HAZARD ASSESSMENT REPORT

Hydrazine

CAS No. 302-01-2

Chemicals Evaluation and Research Institute (CERI), Japan

This report was prepared by CERI in collaboration with National Institute of Technology and Evaluation (NITE) under the sponsorship of New Energy and Industrial Technology Development Organization (NEDO).

Preface to the English Version of the Hazard Assessment Reports

For six years from April 2001 to March 2007, Chemicals Evaluation and Research Institute (CERI/Japan) was engaged in a project named “Chemical Risk Assessment and Development of Risk Assessment Methods” under "Comprehensive Chemical Substance Assessment and Management Program" funded by New Energy and Industrial Technology Development Organization (NEDO/Japan). Under this project, about 150 chemical substances were selected among those designated as Class-I Chemicals in the Law for Pollutant Release and Transfer Register and Promotion of Chemical Management (hereafter PRTR Law)[1)]. The selection criteria of these chemicals were their priorities for risk assessment based on their production levels and environmental/human health concerns.

CERI developed the hazard assessment reports of these selected chemical substances based on the review and evaluation of the environmental and human health hazard data obtained from the existing evaluation documents released by the regulatory agencies and international organizations as well as those from the published scientific literatures. The data review and compilation of the reports were conducted according to the guidelines[2)] and the guidance manual[2)] developed for this project. The proposed hazard assessment reports by CERI were reviewed by the experts in the relevant scientific fields from both inside and outside this project for accuracy, relevance and completeness. The final reports were published in Japanese after going through the deliberation by the “Council on Chemical Substances” under the Ministry of Economy, Trade and Industry (METI/Japan), which is responsible for regulation of chemical substances in Japan.

This project was the first attempt in Japan to develop comprehensive hazard assessments of chemical substances for application in risk assessment. In order to share the outcomes of the project globally, CERI independently selected the following seven chemical substances and developed the English version of the hazard assessment reports:

(1) Acetaldehyde
(2) Chlorobenzene
(3) Hydrazine
(4) *N*, *N*-Dimethylformamide
(5) Poly(oxyethylene) nonylphenyl ether
(6) 3,3’-Dichloro-4,4’-diaminodiphenylmethane
(7) Dimethyl 2,2-dichlorovinyl phosphate (Dichlorvos)

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1) Details of the PRTR Law, the list of designated chemical substances, and release data in Japan are available on Internet at: http://www.prtr.nite.go.jp/index-e.html.

2) Guidelines and the guidance manual in Japanese are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html. Also, the initial risk assessment reports in Japanese developed in this project which include calculations of margin of exposure based on the result of hazard assessment and exposure assessment, are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html.

We hope that the hazard assessment reports from our project contribute to the risk assessment and management of chemical substances globally, and appreciate your feedback.

Date: May, 2007 Chemicals Evaluation and Research Institute
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Summary

In this document, hydrazine is defined as the generic name for hydrazine anhydride and hydrazine hydrate, unless otherwise noted. Hydrazine anhydride is a colorless, weakly basic and hygroscopic liquid with a boiling point of 113.5°C and a vapor pressure of 1.4 kPa at 20°C. It is miscible with water and alcohols. Hydrazine hydrate is a colorless liquid with a boiling point of 118-119°C and a vapor pressure of 1 kPa at 20°C. It is miscible with water and alcohols and has strong alkaline and reducing properties. Hydrazine anhydride is used for rocket fuel and several tons per year was produced in Japan. Hydrazine hydrate is used mainly as raw material for foaming agents of plastics and can cleaning agents. Domestic production and export volumes of hydrazine hydrate in 2001 were 15,373 and 2,702 tons in Japan, respectively.

Considering the uses of hydrazine and the annual emission data for F.Y. 2001 in Japan (the 2001 PRTR data), the main release route is through emmisions during the use process of hydrazine or products containing hydrazine. As the scenario of hydrazine releases in Japan, it was estimated that 65 tons of hydrazine was released annually to air, and 216 tons to water.

Hydrazine released to the aquatic environment is not eliminated by volatilization from the surface of water. Hydrazine is not hydrolyzed but easily oxidized by dissolved oxygen in the aquatic environment and degraded. Hydrazine at a low concentration can be eliminated by biodegradation. Low bioaccumulation is suggested in aquatic organisms.

Many studies have been conducted to assess the toxic effects of hydrazine on organisms in the environment using indices including growth inhibition, mortality, immobilization, growth, anomaly and germination. In a growth inhibition study of hydrazine in algae, the 72-hr EC_{50} was 0.0061 mg/L in freshwater alga. The 72-hr NOEC was 0.001 mg/L in the freshwater alga and the 8-day NOEC was 0.0005 mg/L in the marine alga. The acute toxicity of hydrazine to invertebrates has been reported in freshwater water fleas. The 24-hr EC_{50} values for immobilization in water fleas ranged 0.76 to 2.3 mg/L, and the 48-hr EC_{50} was 0.175 mg/L, and the 48-hr LC_{50} in an amphipod was 0.04 mg/L. The acute toxicity of hydrazine to fish has been studied in freshwater fish, fathead minnow, bluegill, goldfish, zebrafish, guppy and channel catfish. The 96-hr LC_{50}s of hydrazine ranged from 0.61 to 7.7 mg/L and the lowest value was 0.61 mg/L in guppy. The 96-hr LC_{50} in marine three-spined stickleback was 3.4 mg/L. In other effects, it has been reported that exposure of hydrazine anhydride to fish embryos and amphibian larva caused anomalies.

The lowest value of toxicity in aquatic organisms is 0.0005 mg/L as the 8-day NOEC for growth inhibition of the marine alga.

Hydrazine is absorbed rapidly in inhalation, oral and dermal administration to experimental animals. No major differences in distribution pattern of hydrazine in tissues are found in these administration routes. By 0.5 hours after oral administration of hydrazine anhydride to rats, the concentrations in the blood and liver reached the peak. Hydrazine was detected also in the brain of rats after intravenous injection. The

metabolic process (mainly acetylation and free radical generation) and metabolites of hydrazine are same in all administration routes. After administration to rat, hydrazine is metabolized into monoacetylhydrazine, diacetylhydrazine, pyruvic acid hydrazone, urea and a cyclic compound and as well as metabolites, excreted in the urine. Otherwise, hydrazine is eliminated in the expiration as nitrogen gas. It has been reported that in some humans whose hydrazine metabolism (acetylation) is extremely slow due to genetical deficiency of acetylase enzyme, hydrazine absorbed might be accumulated in the plasma.

In human accidents, oral intake of hydrazine hydrate or hydrazine caused vomiting, hepatotoxicity, neurologic and cardiovascular symptoms. Some studies reported no irritation of hydrazine sulfate to the skin, but other study confirmed sensitization of hydrazine. Therefore, the Japan Society for Occupational Health has classified hydrazine and its compounds into Group 2 of skin sensitizer in the recommendation.

In various experimental animals, the acute toxicity values of hydrazine anhydride have been reported. Oral LD_{50} values were 59 mg/kg in mice and 60 to 90 mg/kg in rats. Inhalation LC_{50} values (4-hour exposure) were 330 mg/m^3 in mice and 350 to 760 mg/m^3 in rats, and dermal LD_{50} was 91 mg/kg in rabbits. The oral LD_{50} values of hydrazine hydrate were 83 mg/kg in mice and 129 mg/kg in rats. Acute toxic symptoms were ataxia, hypoactivity, dyspnea, enhanced excitability, salivation, vomiting and convulsion. In acute inhalation exposure, pulmonary edema, lesion in bronchial mucosa, pulmonary congestion and nasal mucosa epithelium degeneration (necrosis, scale and inflammation) were observed.

In application of 35% hydrazine and 55% hydrazine hydrate solutions to rabbit skins, irritation and corrosion were observed, respectively, and in application of 5% hydrazine hydrate solution to the rabbit eyes, no irritation was observed. No reports on sensitization of hydrazine were obtained in this investigation.

In the repeated administration studies, changes were observed in the respiratory system, liver, kidney, central nervous and cardiovascular systems, especially marked in the respiratory system and liver. In an oral study of hydrazine hydrate, body weight gain was suppressed in female mice, and bile duct hyperplasia in male rats was observed at the lowest dose of 2 mg/L (corresponding to 0.13 mg/kg/day of hydrazine in male rats). In halation exposure of hydrazine anhydride to rats, suppression in body weight gain in males and females, inflammation in the larynx and tracheal mucosa epithelium and alveolar epithelial hyperplasia in males were observed at the lowest concentration of 0.066 mg/m^3 (0.05 ppm). Since both in oral and inhalation administrations, the toxicity was observed at the lowest dose, the LOAEL values of hydrazine are 0.13 mg/kg/day in oral administration and 0.066 mg/m^3 in inhalation exposure.

In reproductive and developmental toxicity studies, oral administration of hydrazine anhydride via drinking water to male and female rats for 6 months caused a decrease in the number of surviving embryos and an increase in resorption. No developmental anomaly was found in all fetuses of the treated groups. With regard to developmental effects, intraperitoneal injection of hydrazine anhydride to pregnant mice and rats exhibited decreases in fetal body weight and increases in incidence of extra rib and hydronephrosis. These results suggest that hydrazine anhydride has reproductive and developmental toxicity.

In genotoxicity tests, many *in vitro* tests of hydrazine including reverse mutation, unscheduled DNA synthesis and chromosomal aberration tests showed positive results. Of *in vivo* tests, dominant lethal tests in mice and unscheduled DNA synthesis assays exhibited negative results, while mouse spot tests and gene mutation assay in *Drosophila* showed positive results. The overall evaluation of these results indicates that hydrazine is genotoxic.

With regard to carcinogenicity, a retrospective cohort study (gender unknown) in humans reported that exposure to hydrazine did not increase a risk of cancer incidences. However, carcinogenic responses of hydrazine were observed in experimental animal studies of oral administration and inhalation exposure. Inhalation exposure to hydrazine anhydride developed tumors in the respiratory system and lung of mice and tumors in the nasal cavity of rats and hamsters. Oral administration of hydrazine hydrate caused lung tumors in mice and liver and uterine tumors in rats, and oral administration of hydrazine sulfate caused liver and lung tumors in mice and liver tumors in rats. Hydrazine has been categorized as Group 2B (the agent is possibly carcinogenic to humans) by the IARC.

Contents

1. Identity of the substance

Hydrazine is used as the generic name for hydrazine anhydride and hydrazine hydrate in the law for PRTR and Promotion of Chemical Management (PRTR Law). In this document, the term of hydrazine is used in the same manner as the generic name for hydrazine anhydride and hydrazine hydrate, unless otherwise noted. Hydrazine anhydride or hydrazine hydrate is specifically stated as is, if necessary.

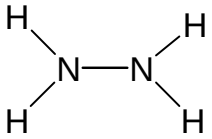
1.1 Chemical name : Hydrazine

1.2 Class reference number in Chemical Substance Control Law[1)] : 1-374

1.3 PRTR[2)] **number (Law for PRTR and Promotion of Chemical Management)** : 1-253

1.4 CAS registry number : 302-01-2 (anhydride)
7803-57-8 (monohydrate)

1.5 Structural formula



(anhydride)

1.6 Molecular formula : N_2H_4 (anhydride)
$N_2H_4 \cdot H_2O$ (monohydrate)

1.7 Molecular weight : 32.05 (anhydride)
50.06 (monohydrate)

2. General information

2.1 Synonyms

Diamine, Diamide, Diazane, Hydrazine monohydrate

2.2 Purity

>99.0 % (anhydride, Commercial products) (CERI, 2002)

[1)] The Low Concerning the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc., Japan. Provisional translation is available on Internet at: http://www.safe.nite.go.jp/english/kasinn/kaiseikasinhou.html

[2)] Pollutant Release and Transfer Register

2.3 Impurities

Iron, Sodium (hydrazine monohydrate, Commercial products) (CERI, 2002)

2.4 Additives/Stabilizers

No additives and stabilizers (hydrazine monohydrate, Commercial products) (CERI, 2002)

2.5 Current regulations in Japan[1)]

Law for PRTR and Promotion of Chemical Management:	Class I-designated chemical substance (anhydride, hydrate)
Chemical Control Substance Law:	Designated chemical substance (Type II monitoring chemical substance) (anhydride, hydrate)
Fire Service Law:	Dangerous goods: class IV second oil division (anhydride) Dangerous goods: class IV third oil division (hydrate)
Poisonous and Deleterious Substances Control Law:	Poisonous substance (anhydride) Deleterious substance (hydrate and hydrate solutions (except aqueous solutions with not more than 30% of hydrazine))
Industrial Safety and Health Law:	Dangerous substance: inflammable substance (anhydride) Hazardous substance to be notified in terms of whose name. (anhydride, hydrate) Mutagenic existing substance (anhydride)
Ship Safety Law:	Corrosive substance (anhydride, hydrate and aqueous solutions with 37-64% of hydrazine) Toxic substance (aqueous solutions with not more than 37% of hydrazine)
Civil Aeronautics Law:	Corrosive substance (anhydride) Toxic substance (aqueous solutions with not more than 37% of hydrazine)
Port Regulation Law:	Corrosive substance (anhydride, hydrate and aqueous solutions with 37-64% of hydrazine)

3. Physico-chemical properties

Hydrazine monohydrate is distributed in the market as commercial products. Therefore, physico-chemical properties of hydrazine monohydrate as well as hydrazine anhydride are also stated.

[1)] As this document covers basic information on Japanese regulations (unofficial translations), you should confirm the details using it.

a. Hydrazine anhydride

Appearance:	Colorless liquid	(IPCS, 1987; Merck, 2001)
Melting point:	2.0°C	(IPCS, 1987; Merck, 2001)
Boiling point:	113.5°C	(IPCS, 1987; Merck, 2001)
Flash point:	38°C (closed-cup)	(IPCS,1999)
	52°C	(Merck, 2001)
Ignition point :	38°C	(NFPA, 2002)
	24°C (rusty iron surface)	(IPCS, 1999 ; NFPA, 2002)
	156°C (stainless-steel surface)	(NFPA, 2002)
	270°C (glass surface)	(IPCS, 1999 ; NFPA, 2002)
Explosion limit :	1.8-100 vol% (in air)	(IPCS, 1999)
	2.9-98 vol% (in air)	(NFPA, 2002)
Specific gravity:	1.0036 (25°C/4°C)	(Merck, 2001)
Vapor density:	1.10 (air = 1)	
Vapor pressure:	1.4 kPa (20°C)	(IPCS, 1999)
Partition coefficient:	log Kow (*n*-octanol/water) = -0.16 (measured),	(METI/Japan, 1992)
	-2.07 (measured), -1.47 (estimated)	(SRC:KowWin, 2002)
Dissociation constant :	pKa = 7.96	(SRC:PhysProp, 2002)
Mass spectrum:	Main mass fragments	(NIST, 1998)
	m/z 31 (base peak = 1.0), 17 (0.76), 29 (0.75)	
Soil adsorption coefficient:	Koc = 14 (estimated)	(SRC:PcKocWin, 2002)
Solubility:	water: miscible	(Merck, 2001)
	methyl alcohol: miscible	(Merck, 2001)
	ethyl alcohol: miscible	(Merck, 2001)
	propyl alcohol: miscible	(Merck, 2001)
Henry's constant:	6.15×10^{-2} Pa·m^3/mol (6.07×10^{-7} atm·m^3/mol) (25°C, estimated)	(SRC:PhysProp, 2002)
Conversion factor:	(Air, 20°C) 1 ppm = 1.33 mg/m^3,	(IPCS, 1999)
	1 mg/m^3 = 0.750 ppm	
Others:	Hydrazine is a hygroscopic liquid and has a strong alkaline property. The substance decomposes at 180°C, producing ammonia fumes and nitrogen. The substance is a strong reducing agent and reacts violently with oxidants. Reacts violently with many metals, metal oxides and porous materials, causing fire and explosion hazard.	(IPCS, 1999)

b. Hydrazine monohydrate

Molecular formula: $N_2H_4 \cdot H_2O$

Molecular weight:	50.06	
Appearance:	Colorless liquid	(IPCS, 1987; Merck, 2001)
Melting point:	-51.7°C	(Merck, 2001)
Boiling point:	118-119°C (99 kPa)	(Merck, 2001)
Flash point:	75°C (open-cup)	(IPCS, 1987)
Ignition point :	270°C	(GDCh BUA, 1996)
Explosion limit :	3.4-100 vol% (in air)	(IPCS, 1987)
Specific gravity:	1.03 (21°C)	(Merck, 2001)
Vapor density:	1.73 (air = 1)	
Vapor pressure:	1 kPa (20°C)	(IPCS, 1987)
Partition coefficient:	No data	
Dissociation constant :	No data	
Mass spectrum:	Main mass fragments: No data	
Soil adsorption coefficient:	No data	
Solubility:	water: miscible	(Merck, 2001)
	ethyl alcohol: miscible	(Merck, 2001)
	chloroform: insoluble	(Merck, 2001)
	ether : insoluble	(Merck, 2001)
Henry's constant:	No data	
Conversion factor:	(Air, 20°C) 1 ppm = 2.08 mg/m^3, 1 mg/m^3 = 0.480 ppm	
Others:	Strong alkaline substance	(Merck, 2001)

4. Sources of release to the environment

4.1 Production, import and export

Hydrazine comprises of hydrazine anhydride (CAS No.: 302-01-2) and hydrazine monohydrate (CAS No.: 7803-57-8). Production and import of hydrazine in F.Y. 2001 was reported as 7,619 tons (METI/Japan, 2003). The production volume means shipment volume not including self consumption one.

In another investigation, production and export of hydrazine hydrate for 5 years from 1997 to 2001 in Japan are shown in Table 4-1 (NITE/Japan, 2003).

Table 4-1 Production and export of hydrazine hydrate (tons)

Year	1997	1998	1999	2000	2001
Production	18,867	18,599	17,086	15,728	15,373
Export	1,281	1,663	1,088	1,071	2,702

(NITE/Japan, 2003)

4.2 Uses

Hydrazine comprises of hydrazine anhydride and hydrazine hydrate and the former is only produced for rocket fuel at several tons per year. Therefore, this assessment describes the use of hydrazine hydrate that is more commonly used.

The estimated use pattern of hydrazine hydrate uses is shown in Table 4-2 (NITE, 2003). Hydrazine hydrate is used mainly as raw material for cellular blowing agents. Some are used as can cleaning agents and raw material for various industrial chemicals (NITE/Japan, 2003).

