DIPHENYLHYDRAZINE

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

1,2-DIPHENYLHYDRAZINE

CRITERIA

Aquatic Life

For 1,2-diphenylhydrazine the criterion to protect freshwater aquatic life as derived using the Guidelines is 17 µg/l as a 24-hour average and the concentration should not exceed 38 µg/l at any time.

For saltwater aquatic life, no criterion for 1,2-diphenylhydrazine can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to 1,2-diphenylhydrazine through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of 1,2-diphenylhydrazine estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 0.4 µg/l, 0.04 µg/l and 0.004 µg/l, respectively.

Introduction

Diphenylhydrazine exists as an assymmetrical isomer, 1,1-diphenylhydrazine, and a symmetrical isomer, 1,2-diphenylhydrazine (hydrazobenzene). The hydrochloride of 1,1-diphenylhydrazine is used as a reagent for the sugars, arabinose and lactose (Windholtz, 1976). 1,2-Diphenylhydrazine is used in organic synthesis (Bennett, 1974) and has a major use as the starting material in the production of benzidine, for use in dyes (Lurie, 1964).

No data were found on the environmental presence or persistence of diphenylhydrazines, except for one report of detection in drinking water at a concentration of 1 µg/l (U.S. EPA, 1975). 1,1- and 1,2-diphenylhydrazines have been characterized as slightly soluble and insoluble in water, respectively (Windholtz, 1976; Bennett, 1974). No quantitative data were found for the water solubilities and vapor pressures of these compounds; consequently, no predictions can be made about their presistence in water.

Since no data are available on levels of diphenylhydrazines in surface waters, ambient water levels cannot be compared to the levels of these chemicals determined to be toxic in laboratory studies. Experimental data indicate that 1,2-diphenylhydrazine is toxic to freshwater aquatic organisms and reported LC50 values range from 0.27 to 4.1 mg/l (U.S. EPA, 1978). Rats and mice developed a variety of malignancies after dermal exposures to 1,2-diphenylhydrazine (Spitz, et al. 1950; Pliss, 1974). Oral doses of 1,2-diphenylhydrazine did

not produce malignancies (Marhold, et al. 1968). The documented carcinogenicity of 1,2-diphenylhydrazine is of primary concern to industrial workers, who are exposed to higher concentrations than other segments of the population.

Although there are few data describing the fate of diphenylhydrazines in water, the carcinogenic effects of 1,2-diphenylhydrazine warrant its regulation, to protect humans and aquatic organisms from possible water-related hazards associated with this chemical.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Toxicity tests with the bluegill and Daphnia magna have been conducted using static procedures, and the results demonstrated adverse effects as low as 251 µg/l.

Acute Toxicity

The unadjusted 96-hour LC50 for the bluegill is 270 µg/l (Table 1), and when this concentration is adjusted for testing procedures and species sensitivity a Final Fish Acute Value of 38 µg/l is obtained.

Daphnia magna is less sensitive with an unadjusted 48-hour EC50 of 4,100 µg/l (Table 2). The resultant Final Invertebrate Acute Value of 170 µg/l is higher than that value for fish, so the latter, 38 µg/l, becomes the Final Acute Value.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Chronic Toxicity

The chronic effects of 1,2-diphenylhydrazine on *Daphnia magna* have been determined (U.S. EPA, 1978) and adverse effects were observed at 420 µg/l (Table 3). No detectable effects occurred at 150 µg/l. The latter concentration is 0.037 of the 48-hour EC50 (Table 2). A Final Invertebrate Chronic Value of 49 µg/l is obtained from these results and, since there are no data on chronic toxicity to fish, plant effects, or Residue Limited Toxicant Concentration, this concentration also becomes the Final Chronic Value.

Residues

No measured steady-state bioconcentration factor (BCF) is available for 1,2-diphenylhydrazine. A BCF can be estimated using the octanol-water coefficient of 870. This coefficient is used to derive an estimated BCF of 100 for aquatic organisms that contain about 8 percent lipids. If it is known that the diet of the wildlife of concern contains a significantly different lipid content, an appropriate adjustment in the estimated BCF should be made.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

Final Fish Acute Value = 38 µg/l

Final Invertebrate Acute Value = 170 µg/l

Final Acute Value = 38 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 49 µg/l

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 49 µg/l

0.44 x Final Acute Value = 17 µg/l

The maximum concentration of 1,2-diphenylhydrazine is the Final Acute Value of 38 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For 1,2-diphenylhydrazine the criterion to protect freshwater aquatic life as derived using the Guidelines is 17 µg/l as a 24-hour average and the concentration should not exceed 38 µg/l at any time.

