

## Hydrazine/Hydrazine sulfate; CASRN 302-01-2

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 Hydrazine/Hydrazine sulfate

**File First On-Line 09/07/1988**

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	09/07/1988

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Hydrazine/Hydrazine sulfate  
CASRN — 302-01-2

Not available at this time.

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

Substance Name — Hydrazine/Hydrazine sulfate  
CASRN — 302-01-2

Not available at this time.

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Hydrazine/Hydrazine sulfate  
CASRN — 302-01-2  
Last Revised — 09/07/1988

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 — Tumors have been induced in mice, rats and hamsters following oral, inhalation or intraperitoneal administration of hydrazine and hydrazine sulfate. Hydrazine is mutagenic in numerous assays.

## **II.A.2. Human Carcinogenicity Data**

Inadequate. A Letter to the Editor by Roe (1978) is the only available report on effects of hydrazine exposure in humans. Mortality data from two hydrazine manufacturing plants (from one company of nine in the field) are presented. Between 1963 and 1975, one company reported two deaths. Both were due to heart disease and were presumed to be unrelated to hydrazine exposure. A second company reported 26 deaths among 272 workers who had been employed at the plant between 1945 and 1970. Two of these deaths were due to stomach cancer. The author noted that the observed and expected deaths were similar and that these occupational exposures to hydrazine are not associated with an increased risk of cancer.

## **II.A.3. Animal Carcinogenicity Data**

Sufficient. Biancifiori (1970) conducted a multiple-dose study in which hydrazine sulfate was administered by gavage to groups of 24 to 30 8-week-old CBA/Cb/Se mice of each sex at doses of 0.0, 0.14, 0.28, 0.56, or 1.13 mg/day, 6 days/week for 25 weeks. Animals were observed throughout their lifetimes. Liver carcinomas were induced in a dose-related manner in both sexes and lung metastases were observed in some of the mice treated with 1.13 mg/kg/day. Pulmonary tumors were reportedly present in many of the treated mice, but incidences were not reported because the purpose of the study was to describe hepatic tumors.

Many other water gavage studies of hydrazine sulfate in mice have resulted in increased incidence of lung adenomas/carcinomas. Strains tested included BALB/c (Biancifiori and Ribacchi, 1962), CBA/Cb/Se (Biancifiori et al., 1964; Severi and Biancifiori, 1968), BALB/c x DBA/2 (Kelly et al., 1969) and Swiss (Roe et al., 1967). Hepatomas and hepatocarcinomas were also observed in some strains as a consequence of treatment. Cb/Se rats gavaged with 18 (males) or 12 (females) mg hydrazine sulfate/day showed an increased incidence of lung tumors in both sexes and hepatomas in males only (Severi and Biancifiori, 1968).

Toth (1969) administered 0.012% hydrazine sulfate in the drinking water to groups of 6-week old Swiss, C3H, and AKR mice (40 to 50/sex) for their lifetimes. Groups of 110 Swiss mice and 30 C3H and AKR mice of each sex served as untreated controls. Lung adenomas and adenocarcinomas were reported in 46-50% of the treated Swiss mice (25/50 males and 24/50 females), compared with 9-11% in the controls (11/110 males and 14/110 females). Hydrazine sulfate did not induce significantly increased incidence of tumors at other sites in the Swiss mice, or at any site in the C3H or AKR mice. In a later study, Toth (1972) administered 0.001% hydrazine continuously in the drinking water to 50 Swiss mice/sex for their lifetimes. Lung adenomas and adenocarcinomas were induced in 24/50 of the males and 27/50 of the females (48-54%). Yamamoto and Weisburger (1970) reported a 100% induction of lung adenomas and

adenocarcinomas (38/38 by comparison with 12/20 in the controls) in A/J male mice given 325 mg/L hydrazine sulfate in the drinking water for 48 weeks.

