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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR 1,2-DIPHENYLHYDRAZINE

Prepared for

OFFICE OF SOLID WASTE AND
EMERGENCY RESPONSE

Prepared by

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NOTICE

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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, 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 focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, RfDs are not estimated. Instead, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980b) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

1,2-Diphenylhydrazine is a solid at ambient temperatures; it is insoluble in water but highly soluble in ethanol (Weast, 1985). It is unstable in both air and water under normal conditions (U.S. EPA, 1981; Riggin and Howard, 1979). 1,2-Diphenylhydrazine is commonly produced by the reduction of nitrobenzene with zinc dust in alkaline solution (U.S. EPA, 1981). In 1977, one company in the United States produced between 0.1 and 1.0 million pounds of this chemical. Because of its adverse health effects, the production of 1,2-diphenylhydrazine in the United States has been greatly reduced in recent years (U.S. EPA, 1981). Data regarding current producers or production volumes of 1,2-diphenylhydrazine in the United States were not available (USITC, 1986; SRI, 1987). 1,2-Diphenylhydrazine is used primarily in the production of benzidine-based dyes and in the manufacture of such pharmaceuticals as sulfinpyrazone and phenylbutazone (U.S. EPA, 1981).

Limited data were available in the literature regarding the fate and transport of 1,2-diphenylhydrazine in any environmental media. In air, direct photolysis, oxidation by molecular oxygen and reaction with HO• are expected to convert 1,2-diphenylhydrazine into azobenzene. The half-life for the conversion of 1,2-diphenylhydrazine to azobenzene by photochemically produced HO• is estimated to be ~7 hours (U.S. EPA, 1986b). The fate and transport of 1,2-diphenylhydrazine in the atmosphere will be controlled indirectly by its oxidation product azobenzene. Photolysis, reaction with molecular oxygen and biodegradation may be responsible for the loss of 1,2-diphenylhydrazine from water (Callahan et al., 1979). The half-life of

1,2-diphenylhydrazine in clean water may be 7 hours and in wastewater 15 minutes (Riggin and Howard, 1979); however, 1,2-diphenylhydrazine may not be degraded in water but may be converted into azobenzene (Callahan et al., 1979). As in the case of air, the fate of 1,2-diphenylhydrazine in water will be controlled by azobenzene, which may undergo further degradation into aniline and other products (Callahan et al., 1979). Similarly, the transport of 1,2-diphenylhydrazine in water will be controlled by azobenzene formed as a result of oxidation of 1,2-diphenylhydrazine. In soils, 1,2-diphenylhydrazine will undergo rapid oxidation in the presence of O_2 and certain metal cations; it may undergo both aerobic (primarily in top layers) and anaerobic (in deeper soil layers) biodegradation. 1,2-Diphenylhydrazine and particularly its oxidation product (azobenzene) will be moderately to strongly adsorbed in soils and are not likely to leach to groundwater from most soils.

Aquatic toxicity information for 1,2-diphenylhydrazine is limited to acute lethality data for two freshwater animal species. These data indicate that the no-discernible-effect concentration for Daphnia magna is 0.41 mg/ℓ, that 24-hour LC_{50}s for Lepomis macrochirus and Daphnia magna are 1.2 and 8.1 mg/ℓ, respectively, and that 96-hour LC_{50}s for Lepomis macrochirus and Daphnia magna are 0.27 and 4.1 mg/ℓ, respectively.

Limited pharmacokinetic data for rats indicate that 1,2-diphenylhydrazine is absorbed by the gastrointestinal and respiratory tracts and excreted as unchanged compound and metabolites in the urine. Specific information regarding the rate and extent of absorption or excretion, other excretory pathways or distribution of 1,2-diphenylhydrazine is not available. Identified urinary metabolites in rats include aniline, benzidine and aminophenols.

Limited toxicity data are available for 1,2-diphenylhydrazine. Four-week feeding studies conducted by the NCI (1978) showed that diets containing ≥0.108 and 0.301% of compound produced deaths in rats and mice, respectively. Intestinal hemorrhage in mice at unspecified concentrations was the only gross pathologic effect attributed to treatment. In chronic oral studies, rats and mice were given 1,2-diphenylhydrazine in the diet for 78 weeks at concentrations of 0.008 or 0.03% (male rats), 0.004 or 0.01% (female rats), 0.008 or 0.04% (male mice) and 0.004 or 0.04% (female mice) (NCI, 1978). Effects included decreased body weight gain in the high-dose male and low- and high-dose female rats, decreased survival in the high-dose female rats, and decreased body weight and decreased survival in the high-dose male and female mice. NCI (1978) concluded that there were no treatment-related nonneoplastic gross or histological alterations in either species.

Treatment-related neoplastic effects occurred in the NCI (1978) study, including hepatocellular carcinomas in the low- and high-dose male rats, squamous-cell carcinomas and papillomas of the Zymbal's gland in high-dose male rats, adrenal pheochromocytomas in high-dose male rats, neoplastic nodules in the liver and mammary gland adenocarcinomas in high-dose female rats, and hepatocellular carcinomas in high-dose female mice. Also, 1,2-diphenylhydrazine was tumorigenic in rats and mice in inadequately reported chronic oral, subcutaneous and dermal carcinogenicity studies (Pliss, 1974), and produced positive responses in a Strain A mouse pulmonary tumor assay (Maronpot et al., 1986). 1,2-Diphenylhydrazine was not tumorigenic when administered to rats by subcutaneous injection once weekly for life (Spitz et al., 1950).

1,2-Diphenylhydrazine induced reverse mutations in S. typhimurium strain TA100 but not in other strains of S. typhimurium or in E. coli WP2 uvrA (Haworth et al., 1983; Dunkel et al., 1985). 1,2-Diphenylhydrazine inhibited thymidine incorporation into mouse testicular DNA when administered by a single intraperitoneal injection (Seiler, 1977), but did not induce sex-linked recessive lethal mutations in Drosophila melanogaster (Yoon et al., 1985).

Information is not available regarding the toxicity or carcinogenicity of inhaled 1,2-diphenylhydrazine, or teratogenicity or other reproductive effects of 1,2-diphenylhydrazine by the oral or inhalation routes.

Using the dose-response data for hepatocellular carcinoma and liver neoplastic nodules in male rats from the NCI (1978) carcinogenicity bioassay, a q_1^* of 0.8 $(mg/kg/day)^{-1}$ was calculated for oral exposure to 1,2-diphenylhydrazine (U.S. EPA, 1980a). This q_1^* was verified and adopted as the inhalation q_1^* (U.S. EPA, 1987b). An RQ of 100 for systemic toxicity was calculated on the basis of decreased survival of rats in the NCI (1978) bioassay. An RQ of 10 for carcinogenicity was calculated from the NCI (1978) male rat liver tumor/nodule incidence data.

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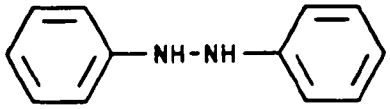
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration producing 50% immobilization
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose rating value
RV_e	Effect rating value
RfD	Reference dose
TWA	Time weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as 1,2-diphenylhydrazine is also known as hydrazobenzene; sym-diphenylhydrazine; N,N-bianiline; and benzene, 1,1-hydrazobis- (HSDB, 1987). The structure, empirical formula, molecular weight and CAS Registry number for 1,2-diphenylhydrazine are as follows:



Empirical formula: $C_{12}H_{12}N_2$

Molecular weight: 184.24

CAS Registry number: 122-66-7

1.2. PHYSICAL AND CHEMICAL PROPERTIES

1,2-Diphenylhydrazine is a solid at ambient temperatures (Weast, 1985). It is insoluble in water and acetic acid, slightly soluble in benzene but very soluble in ethanol (HSDB, 1987). Selected physical properties of 1,2-diphenylhydrazine are listed below (Weast, 1985, unless otherwise stated):

Melting point:	131°C
Boiling point:	not determined
Density:	1.158 g/cm³ at 16/4°C
Water solubility:	314.5 mg/ℓ (estimated from the K_{ow} value and the regression equation, log S (μmol/ℓ) = -1.37 log K_{ow} + 7.26 as given in Lyman et al., 1982)
Vapor pressure:	not determined
Log K_{ow}:	2.94 (Hansch and Leo, 1985)

1,2-Diphenylhydrazine is a reactive chemical; it is not stable in air or in water. It autooxidizes in air, rearranges to benzidine in strong mineral acids and decomposes when heated (U.S. EPA, 1981). 1,2-Diphenylhydrazine is unstable even in aqueous solutions of moderate pH. At a pH of 10, it apparently decomposes primarily to azobenzene; at a pH of 2, it degrades to benzidine; and at a pH of 7, it degrades to an unidentified oxidizable product(s) (Riggin and Howard, 1979).