Table 1 Freshwater fish acute values for 1,2-diphenylhydrazine (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Bluegill, *Lepomis macrochirus*	S	U	96	270	150

* S = static

** U = unmeasured

Geometric mean of adjusted values = 150 µg/l $\frac{150}{3.9}$ = 38 µg/l

Table 2. Freshwater invertebrate acute values for 1,2-diphenylhydrazine (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Cladoceran, Daphnia magna	S	U	48	4,100	3,470

* S = static

** U = unmeasured

Geometric mean of adjusted values = 3,470 µg/l $\frac{3,470}{21}$ = 170 µg/l

Table 3. Freshwater invertebrate chronic values for 1,2-diphenylhydrazine (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Cladoceran, Daphnia magna	LC	150-420	251

* LC = life cycle or partial life cycle

Geometric mean of chronic values = 251 µg/l $\frac{251}{5.1}$ = 49 µg/l

Lowest chronic value = 251 µg/l

SALTWATER ORGANISMS

Introduction

No acute toxicity, chronic toxicity or residue data are available for saltwater organisms and 1,2-diphenylhydrazine.

CRITERION FORMULATION

Saltwater-Aquatic Life

No saltwater criterion can be derived for 1,2-diphenylhydrazine using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

1,2-DIPHENYLHYDRAZINE

REFERENCES

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. Contract No. 68-01-4646.

EXPOSURE

Introduction

1,2-diphenylhydrazine (DPH) is a precursor in the manufacture of benzidine, an intermediate in the production of dyes. 1,2-diphenylhydrazine is used in the synthesis of phenylbutazone, a potent anti-inflammatory (anti-arthritic) drug (Wenner, 1967).

The commercial production of 1,2-diphenylhydrazine per se in 1977 was in excess of 1000 lbs. (SRI, 1977). However, this figure is probably an underestimate of the amount of diphenylhydrazine that was actually available. Diphenylhydrazine is produced in several synthetic processes as an intermediate and a contaminant but there is no way of estimating these quantities which are substantial.

Industrial exposure to 1,2-diphenylhydrazine is primarily limited to workers in the dye manufacturing industry and in the pharmaceutical industry.

Derivatives of hydrazine are reported to be hepatotoxic, hemolytic, convulsants, and irritants. They are absorbed from all routes (Sutton, 1967).

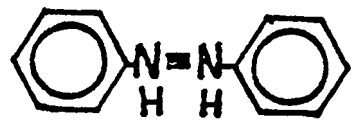
The basis for concern over 1,2-diphenylhydrazine includes: (1) its presence in drinking water (highest concentration reported was 1 µg/l (1ppb), U.S. EPA, (1975); (2) the likely production of benzidine from DPH in the stomach due to gastric acidity (IARC, 1972); (3) the documented carcinogenicity of hydrazine and selected substituted hydrazines (IARC, 1974); (4) the increased incidence of bladder cancer among workers involved in the manufacture of dyes (Wynder, et al.

1963); Anthony, et al. 1970); (5) the carcinogenicity of azobenzene, a metabolite of DPH, as well as the established carcinogenicity of benzidine to which DPH is converted.

The structure and physical data for 1,2-diphenylhydrazine are presented in Figure 1.

The primary commercial method of production of this compound is the reduction of nitrobenzene by catalysts such as Fe^{+3} or Zn^{+2} in alkaline solution. By this procedure, one obtains nearly quantitative yields (Kirk-Othmer, 1963). Figure 2 depicts this process as well as the by-products of diphenylhydrazine, azobenzene and azoxybenzene.

The reaction of 1,2-diphenylhydrazine with acid results in the benzidine rearrangement (Kenner, 1968). This reaction is presented in Figure 3. In addition to benzidine, other products formed include diphenyline, o-benzidine, and o-semidine. In the stomach, 1,2-diphenylhydrazine can be converted into benzidine, a human carcinogen (Haley, 1975; IARC, 1972).



Synonyms - Hydrazobenzene

Symmetrical diphenylhydrazine

N,N' Diphenylhydrazine

N N' - Bianiline

1,1' Hydrazodibenzene

Cas No. 530-50-7[b]

Molecular weight = 184.24

Melting Point = 131°C

Boiling Point = 220°C

Solubility = Slightly soluble in water
Very soluble in benzene, ether, alcohol

Figure 1. 1,2-diphenylhydrazine: Chemical and Physical Properties[a]