Table 4-2 Estimated use patterns

Use	Ratio (%)	Detailed
Raw material for blowing agents (as a derivative)	40.8	Production of plastic blowing agents (Azodicarboxylic amide)
Can cleaning, water treatment agents	28.1	Deoxidant of boiler water supply, pH adjuster, water treatment agent（Metal collection, liquid waste treatment, etc.）
Raw material for the synthesis of industrial chemicals	21.4	As reducer or derivative for organic synthesis, radical polymerization initiator for azo compounds, epoxy resin hardener, fiber modification agents, etc.
Raw material for the synthetic of agricultural chemicals	2.6	Plant growth regulator and the herbicide as maleic acid hydrazide, etc.,
Raw material for the synthesis of medical drug	0.6	A tuberculosis drug（Isonicotinic acid hydrazide）
Others	6.5	
Total	100	

(NITE/Japan, 2003)

4.3 Releases

4.3.1 Releases under PRTR system

According to the “Total Release and Transfers for F.Y. 2001 (hereafter the 2001 PRTR Data)” under the PRTR system (METI/Japan and MOE/Japan, 2003a), 3 tons of hydrazine was released into air, 11 tons into public water, 1 tons into sewers and 208 tons was transferred as wastes from the business institutions required to report their releases and transfer. In addition, it was estimated that 268 tons of hydrazine was released in one year from the business institutions in the business categories designated under the PRTR system but were exempted from notification. No estimation was made for the amounts of releases from the business categories outside the scope of the PRTR system and those from households and those from mobile sources. The PRTR system specifies that hydrazine comprises of hydrazine anhydride and hydrazine hydrate. Therefore, the amount of hydrazine hydrate is reported as the amount converted into hydrazine anhydride.

a. Release and transfer from the industries within the scope of PRTR system

The amounts of releases into the environmental media (air, water and land) and transfer by the designated industries summarized from the 2001 PRTR Data are shown in Table 4-3. METI/Japan and MOE/Japan (2003a) do not provide the amounts of releases by environmental media for the estimations of releases from the business institutions exempted from notification. The ratio for each environmental medium of the releases estimated for the business institutions exempted for notification is calculated based on the assumption that ratios of releases into the air, water and land were the same as those obtained by notification (NITE/Japan, 2003).

Table 4-3 Releases and transfer of hydrazine to environmental media by industries (tons/year)

Industries	By Notification					Notification Exempted			Total amount of releases by notification and by estimation	
	Release			Transfer		Release (estimated)[1)]				
	Air	Water	Land	Sewer	Wastes	Air	Water	Land	Total release[3)]	Ratio (%)
Electrical machinery and appliances	<0.5	1	0	0	<0.5	19	63	0	84	30
Waste disposal business	0	0	0	0	0	8	27	0	35	12
Chemical and allied products	2	9	0	1	113	5	15	0	31	11
Textile mill products	0	<0.5	0	0	0	6	19	0	25	9
Machine repair shops	-	-	-	-	-	3	10	0	13	4
Transportation equipment	-	-	-	-	-	3	9	0	11	4
Petroleum and coal products	0	<0.5	0	0	0	3	9	0	11	4
Ceramic, stone and clay products	-	-	-	-	-	3	8	0	11	4
Lumber and wood products	-	-	-	-	-	2	7	0	10	3
Other[2)]	1	<0.5	0	1	94	12	38	0	51	18
Total[3)]	3	11	0	1	208	63	205	0	282	100

(NITE, 2003)

1) Based on the assumption that ratios of releases into the air, water and land were the same as those of the releases obtained by notification, the amounts of releases from the business institutions exempted from notification were estimated

2) "Others" indicates the total release in the industries other than the above.

3) The total may not correspond with the sum of rounded values in each column of the table.

-: Not notified or estimated

The release and transfer of less than 0.5 tons was mentioned as "<0.5" without exception.

Based on the production volume and the emission factor in manufacturing sites of hydrazine in 2001 (Japan Chemical Industry Association, 2002), the amounts of releases into the air and water are estimated to be 434 kg and 7 tons per year, respectively (NITE/Japan, 2003). Therefore, from the 2001 PRTR Data, most of the releases of hydrazine from the business categories within the scope of PRTR system are

considered to occur not in the manufacture process but in the application process.

b. Releases from the non-designated industries, households and mobile sources

In the 2001 PRTR Data, the amounts of hydrazine releases from the industries outside the scope of the PRTR system, households and mobile sources are outside the scope of estimation required under PRTR (METI/Japan and MOE/Japan, 2003b).

4.3.2 Releases from other PRTR

The possible sources of hydrazine other than those included in the 2001 PRTR data are as follows. When hydrazine derivatives such as hydrazine hydrochloride are used as water treatment chemicals, hydrazine itself can be released into the environment. Farm products can absorb hydrazine, an impurity of plant growth regulators to prevent germination of onion, garlic and potato. Hydrazine is used as epoxy resin curing agent for inner coating of water utilities and water supply equipments, and hydrazine can be transferred to tap water. At present, hydrazine is designated as one of the inspection substances for the drinking water quality standard (enforced on April 1, 2004; no target value is established) by the Water Supply Law (MHLW/Japan, 2004). Therefore, the Japan Water Works Association specifies the elution from epoxy resin curing agent for inner coating of ductile cast iron pipes for drinking water as 0.005 mg/L and lower (Japan Water Works Association, 2004).

Other release sources are cigarette smoke (Liu et al., 1974) and nitrogen fixation by azotobacter (IARC, 1972).

Bayer (1993) reported the rare possibility that hydrazine remains in products that are treated with vapor containing hydrazine and explained that oxygen in the air degrades hydrazine in catalysis on the surface of paper, wood and fiber even if hydrazine is contained in vapor.

However, the detailed information about the above sources was not obtained in this investigation.

4.4 Estimated routes of releases

From the 2001 PRTR Data and the information that most of hydrazine is used as raw material for cellular blowing agents, can cleaning agents, and raw material for various industrial chemicals, it is considered that the main route of releases is discharges in the application process of using hydrazine or products containing hydrazine as raw materials. Since no quantitative data on hydrazine production from cigarette smoke and nitrogen fixation are available, these resources are not included in estimating release amounts.

As the scenario of acetaldehyde releases in Japan, it has been estimated that 65 tons of hydrazine is released annually into the air, and 216 tons into the water. Releases of residual hydrazine into the environment after processing at sewage treatment plants and waste disposal facilities are not considered for estimation of release amounts from sewage and wastes.

5. Environmental fate

5.1 Stability in the atmosphere

Hydrazine anhydride is highly hygroscopic liquid, and reacts with water in the atmosphere to form hydrazine monohydrate.

a. Reaction with OH radical

The reaction rate constant of hydrazine anhydride with OH radical is 6.1×10^{-11} cm^3/molecule-sec in the tropospheric air (U.S. NLM; HSDB, 2002). On the assumption of OH radical concentration of 5×10^5 to 1×10^6 molecule /cm^3, the half-life is calculated as 4 to 7 hours.

b. Reaction with ozone

The reaction rate constant of hydrazine anhydride with ozone is 3×10^{-17} cm^3/molecule-sec in the tropospheric air (Atkinson and Carter, 1984). On the assumption of ozone concentration of 7×10^{11} molecule /cm^3, the half-life is calculated as 9 hours.

c. Reaction with nitrate radical

No reports on reaction of hydrazine with nitrate radical were obtained in this investigation.

However, hydrazine anhydride is assumed to react rapidly with nitrogen oxides in the air (U.S. NLM: HSDB, 2002).

5.2 Stability in water

Hydrazine anhydride reacts immediately with water to form hydrazine monohydrate.

5.2.1 Abiotic degradation

As hydrazine has no chemical bonds that are subject to hydrolysis, it is not hydrolyzed in the aquatic environment. However, it has been reported that 90% of hydrazine anhydride contained in an aqueous solution at 6.41 mg/L was autoxidized by dissolved oxygen of 8.8 mg/L at 25°C for 60 days. The autoxidation rate depends on the concentrations of cupric and orthophosphate ions (GDCh BUA, 1998). Hydrazine auto-oxidizes in water and produces nitrogen and water (U.S. NLM:HSDB, 2002).

5.2.2 Biodegradation

Hydrazine is ranked as a “persistent substance” based on the result of the aerobic biodegradation study required under the Chemical Substance Control Law. The study result indicated that the degradation rate of hydrazine was 2% in biochemical oxygen demand (BOD) determination under the conditions of 100 mg/L of test substance concentration, 30 mg/L of activated sludge concentration and 4 weeks of test period. The degradation rate directly determined by ion chromatography (IC) was 0% (MITI/Japan, 1992).

Hydrazine in an aerobic condition was co-metabolized by nitrifying bacteria and degraded to nitrogen gas (Kane and Williamson, 1983).

No reports on anaerobic biodegradation of hydrazine were obtained in this investigation.

5.2.3 Removal in sewage treatment

Hydrazine was added into continuous sewage treatment system and then, hydrazine was completely degraded at concentrations of 1 mg/L and lower and was not detected in the treated water. However, at concentrations of 10 mg/L and above, hydrazine was not degraded in a chemical oxygen demand (COD) determination for several days. Furthermore, it has been reported that hydrazine inhibited nitrification by nitrifying bacteria at concentrations of 20 mg/L and above (Farmwald and MacNaughton, 1981).

5.3 Behavior in the aquatic environment

Hydrazine anhydride is hydrated in water to form hydrazine hydrate immediately. Considering soil adsorption coefficient (Koc) of 14 (anhydride, see Chapter 3), it is assumed that hydrazine is hardly adsorbed to suspended solids in water and sludge. Hydrazine is miscible with water and its vapor pressure is 1 kPa (monohydrate at 20°C) and Henry's constant is low (6.15×10^{-2} Pa･m^3/mol for anhydride at 25°C) (see Chapter 3).

Based on the information summarized here and in Section 5.2, it is not assumed that hydrazine released into the aquatic environment is eliminated by volatilization from the surface of water. Hydrazine is not hydrolyzed but easily oxidized by dissolved oxygen in the aquatic environment and degraded. Hydrazine at low concentrations can be eliminated by biodegradation, but this is slower than degradation by auto-oxidation.

5.4 Bioaccumulation

There is no bioaccumulation study of hydrazine required under the Chemical Substance Control Law. However, from the log Kow (octanol-water partition coefficient) of -0.16 for hydrazine anhydride (see Chapter 3), hydrazine is ranked as “no or low bioaccumulative substance” (MITI/Japan, 1992).

It has been reported that a bioconcentration factor (BCF) of hydrazine in guppy was 316 (Slonim and Gisclard, 1976).

6. Effects on organisms in the environment

6.1 Effects on aquatic organisms

6.1.1 Microorganisms

The toxicity studies of hydrazine for microorganisms are summerized in Table 6-1.

The toxicity of hydrazine to bacteria and protozoa has been reported and the lowest values in bacteria and protozoa were 0.01 mg/L as the 20-min EC_{50} for luminescence inhibition in marine luminescent bacteria *Photobacterium phosphoreum* (Yates, 1985) and 0.0017 mg/L as the 48-hr hazardous threshold (EC_5) for growth inhibition in flagellate (*Chilomonas paramaecium*) (Bringmann et al., 1980).

Table 6-1 Toxicity of hydrazine for microorganisms

Species	Tem-perature (°C)	Endpoint		Concentration (mg/L)	Reference
Bacteria *Pseudomonas putida* (*Pseudomonas* bacteria)	20	16-hr toxic threshold (EC_3) [1)]	Growth inhibition	0.019 (n) hydrazine hydrate	Bringmann & Kuhn, 1976, 1977a
Mycrocystis aeruginosa (blue green alga)	27	8-day toxic threshold (EC_3) [1)]	Growth inhibition	0.00008 hydrazine	Bringmann & Kuhn, 1976, 1978
Photobacterium phosphoreum K57 (marine photobacteria)	15	20-min EC_{50}	luminescence inhibition	0.01 (n) hydrazine	Yates, 1985
Activated sludge	ND	Toxic threshold	Inhibition of ammonia nitrification	<3 hydrazine	Farmwald & MacNaughton, 1981
Nitrobacter sp. (nitrite-oxidizing bacteria)	ND	10 days< Toxic threshold	Inhibition of substrate consumption	14.6 hydrazine	Kane & Williamson, 1983
Nitrosomonas sp. (ammonia-oxidizing bacteria)	ND			94.8 hydrazine	
Protozoa *Entosiphon sulcatum* (flagellate protozoans)	25	72-hr toxic threshold (EC_5)[2)]	Growth inhibition	0.93 (n) hydrazine hydrate	Bringmann, 1978
Chilomonas paramaecium (flagellate protozoans)	20	48-hr toxic threshold (EC_5)	Growth inhibition	0.0017 (n) hydrazine hydrate	Bringmann et al., 1980
Uronema parduczi (ciliate protozoans)	25	22-hr toxic threshold (EC_5)	Growth inhibition	0.24 (n) hydrazine hydrate	Bringmann & Kuhn, 1980

ND: No data available; (n): Nominal concentration

1) Concentration giving 3% effect compared to the control (EC_3); 2) Concentration giving 5% effect compared to the control (EC_5)

6.1.2 Algae

The toxicity studies of hydrazine for algae are summerized in Table 6-2.

In growth inhibition studies of hydrazine in green alga (freshwater), the 72-hr EC_{50} was 0.0061 mg/L and the NOEC was 0.001 mg/L in *Selenastrum capricornutum* (Harrah, 1978) and the 48-hr EC_{50} was 10 mg/L in *Chlorella* (Heck et al., 1963). In other growth inhibition studies, the 8-day toxicity threshold (EC_3) values were 0.005 mg/L in green alga *Scenedesmus*, (Bringmann and Kuhn, 1977a, 1978) and 0.00008 mg/L in blue green alga (Bringmann and Kuhn, 1976; 1978). However, endpoints of the studies were different from those of standard test guidelines including the OECD guideline, and the results could not be evaluated.

In marine algae, the 8-day EC_{50} was 0.0008 mg/L and the NOEC was 0.0005 mg/L in *Dunaliella tertiolecta* (Harrah, 1978).

In a non standard guideline study, growth inhibition as the 10-day EC_{50} and NOEC of three species of freshwater green alga *Selenastrum capricornutum*, marine green algae *Chlorella* and *Dunaliella tertiolecta*

were estimated in respective growing conditions (freshwater or marine) with oligotrophic and eutrophic cultures (*Selenastrum* under eutrophic condition: 8 days). The 10-day EC_{50} ranged from 0.0012 (*Dunaliella* under oligotrophic condition) to 0.0756 (*Selenastrum* under oligotrophic condition). The 10-day NOEC values of *Selenastrum, Chlorella* and *Dunaliella* were 0.0020, 0.0080 to 0.0202 and 0.0003 to 0.0008 mg/L, respectively. Hydrazine had the strongest hazardous effect on *Dunaliella*, followed by *Chlorella* and *Selenastrum* in order. No remarkable differences in the 10-day EC_{50} were observed between culture components, but the 10-day NOEC varied among culture components and the lowest values were found under oligotrophic conditions in all species (Scherfig et al., 1978 ; Dixon et al., 1979).

Table 6-2 Toxicity of hydrazine for algae

Species	Method/ Condition	Temperature (°C)	Endpoint		Concentration (mg/L)	Reference
Freshwater species						
Selenastrum capricornutum[1)] (green alga, *Scenedesmus* sp.)	Static	ND	72-hr EC_{50} 72-hr NOEC	Growth inhibition	0.0061 0.001 (a, n) hydrazine	Harrah, 1978
	Oligotrophic culture Closed	23±3	10-day EC_{50} 10-day NOEC	Growth inhibition	0.0756 0.0020 hydrazine	Scherfig et al., 1978; Dixon et al., 1979
	Eutrophic culture Closed		8-day EC_{50} 8-day NOEC		0.0353 0.0192 hydrazine	
Scenedesmus quadricauda (green alga, *Scenedesmus* sp.)	Static pH7.0	27	8-day toxic threshold (EC_3) [2)]	Growth inhibition	0.005 (n) hydrazine	Bringmann & Kuhn, 1977a, 1978
Chlorella pyrenoidosa (green alga, *Chlorella* sp.)	Static pH6.8-7.5	23	48-hr EC_{50} 48-hr EC_{100}	Growth inhibition	10 100 (n) hydrazine	Heck et al., 1963
Mycrocystis aeruginosa (blue green alga)	Static	27	8-day toxic threshold (EC_3)	Growth inhibition	0.00008 hydrazine	Bringmann & Kuhn, 1976, 1978
Marine species						
Chlorella stigmatophora (green alga, *Chlorella* sp.)	Oligotrophic culture Closed	23±3	10-day EC_{50} 10-day NOEC	Growth inhibition	0.0192 0.0080 hydrazine	Scherfig et al., 1978; Dixon et al., 1979
	Eutrophic culture Closed				0.0343 0.0202 hydrazine	
Dunaliella tertiolecta (green alga, *Dunaliella sp.*)	Oligotrophic culture Closed				0.0012 0.0003 hydrazine	
	Eutrophic culture Closed				0.0017 0.0008 hydrazine	

Species	Method/ Condition	Temperature (°C)	Endpoint		Concentration (mg/L)	Reference
	Static	ND	8-day EC_{50} 8-day NOEC	Growth inhibition	0.0008 0.0005 (a, n) hydrazine	Harrah, 1978

ND: No data available; (a, n): Test substance was determined but nominal concentration is described. (n): Nominal concentration, Closed system: a test container and water bath is closed with a cover such as a lid, and a headspace is kept. 1) Current scientific name: *Pseudokirchneriella subcapitata,* 2) Concentration giving 3% effect compared to the control (EC_3)

6.1.3 Invertebrates

The toxicity studies of hydrazine for invertebrates are summerized in Table 6-3.

The toxicity of hydrazine to crustacea (*Daphnia magna, Daphnia pulex*, amphipod, etc.) has been reported.

The 24-hr LC_{50} of hydrazine in *Daphnia magna* was 0.81 mg/L (Bringmann and Kuhn, 1977b) and the 24-hr EC_{50} (immobilization) was 2.3 mg/L (Bringmann and Kuhn, 1982).

In *Daphnia pulex*, the 24-hr LC_{50} was 1.16 mg/L (Heck et al., 1963), and the 24- and 48-hr EC_{50} (immobilization) values were 0.76 mg/L and 0.175 mg/L, respectively (Velte, 1984).

The 48-hr LC_{50} of hydrazine in one of scud (*Hyalella azteca*) was 0.04 mg/L (Fisher et al., 1980a) and this is the lowest value of toxicity to crustacea.