1.3. PRODUCTION DATA

Bofors Lakeway Inc., Muskegon, MI, reported that production of 1,2-diphenylhydrazine in 1977 ranged from 0.1-1.0 million pounds (U.S. EPA, 1981). No production data for this compound were available from 1979 to date (U.S. EPA, 1981; SRI, 1987; USITC, 1986). It is likely that the production of this compound in the United States has been greatly reduced because of the known adverse health effects; however, Fabricolor Inc., Patterson, NJ, which manufactures benzidine-based dyes and both Ciba-Geigy Corp., Suffern, NY, and R.S.A Corp., Ardsley, NY, which manufacture 1,2-diphenylhydrazine-based drugs may still use this chemical (U.S. EPA, 1981; SRI, 1987). It is not known whether these companies produce this chemical on site or use imported 1,2-diphenylhydrazine. In 1983, only 22,161 pounds of 1,2-diphenylhydrazine was imported in the United States through principal custom districts (USITC, 1984). 1,2-Diphenylhydrazine is produced by the reduction of nitrobenzene with zinc dust or iron powder in an alkaline solution or by the electrolytic reduction of nitrobenzene (U.S. EPA, 1981).

1.4. USE DATA

1,2-Diphenylhydrazine is used mainly as the starting material for the production of benzidine-based dyes and as an intermediate in the manufacture of pharmaceuticals such as sulfinpyrazone and phenylbutazone (U.S. EPA, 1981).

1.5. SUMMARY

1,2-Diphenylhydrazine is a solid at ambient temperatures; it is insoluble in water but highly soluble in ethanol (Weast, 1985). It is unstable in both air and water under normal conditions (U.S. EPA, 1981; Riggin and Howard, 1979). 1,2-Diphenylhydrazine is commonly produced by the reduction of nitrobenzene with zinc dust in alkaline solution (U.S. EPA, 1981). In 1977, one company in the United States produced between 0.1 and 1.0 million pounds of this chemical. Because of its adverse health effects, the production of 1,2-diphenylhydrazine in the United States has been greatly reduced in recent years (U.S. EPA, 1981). Data regarding current producers or production volumes of 1,2-diphenylhydrazine in the United States were not available (USITC, 1986; SRI, 1987). 1,2-Diphenylhydrazine is used primarily in the production of benzidine-based dyes and in the manufacture of such pharmaceuticals as sulfinpyrazone and phenylbutazone (U.S. EPA, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

Limited information regarding the fate of 1,2-diphenylhydrazine in the atmosphere was located in the available literature. In air, 1,2-diphenylhydrazine will be rapidly converted to azobenzene (Callahan et al., 1979); however, the species responsible for this oxidation is not known with certainty. Although molecular oxygen may convert 1,2-diphenylhydrazine to azobenzene in aerated aqueous solution (Callahan et al., 1979), the most likely species to oxidize 1,2-diphenylhydrazine in the atmosphere is HO•. No experimental value for the rate constant of HO• reaction with 1,2-diphenylhydrazine is available. Based on the Graphical Exposure Modeling System (GEMS) of the U.S. EPA (1986b), the rate constant for this reaction was estimated as 3.4×10^{-11} cm^3/molecule-sec. If the concentration of these radicals in the atmosphere is assumed to be 8×10^5 molecules/cm^3 (U.S. EPA, 1986b), the half-life of this reaction is ~7 hours. Because 1,2-diphenylhydrazine absorbs substantial amounts of light of wavelength >290 nm (HSDB, 1987), direct photolysis of 1,2-diphenylhydrazine in the atmosphere is also likely to occur, although the half-life of this reaction cannot be estimated.

The fate of 1,2-diphenylhydrazine with respect to transport in and out of the atmosphere is uncertain. Based on the expected short half-life for the oxidation of 1,2-diphenylhydrazine to azobenzene, it is the transport of azobenzene (azobenzene may be stable in air) that may determine the ultimate fate of 1,2-diphenylhydrazine in air.

2.2. WATER

Limited experimental data are available regarding the fate of 1,2-diphenylhydrazine in water. The photolysis of 1,2-diphenylhydrazine with UV

light consisting of wavelengths <290 nm (solar cutoff wavelength) was reported by Callahan et al. (1979) and Shizuka et al. (1970). In aerated solutions, 1,2-diphenylhydrazine was oxidized to azobenzene, and in the presence of hydrogen-donating solvents both azobenzene and aniline were formed. Since the photooxidation reaction is easily reversible and azobenzene may not undergo further photolysis, this reaction may not serve as a significant process for the degradation of 1,2-diphenylhydrazine. If 1,2-diphenylhydrazine or its oxidized product (azobenzene), however, remain sorbed to organic particulate matters that are capable of producing hydrogen donors (e.g., chlorophyll or its derivatives) in water, 1,2-diphenylhydrazine may be degraded to aniline during photolysis (Callahan et al., 1979). Therefore, 1,2-diphenylhydrazine which can absorb significant solar radiation may undergo significant photodegradation by the above pathway (Callahan et al., 1979). 1,2-Diphenylhydrazine is rapidly and reversibly oxidized to azobenzene by molecular oxygen in aerated solution, even in the absence of light. This reaction is pH-dependent and is catalyzed by common cations, e.g., Cu(+2) found in natural water. At a pH of 10, the half-life for the formation of azobenzene in this reaction is ~6 minutes in the absence of Cu(+2) catalyst and 1 minute in the presence of Cu(+2) catalyst (Callahan et al., 1979). The stability of 1,2-diphenylhydrazine in aqueous solution in the pH range of 2-10 at room temperature and 4°C was studied by Riggin and Howard (1979). More than 90% of 1,2-diphenylhydrazine disappeared in <1 day under all conditions, and the rate of disappearance was even faster in the presence of chlorine. Riggin and Howard (1979) concluded that azobenzene is formed at a pH of 10 and benzidine is formed at a pH of 2. The product formed at pH 7 could not be identified.

The hydrolysis of 1,2-diphenylhydrazine in aqueous solutions is not expected to be significant (Callahan et al., 1979). 1,2-Diphenylhydrazine was not readily biodegradable with aniline-acclimated mixed microorganisms (Malaney, 1960). Tabak et al. (1981) used the static-culture flask-screening procedure with settled domestic wastewater as microbial inoculum to assess the biodegradability of 1,2-diphenylhydrazine, and concluded that 1,2-diphenylhydrazine may undergo significant degradation with gradual adaptation, followed by a decrease in degradation rate because of the toxicity of the compound toward the microorganisms. The study by Riggin and Howard (1979), although not designed to test biodegradability, provided some evidence for the biodegradability of 1,2-diphenylhydrazine. The disappearance time of 1,2-diphenylhydrazine in wastewater (half-life of 15 minutes) was much faster than its disappearance from distilled water solution (half-life of 7 hours) under similar conditions. In wastewater, the half-life of disappearance of 1,2-diphenylhydrazine under anaerobic conditions was 1 hour.

No experimental data regarding the transport of 1,2-diphenylhydrazine in water were located in the available literature. According to Callahan et al. (1979), volatilization of 1,2-diphenylhydrazine from water is likely to be insignificant. The estimated K_{oc} value of 561 (HSDB, 1987) for 1,2-diphenylhydrazine indicates moderate adsorption to suspended particles and sediments in water; however, this compound is expected to exist in equilibrium with azobenzene in aerated water. Since the K_{oc} value for azobenzene is much higher (670-6410) (HSDB, 1987) than 1,2-diphenylhydrazine, adsorption and subsequent possible donation of hydrogen by the adsorbent during photolysis may become an important process (HSDB, 1987; Callahan et al., 1979).