(a) from CRC Handbook - 59th Ed.
(b) DHEW report, 1978

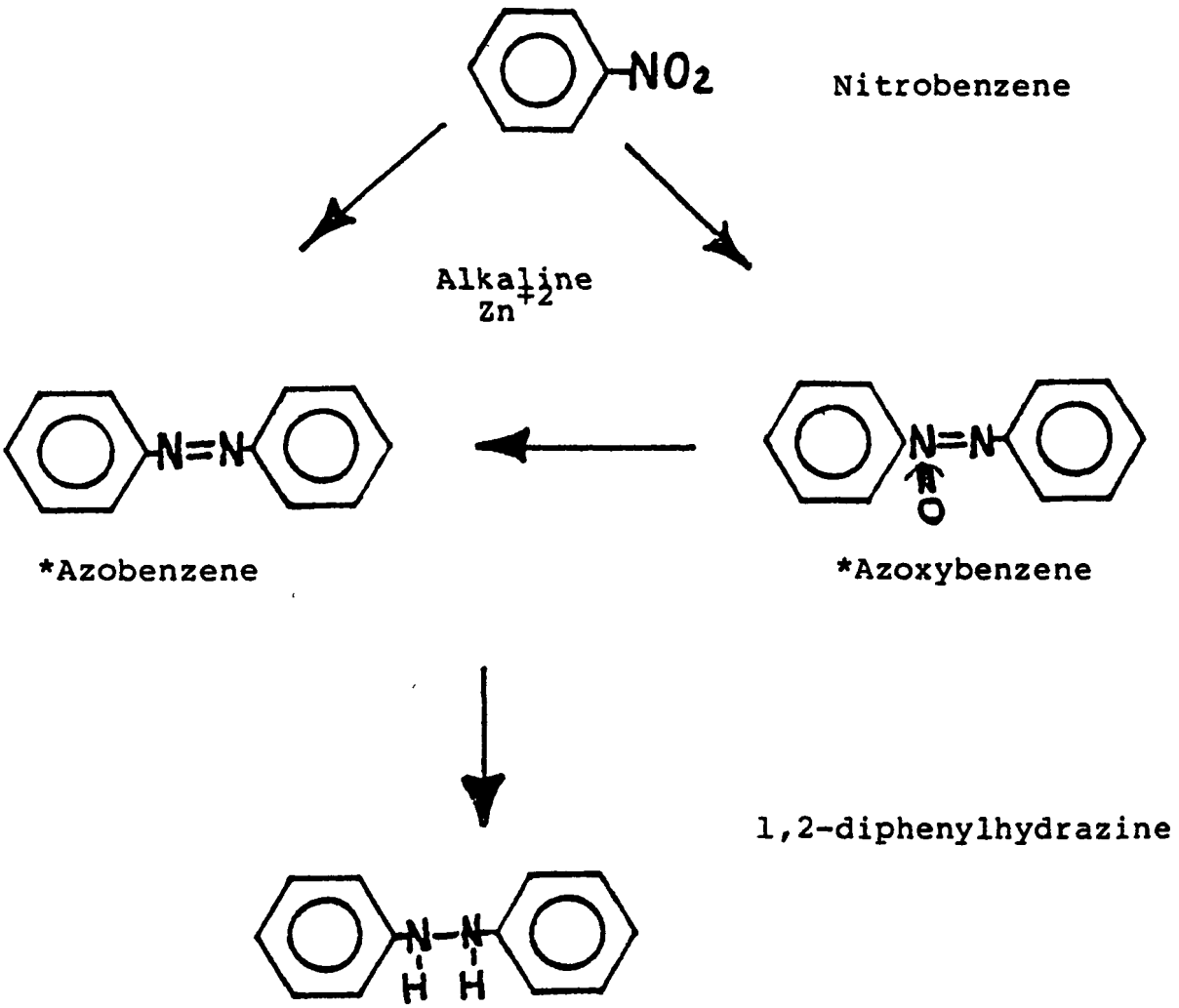


Figure 2. Synthesis of 1,2-diphenylhydrazine (Williams, 1959)

