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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR 1,2-DIPHENYLHYDRAZINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

DISCLAIMER

This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,2-diphenylhydrazine. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for 1,2-Diphenylhydrazine. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-062. NTIS PB81-117731.

U.S. EPA. 1980b. Hazard Profile for 1,2-Diphenylhydrazine. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data was limited in scope, which tended to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The oral carcinogenicity of 1,2-diphenylhydrazine was demonstrated in 2-year feeding studies using rats and mice (NCI, 1978). Based on the concentration-related increase in hepatic carcinomas and neoplastic nodules in treated male rats, the U.S. EPA (1980a) calculated a human q_1^* of 0.768 $(mg/kg/day)^{-1}$.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CAS	Chemical Abstract Service
CS	Composite score
DMBA	Dimethyl benzanthracene
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
TWA	Time-weighted average
UV	Ultraviolet

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 1,2-diphenylhydrazine are reported in Table 1-1.

In the atmosphere, 1,2-diphenylhydrazine has the potential to undergo direct photolysis, as indicated by UV absorption >290 nm (Sadtler, n.d.), autooxidization (U.S. EPA, 1981) and reaction with photochemically generated HO radical (U.S. EPA, 1986). Based on a hydroxyl reaction rate constant of 3.4×10^{-11} cm^3/molecule-sec and an ambient HO radical concentration of 8.0×10^5 molecules/cm^3, the hydroxyl reaction half-life is calculated to be 7.08 hours (U.S. EPA, 1986). The aquatic half-life of 1,2-diphenylhydrazine is based on the observation that 1,2-diphenylhydrazine (10 µg/ℓ) in dilute aqueous solution was found to be unstable, with <10% remaining for longer than 1 day of preservation (in the dark) under any of the conditions tested (i.e., room temperature or 4°C at pH 2, 7 or 10 with or without chlorine). 1,2-Diphenylhydrazine decomposed primarily to azobenzene at pH 10, to benzidine at pH 2 and to an unidentified but oxidizable compound at pH 7 (U.S. EPA, 1981). The half-life of 1,2-diphenylhydrazine at a concentration of 100 µg/ℓ in a municipal sewage effluent was 15 and 60 minutes under aerobic and anaerobic conditions, respectively (U.S. EPA, 1981). 1,2-Diphenylhydrazine should not significantly bioaccumulate or adsorb to sediments. The half-life of 1,2-diphenylhydrazine in soil was not located in the available literature. 1,2-Diphenylhydrazine can undergo sublimation (U.S. EPA, 1981), suggesting that volatilization from soil surfaces may occur. Based on its reactivity in water, it is likely to undergo significant chemical and biodegradation reactions in soil. The estimated K_{oc} value of 947 indicates that 1,2-diphenylhydrazine should have low mobility in soil.

TABLE 1-1

Relevant Physical and Chemical Properties of 1,2-Diphenylhydrazine

Property	Value	Reference
CAS number:	122-66-7	
Chemical class:	substituted hydrazine	
Molecular weight:	184.24	
Vapor pressure:	NA	
Water solubility:	314 mg/ℓ at 25°C (estimated)* 221 mg/ℓ (temperature NA)	Lyman et al., 1982 U.S. EPA, 1981
Log octanol/water partition coefficient:	2.94	Hansch and Leo, 1985
Bioconcentration factor:	101 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	947 (estimated)	Lyman et al., 1982
Half-lives:		
Air	~7 hours (estimated)	U.S. EPA, 1986b
Water	<1 day	U.S. EPA, 1981
Soil	NA	

*Calculated using log K_{OW} value listed above and the following equation: log S = -1.37 log K_{OW} +7.26 (Lyman et al., 1982)

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Rats given an oral dose of either 200 or 400 mg/kg 1,2-diphenylhydrazine excreted hydrazobenzene, benzidine and two unidentified metabolites in the urine, but the proportion of the dose eliminated this way was not quantified and conclusions regarding the rate and amount of gastrointestinal absorption could not be made from these data (Dutkiewicz and Szymanska, 1976).

There are no pertinent human data on the gastrointestinal absorption of 1,2-diphenylhydrazine.

2.2. INHALATION

Dutkiewicz and Szymanska (1976) identified one urinary metabolite after intratracheal administration of 1,2-diphenylhydrazine in rats, but quantitation was not performed. No direct assessment of the respiratory absorption of 1,2-diphenylhydrazine was found in the available animal literature, and pertinent human data could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. NCI (1978) exposed rats and mice to dietary 1,2-diphenylhydrazine for 4 weeks, followed by a 2-week observation period. Dietary concentrations for male rats and mice ranged from 0.007-0.423%, for female rats from 0.00008-5.138% and for female mice from 0.0003-5.138%. Lethality was first observed at 0.108% in rats and 0.301% in mice. Intestinal hemorrhage was grossly observed in mice at unspecified concentration levels.

Because of the lack of sufficient details of the sublethal effects in this study, a NOEL or LOEL cannot be assumed.