The estimated log BCF value of 2.00 indicates that 1,2-diphenylhydrazine will have a relatively low bioconcentration potential in fish. The estimated log BCF of azobenzene, the equilibrium product of 1,2-diphenylhydrazine, is much higher (3.82), however, and azobenzene would therefore have a higher potential for bioconcentration in fish (HSDB, 1987).

2.3. SOIL

No experimental data regarding the fate of 1,2-diphenylhydrazine in soil were located in the available literature. Based on the predicted fate of this chemical in water, 1,2-diphenylhydrazine will probably (because of oxidation by O_2) be unstable on soil surfaces. The oxidation may be further enhanced by the catalytic actions of common cations in soil. Beyond the surficial layer where anaerobic conditions exist, some loss of 1,2-diphenylhydrazine due to biodegradation is expected to occur. Since the compound and its equilibrium product have moderate to high soil sorption coefficients and may not have a long lifetime in soils, they may not leach into groundwater under most circumstances.

2.4. SUMMARY

Limited data were available in the literature regarding the fate and transport of 1,2-diphenylhydrazine in any environmental media. In air, direct photolysis, oxidation by molecular oxygen and reaction with HO• are expected to convert 1,2-diphenylhydrazine into azobenzene. The half-life for the conversion of 1,2-diphenylhydrazine to azobenzene by photochemically produced HO• is estimated to be ~7 hours (U.S. EPA, 1986b). The fate and transport of 1,2-diphenylhydrazine in the atmosphere will be controlled indirectly by its oxidation product azobenzene. Photolysis, reaction with molecular oxygen and biodegradation may be responsible for the loss of 1,2-diphenylhydrazine from water (Callahan et al., 1979). The half-life of

1,2-diphenylhydrazine in clean water may be 7 hours and in wastewater 15 minutes (Riggin and Howard, 1979); however, 1,2-diphenylhydrazine may not be degraded in water but may be converted into azobenzene (Callahan et al., 1979). As in the case of air, the fate of 1,2-diphenylhydrazine in water will be controlled by azobenzene, which may undergo further degradation into aniline and other products (Callahan et al., 1979). Similarly, the transport of 1,2-diphenylhydrazine in water will be controlled by azobenzene formed as a result of oxidation of 1,2-diphenylhydrazine. In soils, 1,2-diphenylhydrazine will undergo rapid oxidation in the presence of O_2 and certain metal cations and may undergo both aerobic (primarily in top layers) and anaerobic (in deeper soil layers) biodegradation. 1,2-Diphenylhydrazine and particularly its oxidation product (azobenzene) will be moderately to strongly adsorbed in soils and are not likely to leach to groundwater from most soils.

3. EXPOSURE

Workers involved in the manufacture of certain dyes and pharmaceuticals are likely to be occupationally exposed to 1,2-diphenylhydrazine both through inhalation and dermal routes of exposure; however, no experimental data other than a reported level of 0.006-3000 µg/ℓ in the air of a Czeckoslovakian benzidine manufacturing plant were located in the available literature to confirm this prediction. Although a survey of drinking water from 10 U.S. cities for the presence of carcinogenic substances found no 1,2-diphenylhydrazine in the finished water at the treatment plant, one tap water sample was found to contain 1 µg/ℓ of 1,2-diphenylhydrazine (U.S. EPA, 1980a). 1,2-Diphenylhydrazine was not found in water from Lake Erie and Lake Michigan (Great Lakes Water Quality Board, 1983), but was quantitatively detected in sediment/soil/water samples from Love Canal, Niagara Falls, NY (Hauser and Bromberg, 1982). 1,2-Diphenylhydrazine has not been detected in any foods in the United States or elsewhere.

4. AQUATIC TOXICITY

4.1. ACUTE TOXICITY

In static tests with 1,2-diphenylhydrazine, 24-hour and 96-hour LC_{50}s of 1.2 and 0.27 mg/ℓ, respectively, were determined for the bluegill, Lepomis macrochirus (Buccafusco et al., 1981; U.S. EPA, 1978).

LeBlanc (1980) and U.S. EPA (1978) determined 24- and 96-hour LC_{50}s of 8.1 and 4.1 mg/ℓ, respectively, for Daphnia magna in static tests; a no-discernible-effect concentration was determined to be 0.41 mg/ℓ. A 48-hour EC_{50} was determined for Daphnia magna (Randall and Knopp, 1980).

4.2. CHRONIC EFFECTS

Pertinent data regarding the chronic effects of 1,2-diphenylhydrazine in aquatic animals were not located in the available literature cited in Appendix A.

4.3. PLANT EFFECTS

Pertinent data regarding effects of 1,2-diphenylhydrazine on aquatic plants were not located in the available literature cited in Appendix A.

4.4. SUMMARY

Aquatic toxicity information for 1,2-diphenylhydrazine is limited to acute lethality data for two freshwater animal species. These data indicate that the no-discernible-effect concentration for Daphnia magna is 0.41 mg/ℓ, that 24-hour LC_{50}s for Lepomis macrochirus and Daphnia magna are 1.2 and 8.1 mg/ℓ, respectively, and that 96-hour LC_{50}s for Lepomis macrochirus and Daphnia magna are 0.27 and 4.1 mg/ℓ, respectively.

5. PHARMACOKINETICS

5.1. ABSORPTION

Pertinent data regarding the rate and extent of absorption of 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A. The identification of unchanged 1,2-diphenylhydrazine and metabolites in the urine of rats following oral and intratracheal dosing with 1,2-diphenylhydrazine (Dutkiewicz and Szymanska, 1973) (Section 5.3.) indicates that absorption by the gastrointestinal and respiratory tracts occurs.

5.2. DISTRIBUTION

Pertinent data regarding the distribution of 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A.

5.3. METABOLISM

The results of thin-layer chromatographic analyses of urine from rats that were treated with 1,2-diphenylhydrazine by different routes were reported in an abstract of a Polish study (Dutkiewicz and Szymanska, 1973). Urine contained 1,2-diphenylhydrazine, benzidine, aniline, two unspecified hydroxy derivatives of benzidine and two unknown compounds following oral doses of 200 or 400 mg/kg, and 1,2-diphenylhydrazine, aniline, benzidine, p-aminophenol and o-aminophenol following intraperitoneal doses of 100 or 200 mg/kg. One urinary metabolite, which appeared to be phenolic but was otherwise uncharacterized, was found after intratracheal or intravenous injection of unspecified doses. Additional information regarding the design or results of these experiments was not reported.

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

5.4. EXCRETION

Pertinent data regarding the rate and extent of excretion of 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A. 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) (see Section 5.3.) indicates that some excretion occurs in the urine.

5.5. SUMMARY

Limited pharmacokinetic data for rats indicate that 1,2-diphenylhydrazine is absorbed by the gastrointestinal and respiratory tracts and excreted as unchanged compound and metabolites in the urine. Specific information regarding the rate and extent of absorption or excretion, other excretory pathways or distribution of 1,2-diphenylhydrazine is not available. Identified urinary metabolites in rats include aniline, benzidine and aminophenols.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. Inhalation Exposures. Pertinent data regarding the subchronic or chronic toxic effects of inhaled 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A.