*Carcinogenic

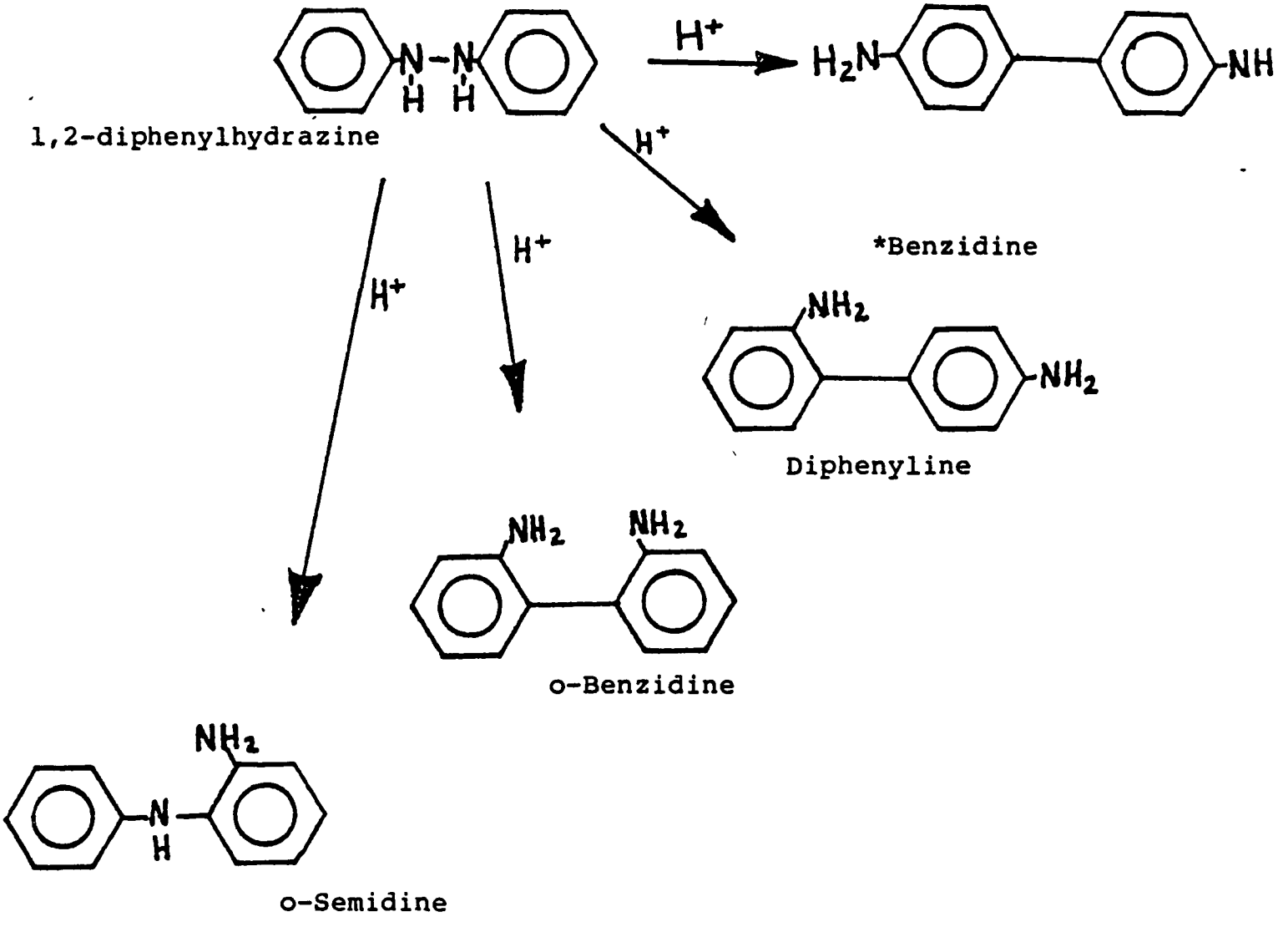


Figure 3. Benzidine Rearrangement of 1,2-diphenylhydrazine (Williams, 1959)

*Carcinogenic

Ingestion from Water and Foods

DPH was not detected in the finished water of any of ten cities selected for a detailed EPA study in 1975. However, the same study demonstrated the presence of DPH in drinking water in concentrations up to 1 µg/l (1 ppb).

There are no available data identifying DPH as a direct or indirect food additive, or as a naturally occurring constituent of any food.

Inhalation, Dermal, and Other Sources

Workers involved in the manufacture of dyes, certain pharmaceuticals and chemicals, laboratory workers, and workers in forensic medicine risk occupational exposure to 1,2-diphenylhydrazine. Both inhalation and dermal contact are possible routes of exposure in these settings. However, no experimental data are available to quantitate either the dermal or inhalation exposure risks to this population.

PHARMACOKINETICS

Absorption, Excretion, and Distribution

There are no available data on the absorption or excretion of 1,2-diphenylhydrazine by mammals. The administration of DPH by various routes results in systemic effects and the presence of DPH metabolites in the urine. This indicates that it is absorbed.

Metabolism

The metabolism of 1,2-diphenylhydrazine in the rat is presented in Figure 4 (Williams, 1959). The 1,2-diphenylhydrazine was administered to rats orally (200, 400 mg/kg), i.p. (200 mg/kg), intratracheally (5, 10 mg/kg), and i.v. (4, 8 mg/kg). Urines were analyzed chromatographically

Route	Dose (mg/kg)	Solvent
p.o.	200, 400	oil
i.p.	100, 200	DMSO[b]
i.t.[a]	5, 10	water
i.v.	4, 8	DMSO

