens in animals (both chemicals) and humans (benzidine) (EPA 1988b,c). Based on the animal evidence for carcinogenicity from the NCI (1978) bioassay and the carcinogenicity of its metabolites, 1,2-diphenylhydrazine is likely to be carcinogenic in humans.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid 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 (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to 1,2-diphenylhydrazine are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells),

2. HEALTH EFFECTS

as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,2-diphenylhydrazine are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to 1,2-Diphenylhydrazine

No studies were located regarding biomarkers of exposure to 1,2-diphenylhydrazine. The metabolites of 1,2-diphenylhydrazine were identified in one study (Dutkiewicz and Szymanska); however, the validity of the findings is uncertain because of the analytical methodology used (see Section 2.3.3 Metabolism). No enzymatic changes that could be used as biomarkers of 1,2-diphenylhydrazine exposure are known.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,2-Diphenylhydrazine

No biomarkers of effects were identified for 1,2-diphenylhydrazine exposure. No specific alterations in the organism that could be recognized as biomarkers were found, and the most susceptible organs or tissues were not identified.

2.6 INTERACTIONS WITH OTHER CHEMICALS

A carcinogenicity study was reported in which groups of rats were given weekly subcutaneous injections of 1,2-diphenylhydrazine (20 mg), or 1,2-diphenylhydrazine (20 mg) concurrently with benzidine sulfate (15 mg) for life (Genin et al. 1975). Combined incidences of tumors (injection site, liver, and other sites) were increased and the mean tumor latent period was decreased in the group with combined 1,2-diphenylhydrazine and benzidine sulfate exposure.. It is unclear whether these findings provide evidence for an interaction between 1,2-diphenylhydrazine and benzidine or additive effects of two carcinogens. The results of this study were also reported by Shabad and Genin (1975) and Kurlyandskiy et al. (1976). Concurrent exposure to 1,2-diphenylhydrazine and benzidine could occur during benzidine production, since 1,2-diphenylhydrazine is used as a starting material in the production of benzidine, which is a degradation or metabolic product of 1,2-diphenylhydrazine.

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2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

No populations with unusual susceptibility to health effects of 1,2-diphenylhydrazine have been identified. It is possible that people with chronic liver disease or possibly compromised hepatic function (e.g., very young or very old people, alcoholics) might be unusually susceptible to 1,2-diphenylhydrazine, because the liver is a target organ of 1,2-diphenylhydrazine in animals.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine.

The following categories of data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substancespecific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of 1,2-Diphenylhydrazine

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-diphenylhydrazine are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2-diphenylhydrazine. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

Information regarding health effects of 1,2-diphenylhydrazine in humans is not available. Except for one dermal study, health effects of 1,2-diphenylhydrazine in animals have been investigated only in oral exposure studies. As indicated in Figure 2-3, animal oral data are available for lethality, systemic effects due to intermediate and chronic duration exposure, and genotoxicity and cancer. These data indicate that oral exposure to 1,2-diphenylhydrazine was life-shortening, hepatotoxic, irritating to the stomach, and carcinogenic to rats and/or mice. Limited animal data are available for neurologic and reproductive effects due to oral exposure, and for cancer due to dermal exposure.