6.1.2. Oral Exposures.

6.1.2.1. SUBCHRONIC -- In dose-selection studies for the NCI (1978) carcinogenesis bioassay, groups of five F344 rats and five B6C3F1 mice of each sex were maintained for 4 weeks on diets that contained technical grade 1,2-diphenylhydrazine, followed by a 2-week observation period. Male rat and male mouse groups received diets containing 0, 0.007, 0.014, 0.028, 0.055, 0.108, 0.214, 0.301 or 0.423% of the compound. Female rat groups received diets containing 0, 0.00008, 0.0003, 0.0011, 0.002, 0.004, 0.015, 0.104, 0.731 or 5.138% of the compound. Female mouse groups received diets containing 0, 0.0003, 0.0008, 0.0011, 0.002, 0.004, 0.015, 0.104, 0.731 or 5.138% of the compound. Deaths occurred in 2/5 male rats at 0.108% and in all rats of both sexes at higher concentrations. Deaths occurred in 1/5 male mice at 0.301%, in 2/5 male mice at 0.423%, in 4/5 female mice at 0.731% and in all female mice at 5.138%. Body weight and gross pathologic evaluations were conducted in both species, but information regarding these endpoints was limited and ambiguous; NCI (1978) indicated that the only consistent effect was intestinal hemorrhage in mice at unspecified concentrations.

6.1.2.2. CHRONIC -- Groups of 50 F344 rats or 47 or 50 B6C3F1 mice of each sex were maintained for 78 weeks on diets that contained technical grade 1,2-diphenylhydrazine in a carcinogenicity bioassay (NCI, 1978). As detailed in Section 6.2.2., the diet concentrations were 0.008% (TWA concentration) and 0.03% for male rats, 0.004% and 0.01% for female rats, 0.008%

(TWA concentration) and 0.04% for male mice and 0.004% and 0.04% for female mice. The rats and mice were observed for 28-30 weeks and 17-18 weeks, respectively, following treatment, and separate control groups of 49-50 rats or 50 mice of each sex were used for each treatment group. Treatment-related effects in the rats included slight mean group body weight depression in the high-dose males and low- and high-dose females, and reduced survival in the high-dose females. In mice, mean group body weights were depressed and survival was reduced in the high-dose male and female groups. NCI (1978) concluded that there were no treatment-related nonneoplastic lesions in the rats or mice.

6.1.3. Other Relevant Information. The average amount of 1,2-diphenylhydrazine ingested by deer mice over a 3-day period without killing >50% of the animals was determined to be 1213 mg/kg/day (Schafer and Bowles, 1985). NIOSH (1987) reported an oral LD_{50} of 301 mg/kg for rats.

6.2. CARCINOGENICITY

6.2.1. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A.

6.2.2. Oral. NCI (1978) conducted a carcinogenicity bioassay in which groups of 50 F344 rats or 47 or 50 B6C3F1 mice of each sex were maintained on diets containing technical grade 1,2-diphenylhydrazine for 78 weeks, followed by untreated observation periods of 28 or 30 weeks (rats) and 17 or 18 weeks (mice). Separate groups of 49-50 rats or 50 mice of each sex served as controls for each treatment group. Comprehensive gross and histological examinations were conducted on all animals that died during the study (unless precluded by unspecified factors), were sacrificed when moribund, or were sacrificed at termination of the study.

The diet concentrations of 1,2-diphenylhydrazine used in the rat study were 0.007% for 9 weeks and 0.008% for the subsequent 69 weeks (0.008% TWA concentration) in low-dose males, 0.03% in high-dose males, 0.004% in low-dose females and 0.01% in high-dose females (NCI, 1978). As detailed in Table 6-1, there were statistically significant increased incidences of hepatocellular carcinomas or neoplastic nodules in the liver in low- and high-dose males and squamous-cell carcinomas and papillomas of the Zymbal's gland, ear canal or skin of the ear and adrenal pheochromocytomas in the high-dose males. Statistically increased incidences of neoplastic nodules in the liver and mammary gland adenocarcinomas occurred in high-dose female rats.

The diet concentrations of 1,2-diphenylhydrazine in the mouse study were 0.007% for 9 weeks and 0.008% for the subsequent 69 weeks (0.008% TWA) in low-dose males, 0.04% in high-dose males, 0.004% in low-dose females and 0.04% in high-dose females (NCI, 1978). An increased incidence of hepatocellular carcinomas or adenomas in the high-dose females was the only treatment-related neoplastic effect in the mice.

Survival and body weight data for the rats and the mice in the NCI (1978) study are summarized in Section 6.1.2.2. Treatment-related decreased survival occurred in the high-dose groups of both species, but adequate numbers of animals survived to be at risk for late-developing tumors.

1,2-Diphenylhydrazine in sunflower oil was administered to mice and rats in the diet at doses of 30 mg/animal, 5 times/week over a period of 588 days, in a Russian study (Pliss, 1974). Neoplasms including pulmonary adenomas, liver tumors or leukemia developed in 50% of the treated mice and rats. Tumor incidence data were not reported for control groups. The only additional information regarding this study reported by U.S. EPA (1980a,

TABLE 6-1

Incidence of Tumors in F344 Rats and B6C3F1 Mice Treated with Technical Grade 1,2-Diphenylhydrazine in the Diet for 78 Weeks[a]

Species	Sex	Diet Concentration (%)[b]	Duration of Study (weeks)	Tumor Site	Tumor Type	Tumor Incidence[c] (p value)[d]
Rat	M	0[e]	108	liver	hepatocellular carcinoma	0/47
					hepatocellular carcinoma or neoplastic nodule	5/47
		0[f]	109	liver	hepatocellular carcinoma	1/48
					hepatocellular carcinoma or neoplastic nodule	1/48
		0.008[g]	107	liver	hepatocellular carcinoma	5/49 (p=0.031)
					hepatocellular carcinoma or neoplastic nodule	13/49 (p=0.040)
		0.03	106	liver	hepatocellular carcinoma	31/49 (p<0.001)
					hepatocellular carcinoma or neoplastic nodule	37/49 (p<0.001)
	M	0[e]	108	Zymbal's gland ear canal, Zymbal's gland and skin of ear	squamous-cell carcinoma	0/47
					squamous-cell carcinoma or papilloma	1/47
		0[f]	109	Zymbal's gland ear canal, Zymbal's gland and skin of ear	squamous-cell carcinoma	0/48
					squamous-cell carcinoma or papilloma	0/48
		0.008[g]	107	Zymbal's gland ear canal, Zymbal's gland and skin of ear	squamous-cell carcinoma	1/50 (NS)
					squamous-cell carcinoma or papilloma	2/50 (NS)
		0.03	106	Zymbal's gland ear canal, Zymbal's gland and skin of ear	squamous-cell carcinoma	5/49 (p=0.030)
					squamous-cell carcinoma or papilloma	7/49 (p=0.007)
	M	0[e]	108	adrenal	pheochromocytoma or malignant pheochromocytoma	7/47
		0[f]	109	adrenal	pheochromocytoma or malignant pheochromocytoma	8/47
		0.008[e]	107	adrenal	pheochromocytoma or malignant pheochromocytoma	7/48 (NS)
		0.03	107	adrenal	pheochromocytoma or malignant pheochromocytoma	16/46 (p=0.042)
	F	0[e]	109	liver	neoplastic nodule	0/47
		0[f]	109	liver	neoplastic nodule	0/50

TABLE 6-1 (cont.)

Species	Sex	Diet Concentration (%)[b]	Duration of Study (weeks)	Tumor Site	Tumor Type	Tumor Incidence[c] (p value)[d]
Rat	F	0.004	108	liver	neoplastic nodule	0/50 (NS)
		0.01	107	liver	neoplastic nodule	6/50 (p=0.013)
	F	0[e]	109	mammary gland	adenocarcinoma NOS	1/48
		0[f]	109	mammary gland	adenocarcinoma NOS	0/50
		0.004	108	mammary gland	adenocarcinoma NOS	3/50 (NS)
		0.01	107	mammary gland	adenocarcinoma NOS	6/50 (p=0.013)
Mouse	F	0[e]	96	liver	hepatocellular carcinoma hepatocellular adenoma or carcinoma	2/47 2/47
		0[f]	96	liver	hepatocellular carcinoma hepatocellular adenoma or carcinoma	1/50 1/50
		0.004	95	liver	hepatocellular carcinoma hepatocellular adenoma or carcinoma	4/39 (NS) 4/39 (NS)
		0.04	96	liver	hepatocellular carcinoma hepatocellular adenoma or carcinoma	20/43 (p<0.001) 22/43 (p<0.001)

QUALITY OF EVIDENCE

Strength of Study: The compound was administered to both sexes of two species at two dose levels by a natural route. Adequate numbers of animals survived to be at risk for late-developing tumors.

