

1,2-Diphenylhydrazine; CASRN 122-66-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR 1,2-Diphenylhydrazine

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	message	11/01/1991*
Carcinogenicity Assessment (II.)	yes	01/31/1987*

*A comprehensive review of toxicological studies was completed (May 24, 2006) - please see section I.B. and II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 1,2-Diphenylhydrazine
CASRN — 122-66-7

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 1,2-Diphenylhydrazine
CASRN — 122-66-7

The health effect data for 1,2-diphenylhydrazine were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC. For additional information on the health effects of this chemical, interested parties are referred to the documentation listed below.

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

U.S. EPA. 1987. Health Effects Assessment for 1,2-Diphenylhydrazine. Prepared by the Environmental Criteria and Assessment Office, Environmental Assessment and Criteria Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA/600/8-88/033. PB88-180211/AS.

U.S. EPA. 1989. Ambient Water Quality Criteria Document Addendum for Diphenylhydrazine. Prepared by the Environmental Criteria and Assessment Office, Environmental Assessment and Criteria Office, Cincinnati, OH. (Final Draft)

Agency Work Group Review — 09/12/1991

A comprehensive review of toxicological studies published through May 2006 indicated that there is insufficient health effects data to derive an RfC for 1,2-Diphenylhydrazine at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

EPA Contacts:

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,2-Diphenylhydrazine

CASRN — 122-66-7

Last Revised — 01/31/1987

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — B2; probable human carcinogen

Basis — Positive results of studies in both rats and mice form the basis for this classification. Two apparently negative studies lack information on compound purity, experimental design, and statistical treatment.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

In a study by NCI (1978), 1,2-diphenylhydrazine was fed to 47-50 each male and female F344 rats and B6C3F1 mice for a period of 78 weeks. TWA food concentrations were 0.008% and 0.03% for male rats, 0.004% and 0.01% for female rats, 0.008% and 0.04% for male mice, and

0.004% and 0.04% for female mice. Rats were observed for 28 to 30 weeks after cessation of treatment and mice for an additional 17 or 18 weeks. Male rats showed a significant treatment-related increase in incidence of hepatocellular carcinoma. Neoplastic liver nodules and mammary adenocarcinomas were significantly increased in the treated female rats. High-dose male rats also showed a significant increase in combined incidence of squamous-cell carcinomas or squamous-cell papillomas of the Zymbal gland, the ear canal, and the skin of the ear. A significant increase of hepatocellular carcinoma was observed in treated female mice, but not male mice.

Pliss (1974) administered diphenylhydrazine in sunflower oil to 110 C57 mice and 163 rats either s.c., topically to the skin, or by addition to food. Tumor incidences of 22-50% were observed in mice treated by all routes; rats administered diphenylhydrazine also had a combined tumor incidence of approximately 22%. While this study suffers from design problems (animals were added in the course of the treatment and control data was missing) it is supportive of the classification of diphenylhydrazine as carcinogenic. Studies by Marhold (1968) and Spitz (1950) found no evidence of diphenylhydrazine carcinogenicity in male Wistar rats and mongrel dogs or in Sherman rats, although study details are lacking.

II.A.4. Supporting Data for Carcinogenicity

Diphenyl hydrazine was shown to depress testicular DNA synthesis in mice when administered i.p. at a dose of 100 mg/kg (Seiler, 1977).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Oral Slope Factor — 8.0E-1 per (mg/kg)/day

Drinking Water Unit Risk — 2.2E-5 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E+0 ug/L

Risk Level	Concentration
E-5 (1 in 100,000)	5E-1 ug/L
E-6 (1 in 1,000,000)	5E-2 ug/L

II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type — hepatocellular carcinomas and neoplastic liver nodules

Test Animals — rat/Fisher 344, male

Route — diet

Reference — NCI, 1979

Administered Dose (% of diet)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	6/95
0.008	4	13/49
0.03	15	37/49