2. HEALTH EFFECTS

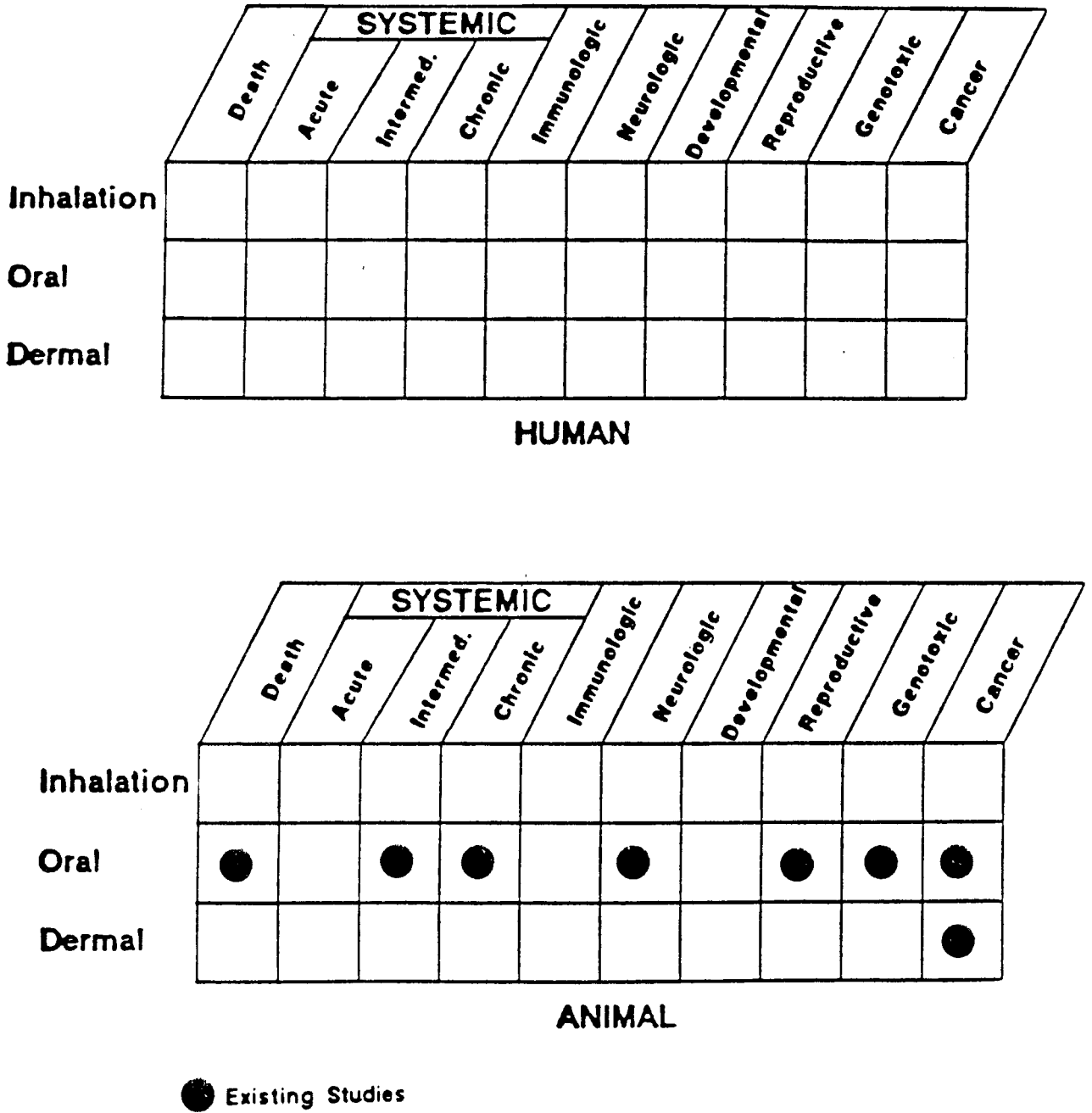


FIGURE 2-3. Existing Information on Health Effects of 1,2-Diphenylhydrazine

2. HEALTH EFFECTS

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Information is not available on the health effects of 1,2-diphenylhydrazine resulting from inhalation exposure in humans or animals. Because 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperatures, it is highly unlikely that inhalation exposure to this chemical in the vapor state would occur (Chapter 5). However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine either free or adsorbed to soil is conceivable. Therefore, acute studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. No studies were located regarding acute oral exposure in humans. The only pertinent acute exposure toxicity studies of 1,2-diphenylhydrazine were conducted in rats; these consist of an oral LD₅₀ assay and methemoglobin determination following intravenous treatment. Additional acute oral exposure studies could corroborate the LD₅₀, identify systemic effects, and provide information on thresholds of effects as well as interspecies differences. However, although ingestion of 1,2-diphenylhydrazine-contaminated soil from waste sites is conceivable, extensive oral studies appear to be unwarranted as the possibility of exposure from ingestion of contaminated soil seems unlikely, and exposure via drinking water is essentially nonexistent because of the rapid oxidation of 1,2-diphenylhydrazine in water (Chapter 5). Because of the lack of dose-effect information, no MRL was derived. Pharmacokinetic data are insufficient for identification of target organs across routes of exposure. No studies were located regarding acute dermal exposure in humans or animals. Acute dermal studies of 1,2-diphenylhydrazine with animals could provide information on skin and eye irritation, lethality, and other toxic effects. Dermal studies of 1,2-diphenylhydrazine appear to be most relevant, as dermal exposure is a likely route of environmental exposure. As discussed in Chapter 5, dermal exposure via direct chemical contact or contact with contaminated soil is possible at hazardous waste sites, where high concentrations of crystalline 1,2-diphenylhydrazine could occur.

Intermediate-Duration Exposure. No information was located regarding intermediate-duration inhalation exposure to 1,2-diphenylhydrazine in humans or animals. As discussed for acute-duration exposure, 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure to this chemical in the vapor state unlikely. However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine either free or adsorbed to soil is conceivable. Therefore, intermediateduration studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. A limited number of intermediateduration oral studies provide information on lethality and/or gross pathology in rats and mice. Because of the lack of reliable information about dose-relationship, no MRL was derived. Pharmacokinetic data were insufficient for identification of target organs across routes of exposure.

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Additional studies examining histology or other sensitive endpoints could elucidate systemic effects and thresholds of toxicity. Intermediateduration dermal studies examining systemic toxicity in animals could provide information on whether repeated dermal exposure of humans poses a threat of toxic effects. This information would be useful for an evaluation of health risk in populations living near hazardous waste sites that might be repeatedly exposed to 1,2-diphenylhydrazine-contaminated soil.

Chronic-Duration Exposure and Cancer. No studies were located regarding chronic inhalation exposure to 1,2-diphenylhydrazine in humans or animals. As discussed for acute- and intermediate-duration exposure, 1,2-diphenylhydrazine is a solid with a low vapor pressure at ambient temperature, which makes inhalation exposure this chemical in the vapor state unlikely. However, the possibility of inhalation exposure to dusts of 1,2-diphenylhydrazine either free or adsorbed to soil is conceivable. Therefore, chronic-duration studies of inhalation exposure to dusts of 1,2-diphenylhydrazine could be designed to provide information on possible toxic effects and exposure levels that cause effects. The NCI (1978) bioassay of 1,2-diphenylhydrazine provides the only sufficient chronic oral toxicity data for this chemical. This study was not, however, subjected to the peer review process used for current NTP bioassays, and it inadequately evaluated nonneoplastic effects. Additional studies would be particularly useful for corroborating and more fully characterizing 1,2-diphenylhydrazine-induced systemic toxicity. In particular, more studies could provide information on cause(s) of death due to chronic exposure, and delineate carcinogenic and noncarcinogenic doses. No studies were located regarding toxic effects after chronic dermal exposure to 1,2-diphenylhydrazine in humans or animals. Because of the lack of reliable data, no MRL for chronic exposure was derived. Pharmacokinetic data were insufficient for identification of target organs across routes of exposure. More information regarding chronic dermal exposure would be useful for possible extrapolation of results to humans that may be exposed to 1,2-diphenylhydrazine near hazardous waste sites for a long period of time.

The paucity of systemic toxicity data for this chemical appears to be related to primary interest in testing for carcinogenicity. Treatment related neoplasms developed in rats and mice that were treated with 1,2-diphenylhydrazine in a diet. An inconclusive chronic dermal carcinogenicity study of 1,2-diphenylhydrazine with mice was available. The development of neoplasia was reported in the exposed group. The results from the controls were not, however, provided. The available data, although scarce, indicate a possible carcinogenic potential for 1,2-diphenylhydrazine. This finding is supported by some genotoxicity studies. Additional chronic dermal studies would be useful to further investigate 1,2-diphenylhydrazine carcinogenicity.

Genotoxicity. A limited number of in vitro assays with bacteria and mammalian cells and an in vivo assay with mice indicate that 1,2-diphenylhydrazine is genotoxic. Replicate essays have not been

2. HEALTH EFFECTS

conducted with the exception of assays with Salmonella, and mutation in mammalian systems and genotoxicity in human cells have not been evaluated. Additional studies, particularly involving mammalian systems and providing information on the potential for heritable mutations, would add to the database on genotoxicity and validate available information.

Reproductive Toxicity. The unremarkable histology of the reproductive organs of the rats and mice in the NCI (1978) bioassay provides limited information on the lack of reproductive toxicity of 1,2-diphenylhydrazine. Multigeneration or continuous breeding studies in animals would provide a basis for evaluation of potential reproductive effects of 1,2-diphenylhydrazine in humans.