Overall Adequacy: Adequate

[a]Source: NCI, 1978

[b]Control groups were used for each treatment group.

[c]Tumor incidence is expressed as number of animals with tumors/number of animals examined histologically.

[d]The p value for the Fisher Exact test is shown next to the incidence in the treated group when p<0.05; otherwise, NS is indicated.

[e]Low dose control group

[f]High dose control group

[g]TWA concentration (see text)

NS = Not significant; NOS = not otherwise specified

1981) is that the rats received a total dose of 12.57 g, that the minimal tumor latency period was 372 days and that some animals (number unspecified) had to be replaced during the experiment because of a parasitic infection.

6.2.3. Other Relevant Information. Additional carcinogenicity studies of 1,2-diphenylhydrazine, inadequately reported, were conducted by Pliss (1974) and summarized by U.S. EPA (1980a, 1981). It appears that these studies also were conducted over a period of 588 days. Epicutaneous application of 2 mg 3 times/week (360 mg total) to mice produced a 22.2% incidence of skin, lung or liver tumors; the incidence of tumors in a control group was 17%. Epicutaneous application of 30 mg 5 times/week to rats was not tumorigenic. Subcutaneous injection of 5 mg/week (370 mg total) to mice produced a 36.6% incidence of rhabdomyosarcomas, and subcutaneous injection of 40 mg/week (3.8 g total) to rats produced a 22.6% incidence of total tumors, consisting of tumors of the uterus, mammary gland, Zymbal's gland, liver and spleen and lymphoid leukemia. The minimal latent period for tumor formation following subcutaneous injection was 188 days, but control data for the subcutaneous studies and additional data for all of the studies were not reported.

1,2-Diphenylhydrazine in olive oil vehicle was administered to 52 Sherman rats of both sexes by subcutaneous injection once a week at an average dose of 60 mg (Spitz et al., 1950). Treatment was continued for life or until grossly obvious tumors appeared, unless contraindicated by weight loss or illness (total amount administered, 6.4 g). A control group consisted of 50 vehicle-treated rats. Histopathologic examination of the liver, external auditory canal, colon and bladder showed a squamous cell carcinoma of the auditory canal sebaceous glands in one of the treated rats.

It appears that comprehensive histopathological examinations were conducted in this study, but data for other sites were not reported and the extent of the examinations was not specified.

The tumorigenicity of 1,2-diphenylhydrazine was evaluated in a Strain A mouse pulmonary tumor assay (Maronpot et al., 1986). Groups of 10 male and 10 female mice were given intraperitoneal injections of 50, 100 or 200 mg/kg in tricaprylin vehicle 3 times/week for 8 weeks. Examinations for adenomas 16 weeks after cessation of treatment showed a positive response in the high-dose males (statistically significant increases in the incidence of tumor-bearing mice and tumors per mouse). There was an equivocal response in the high-dose females (significant increase in tumors per mouse but not incidence of tumor-bearing mice).

Abstracts of several Russian studies report that combined subcutaneous administration of 1,2-diphenylhydrazine (20 mg/week) and benzidine sulfate (15 mg/week) to rats increased the incidence of tumors and decreased tumor latency periods when compared with the activities of the individual compounds (Genin et al., 1975; Shabad and Genin, 1975; Kurlyandskii et al., 1976). The Kurlyandskii et al. (1976) abstract indicates that these observations refer to bladder cancer. Duration of treatment and additional relevant information were not reported in any of the abstracts.

6.3. MUTAGENICITY

1,2-Diphenylhydrazine (practical grade) induced reverse mutations in Salmonella typhimurium strain TA100, but not strains TA1535, TA1537 or TA98, when tested in a liquid suspension assay with rat liver S-9 metabolic activation preparation (Haworth et al., 1983). The compound was not mutagenic in any of the strains when tested with hamster liver S-9 or without S-9 preparations.

Reverse mutation plate incorporation assays were conducted in which Salmonella typhimurium strains TA98, 100, 1535, 1537 or 1538 or Escherichia coli strain WP2 uvrA were exposed to 1,2-diphenylhydrazine (technical grade, purity ≥65%) with or without rat, mouse or hamster liver S-9 metabolic activation preparations (Dunkel et al., 1985). Consistent and unequivocal positive responses were obtained only with S. typhimurium strain TA100 when assayed with rat or mouse liver S-9 preparations.

Thymidine incorporation into testicular DNA was significantly inhibited in mice that received a single intraperitoneal dose of 100 mg/kg 1,2-diphenylhydrazine (purity not stated) (Seiler, 1977).

Practical grade 1,2-diphenylhydrazine in ethanol did not induce sex-linked recessive lethal mutations in male Drosophila melanogaster when administered by feeding for 3 days at a concentration of 50 ppm or by intraperitoneal injection at a concentration of 80 ppm (additional dose information not reported) (Yoon et al., 1985).

6.4. TERATOGENICITY

Pertinent data regarding the teratogenicity of 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A.

6.5. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A.

6.6. SUMMARY

Limited toxicity data are available for 1,2-diphenylhydrazine. Four-week feeding studies conducted by the NCI (1978) showed that diets containing ≥0.108 and 0.301% of compound produced deaths in rats and mice, respectively. Intestinal hemorrhage in mice at unspecified concentrations was the only gross pathologic effect attributed to treatment. In chronic oral

studies, rats and mice were treated in the diet for 78 weeks at concentrations of 0.008 or 0.03% (male rats), 0.004 or 0.01% (female rats), 0.008 or 0.04% (male mice) and 0.004 or 0.04% (female mice) (NCI, 1978). Effects included decreased body weight gain in the high-dose male and low- and high-dose female rats, decreased survival in the high-dose female rats, and decreased body weight and decreased survival in the high-dose male and female mice. NCI (1978) concluded that there were no treatment-related nonneoplastic gross or histological alterations in either species.

Treatment-related neoplastic effects occurred in the NCI (1978) study, including hepatocellular carcinomas in the low- and high-dose male rats, squamous-cell carcinomas and papillomas of the Zymbal's gland in high-dose male rats, adrenal pheochromocytomas in high-dose male rats, neoplastic nodules in the liver and mammary gland adenocarcinomas in high-dose female rats, and hepatocellular carcinomas in high-dose female mice. Also, 1,2-diphenylhydrazine was tumorigenic in rats and mice in inadequately reported chronic oral, subcutaneous and dermal carcinogenicity studies (Pliss, 1974), and produced positive responses in a Strain A mouse pulmonary tumor assay (Maronpot et al., 1986). 1,2-Diphenylhydrazine was not tumorigenic when administered to rats by subcutaneous injection once weekly for life (Spitz et al., 1950).

1,2-Diphenylhydrazine induced reverse mutations in S. typhimurium strain TA100 but not in other strains of S. typhimurium or in E. coli WP2 uvrA (Haworth et al., 1983; Dunkel et al., 1985). 1,2-Diphenylhydrazine inhibited thymidine incorporation into mouse testicular DNA when administered by a single intraperitoneal injection (Seiler, 1977), but did not induce sex-linked recessive lethal mutations in Drosophila melanogaster (Yoon et al., 1985).

Information is not available regarding the toxicity or carcinogenicity of inhaled 1,2-diphenylhydrazine, or teratogenicity or other reproductive effects of 1,2-diphenylhydrazine by the oral or inhalation routes.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

U.S. EPA (1980a) recommended ambient water quality criteria of 422, 42 and 4 ng/ℓ for diphenylhydrazine, which correspond to excess cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7}, respectively. The criteria are derived from a q_1^* that is based on the induction of hepatocellular carcinomas and liver neoplastic nodules in male rats (Section 8.1.5.2.). The q_1^* of 0.8 $(mg/kg/day)^{-1}$ has been verified by U.S. EPA (1987a) and corresponds to drinking water levels of 4.5, $4.5x10^{-1}$ and $4.5x10^{-2}$ µg/ℓ and air levels of $4.5x10^{-1}$, $4.5x10^{-2}$ and $4.5x10^{-3}$ $µg/m^3$ for risk levels of 10^{-4}, 10^{-5} and 10^{-6}, respectively.