No reports on long-term toxicity of hydrazine to crustacea or toxicity to marine crustacea were obtained in this investigation.

Table 6-3 Toxicity of hydrazine for invertebrates

Species	Growth Stage	Method/ Condition	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concent-ration (mg/L)	Reference
Freshwater species								
Daphnia magna (crustacean, water flea)	<24 hours	Static, closed	20-22	286	7.6-7.7	24-hr LC_{50}	0.81 (n) hydrazine hydrate: purity: 80%	Bringmann & Kuhn, 1977b
		Static, closed	20	ND	8	24-hr EC_{50} Immobilization	2. 3 (n) hydrazine hydrate: purity: 80%	Bringmann & Kuhn, 1982
Daphnia pulex (crustacean, water flea)	ND	Static	ND	ND	8.2	24-hr LC_{50}	1.16 (n) hydrazine	Heck et al., 1963
	24 hours	U.S. EPA, Semi -static, closed	20	35	7.1-7.2	24-hr EC_{50} 48-hr EC_{50} Immobilization	0.76 0.175 (m) hydrazine hydrate:	Velte, 1984

Species	Growth Stage	Method/ Condition	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concent-ration (mg/L)	Reference
Hyalella azteca (crustacean, amphipod)	ND	APHA[1)] Static	22.5	132	7.3-8.7	48-hr LC_{50}	0.04 (m) hydrazine purity: 95%	Fisher et al., 1980a
Asellus sp. (crustacean, aquatic sowbug)	ND	APHA[1)] Static	23-24	96	6.5-7.8	72-hr LC_{50}	1.3 (m) hydrazine purity: 95%	

ND: No data available; (n): Nominal concentration, (m): Measured concentration
Closed system: a test container and water bath is closed with a cover such as a lid, and a headspace is kept.
1) Test guideline by the American Public Health Association

6.1.4 Fish

The toxicity studies of hydrazine for fish are summerized in Table 6-4, and the effects of hydrazine on the developmental stages are shown in Table 6-5.

The acute toxicity of hydrazine to freshwater fish has been studied in fathead minnow, bluegill, goldfish, guppy, zebra fish, channel catfish, etc. The 96-hr LC_{50} values of hydrazine ranged from 0.61 to 7.7 mg/L and the lowest value was 0.61 mg/L in guppy.

The differences in toxicity of hydrazine were studied under various test conditions. Hunt et al. (1981) compared the 96-hr LC_{50} in bluegill between flow-through and static conditions. No significant difference in toxicity was observed at 21°C, but at 10°C, the 96-hr LC_{50} values were 1.6 mg/L in the flow-through condition and 7.7 mg/L in the static condition, showing that the toxicity to bluegill in the former condition is stronger than that in the latter one.

The toxicity to zebrafish in different developmental stages was examined. The 24-hr LC_{50} values were 1.17 mg/L in 5 day-old fry but 3.18 mg/L in 3 month-old adult fish. The sensitivity of fry to hydrazine was three times as high as that of adult fish (Proteau et al., 1979). Guppy was exposed to hydrazine in hard (400 to 500 mg $CaCO_3$/L) and soft (20 to 25 mg $CaCO_3$/L) water. The 96-hr LC_{50} values were 0.61 mg/L in soft water and 3.85 mg/L in hard water. The toxicity was stronger in the soft water than in the hard water (Slonim, 1977).

The acute toxicity of hydrazine to marine fish was 3.4 mg/L as the 96-hr LC_{50} in three-spined stickleback (Harrah, 1978). No reports on long-term toxicity of hydrazine to fish were obtained.

In a 24-hr and 48-hr exposure study to hydrazine in mid-cleavage eggs of fathead minnow, ventricular enlargement and scoliosis were observed in 24-hr exposed embryos at a concentration of 0.01 mg/L and above, and slightly to moderately abnormal heart beat, decreased hemoglobin level and body movement were found in embryos at 0.1 mg/L. Hydrazine at 1.0 mg/L and above enhanced these responses and symptoms and anomaly, furthermore, suppressed the expression of body color and arrested development. Most of embryos exposed to hydrazine at 1.0 mg/L for 48 hours did not survive. Surviving embryos showed lack of pigmentation, poor development, tubular heart, lack of hemoglobin and abdominal distension (Henderson et al., 1981).

Henderson et al. (1983) conducted a 48-hr exposure study to hydrazine in rainbow trout embryos. The embryos showed dose-dependent symptoms of jaw-fitting failure, palatal anomaly and lack of body movement up to 5 mg/L, but no effects on mortality, heart rate, hatching rate and hatching period were found. After exposure at 1 and 5 mg/L, poor muscular and bone development of larvae was observed but no effects on mortality and heart rate were found (Table 6-5).

Table 6-4 Toxicity of hydrazine for fish

Species	Growth Stage	Method/ Condition	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concent-ration (mg/L)	Reference
Acute toxicity: freshwater species								
Danio rerio (zebra fish)	5 days	AFNOR[1)] 90303 Static	26±0.5	110	7.8	24-hr LC_{50}	1.17 (n) hydrazine hydrate	Proteau et al., 1979
	3 months		20±1	110	7.6-8.2	24-hr LC_{50}	3.18 (n) hydrazine hydrate	
Pimephales promelas (fathead minnow)	adult	U.S. EPA 600/ 3-75-009 Flow-through	20	31.2	7.0	24-hr LC_{50} 48-hr LC_{50} 96-hr LC_{50}	7.63 6.19 5.98 (m) hydrazine hydrate	Velte, 1984
Lepomis macrochirus (bluegill)	51-74 mm 2.3 g	Static	20-24	240-292	7.2-8.4	96-hr LC_{50}	1.08 (m) hydrazine	Fisher et al., 1978
	ND	Flow-through	23-24	164	7.8-7.9	96-hr LC_{50}	0.43 (m) hydrazine	Fisher et al., 1980b
		Static		239	7.1-7.9		0.1 (m) hydrazine	
	ND	Flow-through	10	160-190	6.7-8.0	96-hr LC_{50}	1.6 (m) hydrazine	Hunt et al., 1981
			15.5				1.0 (m) hydrazine	
			21				1.2 (m) hydrazine	
		Static	10				7.7 (m) hydrazine	
			15.5				3.8 (m) hydrazine	
			21				1.7 (m) hydrazine	

Species	Growth Stage	Method/ Condition	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concent-ration (mg/L)	Reference
Poecilia reticulates (guppy)	4 months 24-36 mm 0.1-0.25 g	Static	22-24	400-500	7.8-8.2	96-hr LC_{50}	3.85 (m) hydrazine	Slonim, 1977
				20-25	6.3-6.9	96-hr LC_{50}	0.61 (m) hydrazine	
Carassius auratus (goldfish)	ND	Static aeration	ND	ND	8.2-8.5	24-hr LC_{50} 48-hr LC_{50}	4.2 2.8 (n) hydrazine	Heck et al., 1963
	8 g	AFNOR[1)] 90303 Static	19±1	245	8.1-8.5	24-hr LC_{50}	1.48 (m) hydrazine hydrate	Proteau et al., 1979
Leuciscus idus (cyprinidae, *Leuciscus* sp)	1.52 ±0.3 g	DIN[2)] 38412-15 Static	20±1	268±54	7-8	48-hr LC_{50}	0.75 (n) hydrazine	Juhnke & Ludemann, 1978
Rutilus rutilus (cyprinidae, roach)	8 g	ANOR[1)] 90303 Static	19±1	245	8.1-8.5	24-hr LC_{50}	0.85 (n) hydrazine hydrate	Proteau et al., 1979
Lepomis cyanellus (centrarchidae, green sunfish)	ND	Static	ND	ND	8.2-8.5	48-hr LC_{50}	5.1 (n) hydrazine	Heck et al., 1963
Micropterus salmoides (large mouth bass)	ND	Static	ND	ND	8.2-8.5	48-hr LC_{50}	3.6 (n) hydrazine	
Ictalurus punctatus (channel catfish)	ND	Static	ND	ND	8.2-8.5	48-hr LC_{50}	1.6 (n) hydrazine	
	7.97 cm 4.76 g	APHA[3)] Static	22.0-22.5	106-113	6.8-8.6	96-hr LC_{50}	1.00 (m) hydrazine purity: 95%	Fisher et al., 1980a
Notomigonus crysoleucas (golden shiner)	5.8 cm 1.41 g	APHA[3)] Static	21.0-21.5	140-173	6.5-7.7	96-hr LC_{50}	1.12 (m) hydrazine purity: 95%	
Acute toxicity: marine species								
Gasterosteus aculeatus (three-spined stickleback)	ND	Semi-static	14-15.5	ND	7.7-8.0	96-hr LC_{50}	3.4 (a, n) hydrazine	Harrah, 1978

ND: No data available; (a, n): Test substance was determined but nominal concentration is described. (n): Nominal concentration, (m): Measured concentration

1) Test guideline by the Association Française de Normalisation,

2) Test guideline by the Deutsches Institut fur Normung,

3) Test guideline by the American Public Health Association

Table 6-5 Toxicity of hydrazine for fish in the developmental stages

Species	Growth Stage/ number of animals	Method/ Condition /Period	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Results	Reference
Pimephales promelas (fathead minnow)	Mid-cleavage 200 eggs/group	hydrazine 0, 0.01, 0.1, 1.0 mg/L 24 or 48 hours exposure	21	150	7-7.5	0.01 mg/L and above: 24-hour exposure: Embryos-ventricular hypertrophy, scoliosis 0.1 mg/L: 24-hour exposure: Embryos- slightly to moderately abnormal heart beat, decreased hemoglobin level and body movement (measured by motion of eye pigment) 1 mg/L: 24-hour exposure: Embryos-increased symptoms and anomaly, suppressed expression of body color and arrested development 48-hour exposure: Larva- retarded growth and following death Surviving embryos- lack of pigmentation, poor growth, tubular heart, lack of hemoglobin, changes in body movement and abdominal distension	Henderson et al., 1981
Oncorhynchus mykiss (rainbow trout)	Embryo	hydrazine nominal concentration: 0, 1, 5 mg/L 48 hours exposure: Flow-through	11.5-12	15	7-7.5	1 mg/L and above: Embryos- dose-dependent jaw-fitting failure, palatal anomaly and lack of body movement, (no effects on mortality, heart rate, hatching rate and hatching period) Larva-poor muscular development and bone growth 5 mg/L: Embryos-death	Henderson et al., 1983

6.1.5 Other aquatic organisms

The toxicity studies of hydrazine for other aquatic organisms are summerized in Table 6-6, and the

effects of hydrazine in the developmental stages are shown in Table 6-7.

In a study of hydrazine in two species of salamander larvae, the 96-hr LC_{50} was 4.1 mg/L in hard water (400 to 500 mg $CaCO_3$/L) and 2.1 mg/L in soft water (20 to 25 mg $CaCO_3$/L) (Slonim, 1986). In a study of hydrazine in African clawed frog larvae, the 120-hr survival rates in 0.01 and 0.1 mg/L were 100% and 87%, respectively, but at 2 mg/L and above, all larvae died 24 to 48 hours after exposure (Greenhouse, 1976a).

To examine teratogenicity of hydrazine, African clawed frog embryos were exposed for 24 to 48 hours and observed for 10 days. Tail curvature, double tails (rare), microcephaly, cyclopia, edema on the body surface, head or fin and spinal overgrowth were found in larvae at 10 mg/L. At 25 mg/L and above, all embryos showed anomaly. The sensitivity was highest in neurulation-stage embryos (Greenhouse, 1976c). The NOEC for teratogenicity was 1 mg/L (Greenhouse, 1975, 1976b).

In African clawed frogs exposed with hydrazine in cleavage to hatch stages, the incidence rates of anomaly in hatching eggs at concentrations of 10 and 25 mg/L were 32% and 100%, respectively. The EC_{50} for teratogenicity (concentration inducing anomaly in 50% of animals) was 12.5 mg/L (Greenhouse, 1976b, 1977).

Table 6-6 Toxicity of hydrazine for other aquatic organisms

Species	Growth Stage	Method/ Condition	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concent-ration (mg/L)	Reference
Ambystoma opacum/ *Ambystoma maculatum* (amphibian, one of salamander)	Larva	Static	22.4-24	400-500	7.8-8.2	24-hr LC_{50}	>10	Slonim, 1986
						48-hr LC_{50}	8.0	
						96-hr LC_{50}	4.1	
				20-25	6.3-6.9	24-hr LC_{50}	>10	
						48-hr LC_{50}	5.2	
						96-hr LC_{50}	2.1 (n) hydrazine sulfate	
Xenopus laevis (African clawed frog)	Larva	ND	ND	ND	ND	120-hr surviving rate 100%	0.01	Greenhouse, 1976a
						87%	0.1	
						0% (24 to 48-hr after)	2 mg/L and above	

(n): Nominal concentration

Table 6-7 Toxicity of hydrazine for other aquatic organisms in the developmental stages

Species	Growth Stage / number of animals	Method/ Condition / Period/ Test article	Tem-perature (°C)	Hardness (mg $CaCO_3$/L)	pH	Results	Reference
Xenopus laevis (African clawed frog)	Embryo 50-150 embryos/L Static	Teratogenicity study hydrazine 0, 0.1, 1.0, 10, 15, 20, 25 mg/L 24 to 48 hours exposure Static Prior to exposure, the egg membrane was removed. 10 days observation Nominal concentration	ND	ND	7.7-8.6	10 mg/L: Larvae-tail curvature, double tails (rare), microcephaly, cyclopia, edema (body surface, head and fin), and spinal overgrowth 25 mg/L and above All embryos- anomaly (anomaly rate of the control group: 2-6%) Exposure in neurulation stage embryos induced anomaly. NOEC (teratogenicity): 1 mg/L	Greenhouse, 1975, 1976b, c
	ND	hydrazine Nominal concentration: 0, 0.1, 1.0, 10, 15, 20, 25 mg/L Exposure in cleavage to hatch stages	ND	ND	ND	Anomaly rate in hatching eggs 10 mg/L: 32% 15 mg/L: 83% 20 mg/L: 99% 25 mg/L: 100% ED_{50}[1)]: 12.5 mg/L	Greenhouse, 1976b, 1977

ND: No data available, 1) Estimated concentration inducing anomaly in 50% of animals.

6.2 Effects on terrestrial organisms

6.2.1 Microorganisms

No reports on toxicity of hydrazine in terrestrial microorganisms (soil bacteria and fungi) were obtained in this investigation.

6.2.2 Plants

The toxicity studies of hydrazine for plant are summerized in Table 6-8.

Heck et al. (1983) added hydrazine in hydroponic solutions and fumigated hydrazine to investigate the effects on seed germination and germ growth.

Seeds of squash, peanut and corn were immersed in the hydrazine solution at concentrations of 0 to 1,000 mg/L at 30°C for 48 hours. At the highest concentration, germination of peanut and corn seeds was suppressed and germ growth was also suppressed in squash at doses of 10 mg/L and above, in corn at doses

of 100 mg/L and above, and in peanut at doses of 1,000 mg/L.

Cotton buds 16 days after germination were cultured in a hydroponic solution containing hydrazine at concentrations of 0 to 1,000 mg/ m^3 for 9 days. At concentrations of 50 mg/L and above, foliar dehadration without chlorosis or necrosis was observed after 9 days of exposure and at concentrations of 300 mg/L and above, death was found within 24 hours of expoure.

Furthermore, soybean, *Vigna sinensis*, *Phaseolus vulgaris*, cotton, chicory, alfalfa and squash were exposed to hydrazine vapor at concentrations of 0 to 100 mg/L for 4 hours. In all species exposed to hydrazine at 30 mg/m^3 for 2 to 24 hours, withered leaves were observed and then spread over the whole and at this concentration, *Phaseolus vulgaris* and chicory died. At concentrations of 30 mg/m^3 and above, soybean and alfalfa also died. All of surviving plants recovered from 6 days after exposure.

Table 6-8 Toxicity of hydrazine for plant

Species	Test condition	Concentration	Results	Reference
Cucurbita pepo (one of squash)	30°C, 48 hours immersion	hydrazine 0-1,000 mg/L	Suppression of germination: ≥10 mg/L	Heck et al., 1963
Arachis hypogaea (peanut)			Suppression of germination: 1,000 mg/L	
Zea mays (corn)			Suppression of germination: ≥100 mg/L	
Gossypium hirsutum (cotton)	Hydroponic culture at 22-29°C (buds 16 days after germination)	hydrazine 0-1,000 mg/L Added to culture solutions	Foliar dehadration without chlorosis or necrosis: Exposure period 50 mg/L: 9 days 300 mg/L and above: within 24 hours Death: Exposure period 300 mg/L: 48 hours 300 mg/L and above: within 30 hours	
Glycine max (soybean)	exposure to vapor 4 hours	hydrazine 0-100 mg/m^3air	30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole 30mg/m^3 and above: Death, surviving plants recovered 6 days after exposure.	
Vigna sinensis (black eyed bean)			30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole Surviving plants recovered 6 days after exposure.	
Phaseolus vulgaris (kidney bean)			30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole Surviving plants recovered 6 days after exposure.	
Gossypium hirsutum (cotton)			30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole Surviving plants recovered 6 days after exposure.	
Cichorium endivia (one of chicory)			30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole Surviving plants recovered 6 days after exposure.	

Species	Test condition	Concentration	Results	Reference
Medicago sativa (alfalfa)			30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole 30mg/m^3 and above: Death Surviving plants recovered 6 days after exposure.	
Cucurbita pepo (one of squash)			30 mg/m^3: 2 to 24 hours exposure: withered leaves, and spread-out to the whole Surviving plants recovered 6 days after exposure.	
Sorghum bicolor (sorghum)	pH8.5 (borate buffer), 25°C, 24 hours immersion and 0.5 hour washing of seeds	hydrazine hydrate 0, 160.3, 320.5, 480.8, 641, 961.5 mg/L	7 days after: dose-dependent decreases in germination rate, main root length, seed size and coleoptile size	Reddy & Smith, 1984
Oryza sativa (rice)	pH8.5 (borate buffer), 26±1°C, 24 hours immersion and 0.5 hour washing of seeds	hydrazine hydrate 0, 160.3, 480.8, 961.5 mg/L	480.8 mg/L: decrease in seed size Expression of chlorophyll variance: 160.3 mg/L: 0.21% 480.8 mg/L: 0.33% 961.5 mg/L: 0.94%	Reddy et al., 1974
Cicer arietinum (garbanzo bean)	pH7 (borate buffer), 25±2°C, Seed immersion: 6 hours	hydrazine hydrate 0, 0.1%	Decrease in germination rate 3 days after (47%, control 97%), decrease in seed size, damaged germ	Farook & Nizam, 1979
Zea mays (corn)	Seed immersion: 23 hours	hydrazine hydrate 0, 288.5 mg/L	Decrease in germination rate 5 days after (58%, control 96%)	Chandra & Reddy, 1971
Avena sativa (oat)	pH8.5, Seed immersion: 24 hours	hydrazine hydrate 0, 96.2, 160.3 mg/L	96.2 mg/L and above: Lower germination rate/surviving germ rate/bearing rate compared with the control	Kak & Kaul, 1975
Ricinus communis (castor bean)	26±1°C, Seed immersion: 5-6 hours	hydrazine sulfate 0, 0.1%	Delay in anthesis (lower seed setting rate compared with the control), increase in racemed flowers	Athma & Reddy, 1985

6.2.3 Animals

The toxicity studies of hydrazine for animal are summerized in Table 6-9.