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

Dietary doses were calculated from the TWA in diet assuming a weight of 0.38 kg, and an expected lifespan of 104 weeks for male rats. Human equivalent doses were based on a surface area extrapolation for individual animals, and on treatment duration of 546 days and a study duration of 742 days. Significant tumor site data were not pooled for total cancer rates, since data were unavailable. Control data were from pooled low- and high-dose controls. The unit risk value should not be used if the water concentration exceeds 500 ug/L, since above this concentration the unit risk may not be appropriate.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

An NCI bioassay found diphenylhydrazine to produce tumors in a dose- dependent fashion in both rats and mice. Adequate numbers of animals were treated for the majority of their lifespan and observed to the end of their natural lifespan. The combined incidence of carcinomas and nodules was significantly increased at both treatment doses. Stability of the compound in the diet was not determined. The magnitude of effects between species cannot be compared, since the total results were not equivalent for modeling. Data for mice and female rats required mortality adjustment for corroboration, which could not be carried out.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

Inhalation Unit Risk —2.2E-4 per ($\mu\text{g}/\text{cu.m}$)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E-1 $\mu\text{g}/\text{cu.m}$
E-5 (1 in 100,000)	5E-2 $\mu\text{g}/\text{cu.m}$
E-6 (1 in 1,000,000)	5E-3 $\mu\text{g}/\text{cu.m}$

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

The inhalation risk estimates were calculated from the oral exposure data in Section II.B.2.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The unit risk value should not be used if the air concentration exceeds 50 $\mu\text{g}/\text{cu.m}$, since above this concentration the unit risk may not be appropriate.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

See II.B.4.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1980

The values in the Ambient Water Quality Criteria Document for Diphenylhydrazine (1980) received extensive peer and public review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 07/23/1986, 10/29/1986

Verification Date — 10/29/1986

A comprehensive review of toxicological studies published through May 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for 1,2-Diphenylhydrazine and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — 1,2-Diphenylhydrazine
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VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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

U.S. EPA. 1987. Health Effects Assessment for 1,2-Diphenylhydrazine. Prepared by the Environmental Criteria and Assessment Office, Environmental Assessment and Criteria Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA/600/8-88/033. PB88-180211/AS.

U.S. EPA. 1989. Ambient Water Quality Criteria Document Addendum for Diphenylhydrazine. Prepared by the Environmental Criteria and Assessment Office, Environmental Assessment and Criteria Office, Cincinnati, OH. (Final Draft)

VI.C. Carcinogenicity Assessment References

Marhold, J., M. Matrka, M. Hub and F. Ruffer. 1968. The possible complicity of diphenylene in the origin of tumors in the manufacture of benzidine. *Neoplasma*. 15: 3-8.

NCI (National Cancer Institute.) 1978. Bioassay of Hydrazobenzene for Possible Carcinogenicity. U.S. DHEW Publication No. (NIH) 78-1342.

NCI (National Cancer Institute). 1979. Bioassay of Hydrazobenzene for Possible Carcinogenicity. U.S. DHEW Publ. No. NIH 78-1342.

Pliss, G.B. 1974. Carcinogenic properties of hydrazobenzene. *Vop. Onkol.* 20: 50.

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.

Spitz, S. 1950. The carcinogenic action of benzidine. *Cancer.* 3: 789-804.

U.S. EPA. 1980. Ambient Water Quality Criteria for Diphenylhydrazine. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-062. NTIS PB 81- 117731.

VII. Revision History

Substance Name — 1,2-Diphenylhydrazine
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Date	Section	Description
11/01/1991	I.B.	Inhalation RfC message on-line
12/03/2002	I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.
07/05/2006	I.B., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — 1,2-Diphenylhydrazine

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Last Revised — 01/31/1987

- 122-66-7
- benzene, hydrazodi-
- (sym)-dihpenylhydrazine
- 1,2-Diphenylhydrazine
- Diphenylhydrazine, 1,2-
- hydrazine, 1,2-dihpenyl-
- hydrazobenzene
- NCI-C01854
- N,N'-bianiline
- RCRA waste number U109