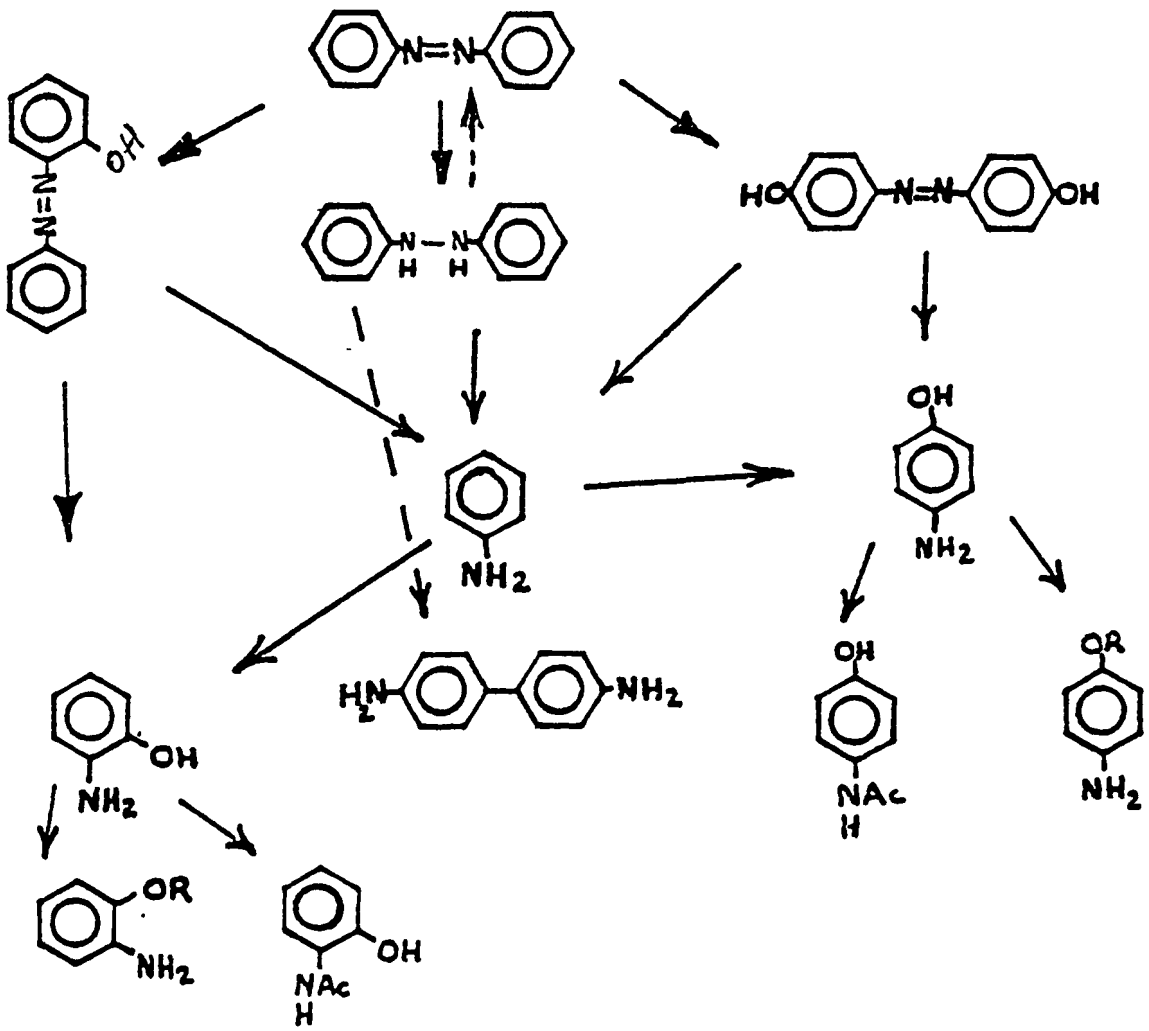


Figure 4. 1,2-diphenylhydrazine Metabolites in Rat Urine (Williams, 1959)

[a]intratracheally
[b]dimethyl sulfoxide

(TLC) and a scheme proposed (Figure 4). Benzidine was identified as a metabolite. The metabolites detected were not dependent upon the dose or the route of administration.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Two studies reporting DPH oral LD_{50}'s were identified. Marhold, et al. (1968) used ten male Wistar rats and administered DPH as a five percent aqueous suspension. The LD_{50} reported was 959 mg/kg. In the Registry of Toxic Effects of Chemical Substances, 1977 (RTECS) the oral LD_{50} is listed as 301 mg/kg. No details were given. The basis for this difference is not known. Liver damage is an important feature of hydrazine toxicity, particularly after chronic exposure, but Sutton (1967) noted that phenylhydrazines cause prominent kidney damage and more diffuse liver damage in animals.

Two rat studies were reported in Reg. Tox. Eff. Chem. Subst. (1977). There were no data available on the strain, sex, doses, or solvents used for these studies. One rat study reported an oral TDLo of 396 gm/kg. Neoplasms were seen by 53 weeks. In the second rat study, a total dose of 16 mg/kg DPH was administered subcutaneously and neoplasms were reported after 52 weeks.