Nematode (*Caenorhabditis briggsae*) cultured in peptone-yeast extract/liver medium was exposed to hydrazine hydrate for 6 days. The EC_{50} of the number of offspring was 540 mg/L (nominal concentration (Kampfe et al., 1986).

Table 6-9 Toxicity of hydrazine for animal

Species	Method	Temperature (°C)	Hardness (mg $CaCO_3$/L)	pH	Endpoint	Concentration (mg/L)	Reference
Caenorhabditis briggsae (nematode)	Culture with peptone-yeast extract/ liver medium	ND	ND	ND	6-day EC_{50} The number of offspring	540 (n) hydrazine hydrate	Kampfe et al., 1986

ND: No data available; (n): Nominal concentration

6.3 Summary of effects on organisms in the environment

Many studies have been conducted to assess the hazardous effects of hydrazine on environmental organisms using indices including growth inhibition, mortality, immobilization, growth, anomaly and germination.

The lowest toxicity values of hydrazine in bacteria and protozoa are 0.01 mg/L for bioluminescence inhibition in marine photobacteria and 0.0017 mg/L for growth inhibition in flagellate, respectively.

In a growth inhibition study of hydrazine in algae, the 72-hr EC_{50} was 0.0061 mg/L in *Selenastrum capricornutum.* The 72-hr NOEC was 0.001 mg/L in *Selenastrum capricornutum* and the 8-day NOEC was 0.0005 mg/L in *Dunaliella tertiolecta.*

The acute toxicity of hydrazine to invertebrates is reported in freshwater crustacea, water fleas (*Daphnia magna*, *Daphnia pulex* and one of scud). The 24-hr EC_{50} of immobilization in water flea ranged 0.76 to 2.3 mg/L, and the 48-hr EC_{50} was 0.175 mg/L, and the 48-hr LC_{50} in one of amphipod (*Hyalella azteca*) was 0.04 mg/L. No reports on long-term toxicity of hydrazine were obtained.

The acute toxicity of hydrazine to fish has been studied in freshwater fish, i.e., fathead minnow, bluegill, goldfish, zebrafish, guppy, and channel catfish. The 96-hr LC_{50} of hydrazine ranged from 0.61 to 7.7 mg/L and the lowest value was 0.61 mg/L in guppy. The acute toxicity of hydrazine to marine fish was 3.4 mg/L as the 96-hr LC_{50} in three-spined stickleback. No reports on long-term toxicity of hydrazine were obtained.

In terrestrial organisms, studies of germination, growth inhibition, seed-setting inhibition and death in plants including squash, corn, peanut, sorghum, rice, chick-pea and oat have been reported. In terrestrial animals, the 6-day EC_{50} for the number of offspring was 540 mg/L in nematode.

Effects on anomaly in fish and amphibian have been reported. In 24-hr exposure to fathead minnow embryos at concentrations of 0.1 to 0.01 mg/L, lack of pigmentation, poor development, scoliosis, changes in body motion, abdominal distension and death were observed. In 48-hr exposure to rainbow trout embryos at concentrations of 1 to 5 mg/L, jaw-fixing failure, palatal anomaly and lack of body activity were found. In exposure of hydrazine to African clawed frogs in cleavage to hatch stages, the incidence rates of anomaly in hatching eggs at concentrations of 10, 20 and 25 mg/L were 32%, 99% and 100%, respectively.

Although formal classification criteria is not used in this investigation, it can be considered that the acute toxicity values of hydrazine to aquatic organisms algae, crustacean and fish is corresponding to the GHS acute toxicity hazard category I (very toxic).

The lowest value of toxicity in aquatic organisms is 0.0005 mg/L as the 8-day NOEC for growth inhibition in marine alga, *Dunaliella. tertiolecta*.

7. Effects on human health

7.1 Kinetics and metabolism

Studies on the kinetics and metabolism of hydrazine to experimental animals are summarized in Table 7-1 and the metabolic pathway of hydrazine is shown in Figure 7-1.

a. Absoption

Hydrazine is absorbed rapidly via inhalation, oral and dermal routes. Absorption of hydrazine via each administration route is summerized below.

a-1. Inhalation exposure

Rats (6 animals/group) were exposed by inhalation to hydrazine in a nose-only chamber for 1 hour at doses of 10, 60 and 500 ppm.The absorption rates were estimated from urinary excretion amounts of hydrazine and its metabolites within 48 hours after administration to be from 8.4% to 29.5%. As the amounts of excretion in the feces and expired air and tissue distribution were assumed high, actual absorption rates were considered to be much higher than these values (Llewellyn et al., 1986).

In a 6-hour inhalation exposure study of hydrazine in SD rats at doses of 17 to 32 mg/m^3, the blood concentration was rapidly elevated for the first 1 hour, however varied thereafter. In a 6-hour inhalation exposure study of hydrazine at doses of 15 to 20 mg/m^3, the blood concentration was 0.64 μg/mL (Dost et al., 1981).

a-2. Oral administration

In oral administration of hydrazine hydrate to rats (15 animals/group) at single doses of 3, 9, 27 and 81 mg/kg, the absorption rates through the gastrointestinal tract, which were estimated from the amounts of urinary excretion of hydrazine and its metabolites for 24 hours after administration, ranged from 19% to 46%. The plasma concentration reached the peak (Cmax) at 10 minutes after administration at 27 mg/kg and at 90 minutes after administration at 81 mg/kg, respectively. The maximum concentrations in the liver were detected at 10 to 30 minutes after administration (Tmax) at all doses. At 3 and 9 mg/kg, the liver concentrations were higher than the plasma concentrations. The ratio of the plasma concentration to the liver concentration and the percentages of hydrazine and acetylhydrazine concentrations to given doses were decreased dose-dependently (Preece et al., 1992b). Some of metabolites could not be detected by GC/MS methods within 24 hours. Therefore, actual absorption rates through the gastrointestinal tract were considered higher than the range between 19% and 46% (Preece et al., 1992a).

In rats orally given hydrazine hydrate at 0.7 and 3.5 mg/kg, the blood concentration reached the peak at 15 minutes after administration (Bayer, 1986).

a-3. Dermal application

In a single dermal application study of hydrazine in anesthetized dogs (mongrel) at doses of 96 to 480 mg/kg (the shaven skin of the chest: approximately 300 cm^2, non-occlusive application), dimethylhydrazine was detected in the arterial blood at 30 seconds after administration. The plasma concentrations varied

individually and reached the peak approximately 60 mintues after administration and were increased dose-dependently (Smith and Clark, 1972). In a similar study in rabbits, the blood concentration reached the peak 50 to 90 minutes after administration and the absorption rate was 86% of given dose (Keller et al., 1984). In F344 rats exposed to hydrazine vapor in an inhalation chamber system, the dermal penetration constant was estimated to be 6×10^{-5} cm/hour, which was similar to that of water vapor (McDougal et al., 1986).

a-4. Subcutaneous administration

In male NMRI mice subcutaneously injected with hydrazine sulfate at a dose of 150 mg/kg, the blood hydrazine concentration reached the peak 15 minutes after administration (Braun, 1976).

b. Distribution

In an oral study of hydrazine in rats at doses of 2.9 to 81 mg/kg, hydrazine concentrations in the plasma and liver reached the peak within 30 minutes after administration, and the plasma concentration ranged from 0.3 to 10 μg/mL and the liver concentration from 0.6 to 6 μg/mL. The liver concentration was 5 times as high as the plasma concentration 24 hours after administration, however, monoacetylhydrazine, a metabolite, was not detected. The liver concentration was not dose-dependently increased, and the saturation was suggested (Preece et al., 1992b).

In an oral (gavage) administration study of hydrazine in rats at 0.7 and 3.5 mg/kg, the blood half-lives were 35 and 90 minutes, respectively. In an oral (via drinking water) study of hydrazine in mice and rats at 10 and 50 ppm for 20 days, the blood concentration at 10 ppm was around the detection limit (13 ng/mL) in rats and mice, and those at 50 ppm were 48 ng/mL in rats and 32 ng/mL in mice (Bayer, 1986).

In male SD rats, hydrazine was subcutaneously administered at a dose of 60 mg/kg and the hydrazine concentration (not including metabolites) was measured at 2 hours and 20 hours after administration. The renal concentration showed the highest (56 μg/g tissue) among the organs measured at 2 hours after administration and hydrazine was distributed almost evenlly in other organs (5.5 to 18.6 μg/g, exception: 0.8 μg/g adipose tissue). By 20 hours after administration, the tissue concentrations were reduced, indicating 8.1 μg/g in the kidney, 0.5 to 1.9 μg/g in other tissues and 0.1 μg/g in adipose tissue. No difference in the order of concentration in organs was found between 2 and 20 hours (Dambrauskas and Cornish, 1964).

In male Wistar rats, hydrazine sulfate (^{15}N-labeled hydrazine hydrate was used as internal standard and measured using GC/MS methods) was subcutaneously administered at a dose of 40 mg/kg and the concentration in organs was measured 0.5, 1, 2, 4 and 8 hours after treatment. At 0.5 hours after administration, the concentrations in the kidney, liver and lung reached the peak, especially the kidney showed a high value compared with other organs (Kaneo et al., 1984). In a subcutaneous study in rats at a dose of 9.9 mg/kg, hydrazine was rapidly distributed and the concentrations in the liver, lung, plasma and kidney reached the peak at 30 minutes after administration (Kaneo et al., 1984).

Therefore, it is considered that hydrazine is rapidly distributed in all organs and not preferentially accumulated in any organs or tissues at a single dose (IPCS, 1987).

In an intravenous study of hydrazine in rats at a dose of 5.1 mg/kg, 0.5 to 1 μg/g of hydrazine was detected in the brain (Matsuyama et al., 1983).

In an intraperitoneal study of ^{15}N-labeled hydrazine in SD rats at a dose of 32 mg/kg, the blood concentration was decreased biphasically with alpha-phase half-life of 0.74 hour and beta-phase half-life (slow phase) of 26.9 hours. The blood concentration of hydrolytic metabolites of hydrazine reached the peak at 30 minutes after administration and thereafter reduced rapidly (Dost et al., 1981).

In an intravenous study of hydrazine hydrate in male rabbits at a dose of 6.25 mg/kg, hydrazine was eliminated from the plasma during 0.25 to 2.56 hours after administration (Noda et al., 1983). It has been reported that the half-life in rat tissues ranged from 2.3 to 3.3 hours (Kaneo et al., 1984).

A biphasic elimination of hydrazine in the blood was reported also in a study of hydrazine sulfate in mice (Nelson and Gordon, 1982) and a study of hydrazine in rats (Dost, 1979).

c. Metabolism

Although there are minor differences in metabolism among the administration routes, the metabolic process and metabolites of hydrazine are similar in all administration routes (ATSDR, 1997). Hydrazine salts (hydrazine sulfate, hydrazine hydrochloride) and hydrate are considered to be existing as hydrazine free base in the body, and therefore, these compounds are evaluated assuming no difference in distribution, metabolism or excretion.

In rats and mice, approximately 20% to 30% of hydrazine given was eliminated as nitrogen gas within the first two hours and approximately 25% of given dose remained in the body as undetected (Nelson and Gordon, 1982; Springer et al., 1981).

Hydrazine is metabolized mainly by acetylation and free radical-producing process, and the hydrazine metabolism by each metabolic process is explained below.

In in vitro study, ^{15}N-labeled hydrazine sulfate was added to the hemolysate of male SD rats and the solution was incubated and at 1, 2 and 3 hours after, approximately 15%, 20% and 30% of given dose were detected as $^{15}N_2$, respectively (Dost, 1979).

c-1. Acetylation

^{15}N-hydrazine subcutaneously, intraperitoneally and intravenously administered was excreted in the urine as unchanged hydrazine and monoacetylhydrazine in dogs (McKennis et al., 1955) and rabbits (McKennis et al., 1959). After acid hydrolysis, a small amount of 1,2-diacetylhydrazine was detected in the urine of rabbits but not dogs.

In a subcutaneous study of hydrazine in mice and rats at a dose of 60 mg/kg, 48.3% (mouse) and 27.3% (rat) of given dose were recovered as hydrazine or monoacetylhydrazine from the urine (Dambrauskas and Cornish, 1964).

In an intraperitoneal study of hydrazine hydrate in rats at a dose of 5 mg/kg, approximately 14% was recovered from the urine. Percentages to given doses were 10.3% of hydrazine, 2.2% of monoacetylhydrazine and 1.2% of diacetylhydrazine (Wright and Timbrell, 1978).

It has been reported that in humans whose hydrazine metabolism (acetylation) is extremely slow due to

acetylation enzyme deficiency (slow acetylator), hydrazine absorbed might be accumulated in the plasma (Blair et al., 1985). It was also reported that one of the isozymes of *N*-acetyltransferase, NAT2, was related to hydrazine metabolism in humans and that 10% of the Japanese workers in a hydrazine production plant where they conducted their investigation were classified into slow acetylator (Koizumi et al., 1998).

In a 1-hour inhalation exposure study of hydrazine in rats at 10 to 500 ppm, unchanged hydrazine (2-10%), monoacetylhydrazine (1.74%) and diacetylhydrazine (4.5-11.4%) were excreted in the urine (Llewellyn et al., 1986).

In a similar study in rats that 30% hydrazine monohydrochloride was subcutaneously administered at doses of 2.6 and 5.1 mg/kg, hydrazine (19%), monoacetylhydrazine (10%) and diacetylhydrazine (small amount) were excreted in the urine (Perry et al., 1981).

In a subcutaneous study of hydrazine sulfate in male Wistar rats (3 to 9 rats/group) at a dose of 40 mg/kg, unchanged hydrazine (24% of given dose), monoacetylhydrazine (2.9%) and diacetylhydrazine (2.5%) were detected in the urine 48 hours after administration (Kaneo et al., 1984).

In a study in which hydrazine was administered at a high dose (427 mg/kg) (animal species was not specified), the following metabolites shown in Figure 7-1 were detected in the urine: monoacetylhydrazine, diacetylhydrazine, pyruvic acid hydrazone, urea and cyclic compound [1,4,5,6-tetrahydro-6-oxo-3-pyridazine-carboxyic acid (a reaction product of 2-oxoglutaric acid and hydrazine)] (Preece et al., 1991). This result suggests that hydrazine is acetylated and reacts with biomolecules *in vivo* (ATSDR, 1997). Nelson and Gordon (1982) reported that some of acid hydrolysis derivatives (same as metabolites identified by Preece et al., 1991) were identified.

c-2. Radical formation

Hydrazine is rapidly metabolized *in vitro* by rat liver microsomes (Timbrell et al., 1982). After incubation of oxyhemoglobin with hydrazine sulfate, radical formation was confirmed (Nelson and Gordon, 1982, Thornalley, 1984) and in the incubation of rat liver microsomes with hydrazine, free radical ($\cdot NHNH_2$, hydrazine radical) formation was confirmed as metabolic intermediate, diazene precursor in oxidation reaction of hydrazine. Therefore, it was considered that rat liver cytochrome P450 was involved in free radical formation (Noda et al., 1985a).

In perfusion culture study of isolated rat liver cells with 5 to 10 mM of hydrazine hydrate, various radicals including acetyl radical were detected in perfusion medium (Sinha, 1987). It was reported that hydrazine generated free radicals with purified NADPH-cytochrome P450 reductase (Noda et al., 1988).

This metabolic process required oxygen, NADPH and active enzyme, and was inhibited by cytochrome P450 inhibitor (GDCh BUA, 1996). In rats given cytochrome P450 inducers (phenobarbital and rifampicin), hydrazine metabolism in the liver was increased, in contrast, in rats given cytochrome P450 inhibitors (metyrapone and piperonyl butoxide), hydrazine metabolism in the liver was decreased (Noda et al., 1985b). Free radicals are considered to be related to mechanism of toxicity (Williams and Weisburger, 1991).

c-3. Another metabolic process

In the blood of dogs, ammoniagenesis with no increase in BUN concentration was confirmed (Floyd,

1980). However, following ^{15}N-hydrazine administration to rats, no ^{15}N-labeled ammonia was detected in the urine (Springer et al., 1981). Therefore, the blood ammonia detected in dogs was not derived from hydrazine but formed in other metabolic pathway on which hydrazine had an effect (Floyd, 1980; Springer et al., 1981).

An *in vitro* study showed that nitrogen (gas) was generated from hydrazine in oxidation catalysis by oxyhemoglobin in erythrocytes and oxygenase in liver microsomes (Clark et al., 1968; Nelson and Gordon, 1982; Springer et al., 1981). After nitrogen release in the first 15 to 30 minutes, nitrogen release was reduced and acetylation and carbonyl reactions were the main metabolic pathways producing urinary metabolites (Nelson and Gordon, 1982).

Hydrazine elimination in the expiration as nitrogen gas (N_2) was reported as follows:

To male SD rats, ^{15}N-labeled hydrazine sulfate was intraperitoneally administered at a dose of 130 mg/kg and the excretion of hydrazine metabolite N_2 via the lung were investigated. The amounts of ^{15}N-labeled N_2 in 0 to 24-hour expiration after administration were measured, which indicated that 15% of given dose in 30 minutes after administration and approximately 23% in 24 hours after administration was eliminated in the expiration. In a comparative study of intraperitoneal and other administration routes at the same dose, $^{15}N_2$ amount in the expiration within 4 hours after administration (no measurement at other time points) was higher in intravenous administration and lower in subcutaneous one, compared with intraperitoneal route (Dost, 1979).