Developmental Toxicity. It is not known whether 1,2-diphenylhydrazine crosses the placenta, but there is no reason to assume that it (or its metabolites) would not do so. Developmental studies in mammals would provide information on possible fetotoxic and teratogenic effects of 1,2-diphenylhydrazine that might be relevant to humans.

Immunotoxicity. No histopathological effects on immunological organs and tissues of rats and mice were found in the NCI (1978) chronic oral bioassay of 1,2-diphenylhydrazine. Adequate evaluation of immunotoxic potential is precluded by a lack of specific immunotoxicity tests of 1,2-diphenylhydrazine. Dermal sensitization tests in animals might provide information on whether an allergic response to 1,2-diphenylhydrazine is likely.

Neurotoxicity. No clinical signs of central nervous system toxicity or histological alterations of nervous system organs and tissues were observed in rats or mice in the NCI (1978) chronic oral bioassay. Tests for neurotoxicity in animals may be appropriate if there is clinical evidence of neurological dysfunction in general oral or dermal toxicity studies of 1,2-diphenylhydrazine.

Epidemiological and Human Dosimetry Studies. Health effects of 1,2-diphenylhydrazine have not been described in humans. As discussed in Chapter 5, the potential for environmental exposure to 1,2-diphenylhydrazine is extremely low. Although dermal exposure to 1,2-diphenylhydrazine could occur at a contaminated waste site, it is highly unlikely that segments of the general population will be exposed to 1,2-diphenylhydrazine.

If 1,2-diphenylhydrazine or its metabolites in urine can be correlated with dermal exposure in humans, it may be possible to monitor humans for exposure. If toxic effects resulting from dermal exposure to 1,2-diphenylhydrazine are identified in humans, it may then be possible to correlate urinary levels of 1,2-diphenylhydrazine or a metabolite with systemic effects.

2. HEALTH EFFECTS

Biomarkers of Exposure and Effect. No biomarkers are known that are specific for 1,2-diphenylhydrazine exposure. Continued efforts to devise more sensitive and more specific early biomarkers of disease (especially cancer) would be valuable.

Absorption, Distribution, Metabolism, Excretion. The general metabolic pathways of 1,2-diphenylhydrazine are identifiable based on limited evidence for 1,2-diphenylhydrazine in oral, intratracheal, and injection experiments with rats (Dutkiewicz and Szymanska 1973), metabolism data for azobenzene (which is metabolized to 1,2-diphenylhydrazine), and metabolism data for aniline (an initial metabolite). The relative contribution of the different pathways is not established. Although oral absorption of 1,2-diphenylhydrazine and urinary excretion of 1,2-diphenylhydrazine and its metabolites are apparent, there is no information on the rate and extent of absorption, or excretion, or tissue distribution following oral exposure. Investigations of the toxicokinetics of 1,2-diphenylhydrazine following dermal exposure have not been conducted. Additional studies of absorption, distribution, metabolism, and excretion in animals by the oral and dermal routes of exposure would provide information needed for sufficient characterization of the toxicokinetics of 1,2-diphenylhydrazine. Studies addressing differences in metabolism between oral and dermal routes would be particularly informative, as benzidine may be formed by acidity in the stomach.

Comparative Toxicokinetics. No data are available to determine if there are differences in the toxicokinetics of 1,2-diphenylhydrazine among species. Toxicokinetic studies with different species could help explain observed differences in toxicity and carcinogenicity between rats and mice, and help identify the animal species that serves as the best model for extrapolating results to humans.

2.8.3 On-going Studies

No ongoing studies of 1,2-diphenylhydrazine were identified.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

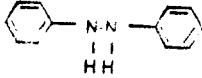
Data pertaining to the chemical identity of 1,2-diphenylhydrazine listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,2-diphenylhydrazine are presented in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 1,2-Diphenylhydrazine

	Value	Reference
Chemical name	1,2-Diphenylhydrazine	CAS 1988
Synonyms	Hydrazobenzene N,N'-diphenylhydrazine sym-diphenylhydrazine	CAS 1988; SANSS 1988
Trade names	No data	
Chemical formula	C ₁₂ H ₁₂ N ₂	CAS 1988
Chemical structure		SANSS 1988
Identification numbers:		
CAS Registry	122-66-7	CAS 1988
NIOSH RTECS	MW2625000	HSDB 1988
EPA Hazardous Waste	U109	HSDB 1988
OHM-TADS	8100209	HSDB 1988
DOT/UN/NA/IMCO Shipping	No data	
HSDB	2882	HSDB 1988
NCI	C01854	HSDB 1988

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 Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; OHM/TADS = Oil and Hazardous Materials/Technical Assistance data System.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Properties of
1,2-Diphenylhydrazine

Property	Value	Reference
Molecular weight	184.24	
Color	White	Ahuja et al. 1988
Physical state	Crystalline solid	Dean 1985
Melting point	123-126°C	Aldrich Catalog 1988
Boiling point	309°C	PCGEMS Estimation
Specific gravity, 16/4°C	1.158	Dean 1985
Odor	No data	
Odor threshold	No data	
Solubility:		
Water at 20°C	66.9 mg/L (calculated using equation 40)	Neely and Blau 1985
Organic solvents	Very soluble in alcohol; slightly soluble in benzene	Dean 1985
Partition coefficients:		
Log octanol/water	2.94 (experimental)	Hansch and Leo 1985
Log K _{oc}	2.73 (calculated using equation 4-10)	Lyman et al. 1982
Vapor pressure at 25°C	2.6 x 10 ⁻⁵ mmHg	Mabey et al. 1981
Henry's law constant	9.42 x 10 ⁻⁸ atm-m ³ /mol (calculated from water solubility and vapor pressure)	
Autoignition temperature	No data	
Flashpoint, open cup	No data	
Flammability limits	No data	
Conversion factors	No data	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

1,2-Diphenylhydrazine is produced in the stepwise reduction of nitrobenzene by the action of iron or zinc powder in caustic solution (e.g., caustic soda, alcoholic alkaline) first to azoxybenzene, then azobenzene, and finally 1,2-diphenylhydrazine (Sandridge and Staley 1978). A batch process is used in which a caustic soda solution is added to a heated vessel charged with nitrobenzene and iron borings. Additions of iron in caustic soda solution are made to continue the reaction. When the reaction is complete, separation of the 1,2-diphenylhydrazine from the iron sludge is accomplished by solvent extraction or by alternative methods, such as stopping the reaction at the azobenzene step and performing the final reduction in a zinc-alcoholic alkali solution followed by filtration and washing of the sodium zincate mass.