3.1.2. Inhalation. Pertinent data regarding the subchronic toxicity of 1,2-diphenylhydrazine after inhalation exposure could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. NCI (1978) conducted 78-week bioassays of dietary 1,2-diphenylhydrazine in groups of ~50 rats/sex and ~50 mice/sex. Rats were observed for 28-30 weeks following the end of treatment and mice for 17-18 weeks following the end of treatment. TWA dietary concentrations were 0.008 or 0.03% (80 or 300 ppm) for male rats, 0.004 or 0.01% (40 or 100 ppm) for female rats, 0.008 or 0.04% (80 or 400 ppm) for male mice and 0.004 or 0.04% (40 or 400 ppm) for female mice. Controls consisted of 49-50 animals/sex of each species for both the low and high groups. Reduced survival was observed in female rats and in mice of both sexes in the high-dose groups. High-dose mice also had reduced mean body weights at termination. Although the authors concluded that no compound-related nonneoplastic lesions were observed, an examination of the raw data suggested that inflammation of the lung, splenic hyperplasia and hyperkeratosis and acanthosis of the stomach in both species may have been related to treatment.

3.2.2. Inhalation. Pertinent data regarding toxicity after chronic inhalation exposure to 1,2-diphenylhydrazine could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive toxicity of 1,2-diphenylhydrazine, after either oral or inhalation exposure, could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Several authors (Marhold et al., 1968; Genin et al., 1975; Kurlyandskii et al., 1976) demonstrated synergism between 1,2-diphenylhydrazine, or related compounds, and benzidine, in tumor induction (U.S. EPA, 1980a).

4. CARCINOGENICITY

4.1. HUMAN DATA

There were no pertinent epidemiological or occupational data in the available literature regarding oral or inhalation exposure specifically to 1,2-diphenylhydrazine. The U.S. EPA (1980a) expressed concern over the oncogenic potential of 1,2-diphenylhydrazine because of evidence that workers involved in dye manufacturing had increased incidences of bladder cancer (Wynder et al., 1963; Anthony et al., 1970).

4.2. BIOASSAYS

4.2.1. Oral. The most pertinent cancer data from the chronic NCI (1978) bioassay in rats and mice (see Section 3.2.1.) are presented in Tables 4-1 and 4-2, respectively. Of the several treatment-related tumor types found, the U.S. EPA (1980a) considered the increased incidence of hepatic neoplastic nodules/hepatocellular carcinomas in male rats to be of the greatest biological significance. Assuming rats consume the dietary equivalent of 5% of their body weight daily (U.S. EPA, 1980c), the TWA concentrations correspond to 4 and 15 mg/kg/day for male rats.

Qualitative evidence of carcinogenicity was provided by Pliss (1974), who studied the carcinogenicity of oral 1,2-diphenylhydrazine given for 588 days to rats and mice; 30 mg of 1,2-diphenylhydrazine/mouse or rat was added to the food 5 times/week. Tumors (primarily pulmonary adenomas, leukemias and liver tumors) developed in 50% of all treated mice. Incidence data for rats or control mice were not given in the descriptions provided by U.S. EPA (1980a, 1981). Apparently, Pliss (1974) replaced some animals that had parasitic infections during the course of the experiment.

TABLE 4-1

Carcinogenic Potency of Technical Grade 1,2-Diphenylhydrazine Administered in the Diet to F344 Rats[a]

Sex	Concentration (%)[b]	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence (p value)[c]
M	0	0	108-109	liver	neoplastic nodule or	6/95
	0.008	78	107		hepatocellular carcinoma	13/49 (0.001)
	0.03	78	106			37/49 (<0.001)
	0	0	108-109	ear canal	squamous cell carcinoma	1/95
	0.008	78	107	Zymbal gland	or papilloma	2/50 (NS)
	0.03	78	106	skin of the ear		7/49 (0.002)
	0	0	108-109	adrenal	pheochromocytoma	15/94
	0.008	78	107			7/48 (NS)
	0.003	78	106			16/46 (0.01)
F	0	0	109	mammary gland	adenocarcinoma	1/98
	0.004	78	108			3/50 (NS)
	0.01	78	107			6/50 (0.006)

[a]Source: NCI, 1978

[b]Time-weighted average

[c]Probability value of treated group vs. combined control data, by Fisher exact test

NS = Not significant ($p>0.05$)

TABLE 4-2

Carcinogenic Potency of Technical Grade 1,2-Diphenylhydrazine Administered in the Diet to Female B6C3F1 Mice[a]

Concentration (%)[b]	Duration of Treatment (weeks)	Duration of Study (weeks)	Target Organ	Tumor Type	Tumor Incidence (p value)[c]
0	78	96	liver	hepatocellular adenoma or carcinoma	3/97
0.004		95			4/39 (NS) →
0.04		96			22/43 (<0.001)

[a]Source: NCI, 1978

[b]Time-weighted average

[c]Probability value of treated group vs. combined control data, by Fisher exact test

NS = Not significant (p>0.05)

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of 1,2-diphenylhydrazine after inhalation exposure in experimental animals could not be located in the available literature.