Two mouse studies were reported in Reg. Tox. Eff. Chem. Subst. (1977). When 1,2-diphenylhydrazine was applied topically for 25 weeks (total dose of 5,280 mg/kg) neoplasms were found. Subcutaneous injection of DPH (8,400 mg/kg) resulted in neoplasms after 38 weeks. These results are presented in Table 1.

TABLE 1

1,2-diphenylhydrazine Toxicity Data

Species/Strain	Sex	No.	Dose	Solvent	Conc	Route	T.I.[a]	Duration	Effects	References
Rat/Wistar	M	10	N.O.S.	water (Suspension)	5%	p.o.	LD_{50} (mg/kg) 959	N.O.S.	N.O.S.	Marhold, et al. (1968)
Rat/N.O.S.[d]	N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	p.o.	LD_{50} 301	N.O.S.	N.O.S.	RTECS[b]
Rat/N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	p.o.	TDLo[e] 39,600	53 wks.	Neoplasms	RTECS
Rat/N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	s.c.[c]	TDLo 16,000	52 wks.	Neoplasms	RTECS
Mouse/N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	skin	TDLo 5,280	25 wks.	Neoplasms	RTECS
Mouse/N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	N.O.S.	s.c.	TDLo 8,400	38 wks.	Neoplasms	RTECS

(a) Toxicity Index

(b) Registry of Toxic Effects of Chemical Substances, 1977

(c) Subcutaneous

(d) Not Otherwise Specified

(e) TDLo-Toxic Dose Low - the lowest dose of a substance introduced by any route, other than inhalation, over any given period of time and reported to produce any toxic effect in humans or to produce carcinogenic, teratogenic, mutagenic, or neoplastigenic effects in humans of animals.

No epidemiological studies have been carried out on the effects of DPH in humans.

Synergism and/or Antagonism

Marhold, et al. (1968) demonstrated that diphenyline, a product of benzidine rearrangement, acts synergistically with benzidine to produce tumors. Genin (1975) showed a synergistic effect of hydrazobenzene and benzidine sulfate. Kulyanskii, et al. (1976) observed that benzidine sulfate-hydrazobenzene or benzidine sulfate-dianisidine sulfate mixtures when administered subcutaneously to rats increased the incidence of bladder cancer and decreased the latent period for tumor development when compared with the carcinogenic activity of the individual compounds. The authors emphasize the importance of preventing the possible exposure of industrial workers to combinations of 1,2-diphenylhydrazine and benzidine during the manufacture of benzidine-sulfate.

Teratogenicity

There are no studies available on the teratogenicity of DPH.

Mutagenicity

Sieler (1977) studied the incorporation of ^{3}H-thymidine into testicular DNA using the technique developed by Friedman and Staub (1976). DPH was administered i.p. in a dose of 100 mg/kg and an inhibitory effect on testicular DNA synthesis was observed. Seiler implied from this study that DPH has a mutagenic potential.

Carcinogenicity

There are several reports on the possible carcinogenicity of DPH. The most comprehensive study was reported in 1978 (NCI, 1978). Technical grade DPH* was fed as a dietary admixture to rats (Fischer 344) and mice (B6C3F1) of both sexes. Dietary concentrations (DPH) fed to rats and mice are indicated in Tables 2 and 3. DPH was fed to mice and rats for 78 weeks followed by observation periods of 17 to 96 weeks and 28 to 109 weeks, respectively. Controls consisted of 47 to 50 animals of each sex. The results of this study are summarized in Tables 2 and 3. There were differences in the nature and organ distribution of tumors between sexes and species. DPH was carcinogenic to Fischer 344 rats of both sexes and caused significant increases in hepatocellular carcinoma at 5 µg/kg/day and 18.8 µg/kg/day; Zymbal's gland squamous-cell tumors in male rats at 18.8 µg/kg/day and neoplastic liver nodules in female rats at 7.5 µg/kg/day. Female mice showed an increase in hepatocelluar carcinomas only at 3.75 µg/kg/day. DPH was not carcinogenic in B6C3F1 male mice.

*mp = 120 - 124 C, K & K labs.

TABLE 2

Carcinogenicity of 1,2-diphenylhydrazine in Mice*

Sex	#	Dose	Weeks		Effects	
			Treated	Observed Post treatment	Hepatocellular Carcinomas	Pulmonary Carcinomas
male	50	LD control	0	95	12/50	5/50
	50	HD control	0	96	6/48	5/49
	50	0.75 µg/kg/day	78	17	11/47	1/47
	50	3.75 µg/kg/day	78	17	8/46	0/46
female	50	LD control	0	96	2/47	2/46
	50	HD control	0	96	1/50	3/50
	47	0.375 µg/kg/day	78	17	4/39	3/38
	50	3.75 µg/kg/day	78	18	20/43 $p<0.001$	2/40