No recent information was located regarding production volumes of 1,2-diphenylhydrazine. The U.S. International Trade Commission last reported production of 1,2-diphenylhydrazine for the 1978 production year (USITC 1979). In that year, Bofors Lakeway, Muskegon, MI, reportedly produced and isolated 1,2-diphenylhydrazine, but no volumes were published. The USITC will not publish production volumes of chemicals for which there are less than three manufacturers. No producers have been reported by the USITC since 1978, indicating either that less than 5000 pounds were produced or that the product was never isolated, but was used directly in the next reaction step.

4.2 IMPORT

No information concerning the importation or exportation of 1,2-diphenylhydrazine in the United States was located in the literature.

4.3 USE

One of the major uses of 1,2-diphenylhydrazine is as a starting material in the production of benzidine; however, it is no longer produced in the United States. 1,2-Diphenylhydrazine rearranges to benzidine upon treatment with strong acid; benzidine is used by the dye industry for the production of benzidine-based dyes including many of the Direct dyes (e.g., Direct Red 28, Direct Black 4, Direct Blue 2) (Ferber 1978; Lurie 1964). Fabricolor, the last producer of benzidine based dyes, discontinued production in 1988 (Personal communication, Alvarez 1989).

1,2-Diphenylhydrazine is used for the production of the drugs phenylbutazone (trade name Butazolidin, an anti-inflammatory agent) and sulfinpyrazone (trade name Anturane, a uricosuric agent for the treatment of gouty arthritis) (Barnhart 1988; Hughes 1981; Kornis 1982). These drugs are made by the condensation of 1,2-diphenylhydrazine with malonic acid derivatives to form pyrazolidinedione structures. It is not clear from the literature if the 1,2-diphenylhydrazine used in the condensation reaction is

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

produced by the manufacturers that use it or if it is purchased by them as an isolated product.

4.4 DISPOSAL

Very little information was located in the literature concerning the disposal of 1,2-diphenylhydrazine. Dietrich et al. (1985) reported that wet air oxidation (heating wastewater under pressure with the addition of an oxygen-containing gas such as air) would remove 99.88% of the 1,2-diphenylhydrazine in the water (initial concentration, 5000 mg/L). Wet air oxidation can effectively treat aqueous waste streams that are too dilute to incinerate, yet too toxic to treat using biological processes. Results of treatment by wet air oxidation are in keeping with the observation that 1,2-diphenylhydrazine oxidizes on standing to azobenzene (Riggin and Howard 1979). Information regarding the amount of 1,2-diphenylhydrazine disposed of in the United States was not located in the literature.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Diphenylhydrazine oxidizes rapidly in the environment under aerobic conditions, with a half-life in water as short as 15 minutes. This rapid oxidation coupled with the lack of straightforward sampling methods makes the assessment of the literature difficult. For example, while a few monitoring papers report the detection of 1,2-diphenylhydrazine in the environment, their analytical methodology suggests that it is unlikely that 1,2-diphenylhydrazine would have been detected even if present. In addition, little information is available to assess the potential for environmental contamination, making the estimation of environmental releases difficult. Therefore, not only is the significance of reported environmental concentrations difficult to interpret, environmental concentrations are difficult to predict. The fate, transport, and distribution of 1,2-diphenylhydrazine in the environment are uncertain. 1,2-Diphenylhydrazine has been reported at 7 of 1177 sites in the National Priority List database (ATSDR 1990); the frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

No information concerning the release of 1,2-diphenylhydrazine to air was located in the literature. The vapor pressure of 1,2-diphenylhydrazine is low (2.6×10^{-5} mmHg at 25 C), indicating that little 1,2-diphenylhydrazine will volatilize from manufacturing and use operations. Dust generated from the loading and off-loading of 1,2-diphenylhydrazine during use may cause local atmospheric concentrations. If present in water, 1,2-diphenylhydrazine will probably oxidize to azobenzene before it volatilizes. Volatilization of 1,2-diphenylhydrazine is not expected to be an environmentally relevant fate process given the low Henry's Law constant (9.42×10^{-8} atm-m³ mol⁻¹).

5.2.2 Water

No information concerning the release of 1,2-diphenylhydrazine to water was located in the literature. If discharged to water, detectable concentrations will probably persist for only a short time, since the halflife of (100 µg/L) 1,2-diphenylhydrazine in wastewater is about 15 minutes (Riggin and Howard 1979, 1982)

5.2.3 Soil

No information concerning the release of 1,2-diphenylhydrazine to soil was located in the literature. The manufacturing process for 1,2-diphenylhydrazine generates a sludge containing iron and/or zinc

5. POTENTIAL FOR HUMAN EXPOSURE

compounds, probably along with small amounts of unextracted 1,2-diphenylhydrazine. Some of this material may be disposed of in landfills, but no information is available concerning the 1,2-diphenylhydrazine disposal practices of the manufacturing industry.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

No information concerning the transport and partitioning of 1,2-diphenylhydrazine in the environment was located in the literature. In water, 1,2-diphenylhydrazine is not expected to volatilize because of its rapid oxidation in aerated water (near-surface water) to azobenzene and its low calculated Henry's Law constant ($9.42 \times 10^{-8} \text{ atm-m}^3 \text{ mol}^{-1}$) (Lyman et al. 1982). The calculated $\log K_{oc}$ (2.76) suggests that 1,2-diphenylhydrazine may sorb to sediments or suspended particles. This is based on the analysis of Kenaga (1980), who stated that chemicals with a $K_{oc} < 100$ tend to be mobile in soil, while those with a $K_{oc} > 1000$ tend to sorb. In soil, 1,2-diphenylhydrazine is not expected to leach to groundwater, based on its physical and chemical properties (i.e., 1,2-diphenylhydrazine reacts rapidly under environmental conditions and, based on its K_{oc} , will not rapidly leach downward in the soil column).