4.3. OTHER RELEVANT DATA

A variety of tumor types was observed by Pliss (1974) after repeated subcutaneous or epicutaneous administration of 1,2-diphenylhydrazine to mice, or subcutaneous injections in rats. Increased incidences of rhabdomyosarcoma, pulmonary and hepatic tumors, Zymbal's gland tumors, leukemia, and neoplasia of the spleen, uterus and mammary glands were observed. U.S. EPA (1980a) noted that control data were provided only for epicutaneous administration.

Spitz et al. (1950) have suggested that 1,2-diphenyl- hydrazine is not carcinogenic by the subcutaneous route (further details not provided), although several Soviet authors (Genin et al., 1975; Shabad and Genin, 1975; Kurlyandskii et al., 1976) have shown the additivity of subcutaneous 1,2-diphenylhydrazine and benzidine sulfate in causing bladder tumors. Maronpot et al. (1983) demonstrated the carcinogenicity of 1,2-diphenylhydrazine in a mouse strain A pulmonary test system.

There is evidence in rats (see Sections 2.1. and 2.2.) that 1,2-diphenylhydrazine is metabolized to hydrazobenzene and benzidine as well as other intermediates. Given that azobenzene and benzidine have known human carcinogenic potential, the weight of evidence for probable human carcinogenicity is further substantiated

Diphenylhydrazine was mutagenic toward Salmonella typhimurium strain TA100, in the presence of rat liver S-9 (Haworth et al., 1983). The technical grade material was not genotoxic in an Escherichia coli WP2 uvrA reversion assay (Dunkel et al., 1985), and practical grade diphenylhydrazine

did not cause sex-linked recessive lethal mutations in Drosophila (Yoon et al., 1985). Seiler (1977), however, showed that an intraperitoneal dose of 1,2-diphenylhydrazine had an inhibitory effect upon testicular DNA synthesis in male mice.

4.4. WEIGHT OF EVIDENCE

IARC (1974) did not evaluate 1,2-diphenylhydrazine for carcinogenic potency. There are sufficient data in both rats and mice to consider 1,2-diphenylhydrazine a potential human carcinogen (NCI, 1978). In the absence of definitive human data and in the presence of sufficient evidence in rats and mice (NCI, 1978), 1,2-diphenylhydrazine can be classified an EPA Group B2 (U.S. EPA, 1986a), or IARC Group 2B, carcinogen.

U.S. EPA (1980a) recommended ambient water quality criteria of 4, 42 and 422 µg/ℓ for diphenylhydrazine, corresponding to excess cancer risk levels of 10^{-7}, 10^{-6} and 10^{-5}, respectively. The criteria are based on the induction of hepatocellular carcinomas and neoplastic nodules in male F344 rats (NCI, 1978).

Other pertinent guidelines and standards, including drinking water standards, ADIs, HAs, AADIs and ACGIH, OSHA or NIOSH occupational exposure limits could not be located in the available literature.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Because of the demonstrated oncogenicity of 1,2-diphenylhydrazine in experimental animals (NCI, 1978), calculation of an RfD_{SO} or RfD_{SI} is inappropriate.

6.2. REFERENCE DOSE (RfD)

Because of the demonstrated oncogenicity of 1,2-diphenylhydrazine in experimental animals (NCI, 1978), calculation of an RfD_O or RfD_I is inappropriate.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. U.S. EPA (1980a) calculated a human q_1^* of 0.768 $(mg/kg/day)^{-1}$ for 1,2-diphenylhydrazine, using the linearized multistage model that was adopted by the U.S. EPA (1980c). This value was based upon the incidence of hepatocellular carcinomas and neoplastic nodules in male F344 rats treated chronically with 0.008% or 0.03% dietary 1,2-diphenylhydrazine (NCI, 1978). The data used in this computation are reported in Table 6-1. Because the incidence of liver tumors in the male rats is the most convincing carcinogenicity data available, the q_1^* derived by the U.S. EPA (1980a), which has undergone both internal Agency and external review, is adopted for the purposes of this document.

6.3.2. Inhalation. In the absence of pertinent data regarding the carcinogenicity of 1,2-diphenylhydrazine after inhalation exposure, a unit risk for inhalation exposure is not listed in this document.

TABLE 6-1

Cancer Data Sheet for Derivation of a q_1^*
for 1,2-Diphenylhydrazine

Reference: NCI, 1978; U.S. EPA, 1980a

Species/strain/sex: rats, F344, male

Route/vehicle: diet

Length of exposure (le) = 78 weeks

Length of experiment (LE) = 104 weeks

Lifespan of animal (L) = 104 weeks

Body weight = 0.380 kg (measured)

Tumor site and type: hepatocellular carcinomas and neoplastic nodules

Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0	6/95
4	13/49
15	37/49

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APPENDIX

Summary Table for 1,2-Diphenylhydrazine

Route	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	q_1^* or Unit Risk	Reference
Oral, diet	rat, male	0, 0.008 and 0.03% (0, 4 and 15)	hepatocellular carcinomas and neoplastic nodules	0.768 $(mg/kg/day)^{-1}$	NCI, 1978; U.S. EPA, 1980a