MacEwen et al. (1981) reported on the carcinogenic effect of inhaled hydrazine in C57BL/6 mice, F344 rats, Syrian golden hamsters and beagle dogs. Hydrazine vapor (97% pure) was administered to 400 female mice at 0.05, 0.25 or 1.0 ppm; to 100 rats of each sex at 0.05, 0.25, 1.0, or 5.0 ppm; to 160 male hamsters at 0.25, 1.0 or 5.0 ppm; and to 4 dogs of each sex at 0.25 or 1.0 ppm. Exposure was 6 hours/day, 5 days/week for 1 year, followed by a variable observation period (12-38 months). Appropriate controls were maintained for each species. Significantly increased incidences of tumors were reported at the highest exposures administered in mice (lung adenoma), male and female rats (nasal cavity adenoma and adenocarcinoma), and hamsters (nasal cavity polyp) as well as in male and female rats treated with 1.0 ppm hydrazine (nasal cavity adenoma and adenocarcinoma). No significant increase in tumor induction was observed at the lower doses nor were treatment-related neoplasms reported in the dogs. The observation period is considered to be insufficient for dogs.

Juhasz et al. (1966) injected white mice of both genders with hydrazine (0.5 mg x 16 injections) over a period of 46 days, then observed the animals for 1 year. Mediastinum reticulum-cell sarcomas were observed in 4/34 mice, and 9/34 had myeloid leukemias. A single thymic leukemia was reported out of 60 control animals. Kelly et al. (1969) injected (BALB/c\c x DBA/2)F1 male mice i.p. with a total dose of 20.8 mg hydrazine sulfate/animal (given in 8 weekly injections). Lung tumors were reported in 6/30 of the treated animals and 1/9 of the control animals.

#### **II.A.4. Supporting Data for Carcinogenicity**

The mutagenicity of hydrazine has been demonstrated in both in vitro and in vivo assays tested as hydrazine sulfate, hydrazine hydrate or hydrazine hydrochloride. Hydrazine induced reverse mutations in histidine auxotrophs of *S. typhimurium* (Kimball, 1977; Anderson and Styles, 1978; McMahan et al., 1979; Tosk et al., 1979; Parodi et al., 1981; Rogan et al., 1982), in tryptophan auxotrophs of *E. coli* (McMahan et al., 1979; Von Wright and Tikkanen, 1980), and in a host-mediated assay with mice given a single dose of hydrazine sulfate by gavage (Simmon et al., 1979). Intraperitoneal treatment of mice with hydrazine sulfate and radiolabeled formate or methionine produced radiolabeled 7-methylguanine in liver DNA and RNA, indicating that hydrazine mediated indirect alkylation of nucleic acids in vivo (Quintero-Ruiz et al., 1970). Hydrazine induces DNA strand breaks in rat hepatocytes treated in vitro (Sina et al., 1983) and in the liver and lung of mice treated intraperitoneally with hydrazine hydrate (Parodi et al., 1981). sister chromatid exchange was induced by in vitro treatment with hydrazine in Chinese hamster V-79 cells (Speit et al., 1980), Chinese hamster ovary cells (MacRae and Stitch, 1979), and Chinese hamster Don (lung) cells (Baker et al., 1983). Hydrazine induced specific locus and

recessive lethal mutations in *D. melanogaster* (Jain and Shukla, 1972; Shukla, 1972) but did not induce dominant lethal mutations in mice (Epstein and Shafner, 1968; Epstein et al., 1972).

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

### **II.B.1. Summary of Risk Estimates**

Oral Slope Factor — 3.0 per (mg/kg)/day

Drinking Water Unit Risk — 8.5E-5 per (ug/L)

Extrapolation Method — Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

<b>Risk Level</b>	<b>Concentration</b>
<b>E-4 (1 in 10,000)</b>	1E+0 ug/L
<b>E-5 (1 in 100,000)</b>	1E-1 ug/L
<b>E-6 (1 in 1,000,000)</b>	1E-2 ug/L

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

Tumor Type — hepatoma

Test animals — mouse, CBA/Cb/Se; male

Route — gavage (hydrazine sulfate in water)

Reference — Biancifiiori, 1970

<b>Administered Dose (ppm)</b>	<b>Human Equivalent Dose (mg/kg)/day</b>	<b>Tumor Incidence</b>
<b>0</b>	0	3/30
<b>0.14</b>	0.044	1/26
<b>0.28</b>	0.103	7/25
<b>0.56</b>	0.222	12/25
<b>1.13</b>	0.403	15/25