5.3.2 Transformation and Degradation

5.3.2.1 Air

No studies were located regarding the rates or products of reaction of 1,2-diphenylhydrazine in the atmosphere. Based on its behavior in aerated water, 1,2-diphenylhydrazine may react rapidly in air to form azobenzene as well as other products resulting from the abstraction of a hydrogen from a nitrogen by hydroxyl radical. Atkinson (1987) developed a method to estimate the hydroxyl radical ($\text{HO}\bullet$) reaction rate based on structure. This method, an overall reaction rate of $211 \times 10^{-12} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$ was calculated, which yields a half-life of less than 2 hours for an atmospheric $\text{HO}\bullet$ concentration of $0.5 \times 10^6 \text{ molecules cm}^{-3}$. This is an estimated annually averaged concentration for a 24-hour period (Atkinson 1985). 1,2-Diphenylhydrazine also absorbs light above 290 nm (Sadler Index, no date) and may be susceptible to photolysis. No information was found concerning the characteristics of this potential reaction.

5.3.2.2 Water

Very little information was located concerning the fate of 1,2-diphenylhydrazine in water. Riggan and Howard (1979, 1982) reported the results of a study on the stability of 1,2-diphenylhydrazine in a number of solvents including distilled water and wastewater. In distilled water at pH values of 2, 4.7, 7, and 10 and at 4°C or at room temperature, less than 10% of the initial 10 µg/L of 1,2-diphenylhydrazine remained in the water after

5. POTENTIAL FOR HUMAN EXPOSURE

1 day. At pH 2, 1,2-diphenylhydrazine degraded to benzidine, while at pH 7 it degraded to an unidentifiable oxidizable product. At pH 10, 1,2-diphenylhydrazine degraded to azobenzene, and at pH 4.7, it degraded into two unidentifiable products, which were not azobenzene or benzidine. In secondary municipal sewage effluent, Riggin and Howard (1979, 1982) reported that 100 µg/L of 1,2-diphenylhydrazine had a half-life of about 15 minutes in the presence of oxygen, and about 60 minutes when no oxygen was present. These results suggest that 1,2-diphenylhydrazine is unlikely to persist in the environment, particularly under aerobic conditions.

Weber and Wolfe (1986, 1987) reported that azobenzene, when incubated in air with four anaerobic lake sediments containing about 2-4% organic matter, was reduced to aniline with a reaction half-life of about 2700-5700 minutes, depending on the source and date of specimen collection. 1,2-Diphenylhydrazine was not detected as an intermediate. The authors postulate a four-electron mechanism involving the intermediate formation of 1,2-diphenylhydrazine.

In reporting the same data, Tabak et al. (1981a,b) and Patterson and Kodukala (1981) stated that 5 or 10 mg/L of 1,2-diphenylhydrazine was degraded up to 80% when initially cultured with settled domestic wastewater. This degradation rate, however, was reduced to 40% in the case of the 10 mg/L concentration, after the third subculture. The authors suggested that a de-adaptive and toxification process was occurring with 1,2-diphenylhydrazine. It is unclear if the analytical methods used by these authors would have been able to detect 1,2-diphenylhydrazine if present. Both dissolved organic carbon and gas chromatography (GC) analyses were performed on the samples. Considering the sample preparation procedures, however, the compound detected might not have been 1,2-diphenylhydrazine, but a decomposition product such as azobenzene.

5.3.2.3 Soil

No information concerning the fate of 1,2-diphenylhydrazine in soil was located in the literature. Based on the fate of 1,2-diphenylhydrazine in water and sediment, detectable concentrations probably will not persist for long periods, but this may depend on the initial concentration.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

The rapid oxidation of 1,2-diphenylhydrazine in water to form azobenzene and other compounds makes its sampling and analysis difficult. Storing a sample containing 1,2-diphenylhydrazine for even short periods can result in complete oxidation; in gas chromatography, 1,2-diphenylhydrazine is oxidized to azobenzene upon injection onto the chromatographic column (Riggin and Howard 1982). Therefore, unless sampling and analysis are performed under conditions that will prevent oxidation or unless concentrations of 1,2-diphenylhydrazine in the sample are very high, analyses of environmental samples for 1,2-diphenylhydrazine are inaccurate

5. POTENTIAL FOR HUMAN EXPOSURE

(Ahuja et al. 1988; Riggin and Howard 1979). It is doubtful that the concentrations measured reflect on the concentrations present in the sample at the time of collection (i.e., measured concentrations would underestimate actual concentrations (Riggin and Howard 1982)).

5.4.1 Air

No ambient air monitoring for 1,2-diphenylhydrazine was located in the literature. This may be due to both the rapid oxidation of 1,2-diphenylhydrazine and its low vapor pressure, which limit the amount of 1,2-diphenylhydrazine entering the atmosphere. In addition, no information was located suggesting that any studies have sought but not found 1,2-diphenylhydrazine.

5.4.2 Water

Two reported identifications of 1,2-diphenylhydrazine in water samples were located in the literature. Melton et al. (1981) reported that 1,2-diphenylhydrazine was present in Cincinnati, OH, drinking water (river water treated by coagulation, sand filtration, and chlorination). 1,2-Diphenylhydrazine was reported at a concentration of 1 ng/L. Since the sample preparation involved aeration and the original sample was chlorinated, it is unclear if the detected material was 1,2-diphenylhydrazine. Riggin and Howard (1982) found that, in addition to injection onto a GC column, either chlorination or aeration of a sample resulted in total disappearance of 1,2-diphenylhydrazine. Tang et al. (1983) reported 1,2-diphenylhydrazine in coal gasification wastewater at concentrations of 0.149 and 1.786 µg/L. Sample preparation in this case involved separation into classes by pH, liquid-liquid extraction, concentration, and gas chromatography/mass spectroscopy (GC/MS) analysis. No precautions were taken to reduce the aeration of the sample. Also, the analytical procedure indicates that no 1,2-diphenylhydrazine would have been able to survive the conditions of the sample preparation and the detection may be of another chemical or of 1,2-diphenylhydrazine from another source (e.g., decomposition of another compound to 1,2-diphenylhydrazine).

