

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			390 (intestinal hemorrhage)	NCI 1978
				Other	6700			
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.

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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

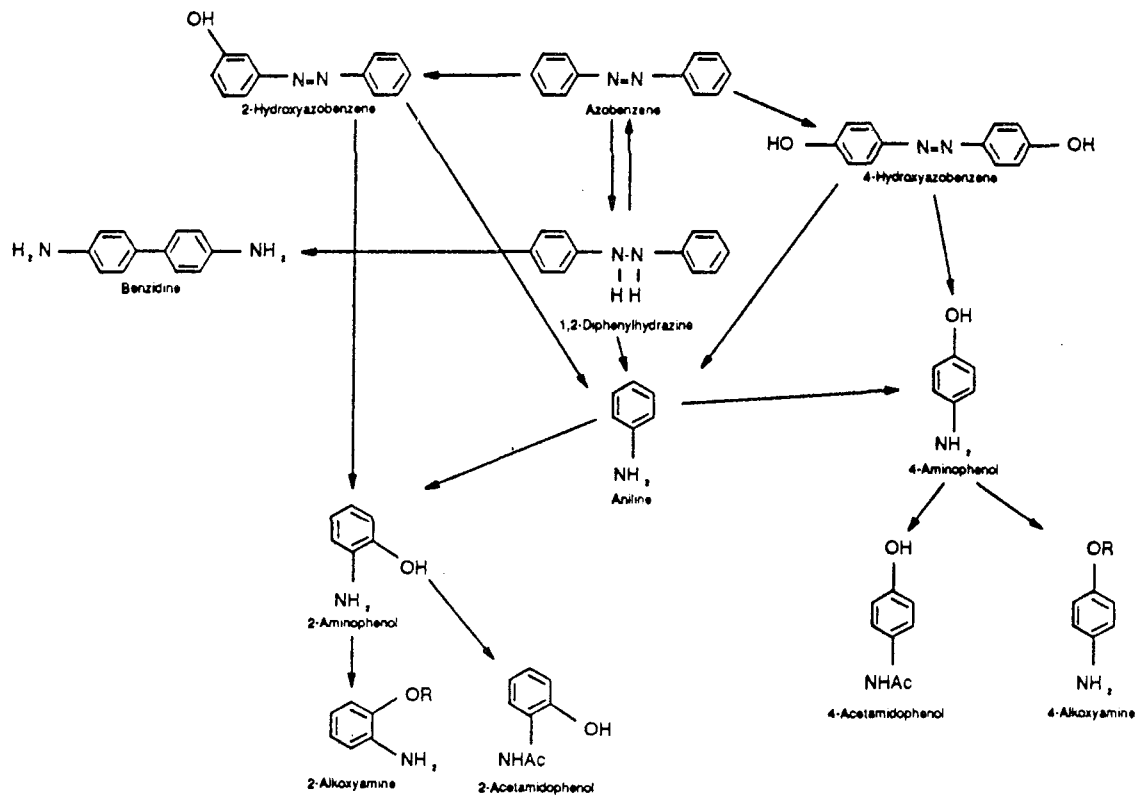
No studies were located regarding distribution in humans or animals after dermal exposure to 1,2-diphenylhydrazine.

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),

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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.

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

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

● Existing Studies

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

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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. Intermediate duration 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 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, 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

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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.

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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.