^{15}N-Labeled hydrazine sulfate was intraperitoneally administered to male Swiss-Webster mice at a dose of 130 mg/kg to determine concentration of $^{15}N_2$ in the expiration air for 1 to 48 hours after administration. Within the first 1 to 2 hours after administration, approximately 20% of given dose was already eliminated in the expiration as $^{15}N_2$ and 48 hours after administration approximately 35% was excreted. The authors suggested that hydrazine is oxidized to N_2 in catalysis by oxyhemoglobin in the blood (Nelson and Gordon, 1982).

Hydrazine hydrate was intraperitoneally administered to male rats at doses of 15 to 80 mg/kg and the urine collected 0 to 6 and 6 to 12 hours after administration was analyzed using proton-NMR spectroscopy. In addition to the metabolites shown in Figure 7-1, methylamine was detected (Sanins et al., 1988). In their early NMR study, methylhydrazine and α-ketoglutarate hydrazone as hydrazine metabolites were detected (Sanins et al., 1986).

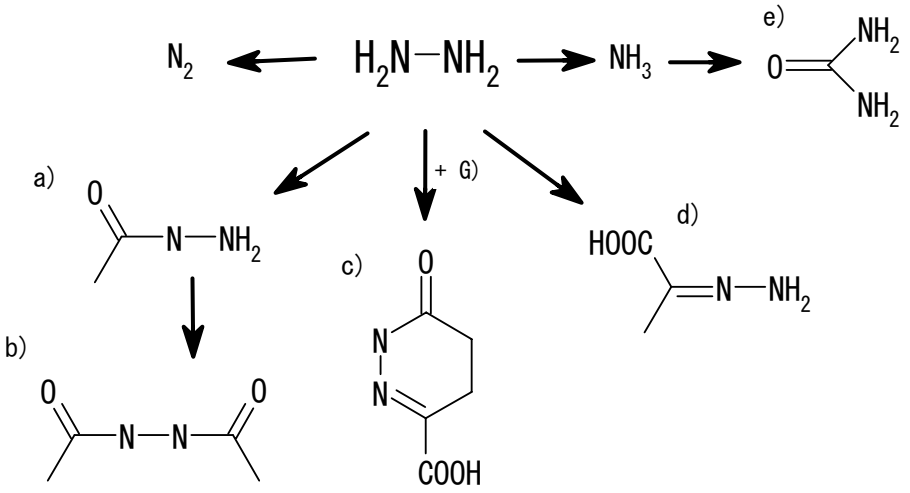


Figure 7-1 Metabolic pathway of hydrazine (Preece et al., 1991)

a) Acetylhydrazine, b) Diacetylhydrazine, c) 1,4,5,6-Tetrahydro-6-oxo-3-pyridazine-carboxyic acid, d) Pyruvic acid hydrazone, e) Urea, +G) 2-Oxoglutaric acid

d. Excretion

The results of urinary excretion study of hydrazine (or its hydrate and salts) in inhalation, oral, intravenous, dermal and subcutaneous administration routes are summarized below.

In a 1-hour inhalation exposure study of hydrazine in rats at 10, 60 and 500 ppm, 8.4% to 29.5% of the given doses were excreted in the urine 48 hours after the completion of exposure (Llewellyn et al., 1986). Most of the excretion occured during the first 24 hours. In an intravenous study of hydrazine in rats at single doses of 2 to 12 mg/kg, 13.8% to 37.3% of the given doses were excreted in the urine in 48 hours after administration (Llewellyn et al., 1986).

In an oral study of hydrazine in 3 rats at single doses of 0.7 and 3.5 mg/kg, the amount excreted in the urine as unchanged hydrazine 24 hours after administration was 13 and 17% of the given doses, respe ctively (Bayer, 1986).

In an oral study of hydrazine in SD rats at single doses of 3, 9, 27 and 81 mg/kg, 19% to 81% of the given doses were excreted in the urine within 24 hours after administration (Preece et al., 1992a). At doses of 3 and 9 mg/kg, 40% of the given dose was excreted in the urine as unchanged hydrazine and 5% as monoacetylhydrazine. At higher doses of 27 and 81 mg/kg, the excretion was decreased dose-depedently, and 20.5% and 17.5% of the given dose were excreted as hydrazine and 2.1% and 1.1% as monoacetylhydrazine, respectively, indicating higher excretion percentages in the low-dose group than those in the high-dose group (Preece et al., 1992b).

In a dermal application study (non-occlusive) of hydrazine in dogs (mongrel) at doses of 96 to 480 mg/kg (the shaven skin of the chest (approximately 300 cm^2), the urinary concentration of hydrazine reached the peak approximately 1.5 to 2 hours after administration at 118 mg/kg and below, but 4 hours

after administration at 128 mg/kg and above (Smith and Clark, 1972).

In a subcutaneous study of hydrazine in rats at a single dose of 9.9 mg/kg, 29.2% of the given dose was excreted in the urine 48 hours after administration and the percentages of monoacetylhydrazine and diacetylhydrazine were 2.9% and 2.5%, respectively (Kaneo et al., 1984).

Hydrazine was intravenously or subcutaneously administered to male Swiss ICR mice (3 to 8 animals/group) at doses of 40 to 100 mg/kg once or twice (administration interval: 0.5 hours) and the cumulative ratio of unchanged hydrazine excreted in the urine and the recovery rates from the animal body were measured at 0.5 to 48 hours after administration. At doses up to 60 mg/kg, approximately 50% of the given dose was excreted within 48 hours after administration. The recovery ratio of hydrazine were approximately 30% and 60% in the early period, but approximately 1% at 48 hours after and none of hydrazine was detected in the body 72 hours after administration (the detection limit unknown). At doses up to 60 mg/kg, the ratio of metabolized hydrazine ranged from 50% to 60% but 40% to 50% at higher doses. Hydrazine is mainly metabolized within 30 minutes after administration (Dambrauskas and Cornish, 1964).

In an intraperitoneal study of hydrazine in male SD rats at a dose of 32 mg/kg, the total amounts of hydrazine and its metabolites excreted in the urine were 5%, 3%, 1% and 0.25% of the given dose at 1, 6, 24 and 48 hours after administration, respectively. The cumulative excretion ratio in the urine were 28% as hydrazine and 24% as hydrolysis derivatives (Dost, 1979).

Hydrazine sulfate was intraperitoneally administered to male Swiss-Webster mice at a dose of 130 mg/kg to determine cumulative urinary excretion ratio and detect its metabolites 6 to 48 hours after administration. In 48 hours after administration, 15% of the given dose was excreted in the urine as free hydrazine or unstable compounds (no detailed description) and 25% as acid hydrolysates of hydrazine. In 6 hours after administration, approximately 10% and 15% were excreted in the urine, respectively (Nelson and Gordon, 1982).

Hydrazine hydrate was administered to rats at a dose of 5 mg/kg in different administration routes and the urinary excretion of unchanged hydrazine was compared during the period from 0 to 48 hours after administration. The recovery rates were 23% in oral administration, 51% in subcutaneous administration, 28% in intratracheal instillation and 7.5% in dermal application (Bayer, 1986).

In an intravenous (catheterization) study of hydrazine in rats at doses of 16 to 64 mg/kg, 20% of unidentified hydrazine metabolites and 30% of unchanged hydrazine were excreted in the urine and 25% of hydrazine nitrogen was eliminated into the expiration as nitrogen gas (Springer et al., 1981).

In an intrapetroneal study of hydrazine in rats at a dose of 32 mg/kg, only 1% of the given dose was excreted into the bile in 24 hours after administration, suggesting that biliary excretion was not a main excretion route of hydrazine (Dost et al, 1981).

Table 7-1 Kinetic and metabolism of hydrazine

Species sex/number of animals	Route	Dose	Results	Reference
Absorption				
Rat (6 animals /group)	Inhalation exposure (nose only) 1 hour hydrazine	10, 60, 500 ppm	Absorption rate estimated from urinary excretion amounts of hydrazine and its metabolites 48 hours after administration: 8.4-29.5% The amounts of excretion into the feces and expiration and tissue distribution were assumed high, therefore, actual absorption rate was considered much higher than these values.	Llewellyn et al., 1986
Rat SD	Inhalation exposure 6 hours hydrazine	17-32 mg/m^3	Blood hydrazine concentration: rapidly increased up to 1 hour after the beginning of exposure, but thereafter not constant.	Dost et al., 1981
	6 hours hydrazine	15-20 mg/m^3	Blood concentration: 0.64 μg/mL	
Rat (15 animals /group)	Oral Single hydrazine hydrate	3, 9, 27, 81 mg/kg	Estimated absorption rate based on urinary excretion amounts of hydrazine and its metabolites 24 hours after administration: 19-46%. Plasma Cmax[1]: 27 mg/kg: 10 minutes after 81 mg/kg: 90 minutes after 3 and 9 mg/kg: plasma concentration<liver concentration Plasma/liver concentration ratio, plasma concentration/given dose ratio, liver concentration/given dose ratio: decreased dose-dependently Tmax[2] liver: 10 to 30 minutes at all doses Some of metabolites could not be detected and unchanged hydrazine and metabolites remaining in the body were excreted in the urine even after the 24 hours urine collection period, therefore, actual absorption rates through the gastrointestinal tract were considered higher than the range between 19% and 46%.	Preece et al., 1992a, b
Rat	Oral hydrazine hydrate	0.7, 3.5 mg/kg	Tmax for blood hydrazine: 15 minutes after administration	Bayer, 1986
Dog (hybrid, anesthetized)	Percutanous exposure (shaven chest skin: approximately 300 cm^2 not covered) Single dose hydrazine	96-480 mg/kg	30 seconds after administration: dimethylhydrazine was detected in the arterial blood. Plasma concentration: reached the peak (Tmax) approximately 1 hour after administration and increased dose-dependently (considerable individual variance)	Smith & Clark, 1972
Rabbit	Percutanous exposure	ND	Tmax for blood hydrazine: 50 to 90 minutes Absorption rate: 86% of given dose	Keller et al., 1984

Species sex/number of animals	Route	Dose	Results	Reference
Rat F344	Percutanous exposure in vapor inhalation chamber system hydrazine	ND	Penetration constant: 6×10^{-5} cm/hour(low similar to water vapor)	McDougal et al., 1986
Mouse NMRI (male)	Dermal hydrazine sulfate	150 mg/kg	Tmax for blood hydrazine: 15 minutes	Braun, 1976
Distribution				
Rat	Oral Hydrazine	2.9-81 mg/kg	Plasma and liver hydrazine Tmax: within 30 minutes Cmax: Plasma: 0.3-10 μg/mL and above; Liver: 0.6-6 μg/mL) 24 hours after administration: Liver concentration was 5-fold of plasma one. Monoacetylhydrazine was not detected. Liver concentration was not dose-dependently increased (suggesting its saturation effect).	Preece et al., 1992b
Rat	Oral Single dose Hydrazine	0.7, 3.5 mg/kg	Half-life: 0.7 mg/kg: 35 minutes 3.5 mg/kg: 90 minutes	Bayer, 1986
Mouse Rat	Oral (via drinking water) 20 days hydrazine	10, 50 ppm	Blood hydrazine concentration 10 ppm: around the detection limit in rats and mice (13 ng/mL) 50 ppm: 48 ng/mL in rats, 32 ng/mL in mice	
Rat SD (male)	Subcutaneous hydrazine	60 mg/kg	Hydrazine concentration: 2 hours after administration: Max concentration in the liver (56 μg/g tissue) and distribution was almost equal in other tissues (5.5-18.6 μg/g, exception: 0.8 μg/g in adipose tissue) 20 hours after administration: 8.1 μg/g in the liver, 0.5-1.9 μg/g in other organs, 0.1μg/g in adipose tissue	Dambrauskas & Cornish, 1964
Rat Wistar Male (3-9 animals/group)	Subcutaneous hydrazine sulfate (internal standard: ^{15}N-labeled hydrate was used and measured using GC/MS) Determination point: 0.5, 1, 2, 4 and 8 hours after administration	40 mg/kg	Hydrazine concentration: kidney, liver and lung: T_{max} 0.5 hours kidney concentration was higher than others.	Kaneo et al., 1984
Rat	Subcutaneous	9.9 mg/kg	Hydrazine was distributed rapidly to tissues. Tmax of hydrazine concentration in the liver, lung, plasma and kidney: T_{max} 0.5 hours in all tissues	Kaneo et al., 1984
Rat	Intravenous Hydrazine	5.1 mg/kg	Brain: 0.5-1 μg/g distributed	Matsuyama et al., 1983

Species sex/number of animals	Route	Dose	Results	Reference
Rat SD	Intraperitoneal ^{15}N-labeled hydrazine	32 mg/kg	Blood concentration: decreased (biphasically) $T_{1/2}$ (α phase): 0.74 hour $T_{1/2}$ (β phase): 26.9 hours Blood concentration of hydrolytic metabolites of hydrazine: T_{max}: 0.5 hour and thereafter reduced rapidly	Dost et al., 1981
Rabbit Male	Intravenous hydrazine hydrate	6.25 mg/kg	Elimination from the plasma: 0.25-2.56 hours after administration	Noda et al., 1983
ND	ND	ND	Half-life in rat tissue: 2.3-3.3 hours	Kaneo et al., 1984
Mouse	ND hydrazine sulfate	ND	Hydrazine elimination from the blood: biphasic	Nelson & Gordon, 1982
Rat	ND Hydrazine	ND		Dost, 1979
Metabolism				
in vitro	Culture with the hemolysate of male SD rats ^{15}N-labeled hydrazine sulfate	ND	1, 2 and 3 hours after incubation, approximately 15%, 20% and 30% of given dose were detected as $^{15}N_2$.	Dost, 1979
Dog	Subcutaneous, intraperitoneal, intravenous hydrazine	ND	Urinary excretion: unchanged hydrazine or monoacetylhydrazine 1,2-diacetylhydrazine was not excreted.	McKennis et al., 1955
Rabbit	Subcutaneous, intraperitoneal, intravenous hydrazine	ND	Urinary excretion: unchanged hydrazine or monoacetylhydrazine After acid hydrolysis, a small amount of 1,2-diacetylhydrazine was excreted in the urine.	McKennis et al., 1959
Mouse Rat	Subcutaneous hydrazine	60 mg/kg	Urinary excretion: 48.3% (mouse) and 27.3% (rat) of given dose were excreted in the urine as unchanged hydrazine or monoacetylhydrazine and hydrazine did not remain in the body.	Dambrauskas & Cornish, 1964
Rat	Intraperitoneal hydrazine hydrate	5 mg/kg	Recovery rate from the urine (to given dose): approximately 14% (hydrazine 10.3%, monoacetylhydrazine 2.2%, diacetylhydrazine 1.2%)	Wright & Timbrell, 1978
Humans	ND	ND	Patients with acetylase enzyme (NAT1) deficiency (slow acetylator whose hydrazine metabolism via acetylation pathway is extremely slow) might accumulate hydrazine in the plasma.	Blair et al., 1985
Humans hydrazine production plant (Japanese worker)	ND	ND	Acetylase enzyme (NAT2) is related to human hydrazine metabolism. 10% of subjects were classified into slow acetylator.	Koizumi et al., 1998
Rat	Inhalation exposure 1 hour hydrazine	10-500 ppm	Urinary excretion (of given dose): hydrazine 2-10% monoacetylhydrazine 1.74% diacetylhydrazine 4.5-11.4%	Llewellyn et al., 1986

Species sex/number of animals	Route	Dose	Results	Reference
Rat	Inhalation exposure 1 hour 30% hydrazine monohydrochloride	2.6, 5.1 mg/kg	Urinary excretion (of given dose): hydrazine 19% monoacetylhydrazine 10% diacetylhydrazine small amount	Perry et al., 1981
Rat Wistar male (3-9 animals/group)	Subcutaneous hydrazine sulfate	40 mg/kg	Urinary excretion (of given dose 48 hours after administration): hydrazine 24% monoacetylhydrazine 2.9%, diacetylhydrazine 2.5%	Kaneo et al., 1984
in vitro	Addition to oxyhemoglobin hydrazine sulfate	ND	Radical formation was confirmed.	Nelson & Gordon, 1982; Thornalley, 1984
in vitro	Addition to rat liver microsome (addition to cytochrome P450) hydrazine	1 mM	In oxidation reaction of hydrazine by microsome, free radical ("·$NHNH_2$, hydrazine radical") might be formed as diazene (diimide) precursor, intermediate metabolite.	Noda et al., 1985a
in vitro	Addition to purified NADPH-cytochrome P450 reductase hydrazine	ND	Hydrazine was metabolized by purified NADPH-cytochrome P450 reductase and generated free radicals with purified NADPH-cytochrome P450 reductase. This reaction required NADPH and oxygen, was promoted by FAD (flavin adenine dinucleotide), inhibited by SOD (superoxide dismutase), but received no effect by carbon monoxide.	Noda et al., 1988
in vitro	Addition to perfusion culture of isolated rat liver cells and perfution hydrazine hydrate	5-10 mM	Various radicals including acetyl radical were detected in perfusion medium.	Sinha, 1987
in vitro	Rat liver microsome	ND	Rapid metabolism of hydrazine was confirmed (depending on oxygen, NADPH and active enzyme and inhibited by cytochrome P450 inhibitor)	Jenner & Timbrell, 1990; Timbrell et al., 1982
in vitro	Rat Combined administration of cytochrome P450 inducers (phenobarbital and rifampicin) Combined administration of cytochrome P450 inhibitors (metyrapone and piperonyl butoxide)	ND	Combined administration of P450 inducers: hydrazine metabolism in the liver was increased. Combined administration of P450 inhibitors: hydrazine metabolism in the liver was decreased.	Noda et al., 1987