Hall et al. (1985) reported that no 1,2-diphenylhydrazine (less than 1 µg/L) was detected in the Nanticoke River near the Chesapeake Bay. The analytical method involved liquid-liquid extraction, concentration, and analysis by GC/MS. The Contract Laboratory Program statistical database (queried April 13, 1987) reported that 1,2-diphenylhydrazine has been detected in water at 1 of 357 hazardous waste sites at a concentration of 96 ppb (CLPSDB 1987), and has been reported at 7 of 1177 sites in the National Priority List database (ATSDR 1990). The U.S. EPA Contract Laboratory Program uses GC methods to analyze the contaminants of interest. Since 1,2-diphenylhydrazine oxidizes to azobenzene in the GC injector port and both 1,2-diphenylhydrazine and azobenzene have the same GC retention time and mass spectra, reports of 1,2-diphenylhydrazine from the Contract

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Laboratory Program may actually represent detections of 1,2-diphenylhydrazine, azobenzene, or both (see Chapter 6 for more details).

5.4.3 Soil

1,2-Diphenylhydrazine has been identified in soil only at hazardous waste sites. The Contract Laboratory Program statistical database (queried April 13, 1987) reported that 1,2-diphenylhydrazine has been detected in the soil at 2 of 357 hazardous waste sites in both cases at 18,200 ppm (CLPSDB 1987). The Contract Laboratory Program uses GC methods to analyze the contaminants of interest. As discussed in Section 5.4.2, this may actually represent detections of either 1,2-diphenylhydrazine or azobenzene (see Chapter 6 for more details). Furthermore, the fact that identical concentrations were reported increases uncertainty about the validity of the data.

5.4.4 Other Media

1,2-Diphenylhydrazine has been assayed but not detected in fish samples from the Great Lakes area. Camanzo et al. (1987) reported that no 1,2-diphenylhydrazine was detected in fish samples from 13 Lake Michigan tributaries and Grand Traverse Bay fish. Analyses were made by GC/MS and no detection limits were given. Similarly, DeVault (1985) reported that a GC/MS did not identify any of the peaks present in fish samples from Great Lakes Harbors and Tributaries as 1,2-diphenylhydrazine.

Phenylbutazone and sulfinpyrazone can hydrolyze to yield 1,2-diphenylhydrazine and these drugs may contain some 1,2-diphenylhydrazine (Ahuja et al. 1988; Fabre et al. 1984; Matsui et al. 1983). Phenylbutazone is a drug used for the treatment of inflammatory conditions (e.g., arthritis) and sulfinpyrazone is used to treat gouty arthritis. Although potential exists for exposure to 1,2-diphenylhydrazine via from treatment with these drugs, no information regarding body burden was located in the literature.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Virtually no information concerning general population or occupational exposure was located in the literature. General population exposure may come from those on phenylbutazone or sulfinpyrazone therapy, since these drugs may contain some 1,2-diphenylhydrazine (Fabre et al. 1984; Matsui et al. 1983). The National Institute for Occupational Safety and Health (NIOSH), National Occupational Exposure Survey (NOES) reported as of May 1988 that 977 total employees and 154 female employees are potentially exposed to 1,2-diphenylhydrazine (100% from actual observations) (NIOSH 1988).

The available database limits analysis of exposures in two ways. First, very little information is available concerning the manufacturing

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processes used in the production of phenylbutazone and sulfinpyrazone, the two drugs that use 1,2-diphenylhydrazine as a starting material. A better understanding of these processes would allow the estimation of worker exposure potentials. Second, dye manufacturers in the United States no longer produce benzidine based dyes (the last manufacturer stopped production in 1988) and the number of workers potentially exposed to 1,2-diphenylhydrazine is now less than at the time of the NOES survey cited above. Thus, the survey may no longer accurately reflect the number of workers potentially exposed to 1,2-diphenylhydrazine.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURE

The only populations with potentially high exposure appear to be persons receiving phenylbutazone or sulfinpyrazone therapy, those living near hazardous waste sites, and those in occupations that manufacture or use 1,2-diphenylhydrazine. Very little information concerning these populations, however, is available to clearly understand the extent of these potential exposures.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. 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. Physical and chemical properties are essential for estimating the partitioning of a chemical in the environment. Data are available for only a few physical and chemical properties of 1,2-diphenylhydrazine, and most of these have limited experimental descriptions. Therefore, an evaluation of the accuracy of the data is difficult. Specifically, measured solubility, vapor pressure, K_{oc} , pKa, and Henry's Law constant at environmentally significant temperatures would help to remove any doubt concerning the accuracy of the partitioning estimates, especially in circumstances where 1,2-diphenylhydrazine does not oxidize rapidly (such as when high concentrations are present). These data form the

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basis of much of the input requirements for environmental models that predict the behavior of a chemical under specific conditions including hazardous waste landfills. In addition, the uncertainty in these measurements can be used to estimate the sensitivity of these properties in determining the overall fate of 1,2-diphenylhydrazine in the environment.

Production, Use, Release, and Disposal. Production methods for 1,2-diphenylhydrazine are well described in the literature (including the patent literature); there does not appear to be a need for further information in this area. Uses of 1,2-diphenylhydrazine are documented but no recent production figures or detailed descriptions of uses are available. This information is useful for estimating the potential for environmental releases from manufacturing and use industries as well as the potential environmental burden, but it is difficult to obtain in the detail desired since it is considered confidential business information for those industries that manufacture 1,2-diphenylhydrazine. Release information is similar to use information in that it is not obtained easily and can be used to estimate environmental burdens and potentially exposed populations. A Toxic Release Inventory will provide some of this information in the future. Disposal information is useful for determining environmental burden and potential concentrations where environmental exposures may be high. Data on different disposal methods for 1,2-diphenylhydrazine are lacking. According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Environmental Fate. Photolysis, photooxidation, and chemical oxidation studies in air and water are lacking, as are persistence studies in soil and groundwater. These kinds of studies are important since they address the fundamental removal mechanisms available to 1,2-diphenylhydrazine in the environment. In addition, removal mechanisms such as atmospheric photooxidation may be several orders of magnitude faster than any other removal mechanism; understanding these reactions is crucial to an understanding of the fate of 1,2-diphenylhydrazine in the environment. Biodegradation studies in water may not be important, even though they are lacking, since 1,2-diphenylhydrazine oxidizes rapidly.

Bioavailability from Environmental Media. No studies were located regarding the bioavailability of 1,2-diphenylhydrazine from environmental media, but lack of these data does not necessarily indicate a lack of bioavailability. As exposure to 1,2-diphenylhydrazine could occur at waste sites by dermal contact with contaminated soil or by ingestion of contaminated soil, it would be useful to know if dermal or oral absorption of 1,2-diphenylhydrazine from environmental media could occur. Information on dermal absorption of 1,2-diphenylhydrazine from other media is not

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available, but qualitative evidence indicates that 1,2-diphenylhydrazine in diet or oil media is absorbed from the gastrointestinal tract (Section 2.3).