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

Human equivalent doses were calculated to reflect a treatment period of 175 days and an experimental period of 607 days, the mean length of the experiment for each treatment group. Mouse body weight was assumed to be 0.03 kg and the animal lifespan was assumed to be 730 days. A slope factor of 9.01E-1 per (mg/kg)/day was derived from the lung tumor response in male Swiss mice in the single-dose lifetime drinking water study with 0.012% (0.74 mg/day) hydrazine sulfate (Toth, 1969). The values for hydrazine would be expected to be less than these values for hydrazine sulfate because of the smaller molecular weight of the molecule. Although it is likely that hydrazine is responsible for the tumorigenic response in these experiments, the slope factor calculated on the basis of this compound may not be appropriate for hydrazine, even after converting the dose rate from hydrazine sulfate to that of hydrazine. The absorption rates in the body are likely to differ between the two compounds. The lifetime drinking water study with hydrazine in Swiss mice (Toth, 1972) is inappropriate for the calculation of a slope factor because of the lack of concurrent controls.

The unit risk should not be used if the water concentration exceeds 1E+2 ug/L, since above this concentration the unit risk may not be appropriate.

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

The study showed a dose-response and encompassed the lifespan of the animal. Two independent slope factors are within a factor of 4.

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

### II.C.1. Summary of Risk Estimates

Inhalation Unit Risk — 4.9E-3 per (ug/cu.m)

Extrapolation Method — Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
<b>E-4 (1 in 10,000)</b>	2E-2 ug/cu.m
<b>E-5 (1 in 100,000)</b>	2E-3 ug/cu.m
<b>E-6 (1 in 1,000,000)</b>	2E-4 ug/cu.m

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

Tumor Type — nasal cavity adenoma or adenocarcinoma

Test animals — rat/F344, male

Route — inhalation (hydrazine)

Reference — MacEwen et al., 1981

-----Dose-----		
Administered (ppm)	Human Equivalent (mg/kg)/day	Tumor Incidence
<b>0.0</b>	0.00	0/149
<b>1.0</b>	0.01	11/98
<b>5.0</b>	0.05	72/99

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

Data in Section II.C.2. were described in the Evaluation of the Potential Carcinogenicity of Hydrazine (U.S. EPA, 1986). Global 82 was used to calculate a slope factor of 1.7E+1 per (mg/kg)/day, which was the basis for the inhalation unit risk.

Human equivalent doses reflect a treatment period of 365 days and an experimental period of 910 days. Rat body weight was assumed to be 350 g, and the animal lifespan was assumed to be 910 days.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

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

A sufficient number of animals were treated for less than lifetime and observed until death; a dose-related increase in incidence was observed.

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

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1984, 1986

The values in the 1986 Reportable Quantity Document for Hydrazine (review draft) have received limited Agency Review. The values in the 1984 Health and Environmental Effects Profile for Hydrazine and Hydrazine Sulfate (final draft) have received Agency Review.

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

Agency Work Group Review — 06/03/1987

Verification Date — 06/03/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Hydrazine/Hydrazine sulfate conducted in September 2002 identified one or more significant

new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto: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](mailto:hotline.iris@epa.gov) (internet address).

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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — Hydrazine/Hydrazine sulfate

CASRN — 302-01-2

### **VI.A. Oral RfD References**

None

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### **VI.B. Inhalation RfD References**

None

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### **VI.C. Carcinogenicity Assessment References**

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## VII. Revision History

Substance Name — Hydrazine/Hydrazine sulfate  
CASRN — 302-01-2

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
12/03/2002	II.D.2.	Screening-Level Literature Review Findings message has been added.

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## VIII. Synonyms

Substance Name — Hydrazine/Hydrazine sulfate

CASRN — 302-01-2

Last Revised — 09/07/1988

- 302-01-2
- hydrazine
- hydrazine, anhydrous
- Hydrazine/Hydrazine sulfate