Species sex/number of animals	Route	Dose	Results	Reference
in vivo	ND	ND	After nitrogen release in the first 15 to 30 minutes, acetylation and carbonylation were the main metabolic pathways producing metabolites excreted in the urine.	Nelson & Gordon, 1982
Rat SD male (3 animals/group)	Intraperitoneal Elimination of hydrazine metabolite (N_2) into the expiration ^{15}N-labeled hydrazine sulfate	130 mg/kg	30 min after administration: 15% of given dose, 4 hours after administration: 23% Comparison of expiratory $^{15}N_2$ volume in 4 hours after administration with that in other administration routes at the same dose: high in intravenous administration and low in subcutaneous one	Dost, 1979
Mouse, Rat	Intraperitoneal ^{15}N-labeled hydrazine sulfate	130 mg/kg	Approximately 20% to 30% of hydrazine given was eliminated as nitrogen gas up to the first 2 hours. Approximately 25% of given dose remained in the body as undetected substance.	Nelson & Gordon, 1982; Springer et al., 1981
Rat SD	Intraperitoneal hydrazine	427 mg/kg	Metabolites shown in Figure 7-1 {monoacetylhydrazine, diacetylhydrazine, pyruvic acid hydrazone, urea, cyclic compound [1,4,5,6-tetrahydro-6-oxo-3-pyridazine -carboxyl acid (a reaction product of 2-oxoglutaric acid and hydrazine)]}: detected in the urine Confirmed that hydrazine was acetylated and reacted with biomolecules (*in vivo*).	Preece et al., 1991
Mouse Swiss-Webster Male	Intraperitoneal ^{15}N-labeled hydrazine sulfate	130 mg/kg	Time course of $^{15}N_2$ elimination into the expiration for 1 to 48 hours after administration: first 1 to 2 hours: approximately 20% of given dose was already eliminated into the expiration as $^{15}N_2$. 48 hours after administration: approximately 35% was eliminated into the expiration. Hydrazine is oxidized to nitrogen (gas) in catalysis by oxyhemoglobin.	Nelson & Gordon, 1982
in vitro	ND	ND	Hydrazine was metabolized into nitrogen (gas) in oxidation catalysis by oxyhemoglobin in erythrocytes and oxygenase in liver microsome.	Clark et al., 1968; Springer et al., 1981; Nelson & Gordon, 1982
in vitro	Dog Blood	ND	Ammoniagenesis with no increase in BUN concentration was confirmed.	Floyd, 1980
Rat	ND ^{15}N-hydrazine	ND	^{15}N-ammoia was not detected in the urine. It was assumed that the blood ammonia detected in dogs was not hydrazine metabolite but formed in other metabolic pathway on which hydrazine had an effect.	Floyd, 1980, Springer et al.,1981;
Rat Male	Intraperitoneal hydrazine hydrate	15-80 mg/kg	The urine collected in 0 to 6 and 6 to 12 hours was analyzed using proton-NMR spectroscopy, and in addition to metabolites shown in Figure 7-1, methylamine was detected.	Sanins et al., 1988

Species sex/number of animals	Route	Dose	Results	Reference
ND	NMR analysis	ND	Methylhydrazine and α-ketoglutarate hydrazone were detected as hydrazine metabolites.	Sanins et al., 1986
Excretion				
Rat	Inhalation exposure 1 hour hydrazine	10, 60, 500 ppm	Excretion in the urine in 48 hours after the completion of exposure: 8.4-29.5% of given dose Most of them were excreted in the first 24 hours.	Llewellyn et al., 1986
Rat	Intravenous Single dose hydrazine	2-12 mg/kg	Excretion volume in the urine in 48 hours after administration: 13.8-37.3% of given dose	
Rat (3 animals)	Oral Single dose hydrazine	0.7, 3.5 mg/kg	Excretion volume in the urine in 24 hours after administration: unchanged hydrazine 13% and 17% of given dose	Bayer, 1986
SD rat (3 animals)	Oral Single dose hydrazine	3, 9, 27 and 81 mg/kg	Excretion volume in the urine in 24 hours after administration: 19-81% of given dose Excresion into the feces and expiration was not determined.	Preece et al., 1992a
			9 mg/kg and less: 40% of given dose was excreted in the urine as unchanged hydrazine and 5% as monoacetylhydrazine. 27 mg/kg and above: the excretion was decreased dose-depedently with 20.5%and 17.5% as hydrazine and 2.1% and 1.1% as monoacetylhydrazine.	Preece et al., 1992b
Hybrid dog	Percutanous exposure Non-occlusion Shaven skin of the chest: approximately 300 cm^2 Hydrazine	96-480 mg/kg	118 mg/kg and less: Urinary concentration of hydrazine reached the peak approximately 90 to 120 minutes after administration. 128 mg/kg and above: Urinary concentration of hydrazine reached the peak 4 hours after administration.	Smith & Clark, 1972
Rat	Subcutaneous Single dose Hydrazine	9.9 mg/kg	48 hours after: 29.2% of given dose was excreted in the urine. Percentages of monoacetylhydrazine and diacetylhydrazine were 2.9% and 2.5%.	Kaneo et al., 1984
Mouse Swiss-ICR Male 3-8 animals /group	Intravenous, Subcutaneous Accumulated urinary excretion volume and recovery rate 0.5-48 hours after administration Single dose (intravenous) Two-divided dose (dermal; administration interval: 0.5 hours) Hydrazine	40-100 mg/kg	Up to 60 mg/kg: Accumulated excretion of unchanged hydrazine up to 48 hours after administration: approximately 50% of given dose Hydrazine recovery percentage: Early period: approximately 30% and 60% 48 hours after administration: Approximately 1% 72 hours after administration: not detected (the detection limit unknown) Percentage of hydrazine metabolites (assumption by authors; to given dose): Up to 60 mg/kg: 50-60% 60 mg/kg and above: 40 -50% (no further information)	Dambrauskas & Cornish, 1964

Species sex/number of animals	Route	Dose	Results	Reference
Rat SD Male	Intraperitoneal hydrazine	32 mg/kg	Total urinary excretion of hydrazine and its metabolites: (after administration) 1 hour: 5% 6 hours: 3% 24 hours: 1% 48 hours: 0.25% Accumulated urinary excretion percentage (to given dose): hydrazine: 28% acid hydrolysis derivatives: 24%	Dost, 1979
Mouse Swiss-Webster Male	Intraperitoneal 6 to 48 hours exposure hydrazine sulfate	130 mg/kg	Urinary excretion (percentage to given dose) 6 hours after administration: free hydrazin/unstable compounds (no detailed description): 10% hydrazine acid hydrolysis derivatives: 15% 48 hours after administration: free hydrazin/unstable compounds: 15% hydrazine acid hydrolysis derivatives: 25%	Nelson & Gordon, 1982
Rat	Oral, Subcutaneous, intratracheal, dermal hydrazine hydrate	5 mg/kg	48 hours urinary excretion (percentage to given dose) Oral administration: 23% Subcutaneous administration: 51% Intratracheal instillation: 28% Dermal application: 7.5%	Bayer, 1986
Rat	Intravenous (catheterization) Single dose ^{15}N-hydrazine	16-64 mg/kg	Urinary excretion: Unidentified hydrazine metabolite 20% Unchanged hydrazine 30% In the expiration: nitrogen gas 25%	Springer et al., 1981
Rat	Intraperitoneal hydrazine	32 mg/kg	Biliary excretion: not more than 1% of given dose within 24 hours after administration Hydrazine and its hydrolysis derivatives: biliary excretion was not a main excretion route of hydrazine.	Dost et al., 1981

ND: No data available

1) Cmax: the maximum concentration in the blood, etc. of a compound after administration; 2) Tmax: the time at which the concentration reaches Cmax after administration of a compound.

7.2 Epidemiological studies and case reports

a. Epidemiological studies

The epidemiological studies and case reports of hydrazine are summarized in Table 7-2.

In a retrospective cohort study in 423 workers (gender unknown) in a hydrazine production plant, it was reported that exposure to hydrazine did not increase a risk of cancer incidences (Roe, 1978), and in the follow-up studies with the almost same population, it was concluded that hydrazine did not enhance cancer risks (Henscher, 1985; Wald et al., 1984).

In a cross-sectional study in 172 male workers aged 18 to 60 years who engaged in hydrazine hydrate production for 0.5 to 35 years, no relationship was indicated between the current average hydrazine concentration (0.0109 ppm) and effects of accumulated hydrazine exposure on health, which was detected

by *N*-acetyltransferase phenotype. In a study using questionnaires, no heath effects of hydrazine hydrate except the complaints of "nightmare" were found. The study results indicated that the evidence was insufficient to conclude that hydrazine hydrate caused "nightmare" (Nomiyama et al., 1998).

Table 7-2 Epidemiological studies and case reports of hydrazine

Population Gender/number	Exposure condition/Dose	Results	Reference
423 workers (gender unknown) in a hydrazine production plant	ND	In a retrospective cohort study, hydrazine did not enhance cancer risk.	Roe, 1978
427 workers of the almost same population in the above study (workers engaging in production for 6 months and above)	Exposure period: 1945-1971 Repeated exposure concentration: 78 subjects: 1-10 ppm (sometimes 100 ppm) Others (n=375): 1 ppm and below	In a retrospective cohort study, hydrazine did not enhance cancer risk. Mortality of lung cancer and other cancers and other diseases was within the expected values (unknown whether the number of smokers was investigated).	Wald et al., 1984; Henschler, 1985
Worker engaging in hydrazine hydrate production 172 males 18-60 years old	Current exposure concentration : 0.0109 ppm Exposure period: 0.50-34.17 years	In a ross-sectional study, no effects except "nightmare" complaint Test item: questionnaire for subjective symptoms, laboratory test in liver and kidney function in main, *N*-acetyltransferase (NAT2)	Nomiyama et al., 1998

ND: No data available

b. Occupational and accidental case reports

Reports on the occupational and accidental exposures of hydrazine are summarized in Table 7-3.

Hydrazine has ammonia or amine odor and human olfactory threshold is 3 to 4 ppm (Jacobson et al., 1955). Acute poisoning rarely occurs, but there is a possibility of chronic poisoning (Henschler, 1971).

As an example of acute poisoning, a worker who suffered from burns to 22% of the body surface in hydrazine explosion had no neurologic symptom at the time of admission to a hospital, but showed coma and electroencephalography (EEG) revealed hypoactivity (marked particular in the right hemisphere) 14 hours after the explosion and neurologic symptoms were not improved for 60 hours thereafter. Spontaneous motion recovered 4 hours after pyridoxine (as antidote) treatment and neuropathic symptoms were improved in 12 hours after the initiation of the antidote treatment. This patient, in addition to neuropathy, exhibited hematuria without renal disorder, an increase in blood glucose level and hepatic dysfunction for 3 days after accident (Kirklin et al., 1976).

A worker who was exposed to hydrazine vapor for 4 to 5 hours in accident showed nausea, vomiting, local irritation in the exposed skin, conjunctiva and upper respiratory tract, and a significant increase in hepatotoxicity related enzyme levels (Henschler, 1971).

Two workers who had inhalation of mixture of hydrazine and 1,1-dimethylhydrazine (equivalent

concentration) for 90 minutes at the longest due to a leak from a pipe exhibited neuropathy and pulmonary symptom (edema), but were improved by antidote treatment of pyridoxine (Frierson, 1965).

Oral intake of hydrazine hydrate or hydrazine in accident induced vomiting, hepatotoxicity, neurologic and cardiac symptoms (Drews et al., 1960; Harati and Niakan, 1986; Kulkarni and Nawaz, 1982; Reid, 1965).

A machine operator aged 59 years who used hydrazine hydrate at a concentration of 0.071 mg/m^3 (measured after accident) for 6 months (once a week) showed fatigue, tremor and conjunctivitis on the operation day and the next day. After continuous 1-month exposure, the patient was admitted due to fever, vomiting, diarrhea, abdominal pain, black stool and icterus and died on 15 days after admission. In autopsy, pneumonia, severe nephritis, tubular necrosis, glomerulonephritis and focal hepatocellular necrosis were found (Sotaniemi et al., 1971).

c. Irritation and Sensitization

In 6 volunteers, no irritation was induced by application of 25% hydrazine sulfate or its concentrated solution to the skin for 24 hours (Bayer, 1954). Similarly, dermal application of a photographic stop-bath solution containing 0.1% hydrazine sulfate for 24 hours caused no skin irritation in 6 volunteers (Bayer, 1962).

With regard to sensitization, a sensitization test to 23 volunteers was conducted. After 24 hours pretreatment with 5% sodium lauryl sulfate, 5% hydrazine solution was applied to the upper arm and the application site was occluded for 48 hours. The application for induction was repeated 4 times. For challenge, 0.5% hydrazine solution was applied for 48 hours and then skin response was observed 0 and 48 hours after the challenge treatment. Positive results were obtained for all volunteers (Kligman, 1966). Recently, it has been reported that hydrazine and its salts induced contact allergy in humans (Kayser and Schlede, 1995). The Japan Society for Occupational Health (2002) has classified hydrazine and its compounds into Group 2 of skin sensitizing substance (almost equal to Group 1 substances but its effect has not definitely been confirmed in epidemiological studies).

In summary, in humans, coma and EEG hypoactivity were observed in a poisoning accident at the occasion of hydrazine explosion, and antidote treatment of pyridoxine recovered spontaneous motion impairment and neuropathy. Hematuria, an increase in blood glucose level and hepatic dysfunction were observed also as hydrazine intoxication. Inhalation of hydrazine vapor induced neuropathy and pulmonary edema, however, the patient was improved by pyridoxine treatment. Oral intake of hydrazine or hydrazine hydrate in accidents induced vomiting, hepatotoxicity, neurologic and cardiovascular symptoms. As hydrazine has ammonia- or amine-like odor and human olfactory threshold, which is 3 to 4 ppm, is low, acute exposure accidents at high concentrations rarely occur, but there is a possibility that long term exposures at low concentrations may cause poisoning. Hydrazine sulfate does not induce irritation to the human skin, but hydrazine and its salts have skin sensitization.

Table 7-3 Occupational and accidental exposures of hydrazine

Population Gender/ number	Exposure condition	Dose	Results	Reference
Acute poisoning				
Worker	Explosion	ND	Burn (22% of the body surface) No neuropathy in admission 14 hours after explosion: coma, EGG hypoactivity (marked particular in the right hemisphere), not improved 60 hours thereafter, spontaneous motion recovered 4 hours after antidote treatment of pyridoxine, and neuropathic symptoms were improved 12 hours after the antidote treatment. Other systemic symptoms: 3 days after exposure: hematuria (without renal disorder), an increase in blood glucose level and hepatic dysfunction	Kirklin et al., 1976
Worker	Vapor exposure	ND	4-5 hours after exposure: nausea, vomiting, irritation in the conjunctiva and upper respiratory tract, local irritation in the exposed skin, and a significant increase in hepatotoxicity-related enzyme levels	Henschler, 1971
Worker 2 persons	Inhalation exposure (leak from a pipe)	50% hydrazine 50% 1,1-dimethylhydrazine compound 1.5 hours at the longest	Neurologic symptom,pulmonary symptom (edema) recovered by antidote (pyridoxine) treatment	Frierson, 1965
Humans 40 years old	Oral intake Intake in accident	Immediately after intake (2-3 mL) of 80% hydrazine hydrate solution, spit out.	Course after intake: Up to 24 hours after: vomiting once, no other symptom 2 days after: admitted in hospital due to drowsiness 3 days after: icterus+, serious hepatic coma and others (trembling, localized plantar reflex) 5 days after: antidote treatment without pyridoxine and improved 8 days after	Kulkarni & Nawaz, 1982
Humans	Oral intake	ND	3 days after accident: Hepatotoxicity (increases in ASAT, LDH and total bilirubin), drowsiness, perturbation, confusion	Harati & Niakan, 1986
Humans	Oral intake	ND	Effects on the nervous system (drowsiness, lack of concentration, Cheyne-Stokes breathing, urinary retention, ataxia, hyperactivity, lack of motion coordination, paresthesia) Effects on cardiovascular system (transient atrial fibrillation with absolute arrhythmia)	Drews et al., 1960; Reid, 1965

Population Gender/ number	Exposure condition	Dose	Results	Reference
Chronic poisoning				
Machine operator 59 years old	Exposed to hydrazine hydrate for 6 months (once a week) and continuously used for one month therafter.	0.071mg/m^3: (measured after accident)	Course of the symptoms: Fatigue, trembling and conjunctivitis on the operation day and the following day. After 1 month continuous exposure thereafter, admitted due to fever, vomiting, diarrhea, abdominal pain, black stool and jaundice and died 15 days after admission. Autopsy: pneumonia, severe nephritis, tubulonecrosis, glomerulonephritis and focal hepatocellular necrosis	Sotaniemi et al., 1971
Irritation and Sensitization				
6 volunteers	Cotton ball containing test substance was applied to the skin.	25% hydrazine sulfate or its condensed solution for 24 hours	No irritation to the skin	Bayer, 1954
6 volunteers	Cotton ball containing 0.1% stop solution for photographic development was applied to the skin.	Hydrazine sulfate (0.1%) for 24 hours	No irritation to the skin	Bayer, 1962
23 volunteers	After 24 hours pretreatment with 5% sodium lauryl sulfate (evoking inflammatory reaction), 5% solution was applied and the application site (upper arm) was occluded for 48 hours (sensitization treatment/ repeated 4 times/site)	0.5% hydrazine solution application for 48 hours (challenge)	Positive responses were observed in all volunteers 0-48 hours after the challenge application. Conclusion: Hydrazine has skin sensitization.	Kligman, 1966

ND: No data available

7.3 Studies in experimental animals and *in vitro* studies

7.3.1 Acute toxicity

Summarized data of the acute toxicity of hydrazine and hydrazine hydrate to experimenal animals are shown in Table 7-4 (Becker et al., 1981; Comstock et al., 1954; Ekshtat, 1965; Horton and Conn, 1954; HRC, 1993; Jacobson et al., 1955; Parodi et al., 1981; Scales and Timbrell, 1982; Smith and Clark, 1972 ; Witkin, 1956).

No differences in acute toxic symptoms were shown between oral and other administration routes of hydrazine. Ataxia, hypoactivity, dyspnea, enhanced excitability, salivation, vomiting and convulsion were observed (Henschler, 1971; IPCS, 1987). In a single administration study of hydrazine at a lethal dose, hepatic lipidosis [1)] and renal histopathological changes were found (Henschler, 1971; IPCS, 1987).

Inhalation exposure of hydrazine caused pulmonary edema, bronchial mucosa damage (Comstock et al., 1954), and pulmonary congestion (HRC, 1993). In rats and hamsters exposed to hydrazine at a dose of 1,000 mg/m^3 for 1 hour, degeneration (necrosis, scale and inflammation) was observed in the nasal mucosa epithelium at 24 hours after exposure (Latendresse et al., 1995). Intravenous administration of hydrazine in dogs at a single dose of 20 mg/kg caused renal toxicity, and at 20 to 240 minutes after administration creatinine clearance was reduced and glucose reabsorption in the renal tubules was significantly decreased (Wong, 1966). In an intravenous study of hydrazine sulfate in rhesus monkeys at single doses of 10 to 80 mg/kg, histopathological examination showed hepatic lipidosis at the highest dose, but the clinical biochemistry including hepatic function test showed no effects (Warren et al., 1984).