Food Chain Bioaccumulation. 1,2-Diphenylhydrazine reacts rapidly in water to form azobenzene and other oxidation products (half-life in wastewater is 60 minutes). Because of this and based upon the log octanol/water partition coefficient, no bioaccumulation is expected in any aquatic organism.

Exposure Levels in Environmental Media. Environmental monitoring data are not available or are of questionable accuracy for water, soil, and air. These data would be helpful in determining the ambient concentrations of 1,2-diphenylhydrazine so that exposure estimates for the general population could be made as well as 1,2-diphenylhydrazine exposure estimates for terrestrial and aquatic organisms.

Exposure Levels in Humans. The database for exposure levels in humans is very limited, and it is unclear if an exposed population exists given the rapid disappearance of 1,2-diphenylhydrazine from the environment. While a more complete database would be helpful in determining the current exposure levels and thereby estimating the average daily dose associated with various scenarios (e.g., living near a hazardous waste site, taking phenylbutazone), a number of factors limit establishing such a program, including the lack of appropriate analytical methods.

Exposure Registries. An exposure registry is not available. The development of such a registry would be a useful reference tool in assessing exposure levels and frequency. In addition, a registry would allow an assessment of the variations in exposure concentrations from, for example, geography, season, regulatory actions, presence of hazardous waste landfills, or manufacturing and use facilities. These assessments, in turn, would provide a better understanding of the need for research or data acquisition based on the current exposure concentrations.

5.7.2 On-Going Studies

No on-going studies were located in the literature.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 1,2-diphenylhydrazine in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 1,2-diphenylhydrazine. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 1,2-diphenylhydrazine in environmental samples are the methods approved by federal agencies 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 a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

No adequate methods were located for the analysis of 1,2-diphenylhydrazine in biological materials. While thin-layer chromatography methods have been published, it is not clear if these methods would be capable of resolving 1,2-diphenylhydrazine from degradation products that appear rapidly in a sample upon standing (Bolton and Griffiths 1978; Dutkiewicz and Szymanska 1973). These products (some unidentified) are produced rapidly, and vary depending on the exact conditions (see below). In addition, none of the metabolites identified (e.g., benzidine, aniline) are suitable surrogates since they cannot be linked exclusively to 1,2-diphenylhydrazine exposure, but may result from exposure to other chemicals (and possibly drugs; see above).

6.2 ENVIRONMENTAL SAMPLES

Adequate analytical methods exist for the analysis of 1,2-diphenylhydrazine in environmental samples and are presented below. However, adequate methods are not available for the sampling, sample preservation, and sample preparation (extraction) of environmental media. Neither EPA nor NIOSH have standard methods for analyzing 1,2-diphenylhydrazine in any medium; 1,2-diphenylhydrazine is no longer on the Target Compound List (TCL) for the Contract Laboratory Program, but is identified as a semi-volatile compound (EPA 1987a). Riggin and Howard (1982) reported that 1,2-diphenylhydrazine at 100 µg/L in a municipal sewage effluent (after secondary treatment) had a time to 50% disappearance of 15 minutes (it degraded completely within 1 hour), but the half-life was extended to 60 minutes when the wastewater was deaerated. Also, the authors stated that 1,2-diphenylhydrazine "... analysis in wastewater is virtually meaningless, since the DPH level determined cannot be directly related to the DPH in the sample at the time of collection." This limitation may apply to all environmental media, depending on the exact conditions used to acquire and store the sample, as well as the sample itself. Even excellent

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methods for the analysis of 1,2-diphenylhydrazine will not necessarily yield concentrations that are representative of the concentrations present in the medium sampled.

Extracting and concentrating the 1,2-diphenylhydrazine in an environmental sample may give poor results. Riggin and Howard (1979) reported that 1,2-diphenylhydrazine extraction from water was "irreproducible" because of instability when the extract was concentrated. An extraction efficiency of more than 50% was reported for chloroform extraction at pH 7. If stored for longer than 1 day, however, the extract contained less than 10% of the initial 1,2-diphenylhydrazine concentration. At different pH values, 1,2-diphenylhydrazine degraded into different products, not all of which were identifiable. This lack of clearly identifiable degradation products makes identification of a degradation product as a surrogate for 1,2-diphenylhydrazine difficult. Ahuja et al. (1988) found that extraction of 1,2-diphenylhydrazine in water containing THAM buffer (pH 9.2) showed only 0.9% loss over 30 minutes, although chromatography was performed within 30 minutes of extraction. Although this procedure was applied to pharmaceutical analysis, there is no apparent reason to believe it will not work for environmental analysis.

In addition, Riggin and Howard (1982) reported that analytical standards of 1,2-diphenylhydrazine prepared in benzene, methylene chloride, methanol, triethyl amine, acetonitrile, or acetic acid decomposed completely in 3 days or less. Matsui et al. (1983) reported that 1,2-diphenylhydrazine was oxidized to azobenzene in n-hexane solution at a rate of about 5%/hr; flushing the n-hexane with nitrogen reduced the conversion rate to about 4% in 2 hours. These authors also found that nitrogen flushed standards were stable over a 1-hour period, based on the detector response factors during liquid chromatography. These limitations should be considered when interpreting analytical results.

Riggin and Howard (1982) reported that 1,2-diphenylhydrazine ". . . instantaneously decomposes to azobenzene in the GC injection port." The authors further stated that:

"It is interesting to note that only one peak resulted from DPH injection. Occasionally, it was found that a second, later eluting peak was present . . . but this was not always the case. This additional component may have been a solution decomposition product."

Because of this, GC, including GC/MS, does not appear to be an acceptable analytical tool for the analysis of 1,2-diphenylhydrazine in any sample.

Riggin and Howard (1979, 1982), Matsui et al. (1983), Fabre et al. (1984), and Ahuja et al. (1988) reported that High Performance Liquid Chromatography (HPLC) with UV or electrochemical detection is capable of analyzing 1,2-diphenylhydrazine. Reversed phase chromatographic columns

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have been used most often (Ahuja et al. 1988; Fabre et al. 1984; Riggin and Howard 1979, 1982). Cyano-amino polar bonded phase columns also have been used (Matsui et al. 1983). Using a reversed phase and UV detection, the minimum amount detected (on column amounts) is approximately 6-7 ng and the minimum amount quantifiable is less than 1 µg (Ahuja et al. 1988; Fabre et al. 1984; Matsui et al. 1983).