*Data taken from NCI, 1978

LD = Low dose
HD = High dose
Dose = DPH in diet

TABLE 3

Carcinogenicity of 1,2-diphenylhydrazine in Rats

Sex	#	Dose	Weeks Treated	Weeks Observed	Effects: Hepatocellular Carcinoma	Effects: Zymbal's Gland	Effects: Pulmonary Carcinomas
male	50	Ld control	0	108	0/47	0/47	1/47
	49	HD control	0	109	1/48	1/48	1/48
	50	5 ug/kg/day	78	29	5/49 p 0.031	2/50	3/49
	50	18.8 ug/kg/day	78	28	31/49 p 0.001	7/49 p 0.007	1/48
					Hepatic Neoplastic Nodules		Mammary carcinomas
female	50	LD control	0	109	0/47	0/48	1/48
	50	HD control	0	109	0/50	0/50	0/50
	50	3 ug/kg/day	78	30	0/50	1/50	3/50
	50	7.5 ug/kg/day	78	29	6/50 p 0.013	0/50	6/50 p < 0.013

*Data taken from NCI, 1978.

LD = Low dose
HD = High dose
Dose = % DPH in diet

In an additional study by Pliss in 1974, the carcinogenic properties of DPH were studied over a period of 588 days in rats (N = 163) and C 57 mice (N = 110). DPH was suspended in sunflower seed oil and administered by s.c. injection (40 mg/wk/rat and 5 mg/wk/mouse), and by addition to food (30 mg/5 times/wk), or application to the skin (30 mg/5 times/wk/rat and 2 mg/3 times/wk/mouse).

TABLE 4

Carcinogenicity of DPH in Mice and Rats[a]

Species	Route	% Tumor Incidence	Effects Tumors
mice	s.c.	36.6	rhabdomyosarcoma
	PO	50	pulmonary adenoma, leukemia, liver
	epicutaneous	22.2	skin, lung, liver
rats	s.c.	22.6	uterus, mammary, Zymbal's gland, liver spleen, lymphoid leukemia

The data summarized in Table 4 indicate that DPH produces a wide variety of tumors in both mice and rats.

[a]Data taken from Pliss, 1974.

In contrast to the NCI (1978) study and the report by Pliss (1974), Marhold, et al. (1968) and Spitz (1950) did not find any significant increase in carcinogenicity by DPH. These latter two studies were difficult to interpret due to the lack of specific information on the purity of DPH, experimental design or statistical analysis. The Pliss study (1974) should be used in a cautious manner in indicting DPH as a carcinogen. The author indicates that animals had to be added to the study in order to replace animals afflicted with a parasitic infection. In addition, although the tumor incidence is given for DPH treated animals, the incidence of tumors in control animals is not presented except in the case of the epicutaneous administration of DPH. Values of 17 percent vs. 22.2 percent for control and DPH groups, respectively, are presented but no statistical analysis of these incidences is given. The NCI (1978) report stands in marked contrast to the other published studies on the carcinogenecity of DPH. It represents the only reliable study and indicates that DPH is carcinogenic.

CRITERION FORMULATION

Existing Guidelines and Standards

No existing guidelines or standards were found for 1,2-diphenylhydrazine.

Current Levels of Exposure

No information is available on the concentration of 1,2-diphenylhydrazine in the atmosphere.

1,2-Diphenylhydrazine has been found to be present in drinking water at levels of 1 µg/l = 1 ppb (U.S. EPA, 1975).

1,2-Diphenylhydrazine has not been found to be a natural constituent of food.

Special Groups at Risk

Manufacturers of dyes and pharmaceuticals are subject to occupational exposure. Groups working in the laboratory and forensic medicine may also be subject to 1,2-diphenylhydrazine exposure.

Basis and Derivation of Criterion

An evaluation of the subacute, acute and chronic toxicity, with the exception of carcinogenicity is impossible because of only scanty data. No current guidelines or standards presently exist for DPH. Diphenylhydrazine has been shown to produce carcinogenic responses in rats and mice (NCI, 1978; Pliss, 1974). Since the NCI (1978) study represents the only report in which all the data can be analyzed, it will be used as a basis for formulating a criterion.

More specifically, the data on the induction of cancer in male and female rats and female mice were chosen for

analysis because they all had significantly increased tumor formation following DPH treatment (i.e. dietary). The respective criterion levels obtained from applying the standard water quality dose extrapolation/criteria calculation methodology is given in Table 5.

TABLE 5

1,2-Diphenylhydrazine Induction of Tumors in Mice and Rats[a]

Species	Sex	Estimated Criterion Level at 10^{-5} Risk[b]
Mouse	Female	1.43 µg/l
Rat	Female, liver carcinoma	1.32 µg/l
	mammary carcinoma	1.32 µg/l
	Male, zymbol gland tumor	5.14 µg/l
	liver carcinoma	0.38 µg/l

[a]Data taken from NCI, 1978. (Tech No. 92, 1978)
[b]Calculated by applying a modified "one-hit" extrapolation model described in the Federal Register 1062-5, 1979.