1) Fat accumulation in the reticuloendothelial system

Table 7-4 Acute toxicity of hydrazine and hydrazine hydrate

	Route	Mouse	Rat	Rabbit	Guinea pig	Dog
Hydrazine	Oral LD_{50} (mg/ kg)	59	60-90	ND	ND	ND
	Inhalation LC_{50} (mg/ m^3)	330 (for 4 hours exposure)	350-760 (for 4-hour exposure) 4,200 (for 1-hour exposure)	ND	ND	ND
	Dermal LD_{50} (mg/ kg)	ND	ND	91	ND	96 (LDLo)
	Intravenous LD_{50} (mg/kg)	57	55	ND	ND	25
	Intraperitoneal LD_{50} (mg/kg)	62-156	59	ND	ND	ND
Hydrazine hydrate	Oral LD_{50} (mg/kg)	83	129	55	40	ND
	Intraperitoneal LD_{50} (mg/kg)	56	80-100	ND	ND	ND

ND: No data available; LDLo: the lowest lethal dose

7.3.2 Irritation and corrosion

Studies on the irritation and corrosion of hydrazine to experimental animals are summarized in Table 7-5.

a. Skin

In New Zealand White (NZW) rabbits, 0.5 mL of 35% hydrazine anhydride solution was applied for 4 hours to the shaved skin on the back and the application site was occluded. Irritation response was observed in the applied skin and 2 of 6 rabbits died (Hathaway, 1984).

According to the Draize method, 35% hydrazine solution (corresponding to 60 mg/kg) was applied for 4 hours to the shaved skin on the back of NZW rabbits, and the application site was occluded. Irritation response was observed, although 4 of 6 rabbits died in the study (Mobay Chemical, 1984).

In Japanese albino rabbits, 0.5 mL of 55% hydrazine hydrate solution was applied for 4 hours to the

shaved skin on the back and the application site was occluded. Corrosion response was observed in the applied skin in 7 of 11 rabbits (Otsuka Chemical, 1978).

According to the OECD Test Guideline 404, 0.5 mL of 5% hydrazine hydrate solution was applied for 4 hours to the shaved skin of NZW rabbits and the application site was semi-occluded. No irritation response was observed in the applied skin (Bayer, 1988).

b. Eye

In an eye irritation study of hydrazine according to OECD Test Guideline 405, 0.1 mL of 5% hydrazine hydrate solution was applied to the conjunctival sac of NZW rabbits and washed out after 24hours. Symptoms were observed for 21 days. No irritaition responses were induced in the eye (Bayer, 1988).

As described above, in application of 35% hydrazine and 55% hydrazine hydrate solutions to rabbit skins, irritation and corrosion were observed, respectively, and in application of 5% hydrazine hydrate solution to the rabbit eyes, no irritation was observed.

Table 7-5 Irritation and corrosion of hydrazine

	Species sex/number of animals	Method	Period	Dose	Results	Reference
Skin						
Hydrazine	Rabbit NZW 6 animals	Shaved skin on the back Closed application Draize method	4 hours	35% aqueous solution 0.5 mL	Irritation: 2/6 Death: 2	Hathaway, 1984
	Rabbit NZW 6 animals	Shaved skin on the back Closed application Draize method	4 hours	35% solution (used as catalyst: vehicle unknown) Dose corresponding to 60 mg/kg	Irritation response Irritation response is in doubt because 4 rabbits died 24 hours after application.	Mobay Chemical, 1984
Hydrazine hydrate	Rabbit Japanese albino, male 11 animals	Shaved skin on the back Closed application	4 hours	55% solution (vehicle unknown) 0.5 mL	Corrosion response (7/11)	Otsuka Chemical, 1978
	Rabbit NZW 6 animals	Semi- closed OECD TG 404	4 hours	5% aqueous solution	No irritation	Bayer, 1988
Eye						
Hydrazine hydrate	Rabbit NZW	Dropping in the conjunctival sac Washing eys 24 hours after dropping OECD TG 405	24 hours	5% aqueous solution	No irritation	Bayer, 1988

ND: No data available

7.3.3 Sensitization

No reports on sensitization of hydrazine in experimental animals were obtained in this investigation.

7.3.4 Repeated dose toxicity

Studies on the repeated dose toxicity of hydrazine to experimental animals are summarized in Table 7-6.

a. Oral administration

a-1. Hydrazine

In a drinking water administration study, rats (10 animals/group) were given hydrazine solution at 0, 500, 1,000 and 2,000 mg/L (corresponding to 0, 60, 120 and 240 mg/kg/day) for 3 to 4 weeks or at 0, 100 and 200 mg/L (corresponding to 0, 12 and 24 mg/kg/day) for 14 weeks. Water consumption and body weight gain were dose-dependently decreased in both studies. In the latter study, 4 animals at the 100 mg/L group died at 5 to 9 weeks after administration and 6 in the 200 mg/L group died at 4 to 6 weeks after administration, but no histopathological changes were observed (Weatherby and Yard, 1955).

a-2 Hydrazine hydrate

In an oral administration study in NMRI mice (male and female, 50 animals/group) with drinking water containing 0, 2, 10 and 50 mg/L of hydrazine hydrate (male: corresponding to 0, 0.3, 1.1 and 3.7 mg of hydrazine /kg/day; female: corresponding to 0, 0.3, 0.7 and 3.1 mg of hydrazine /kg/day) for life span, water consumption was dose-dependently reduced in males and females, and coarse fur, hypoactivity and suppression in body weight gain were observed at 50 mg/L group. Remarkable suppression in body weight gain was noted in females of the 50 mg/L group and a slight suppression was found also in females of the 2 mg/L group. No changes in organ weight and histological examination were shown (Steinhoff et al., 1990). Based on these results, the LOAEL is considered to be 2 mg/L (corresponding to 0.3 mg/kg/day of hydrazine) in this assessment.

Wistar rats (6 weeks, male and female each 50 animals/group) were orally administered by drinking water containing hydrazine hydrate at 0, 2, 10 and 50 mg/L (male: corresponding to 0, 0.13, 0.64 and 3.2 mg of hydrazine kg/day; female: corresponding to 0, 0.15, 0.77 and 3.8 mg of hydrazine /kg/day). The body weight gain was suppressed in males and females of the high dose (50 mg/L) group and the survival rate was reduced in females. No differences in organ weight were found between natural death/moribund sacrifice animals and control animals. The histological examination showed bile duct hyperplasia at doses of 10 mg/L and above in females and at all doses in male groups, but no other changes were found (Steinhoff and Mohr, 1988). Based on these results, the LOAEL is considered to be 2 mg/L (corresponding to 0.13 mg of hydrazine/kg/day) in this assessment.

a-3 Hydrazine sulfate

In an oral administration (gavage) study, hydrazine sulfate was administered in male and female CBA mice and Syrian golden hamsters at 0, 1.1, 2.3, 4.9 mg/kg/day for 15 to 25-weeks. In mice and hamster, the mortality was increased at 2.3 mg/kg/day and above, respectively. In mice, adrenal degeneration was found in females at 1.1 mg/kg/day and above and in hamsters, hepatic cirrhosis, reticuloendothelial cell and bile duct hyperplasia were observed at 4.9 mg/kg/day (Biancifiori, 1970b).

In a drinking water administraiton study, male Syrian golden hamsters were given hydrazine sulfate at

doses of 0, 170, 340 and 510 mg/L (corresponding to 0, 4.6, 8.3 and 10.3 mg of hydrazine/kg/day) for 2 years. Water consumption and survival rate were dose-dependently reduced, but no statistical significance was observed. However, in histopathological examination at 18 months after the initiation of the exposure, the dose-dependent incidences of nodular hyperplasia, hypertrophy and necrosis were found in hepatocytes (Bosan et al., 1987; Henschler, 1989).

b. Inhalation exposure

b-1 Hydrazine

In an inhalation exposure study of hydrazine, male and female F344 rats (5 animals/sex) and male Syrian golden hamsters (10 animals/group) were exposed at 0, 750 ppm (0, 1,000 mg/m^3) for 10 weeks (1 hour/week). Nasal mucosa inflammation, necrosis, scale and hyperplasia of the nasal mucosa epithelium and squamous metaplasia (rats only) were found. Hyperplasia of the epithelium was marked in male rats (Latendresse et al., 1995). Inhalation exposure to hydrazine at a high concentration (750 ppm) induced severe lesions in the nasal mucosa.

MacEwen et al. (1981) and Vernot et al. (1985) conducted inhalation exposure studies of hydrazine in mice, rats, hamsters and dogs for 12 months (6 hours/day, 5 days/week) to compare the effects of hydrazine at low concentrations among species.

Inhalation exposure to female C57BL/6 mice (400 animals/group) at 0, 0.066, 0.33 and 1.33 mg/m^3 (0, 0.05, 0.25 and 1 ppm) caused no effects in all dose groups (MacEwen et al., 1981; Vernot et al., 1985).

Male and female F344 rats (100 animals/group) were exposed at 0, 0.066, 0.33, 1.33 and 6.65 mg/m^3 (0, 0.05, 0.25, 1 and 5 ppm) for 12 months. In 0.066 mg/m^3 and above groups, suppression in body weight gain in males and females, inflammation in the larynx and tracheal mucosa epithelium, squamous metaplasia and alveolar epithelial hyperplasia in males were found. In 1.33 mg/m^3 and above groups, hepatocellular hyperplasia in females and myocardial degeneration in males occurred. In 6.65 mg/m^3 groups, squamous metaplasia, hyperplasia and inflammation in the upper respiratory tract mucosa epithelium in males and females were observed (MacEwen et al., 1981; Vernot et al., 1985). From these results, the LOAEL is considered to be 0.066 mg/m^3 in this assessment.

Male Syrian golden hamsters (200 animals/group) were exposed at 0, 0.33, 1.33 and 6.65 mg/m^3 for 12 months. The following findings were dose-dependently induced in 0.33 mg/m^3 and above groups: a suppression in body weight gain, an increase in mortality, amyloidosis in the liver, spleen, kidney, thyroid and adrenal gland, hepatic hemosiderosis and testicular atrophy. Amyloidosis, hemosiderosis and testicular atrophy, which are age-related changes, were promoted by the exposure to hydrazine (MacEwen et al., 1981; Vernot et al., 1985).

Male and female dogs (Beagle, 4 animals/group) were exposed at 0, 0.33 and 1.33 mg/m^3 for 12 months. An increase in alanine aminotransferase (ALT) activity and vacuolation in hepatocytes were found only in a male dog at 1.33 mg/m^3. No histopathological changes were observed in all dose groups (MacEwen et al., 1981; Vernot et al., 1985).

In other inhalation studies, hepatotoxicity (lipidosis) in mice, dogs and monkeys (Haun and Kinkead, 1973) and reversible changes (emphysema and atelectasis) in respiraotry tract (Comstock et al., 1954) were

reported.

An inhalation exposure study of hydrazine in 4 animal species was condected. ICR mice (female, 40 animals/group), SD rats (male, 50 animals/group), Beagle dogs (male, 8 animals/group) and Rhesus monkeys (female, 4 animals/group) were exposed at 0, 0.26 and 1.33 mg/m^3 (0, 0.2 and 1 ppm) for 6 months (6 hours/day, 5 days/week). A dose-related decrease in body weight gain was found in rats. Fatty degeneration in the liver was observed in mice, dogs and monkeys at 0.26 and 1.33 mg/m^3 and significant decreases (approximately 25% to 30%) in hemoglobin value, hematocrit value and red blood cell (RBC) count in dogs at 1.33 mg/m^3 (Haun and Kinkead, 1973).

In summary, rats showed higher sensitivity to hydrazine in the respiraotry mucosa than mice, hamsters and dogs and exhibited changes even at the lowest concentration of 0.066 mg/m^3 (0.05 ppm) in rats. Therefore, the NOAEL could not be estimated. The LOAEL of inhalation exposure is considered to be 0.066 mg/m^3. The hepatotoxic effect of hydrazine through inhalation exposure was the highest in hamsters and the lowest in mice. The NOAEL for hepatotoxicity ranges from 0.33 to 1.33 mg/m^3 in mice, rats and dogs.

c. Intraperitoneal injection

In an intraperitoneal injection study of hydrazine in rats at a lethal dose, serotonin concentrations were increased in the midbrain, diencephalon, medullary and cerebral cortex and noradrenaline concentrations in the cerebral cortex and γ-aminobutyric acid (GABA) in the cerebellum, midbrain and diencephalon (Uchida and O'Brian, 1964).

In intraperitoneal injection of hydrazine sulfate in rabbits around a lethal dose, excitatory threshold was reduced in the visual cortex in the electroencephalogram (EEG) and focal necrosis was found in the visual cortex between white and gray matters in neuropathological examination (Edelwejn, 1967), indicating the effect of hydrazine on the central nervous system.

In an intraperitoneal administration of hydrazine in Rhesus monkeys at doses of 15 to 25 mg/kg/day for 3 days, heart index (measured by Fick method), systolic ejection time, systolic blood pressure × heart rate (tension time index) were significantly reduced and fatty degeneration was observed in the myocardium, indicating the effect of hydrazine on the cardiovascular system (Hayden and Murray, 1965).

From these results described above, hydrazine had effects on the respiratory system, liver, kidney, central nervous system, reticuloendothelial system, adrenal gland and cardiovascular system including the heart in repeated dose toxicity studies. In the respiratory system, inhalation exposure induced proliferative changes including hyperplasia in the respiratory tract mucosa induced by chronic stimuli but not other administration routes. In inhalation exposure, hydrazine caused supression in body weight gain and inflammation in larynx and tracheal mucosa epithelium in rats at the lowest dose (MacEwen et al., 1981; Vernot et al., 1985) and the LOAEL is considered to be 0.066 mg/m^3 in this assessment. In oral administration, bile duct hyperplasia was found in male rats at the lowest dose (Steinhoff et al., 1988). Therefore, the LOAEL is 2 mg/L (corresponding to 0.13 mg of hydrazine /kg/day).

Table 7-6 Repeated dose toxicity of hydrazine

Species sex/number of animals	Route	Period	Dose	Results	Reference
Rat 10 animals/group	Oral (via drinking water)	3 to 4 weeks	Hydrazine 0, 500, 1,000, 2,000 mg/L (corresponding to 0, 60, 120, 240 mg/kg/day)	Dose-dependent reduction in water consumption and suppression in body weight gain	Weatherby & Yard, 1955
		14 weeks	Hydrazine 0, 100, 200 mg/L (corresponding to 0, 12, 24 mg/kg/day)	100 mg/L: 4/10 death (week 5 to 9) 200 mg/L: 6/10 death (week 4 to 6) No histopathological change	
Mouse NMRI Male and female 50 animals/group	Oral (via drinking water)	Life-span	Hydrazine hydrate 0, 2, 10, 50 mg/L (As hydrazine: male: corresponding to 0, 0.3, 1.1 and 3.7 mg of hydrazine /kg/day; female: corresponding to 0, 0.3, 0.7 and 3.1 mg of hydrazine /kg/day) (converted in this assessment)	2 mg/L and above: Male and female: dose-dependent reduction in water consumption Female: suppression in body weight gain (slight) 50 mg/L: Male and Female: coarse fur, hypoactivity, suppression in body weight gain (markedly in females), No changes in organ weight and histopathological examination LOAEL : 2 mg/L (corresponding to 0.3 mg of hydrazine /kg/day) (in this assessment)	Steinhoff et al., 1990
Rat Wistar Male and female 6 weeks old each 50 animals/group	Oral (via drinking water)	Life-span	Hydrazine hydrate 0, 2, 10, 50 mg/L (male:corresponding to 0, 0.2, 1.0, 5.0 mg/kg/day, female: corresponding to 0, 0.24, 1.2, 6.0 mg/kg/day; as hydrazine: male: corresponding to 0, 0.13, 0.64, 3.2 mg of hydrazine /kg/day, female: corresponding to 0, 0.15, 0.77, 3.8 mg of hydrazine /kg/day) (converted in this assessment)	2 mg/L and above: Male and female: dose-dependent reduction in water consumption Male: bile duct hyperplasia 10 mg/L and above: Female: bile duct hyperplasia 50 mg/L: Male and female: suppression in body weight gain Female: decrease in survival rate No differences in organ weight between natural death/moribund sacrifice animals. LOAEL : 2 mg/L (corresponding to 0.13 mg of hydrazine /kg/day) (in this assessment)	Steinhoff & Mohr, 1988

Species sex/number of animals	Route	Period	Dose	Results	Reference
Mouse CBA Male and female Hamster Syrian golden Male and female	Oral (via drinking water)	15 to 25 weeks	Hydrazine sulfate (solvent: water) 0, 1.1, 2.3, 4.9 mg/kg/day	Mouse 1.1 mg/kg/day and above: Female: adrenal degeneration 2.3 mg/kg/day and above: increase in mortality Hamster 2.3 mg/kg/day: increase in mortality 4.9 mg/kg: increase in mortality, hepatic cirrhosis, reticuloendothelial cell and bile duct hyperplasia	Biancifiori, 1970b
Hamster Syrian golden Male 31-34 animals/group	Oral (via drinking water)	2 years	Hydrazine sulfate (purity> 99%) 0, 170, 340, 510 mg/L (corresponding to 0, 4.6, 8.3, 10.3 mg of hydrazine /kg /day)	170 mg/L and above: Dose-dependent reduction in water consumption and survival rate (no significant difference) 18 months after the initiation of the administration, nodular hyperplasia, hypertrophy and necrosis in hepatocytes	Bosan et al., 1987; Henschler, 1989
Rat F344 Male and female 5 animals/sex Hamster Syrian golden Male 10 animals/group	Inhalation exposure	10 weeks 1 hour /week	Hydrazine (purity: 98.8%) 0, 750 ppm (0, 1,000 mg/m^3)	750 ppm: Rat: Nasal mucosa epithelium: inflammation, necrosis, scale, squamous metaplasia and hyperplasia Olfactory epithelium in the anterior nose: apoptosis, necrosis Hamster: Olfactory epithelium in the anterior nose: apoptosis, necrosis	Latendresse et al., 1995
Mouse C57BL6 Female 400 animals/group 800 animals/control group	Inhalation exposure	12 months 6 hours /day, 5 days/week, follow-up 15 months	Hydrazine (purity: 99.8%) 0, 0.066, 0.33, 1.33 mg/m^3 (0, 0.05, 0.25, 1 ppm)	All exposure groups: no change (not including neoplastic change, see 8.3.7) NOAEL : 0.33 mg/m^3(dose with no pulmonary adenoma)	MacEwen et al., 1981; Vernot et al., 1985