U.S. EPA (1987b) has proposed an RQ of 10 for 1,2-diphenylhydrazine.

Other pertinent guidelines or standards, including drinking water standards, FAO/WHO ADIs, and ACGIH, OSHA and NIOSH occupational exposure limits, were not located in the available literature cited in Appendix A.

7.2. AQUATIC

The U.S. EPA (1980a) did not recommend criteria for the protection of aquatic life from the effects of 1,2-diphenylhydrazine. It was stated that acute toxicity to freshwater aquatic life occurs at concentrations as low as 270 µg/ℓ, and would occur at lower concentrations among species that are more sensitive than those tested.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of inhaled 1,2-diphenylhydrazine were not located in the available literature cited in Appendix A.

8.1.2. Oral. NCI (1978) conducted a carcinogenicity bioassay in which groups of 50 F344 rats or 47 or 50 B6C3F1 mice of each sex were maintained on diets containing technical grade 1,2-diphenylhydrazine for 78 weeks, followed by untreated observation periods of 28 or 30 weeks (rats) and 17 or 18 weeks (mice). The dietary concentrations of 1,2-diphenylhydrazine used in the rat study were 0.008% (TWA concentration) or 0.03% in males, and 0.004 or 0.01% in females. The dietary concentrations used in the mouse study were 0.008% (TWA concentration) or 0.04% in males, and 0.004 or 0.04% in females. Separate groups of 49-50 rats or 50 mice of each sex served as controls for for each treatment group. As detailed in Table 6-1, there were statistically increased incidences of hepatocellular carcinomas or neoplastic nodules in the liver in low- and high-dose male rats, squamous-cell carcinomas and papillomas of the Zymbal's gland in high-dose male rats, adrenal pheochromocytomas in high-dose male rats, and neoplastic nodules in the liver and mammary gland adenocarcinomas in high-dose female rats. In mice, there was a statistically increased incidence of hepatocellular carcinomas or adenomas in the high-dose females.

1,2-Diphenylhydrazine in sunflower oil was administered to mice and rats in the diet at concentrations of 30 mg/animal, 5 times/week for 588 days, in an inadequately reported Russian study (Pliss, 1974). Pulmonary adenomas, liver tumors or leukemia occurred in 50% of the treated mice and rats, but incidences of tumors by type and in control groups were not reported.

8.1.3. Other Routes. Inadequately reported subcutaneous studies with mice (5 mg/week) and rats (40 mg/week) and epicutaneous studies with mice (2 mg, 3 times/week) were conducted by Pliss (1974). Various tumors were attributed to treatment (see Section 6.2.3.), but incidences were not reported for specific tumor types and control data were not reported for the subcutaneous injection studies.

1,2-Diphenylhydrazine was not tumorigenic when administered to rats by subcutaneous injection at an average dose of 60 mg once a week for life (total dose 6.4 g) (Spitz et al., 1950).

The tumorigenicity of 1,2-diphenylhydrazine was evaluated in a Strain A mouse pulmonary assay (Maronpot et al., 1986). There was a positive response in males and an equivocal response in females at the highest dose tested (200 mg/kg intraperitoneally).

8.1.4. Weight of Evidence. The carcinogenicity of 1,2-diphenylhydrazine has been demonstrated in both rats and mice in adequate oral bioassays (NCI, 1978). 1,2-Diphenylhydrazine was also tumorigenic in rats and mice in inadequately reported oral, subcutaneous and dermal carcinogenicity studies, and produced positive responses in a Strain A mouse pulmonary tumor assay and in mutagenicity assays. Additionally, the carcinogenicity of other substituted hydrazines has been documented (IARC, 1974). Based on the carcinogenic responses in rats and mice in the NCI (1978) bioassay, 1,2-diphenylhydrazine is classified as an EPA Group B1 carcinogen (U.S. EPA, 1987a).

8.1.5. Quantitative Risk Estimates.

8.1.5.1. INHALATION -- Inhalation carcinogenicity data for 1,2-diphenylhydrazine are not available. The human q_1^* of 0.8 $(mg/kg/day)^{-1}$ for oral exposure was adopted by the U.S. EPA (1987a) as the q_1^* for

inhalation exposure by assuming equal potency by either route. The concentrations of 1,2-diphenylhydrazine in air associated with increased lifetime risk of cancer at risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 4.5×10^{-2}, 4.5×10^{-3} and 4.5×10^{-4} $\mu g/m^3$, respectively (U.S. EPA, 1986b). If it is assumed that absorption by the inhalation route is 50%, the concentrations associated with the 10^{-5}, 10^{-6} and 10^{-7} risk levels are twice as high as those reported above. U.S. EPA (1987a) noted that the q_1^* may differ from that stated above if air concentrations of 1,2-diphenylhydrazine exceed 45 $\mu g/m^3$, and that there is low confidence in the inhalation risk estimate derived from oral data.

8.1.5.2. ORAL -- The U.S. EPA (1980a) used the dose-response data for hepatocellular carcinoma and liver neoplastic nodules in male rats from the NCI (1978) bioassay to calculate a human q_1^* of 0.768 $(mg/kg/day)^{-1}$ for 1,2-diphenylhydrazine. The data reported in Appendix B were used with the linearized multistage model (U.S. EPA, 1980b) for the computation. The q_1^* [0.8 $(mg/kg/day)^{-1}$] has been verified by the Agency CRAVE Work Group Review (U.S EPA, 1987a) and is adopted for this document. Concentrations of 1,2-diphenylhydrazine in drinking water associated with increased lifetime risk of cancer at risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 4.5×10^{-1}, 4.5×10^{-2} and 4.5×10^{-3} $\mu g/\ell$, respectively (U.S. EPA, 1987a). It was noted that the q_1^* may differ from that stated above if the water concentration of 1,2-diphenylhydrazine exceeds 450 $\mu g/\ell$, and that confidence in the q_1^* is low to medium since not all neoplastic nodules may progress to tumors (U.S. EPA, 1987a).

8.2. SYSTEMIC TOXICITY

8.2.1. Inhalation Exposure. Derivation of an RfD for less than lifetime (subchronic) or chronic inhalation exposure to 1,2-diphenylhydrazine is precluded by the lack of inhalation toxicity data and is inappropriate because of carcinogenicity by the oral route.

8.2.2. Oral Exposure. In a 4-week feeding study, diets that contained $\geq$0.108 and 0.301% 1,2-diphenylhydrazine produced deaths in rats and mice, respectively (NCI, 1978). Chronic exposure of rats resulted in decreased body weight gain at dietary concentrations $\geq$0.004% and decreased survival at 0.01% (NCI, 1978). Chronic exposure of mice resulted in decreased body weight and survival at 0.04%. Derivation of an RfD for less than lifetime (subchronic) or chronic oral exposure to 1,2-diphenylhydrazine is inappropriate because of carcinogenicity by the oral route.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

Pertinent toxicity data for 1,2-diphenylhydrazine are available only from the NCI (1978) carcinogenesis bioassay. As discussed in Section 6.1.2.2. and summarized in Table 9-1, 1,2-diphenylhydrazine was administered to rats and mice in the diet for 78 weeks at concentrations of 0.008% (TWA concentration) or 0.03% for male rats, 0.004% or 0.01% for female rats, 0.008% (TWA concentration) or 0.04% for male mice and 0.004 or 0.04% for female mice. Treatment-related nonneoplastic effects included slightly decreased mean group body weight gain in the high-dose male and low- and high-dose female rats, decreased survival in the high-dose female rats, and decreased mean group body weight and decreased survival in the high-dose male and female mice.