It can be seen that male rats appear to have the lowest tolerance for DPH.

Under the Consent Decree in NRDC vs. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." DPH is suspected of being a human carcinogen. Because there is no recognized safe concentration for human carcinogens, the recommended concentration of DPH in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of DPH corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions	Risk Levels and Corresponding Criteria			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish (2)	0	4 ng/l	40 ng/l	400 ng/l
Consumption of fish and shellfish only.	0	.019 µg/l	0.19 µg	1.9 µg/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the FR 15926, 1979. Appropriate bioassay data used in the calculation of the model are presented in Appendix I. Since the extrapolation model is linear to low doses, the additional lifetime risk is directly proportional to the water concentration.

Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1000 and so forth.

(2) Twenty-one percent of the DPH exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 29 fold. The remaining percent of DPH exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amount of DPH, (1) occurring from the consumption of both drinking water and aquatic life grown in water containing the corresponding DPH concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding DPH concentrations.

Although a total exposure evaluation for DPH is desirable there is no data to support a total exposure analysis. The criteria presented, therefore, assume an incremental risk from assumed ambient water exposure only.

For DPH the case for criterion development is based upon the existence of carcinogenicity responses in animals (rats and mice).

Because of the lack of investigations for other chronic and acute responses, there is no information on other effects in either human or animal systems. Thus, the criterion proposed should be considered as precautionary until further studies can be used in the overall toxicity evaluations.

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APPENDIX I

Summary and Conclusions Regarding the Carcinogenicity of 1,2,-Diphenylhydrazine*

1,2-Diphenylhydrazine is used primarily in dye manufacturing industries as a precursor in the synthesis of benzidine. There are no data showing carcinogenic effects of 1,2-diphenylhydrazine in humans. However, two studies have shown that 1,2-diphenylhydrazine is carcinogenic in mice and rats via subcutaneous and oral routes of administration. Male rats, receiving dietary concentrations of 0.03 percent 1,2-diphenylhydrazine, developed hepatocellular carcinomas and squamous cell carcinomas of the Zymbal glands. Female rats, receiving 0.01 percent 1,2-diphenylhydrazine in the diet, developed neoplastic nodules of the liver and mammary adenocarcinomas. Female mice, exposed to 0.04 percent 1,2-diphenylhydrazine in the diet, developed hepatocellular carcinomas.

The carcinogenic responses induced in male and female rats and female mice constitute substantial evidence that 1,2-diphenylhydrazine is likely to be a human carcinogen.

The water quality criterion for 1,2-diphenylhydrazine is based on the induction of hepatocellular carcinoma and neoplastic nodules in male Fischer 344 rats, exposed to a time-weighted average concentration of 0.03 percent (300 ppm) 1,2-diphenylhydrazine in the diet for 78 weeks (NCI, 1978). The concentration of 1,2-diphenylhydrazine in water calculated to keep the lifetime cancer risk below 10^{-5} is 0.40 micrograms per liter.

*This summary has been prepared and approved by the Carcinogens Assessment Group of EPA on June 15, 1979.

Summary of Pertinent Data

The water quality criterion for 1,2-diphenylhydrazine is based on the induction of hepatocellular carcinomas and neoplastic nodules in male Fischer 344 rats, exposed to 0.03 percent (300 ppm) 1,2-diphenylhydrazine in the diet ad libitum for 78 weeks (NCI, 1978). The incidence of hepatocellular carcinomas and neoplastic nodules was 37/49 and 1/48 in the treated and control groups, respectively. The criterion was calculated from the following parameters:

$n_t = 37$ $\quad$ $d^* = 15$ mg/kg/day

$N_t = 49$ $\quad$ $F = .0187$ kg/day

$n_c = 1$ $\quad$ $R = 29$

$N_c = 48$ $\quad$ $W = 0.375$ kg

$Le = 104$ weeks

$le = 78$ weeks

$L = 104$ weeks

Based on these parameters, the "one-hit" slope (B_H) is 0.715 $(mg/kg/day)^{-1}$. The resulting water concentration of 1,2-diphenylhydrazine, calculated to keep the individual lifetime cancer risk below 10^{-5}, is 0.40 µg/l.

* The dose (expressed as mg/kg (body weight) /day) is based on the assumption that the amount of diet consumed by rats each day was five percent of their body weights.

0.05 x 0.375 kg = 0.01875 kg diet/day

0.01875 kg diet/day x 300 mg/kg = 5.625 mg 1,2 DPH/day

5.625 mg 1,2 DPH/day/0.375 kg = 15 mg/kg/day