In conclusion, HPLC is preferred over GC for analysis of 1,2-diphenylhydrazine. Sample preservation and extraction methods need improvement.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-diphenylhydrazine 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 1,2-diphenylhydrazine.

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No biomarker that can be associated quantitatively with exposure to 1,2-diphenylhydrazine has been identified (see Section 2.5). No adequate methods are available for the analysis of 1,2-diphenylhydrazine in biological materials. If this information were available, it would allow both investigators and reviewers to assess the accuracy and uncertainty of the methods used in toxicological studies. Furthermore, the ready availability of tested analytical methods, including sample preservation, would permit a standardized approach to the analysis of biological materials to assist in measuring human exposure and monitoring effects in humans. Adequate methods appear to be available for the analysis of 1,2-diphenylhydrazine metabolites in biological materials. Metabolites include azobenzene and aniline, both of which appear to be amenable to analysis by standard methods. 1,2-Diphenylhydrazine and its metabolites, however, have not been established as a quantitative biomarker of exposure to 1,2-diphenylhydrazine.

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No biomarker that can be associated quantitatively with effect has been identified (see Section 2.5). Thus, there are no analytical methods for the determination of biomarkers of effect for 1,2-diphenylhydrazine.

Methods for Determining Parent Compound and Degradation Products in Environmental Media. While analytical methods appear to be available for the analysis of 1,2-diphenylhydrazine, no methods were found for the preservation of 1,2-diphenylhydrazine in ambient air, water, or soil samples. Such methods would allow the development and analysis of a monitoring program designed to better assess the concentrations of 1,2-diphenylhydrazine in and around hazardous waste sites. Methods for Determining Degradation Products in Environmental Media. Adequate methods are available for the analysis of some 1,2-diphenylhydrazine degradation products in environmental media; however, not all of the major degradation products have been identified. In addition, the number and nature of degradation products appear to change depending on conditions (e.g., pH). The development of adequate analytical methods for identifying degradation products would allow a monitoring program designed to assess the ambient concentrations of 1,2-diphenylhydrazine degradation products in environmental media to be established; this would provide information concerning both human and environmental exposure, since it would allow an estimation of the concentration of 1,2-diphenylhydrazine in environmental media to be established prior to degradation. The development of analytical methods, however, must be subsequent to generalized environmental fate studies that identify the degradation products. A standardized method could then be developed using spike recoveries from different media to determine the recovery efficiencies and precision and accuracy of the method.

6.3.2 On-going Studies

No studies were located regarding on-going analytical methods development for 1,2-diphenylhydrazine.

7. REGULATIONS AND ADVISORIES

National and state regulations and advisories pertinent to human exposure to 1,2-diphenylhydrazine are summarized in Table 7-1. Guidance from the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) is not available.

TABLE 7-1. Regulations and Advisories Applicable to 1,2-Diphenylhydrazine

Agency	Description	Value	Reference
<u>National</u>			
Regulations:			
a. Nonspecific media:			
EPA OERR	Reportable quantity	1 pound (statutory) 10 pounds (proposed)	EPA 1987b 40 CFR 117 and 302
EPA OSW	Hazardous waste Groundwater monitoring list	Not applicable Not applicable	40 CFR 261 40 CFR 264
Guidelines:			
a. Air:			
EPA	Inhalation unit risk	$2.2 \times 10^{-4} (\mu\text{g}/\text{m}^3)^{-1}$ a	EPA 1988a
b. Water:			
EPA	Drinking water unit risk	$2.2 \times 10^{-5} (\mu\text{g}/\text{L})^{-1}$ a	EPA 1988a
EPA OWRS	Ambient water quality criteria Ingesting water and organisms Ingesting organisms only	4 ng/L, 42 ng/L, 422 ng/L ^{a,b} 56 ng/L, 560 ng/L, 5600 ng/L ^{a,b}	EPA 1980 EPA 1980
c. Other:			
EPA	Carcinogenic classification Cancer slope factor	Group B2 ^c $8.0 \times 10^{-1} (\text{mg}/\text{kg}/\text{day})^{-1}$	EPA 1988a
<u>State</u>			
Guidelines:			
a. Air:			
Florida-Tampa	Acceptable ambient air concentration	0.01 mg/m ³ (8 hr)	NATICH 1988
New York		3.3 μg/m ³ (annual)	NATICH 1988
North Dakota		BACT ^d	NATICH 1988
b. Water:			
Kansas	Drinking water	0.45 μg/L	FSTRAC 1988
Minnesota		0.45 μg/L	FSTRAC 1988

^aCalculated from cancer slope factor of $8.0 \times 10^{-1} (\text{mg}/\text{kg}/\text{day})^{-1}$.

^bCriteria corresponding to cancer risk levels of 10^{-7} , 10^{-6} , and 10^{-5} .

^cGroup B2 - Probable human carcinogen, based on sufficient evidence from animal studies.

^dBest available control technology.

EPA = Environmental Protection Agency; OERR = Office of Emergency and Remedial Response; OWRS = Office of Water Regulations and Standards; OSW = Office of Solid Waste.

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9. GLOSSARY

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

Adsorption Coefficient (Koc) -- 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,

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Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.
Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

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

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

In Vivo -- Occurring within the living organism.

Lethal Concentration₍₁₀₎ (LC₅₀) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose₍₁₀₎ (LD₁₀) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

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

Lethal Time₍₅₀₎ (LT₅₀) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

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

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

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

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

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

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-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.

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

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

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 (TD₅₀) -- 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: PEER REVIEW

A peer review panel was assembled for 1,2-diphenylhydrazine. The panel consisted of the following members: Dr. Judith S. Bellin, Private Consultant; Dr. Rolf Hartung, Department of Environmental and Industrial Health, University of Michigan; Dr. Michael Norvell, Private Consultant; and Dr. Richard Carchman, Department of Pharmacology and Toxicology, Medical College of Virginia. These experts collectively have knowledge of 1,2-diphenylhydrazine'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.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with 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 Agency for Toxic Substances and Disease Registry.