The lowest equivalent human doses at which decreased body weight and decreased survival occurred are 0.31 and 0.76 mg/kg/day, respectively (see Table 9-1). Multiplication of these doses by 70 kg yields MEDs of 21.7 and 53.2 mg/day, respectively (Table 9-2). The RV_ds corresponding to the MEDs are 3.5 and 2.9, respectively. The most appropriate RV_e for decreased weight gain is 4 and the RV_e for life shortening is 10. Multiplication of the RV_ds by the RV_es yields CSs of 14 for decreased weight gain and 29 for life shortening. Since the CS of 29 for life shortening is the highest CS, it is the appropriate basis for the RQ. A CS of 29 corresponds to an RQ of 100 (Table 9-3).

9.2. BASED ON CARCINOGENICITY

NCI (1978) conducted a carcinogenicity bioassay in which groups of 47-50 F344 rats or B6C3F1 mice of each sex were maintained on diets containing technical grade 1,2-diphenylhydrazine for 78 weeks, followed by untreated observation periods of 28 or 30 weeks (rats) and 17 or 18 weeks (mice).

TABLE 9-1

Oral Toxicity Summary for Technical Grade 1,2-Diphenylhydrazine[a]

Species/ Strain	Sex	No. at Start	Average Weight[b] (kg)	Vehicle/ Physical State	Exposure	Transformed Animal Dose[c] (mg/kg/day)	Equivalent Human Dose[d] (mg/kg/day)	Response
Rat/F344	M	50	0.35	diet	0.03% for 78 weeks	15	2.56	decreased body weight gain
Rat/F344	F	50	0.25	diet	0.004% for 78 weeks	2	0.31	decreased body weight gain
Rat/F344	F	50	0.25	diet	0.01% for 78 weeks	5	0.76	decreased body weight gain and increased mortality
Mouse/ B6C3F1	M,F	50	0.03 (M) 0.025 (F)	diet	0.04% for 78 weeks	52	3.69[e]	decreased body weight gain and increased mortality

[a]Source: NCI, 1978

[b]Estimated from growth curves in the study

[c]Calculated by multiplying dietary concentration in ppm by reference food consumption estimates (5% bw/day for rats, 13% bw/day for mice) (U.S. EPA, 1985)

[d]Calculated by multiplying the transformed animal dose by the cube root of the ratio of the animal body weight to reference human body weight (70 kg)

[e]Calculated using female mouse body weight

TABLE 9-2

Oral Composite Scores for 1,2-Diphenylhydrazine Using the Rat*

Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
2	21.7	3.5	decreased weight gain	4	14	1000
5	53.2	2.9	decreased survival and decreased weight	10	29	100

*Source: NCI, 1978

TABLE 9-3

1,2-Diphenylhydrazine

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	0.76 mg/kg/day
Effect:	decreased survival and decreased weight
Reference:	NCI, 1978
RV_d:	2.9
RV_e:	10
Composite Score:	29
RQ:	100

*Equivalent human dose

The dietary concentrations were 0.008 or 0.03% in the male rats, 0.004 or 0.01% in the female rats, 0.008 or 0.04% in the male mice, and 0.004 or 0.04% in the female mice. Separate groups of 49-50 rats or 50 mice of each sex served as controls for each treatment group. As detailed in Table 6-1, there were statistically increased incidences of hepatocellular carcinomas or neoplastic nodules in the liver in low- and high-dose male rats, squamous-cell carcinomas and papillomas of the Zymbal's gland in high-dose male rats, adrenal pheochromocytomas in high-dose male rats, and neoplastic nodules in the liver and mammary gland adenocarcinomas in high-dose female rats. In mice, there was a statistically increased incidence of hepatocellular carcinomas or adenomas in the high-dose females.

1,2-Diphenylhydrazine also was tumorigenic in rats and mice in inadequately reported chronic oral, subcutaneous and dermal carcinogenicity studies (Pliss, 1974), and produced positive responses in a Strain A mouse pulmonary tumor assay (Maronpot et al., 1986) (see Section 6.2.). 1,2-Diphenylhydrazine was not tumorigenic when administered to rats by subcutaneous injection at an average dose of 60 mg once a week for life (total dose 6.4 g) (Spitz et al., 1950).

Based primarily on the carcinogenic responses in the rats and mice in the NCI (1978) bioassay, 1,2-diphenylhydrazine is classified as an EPA Group B1 carcinogen (U.S. EPA, 1987a).

The NCI (1978) bioassay provides a basis for derivation of an F factor for 1,2-diphenylhydrazine because it is the only adequate carcinogenicity study and was used for derivation of a verified q_1^* (U.S. EPA, 1980b, 1987a). Using the incidence data for hepatocellular carcinoma and neoplastic nodules in the liver in male rats and the computerized multistage linear model adopted by the U.S. EPA (Howe and Crump, 1982), the unadjusted

$1/ED_{10}$ is calculated to be 0.72 $(mg/kg/day)^{-1}$ (Table 9-4). Multiplying by the cube root of the ratio of reference human body weight (70 kg) to measured rat body weight (0.38 kg) results in an F factor of 4.1. This F factor indicates that 1,2-diphenylhydrazine should be placed in Potency Group 2. A Potency Group 2 and an EPA Group B1 chemical has a Medium hazard ranking under CERCLA. A Medium hazard ranking is assigned an RQ of 10.

TABLE 9-4

Derivation of Potency Factor (F) for 1,2-Diphenylhydrazine

Reference:	NCI, 1978
Exposure route:	oral
Species:	rat
Strain:	F344
Sex:	male
Vehicle or physical state:	diet
Body weight:	0.38 kg (measured)
Duration of treatment:	78 weeks
Duration of study:	108-109 weeks (control), 107 weeks (low dose), 106 weeks (high dose)
Lifespan of animal:	108-109 weeks (control), 107 weeks (low dose), 106 weeks (high dose)
Target organ:	liver
Tumor type:	hepatocellular carcinoma and neoplastic nodules
Experimental doses/exposures:	0%, 0.008%, 0.03%
Transformed doses (mg/kg/day):	0, 2.92, 11.04
Tumor incidence:	6/95*, 13/49, 37/49
Unadjusted $1/ED_{10}$:	0.721407 $(mg/kg/day)^{-1}$
Adjusted $1/ED_{10}$ (F Factor):	4.1047356 $(mg/kg/day)^{-1}$

*Pooled incidences from low dose control and high dose control groups

10. REFERENCES

Buccafusco R.J., S.J. Ells and G.A. LeBlanc. 1981. Acute toxicity of priority pollutants to bluegill (Lepomis macrochirus). Environ. Contam. Toxicol. 26(4): 446-452.

Callahan, M.A., M.W. Slimak, N.W. Gabel, et al. 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Vol. 2. Office of Water Planning and Standards, Office of Water and Waste Management, U.S. EPA, Washington, DC. EPA 440/4-79-029b. p. 104-1 to 104-9.

Dunkel V.C., E. Zeiger, D. Brusick, et al. 1985. Reproducibility of microbial mutagenicity assays. II. Testing of carcinogens and noncarcinogens in Salmonella typhimurium and Escherichia coli. Environ. Mutagen. 7(Suppl. 5): 1-12, 15-19, 37.

Dutkiewicz T. and J. Szymanska. 1973. Chromatographic determination of hydrazobenzene metabolites in rats. Bromatol. Chem. Toksykol. 6(3): 323-327. (CA 80:116838k)

Genin V.A., A.G. Medvedovskii and V.M. Voronin. 1975. Increase of the carcinogenic activity during the joint effect of hydrazobenzene and benzidine sulfate. Gig. Tr. prof. Zabol. 6: 28-31. (CA 83:173640a)

Great Lakes Water Quality Board. 1983. An Inventory of Chemical Substances Identified in the Great Lakes Ecosystem. Report. Great Lakes Water Quality Board, Windsor Ontario, Canada. p. 17.

Hansch, C. and A.J. Leo. 1985. Medchem Project, Issue No. 26. Pomona College, Claremont, CA.

Hauser, T.R. and S.M. Bromberg. 1982. EPA's monitoring program at Love Canal 1980. Environ. Monit. Assess. 2: 249-271.

Haworth, S., T. Lawlor, K. Mortelmas, W. Speck and E. Zeiger. 1983. Salmonella mutagenicity test rules for 250 chemicals. Environ. Mutagen. 5(Suppl. 1): 21, 38, 38, 51, 102.

Howe, R.B. and K.S. Crump. 1982. GLOBAL 82. A Computer Program to Extrapolate Quantal Animal Toxicity Data to Low Doses. Prepared for Office of Carcinogen Standards. OSHA, U.S. Dept. of Labor. Contract No. 41USC252C3.

HSDB (Hazardous Substances Data Bank). 1987. On-line: 10/19/87. CAS No. 122-66-7.

IARC (International Agency for Research on Cancer). 1972. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Benzidine. IARC, WHO, Lyons, France. Vol. 1, p. 80-86.

IARC (International Agency for Research on Cancer). 1974. Monograph on the Evaluation of Carcinogenic Risk of Chemicals to Man. Hydrazine and Its Derivatives. IARC, WHO, Lyons, France. Vol. 4, p. 127-136.

Kurlyandskii, B.A., A.G. Medvedovskii, V.A. Genin, V.M. Voronin and F.D. Mashbits. 1976. Experimental study on the combined effect of some diphenylamino derivatives with regard to the prevention of occupational urinary bladder growths. Gig. Tr. Prof. Zabol. 20(5): 34-38. (CA 85:105041x)

LeBlanc, G.A. 1980. Acute toxicity of priority pollutants to water flea (Daphnia magna). Bull. Environ. Contam. Toxicol. 24(5): 684-691.

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York. p. 2-14.

Malaney, G.W. 1960. Oxidative abilities of aniline-acclimated activated sludge. J. Water Pollut. Control Fed. 32: 1300-1311.

Maronpot R.R., M.B. Shimkin, H.P. Witschi, L.H. Smith and J.M. Cline. 1986. Strain A mouse pulmonary tumor test results for chemicals previously tested in the National Cancer Institute carcinogenicity tests. J. Natl. Cancer Inst. 76(6): 1101-1112.

NCI (National Cancer Institute). 1978. Bioassay of Hydrazobenzene for Possible Carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 92. [Also published as NIH 78-1342.]

NIOSH (National Institute for Occupational Safety and Health). 1987. RTECS (Registry of Toxic Effects of Chemical Substances). Online: Oct. 1987. CAS No. 122-66-7.

Pliss, G.B. 1974. Carcinogenic properties of hydrazobenzene. Vop. Onkol. 20: 53. (Cited in U.S. EPA, 1980a, 1981)

Randall, T.L. and P.V. Knopp. 1980. Detoxification of specific organic substances by wet oxidation. J. Water Pollut. Control Fed. 52(8): 2117-2130.

Riggin, R.M. and C.C. Howard. 1979. Determination of benzidine, dichlorobenzidine, and diphenylhydrazine in aqueous media by high performance liquid chromatography. Anal. Chem. 51: 210-214.

Schafer E.W., Jr. and W.A. Bowles, Jr. 1985. Acute oral toxicity and repellency of 933 chemicals to house and deer mice. Arch. Environ. Contam. Toxicol. 14(1): 111-129.

Seiler, J.P. 1977. Inhibition of testicular DNA synthesis by chemical mutagens and carcinogens. Preliminary results in the validation of a novel short term test. Mutat. Res. 46: 305-310.

Shabad, L.M. and V.A. Genin. 1975. Combined action of amino-substituted biphenyls causing bladder tumors. Urol. Nefrol. 1: 38-42. (CA 83:127207s)

Shizuka, H., H. Kayoiji and T. Morita. 1970. The photolysis of hydrazobenzene in solution. Mol. Photochem. 2: 165-176.

Spitz, S., W.H. Maguigaw and K. Dobriner. 1950. The carcinogenic action of benzidine. Cancer. 3: 789-804.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. United States of America. SRI International, Menlo Park, CA. p. 604, 773, 777.

Tabak, H.H., S.A. Quave, C.I. Mashni and E.F. Barth. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut. Control Fed. 53: 1503-1518.

U.S. EPA. 1978. In-depth Studies on Health and Environmental Impacts of Selected Water Pollutants. Contract No. 68-01-4646. (Cited in U.S. EPA, 1980a)

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

U.S. EPA. 1980b. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Criteria Documents. Federal Register. 45(231): 49347-49357.

U.S. EPA. 1981. CHIP (Chemical Hazard Information Profile). Draft Report. Hydrazobenzene. OTS, OPTS, U.S. EPA, Washington, DC.

U.S. EPA. 1984. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986a. Methodology for Evaluating Carcinogenicity in Support of Reportable Quantity Adjustment Pursuant to CERCLA Section 102. Prepared by the Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986b. Graphical Exposure Modeling System (GEMS) Fate of Atmospheric Pollutants (FAP). Office of Toxic Substances, Washington, DC.

U.S. EPA. 1987a. IRIS (Integrated Risk Information System), CRAVE (Carcinogen Risk Assessment Validation Endeavor) for 1,2-Diphenylhydrazine. Online: Verification date: 10/29/86. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1987b. Reportable Quantity Adjustments. Federal Register. 52(50): 5139.

USITC (U.S. International Trade Commission). 1984. Imports of Benzenoid Chemicals and Products: 1983. USITC Publ. 1548, Washington, DC. p. 19.

USITC (U.S. International Trade Commission). 1986. Imports of Benzenoid Chemicals and Products: 1985. USITC Publ. 1892, Washington, DC.

Weast, R.C., Ed. 1985. CRC Handbook of Chemistry and Physics, 66th ed. CRC Press, Boca Raton, FL. p. c-313.

Yoon, J.S., J.M. Mason, R. Valencia, R.C. Woodruff and S. Zimmering. 1985. Chemical mutagenesis testing in Drosophila. IV. Results of 45 coded compounds tested for the National Toxicology Program. Environ Mutagen. 7(3): 349-367.

APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB

These searches were conducted in October 1987, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1984. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. IARC, WHO, Lyons, France.

Jaber, H.M., W.R. Mabey, A.T. Lieu, T.W. Chou and H.L. Johnson. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Solid Waste. EPA 600/6-84-010. NTIS P884-243906. SRI International, Menlo Park, CA.

NTP (National Toxicology Program). 1987. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1984. Dangerous Properties of Industrial Materials, 6th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1987. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1986. Report on Status Report in the Special Review Program, Registration Standards Program and the Data Call in Programs. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

USITC (U.S. International Trade Commission). 1986. Synthetic Organic Chemicals. U.S. Production and Sales, 1985, USITC Publ. 1892, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

APPENDIX B

Cancer Data Sheet for Derivation of q_1^* for Oral Exposure†

Compound:	1,2-diphenylhydrazine
Reference:	NCI, 1978
Species, strain, sex:	rat, F344, male
Body weight:	0.38 kg (measured)
Length of exposure (le):	78 weeks
Length of experiment (Le):	104 weeks
Lifespan of animal (L):	104 weeks
Tumor site and type:	liver, hepatocellular carcinoma and neoplastic nodules
Route, vehicle:	oral, diet

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

Human $q_1^* = 0.768\ (mg/kg/day)^{-1}$

†Parameters reported by U.S. EPA (1980a); see text for additional information. Le was reported to be 107 weeks (low dose) and 106 weeks (high dose) by NCI (1978).

APPENDIX C

Summary Table for 1,2-Diphenylhydrazine

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	NA	NA	NA	RfD = NA	NA
Chronic	NA	NA	NA	RfD = NA	NA
Carcinogenicity	rat	NA	NA	q_1^*:0.8 $(mg/kg/day)^{-1}$†	NA
Oral Exposure					
Subchronic	NA	NA	NA	RfD = NA	NA
Chronic	NA	NA	NA	RfD = NA	NA
Carcinogenicity	rat	0.008 and 0.03% in diet for 78 weeks	hepatocellular carcinoma and neoplastic nodules in liver	q_1^*: 0.8 $(mg/kg/day)^{-1}$	NCI, 1978

REPORTABLE QUANTITIES

Based on chronic toxicity: 100

Based on carcinogenicity: 10

†The oral q_1^* was adopted as the inhalation q_1^* (U.S. EPA, 1987a)

NA = Not applicable