Species sex/number of animals	Route	Period	Dose	Results	Reference
Mouse ICR Female 40 animals/group Rat SD Male (50 animals/ group) Dog Beagle Male 8 animals/ group Monkey Rhesus Female 4 animals/ group	Inhalation exposure	6 months 6 hours /day 5 days /week	Hydrazine 0, 0.26, 1.33 mg/m^3 (0, 0.2, 1 ppm)	0.26 mg/m^3 and above: Mouse, dog, monkey: lipidosis in the liver 1.33mg/m^3 : Dog: decreases in hemoglobin value, hematocrit and RBC[1)] count (approximately 25-30%) Possible recovery	Haun & Kinkead, 1973
Rat F344 Male and female 100 animals/group 150 animals/control group	Inhalation exposure	12 months 6 hours /day 5 days /week follow-up 18 months	Hydrazine (purity: 99.8%) 0, 0.066, 0.33, 1.33, 6.65 mg/m^3 (0, 0.05, 0.25, 1, 5 ppm)	0.066 mg/m^3 and above: Male and female: suppression of body weight gain Male: squamous metaplasia and inflammation in the larynx and tracheal mucosa epithelium, alveolar epithelial hyperplasia 1.33 mg/m^3 and above: Female: hepatocellular hyperplasia Male: myocardial degeneration 6.65 mg/m^3: Male and female: squamous metaplasia, hyperplasia of the nasal mucosa epithelium, squamous metaplasia and inflammation of the larynx and tracheal mucosa epithelium Female: endometrial hyperplasia, endometritis, ovarian atrophy, salpingitis Male: Leydig cell hyperplasia in the testis LOAEL : 0.066 mg/m^3: (in this assessment)	MacEwen et al., 1981; Vernot et al., 1985
Hamster Syrian golden Male 200 animals/ group	Inhalation exposure	12 months 6 hours /day 5 days /week follow-up 12 months	Hydrazine (purity: 99.8%) 0, 0.33, 1.33, 6.65 mg/m^3 (0, 0.25, 1, 5 ppm)	0.33 mg/m^3 and above: suppression in body weight gain, increase in mortality dose-dependent age-related changes amyloidosis (liver, spleen, kidney, thyroid and adrenal gland), hepatic hemosiderosis, testicular atrophy	MacEwen et al., 1981; Vernot et al., 1985

Species sex/number of animals	Route	Period	Dose	Results	Reference
Dog Beagle Male and female each 4 animals/group	Inhalation exposure	12 months 6 hours /day 5 days /week follow-up 38 months	Hydrazine (purity: 99.8%) 0, 0.33, 1.33 mg/m^3 (0, 0.25, 1 ppm)	1.33 mg/m^3: increase in ALT[2], hepatocellular vacuolation	MacEwen et al., 1981; Vernot et al., 1985
Rat	Intraperi-toneal	ND	Hydrazine lethal dose	Midbrain, diencephalon, medullary and cerebral cortex: increase in serotonin concentration Cerebral cortex: increase in noradrenaline concentration Cerebellum, midbrain and diencephalon: increase in γ-aminobutyric acid	Uchida & O'Brian, 1964
Rabbit	Intraperi-toneal	Repeated dose (period unknown)	Hydrazine sulfate around lethal dose	EEG[3]: reduction in excitability threshold in the visual cortex Neuropathological examination: focal necrosis in the visual cortex between white and gray matters	Edelwejn, 1967
Rhesus monkey 7 animals	Intraperi-toneal	3 days	Hydrazine 15-25 mg/kg/day	Significant reduction in heart index (Fick method), systolic ejection time, tension time index (systolic blood pressure × heart rate) myocardial fatty degeneration	Hayden & Murray, 1965

ND: No data available; 1) RBC: red blood cell; 2) ALT: alanine aminotransferase; 3) EEG: electroencephalogram.

7.3.5 Reproductive and developmental toxicity

Studies on the reproductive and developmental toxicity of hydrazine to experimental animals are summarized in Table 7-7.

a. Reproductive toxicity

In an oral administration (gavage) study, male and female rats were given hydrazine nitrate at 0, 13 mg/kg/day for 30 days before mating, the effects on reproductive function (female fertility, the number of newborns and resorption) were investigated. No difference was observed in the development of the surviving litters between the control and treated groups (Savchenkov and Samoilova, 1984).

Hydrazine (purity: 99.5%) contained in drinking water was administered to male and female rats (10 animals/treated group and 20 animals/control group) at concentrations of 0, 0.002, 0.018 and 0.82 mg/L (corresponding to 0, 0.00016, 0.0014 and 0.016 mg/kg/day) for 6 months. At 0.82 mg/L group, the number of surviving embryos were decreased and resorption was increased compared with the control group. No developmental anomaly was found in 293 fetuses of the treated groups. Six months after administration, lesion in the gonadal epithelial cells of male rats (parent) was observed at 0.018 and above (Duamin et al., 1984).

Hydrazine was exposed by inhalation to rats at 0, 0.01, 0.13 and 0.85 mg/m^3 (corresponding to 0, 0.0012,

0.016 and 0.10 mg/kg/day) for 4 months (5 hours/day, 5 days/week). Toxic effects on embryos (resorption and death) were found, which were similar severity to those that were found at middle to high doses of oral toxicity study. No anomaly was found in 315 fetuses. No toxic effect on the gonad in male rats was observed (Duamin et al., 1984).

In some studies in male and female rats and hamsters, some effects on reproductive organs were reported. In an inhalation exposure study, hydrazine was exposed to male and female F344 rats (each 100 animals/group) at 0, 0.066, 0.33, 1.33 and 6.65 mg/m^3 for one year. Endometrial hyperplasia, endometritis, ovarian atrophy, salpingitis and progressive glomerulopathy were found in females and Leydig cell hyperplasia in the testis in the 6.65 mg/m^3 group (MacEwen et al., 1981).

Following inhalation exposure of hydrazine in rats and hamsters for one year, age-related testicular atrophy was observed at 1 ppm, and ovarian atrophy, endometritis and salpingitis were observed at 5 ppm in rats. In hamsters, spermatogenic deficiency was observed at 5 ppm. These changes are age-related and observed also in normal animals, but exposure to hydrazine might promote them (Vernot et al., 1985; MacEwen et al., 1981).

b. Developmental toxicity

In a dermal application study, hydrazine was administered in pregnant female F344 rats (11 to 13 animals/group) at 0, 5 and 50 mg/kg/day on gestation day 9, and Caesarian section was conducted on gestation day 20. At 5 mg/kg/day and above groups, suppression of body weight gain and epidermal necrosis at the application sites in maternal animals after 24 hours of treatment, but effects on implantation and resorption rates, fetal body weight and external, visceral or skeletal anomalies in fetus were not observed. At 50 mg/kg/day, complete resorption was observed in 10 of 12 maternal animals (Keller et al., 1982).

In a subcutaneous administration study, hydrazine hydrochloride was injected in Wistar rats (26 animals/group) at 0 and 8 mg of hydrazine/kg/day from gestation day 11 to 20, and Caesarian section was conducted on gestation day 21. Maternal body weight was reduced by 20% and two rats died. The number of survival fetuses was decreased (survival/total fetuses, treated group: 63/172, control group: 142/179) in 9 animals of the treated group, but no change in the number of implantation was found. In fetuses, a reduction in body weight, pale appearance and edema occurred (region and the number unknown, assumed as systemic changes), but no malformation was observed (Lee and Aleyassine, 1970).

In an intraperitoneal administration study, hydrazine was injected in F344 rats (6 to 27 animals/group) at 0, 2.5, 5 and 10 mg/kg from gestation day 6 to 15, and Caesarian section was conducted on gestation day 20. Maternal body weight was reduced, and the number of resorption and fetuses per maternal animal were dose-dependently increased (statistically significant at 5 and 10 mg/kg). At all doses, the number of implantation per maternal animal and fetal body weight were not affected and the number of maternal animals with abnormal offsprings and fetuses was not increased (Keller et al., 1980).

In a subsequent intraperitoneal administration study, pregnant rats (10 to 11 animals/treated group, 27 animals/control group) were treated at 0, 10 mg/kg/day from gestation day 7 to 9, the incidences of abnormal litters and fetuses at 10 mg/kg group were 6/8 and 8/16, respectively, which were higher than that

in the control group (8/27 and 11/181). Anomalies observed were extra rib, fused rib delayed osteogenesis, moderate hydronephrosis and moderate ventriculomegaly (Keller et al., 1982).

In an intraperitoneal study of hydrazine in ICR mice at 0, 4, 12, 20, 30 and 40 mg/kg/day from gestation day 6 to 9, maternal body weight was reduced at 12 mg/kg and above groups ,and 17 days fetal body weight was also decreased at doses of 12 and 20 mg/kg. At 12 mg/kg and above groups, the incidence of abnormalities in offspring (exencephalia, hydronephrosis and extra rib in main) was dose-dependently increased and at 30 mg/kg and above groups, the number of resorption was increased. At 40 mg/kg group, some maternal animals died (Lyng et al., 1980).

As described avobe, in reproductive toxicity studies, oral administration of hydrazine via drinking water to male and female rats caused a decrease in the number of surviving embryos and an increase in resorption, showing that hydrazine has reproductive toxicity. Oral and inhalation administrations caused damage in the gonadal epithelial cells of male rats (parent). However, the original articles were not obtained and experimental conditions were unknown, and thus, these studies are considered as secondary information in this assessment. In developmental toxicity studies, hydrazine caused a reduction in fetal body weight, an increase in the number of resorption and an increase in the incidences of exencephalia, hydronephrosis and extra rib in mice and rats with intraperitoneal administration, which hydrazine has developmental toxicity including teratogenicity.

Table 7-7 Reproductive and developmental toxicity of hydrazine

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Reproductive toxicity					
Rat Male and female	Oral (gavage)	Once a day, 30 days before mating	Hydrazine nitrate 0, 13 mg of hydrazine /kg/day	13 mg/kg/day: no changes in female fertility, the number of newborns and resorptions and in the development of the surviving litters	Savchenkov & Samoilova, 1984
Rat Male and female 10 animals /treated group and 20 animals /control group	Oral (via drinking water)	6 months Study procedure and mating period unknown	Hydrazine (purity: 99.5%) 0, 0.002, 0.018, 0.82 mg/L (corresponding to 0, 0.00016, 0.0014, 0.016 mg/kg/day)	0.018 mg/L and above: lesion in the gonadal epithelial cells of male parent rats 0.82 mg/L: Dam: a reduction in surviving embryo, an increase in resorptions and death before and after implantation No developmental anomaly was found in all of 293 fetuses of the treated groups.	Duamin et al., 1984
Rat	Inhalation exposure	4 months 5 days/week, 5 hours/day Study procedure and mating period unknown	hydrazine 0, 0.01, 0.13, 0.85 mg/m^3 (corresponding to 0, 0.0012, 0.016 and 0.10 mg/kg/day)	0.13 mg/m^3 and above: increases in resorption and fetal death No effect on 315 fetuses No effects on the gonad of male parents	Duamin et al., 1984

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
Effects on reproductive organs in repeated dose study					
Rat F344 Male and female 100 animals /group	Inhalation exposure	1 year	hydrazine 0, 0.25, 1, 5 ppm (0, 0.33, 1.33, 6.65 mg/m^3)	1 ppm: age-related testicular atrophy 5 ppm: ovarian atrophy, endometritis, salpingitis NOAEL : 0.25 ppm (0.33 mg/m^3) (in this assessment)	Vernot et al., 1985; MacEwen et al., 1981
Hamster Syrian golden Male 200 animals /group)				5 ppm: spermatogenic deficiency (age-related changes but promoted by exposure to hydrazine)	
Rat F344 male and female each 100 animals /group	Inhalation exposure	1 year	0, 0.066, 0.33, 1.33, 6.65 mg/m^3	6.65 mg/m^3: Female: endometrial hyperplasia, endometritis, ovarian atrophy, salpingitis, progressive glomerulopathy Male: Leydig cell hyperplasia in the testis	MacEwen et al., 1981
Developmental toxicity					
Hamster Syrian golden 24 animals /group	Oral	Gestation day 12	hydrazine hydrate 0, 260 mg/kg	Postnatal effects on the enzyme activity in the brush border of fetal intestinal ciliated border. No incidence of cleft palate Other items were not examined.	Schiller et al., 1979
Rat F344 11-13 animals /treated group	Dermal	Gestation day 9 Caesarian section on gestation day 20	Hydrazine (purity: >95%) 0, 5, 50 mg/kg/day	5 mg/kg and above: suppression of body weight gain and epidermal necrolysis in the application site 24 hours after treatment. No abnormal findings in implantation and resorption rates, fetal body weight and external, visceral or skeletal anomalies in Caesarian section on gestation day 20 50 mg/kg: complete fetal resorption (10/12 of maternal animals)	Keller et al., 1982
Rat Wistar 26 animals /group	Sub-cutaneous	Gestation day 11-20 Caesarian section on gestation day 21	Hydrazine hydrochloride 0, 8 mg of hydrazine/kg/day	8 mg/kg: Dam: reduction in body weight (20%), death (2 animals) decrease in surviving fetuses (9/26) (surviving/total fetuses: treated group 63/172, control group 142/179) No effect on the number of implantation Fetus: a reduction in body weight, pale appearance, edema; no malformations	Lee & Aleyassine, 1970
Mouse ICR	Intraperi-toneal	Gestation day 6-9 Caesarian section on gestation day 17	Hydrazine 0, 4, 12, 20, 30, 40 mg/kg/day	12 mg/kg and above: Dam: suppression of body weight gain 12, 20 mg/kg: Fetus: reduction in body weight, dose-related increase in incidences of exencephalia, hydronephrosis and extra rib 30 mg/kg and above:	Lyng et al., 1980

Species sex/numbers of animals	Route	Period	Dose	Results	Reference
				Fetus: fetal toxicity (no detailed description) 40 mg/kg: Dam: some died	
Rat F344 6-19 animals /treated group 27 animals /control group	Intraperi-toneal	Gestation day 6-15 Caesarian section on gestation day 20	Hydrazine (purity: >95%) 0, 2.5, 5, 10 mg/kg/day	2.5 mg/kg/day and abov: Dam: no significant change in implantation rate Fetus: no anomaly in fetal appearance, organs and skeleton 5 mg/kg/day and above: Dam: suppression in body weight gain, increase in the number of resorption and/or dead fetus per maternal animal Fetus: decrease in body weight 10 mg/kg: Dam: resorption of all fetuses except 6 live fetuses in one litter	Keller et al., 1980
Rat F344 10-11 animals /treated group the control group of the above study (1980) was used.	Intraperit-oneal	Gestation day 7-9 (a) or 13-15 (b) Caesarian section on gestation day 20	Hydrazine (purity: >95%) 0, 10 mg/kg/day	10 mg/kg/day: suppression in maternal body weight gain and significant decrease in fetal body weight (groups a and b) significant increase in the incidences of resorption and abnormal fetus (hydronephrosys, hydrocephaly and extra rib) No difference in growth of neonates compared with the control group Incidence of abnormal maternal animals and fetuses: 6/8 and 8/16, significantly higher than that in the control group (8/27 and 11/181)	Keller et al., 1982

7.3.6 Genotoxicity

Studies on the genotoxicity of hydrazine and its salts are summarized in Table 7-8, and the summary of these data is shown in Table 7-9.

It is considered that the metabolic process and metabolites of hydrazine are same in all administration routes (ATSDR, 1997). Therefore, hydrazine hydrate and hydrazine salts used in the studies summarized in this section are assessed under assumption that there is no difference in manifestation of genotoxicity between them.

a. *in vitro* studies

The results of reverse mutation assays of hydrazine (Chu et al., 1973; Herbold, 1978; Herbold and Buselmaier, 1976; McMahon et al., 1979; Noda et al., 1986) and its hydrate (Bayer, 1989; De Flora, 1981; Fraunhofer Institute, 1990a; Parodi et al., 1981) in *Salmonella typhmurium* were positive regardless of the presence and absence of metabolic activation system. In gene mutation assays using other bacteria and

eukaryotic cells, the results were positive (Kumari et al., 1992; Lemontt and Lair, 1982; Rogers and Back, 1981).

In an alkaline elution assay for DNA breaks with hepatocytes (Sina et al., 1983) and an unscheduled DNA synthesis test (Mori et al., 1988), genotoxicity of hydrazine was confirmed. In a sister chromatid exchange test of hydrazine at a noncytotoxic concentration, an increase in sister chromatid exchange was found without metabolic activation system and positive results were shown in a micronucleus test. In an chromosome aberration test of hydrazine in accordance with the OECD Guideline 473, no effects on chromosome aberration were found in human lymphocytes regardless of the metabolic activation system (Fraunhofer Institute, 1990b).

In gene mutation assays with yeast *Sacchromyces cerevisiae*, hydrazine hydrochloride and hydrazine sulfate exhibited positive results (Lemontt and Lair, 1982; Loprieno, 1981). Similarly, in a host-mediated gene mutation assay of hydrazine sulfate with bacteria srains of *S. typhmurium* (Braun et al., 1976; Rohrborn et al., 1972; Simmon et al., 1979), mutagenicity was confirmed, inducing DNA damage in *Eschericia coli* (Green, 1981; Hellmer and Bolcsfoldi, 1992).

However, most of mutation assays for hydrazine sulfate using mammalian and human cell lines (Amacher et al., 1980; Carver et al., 1981; Gupta and Goldstein, 1981; Hsie et al., 1981) as well as unscheduled DNA synthesis test with human cell lines (Martin and McDermid, 1981; Robinson and Mitchell, 1981) showed negative or weak positive results, but a cell transformation assay exhibited positive result (Pienta, 1980; Pienta et al., 1978).

b. *in vivo* studies

Of *in vivo* studies, dominant lethal tests of hydrazine in mice (Epstein et al., 1972 ; Epstein and Shafner, 1968) and unscheduled DNA synthesis assay of hydrazine hydrochloride (Sotomayor et al., 1982) showed negative results, but a gene mutation assay for hydrazine in *Drosophila* (Jain and Shukla, 1972) exhibited positive result.

In an alkaline elution assay of hydrazine hydrate in mice, an increase in the incidence of DNA single strand break was found (Parodi et al., 1981), and mouse spot tests of hydrazine hydrate and hydrazine hydrochloride showed positive results (Fraunhofer Institute, 1989; Neuhauser-Klaus and Chauhan, 1987), suggesting that mutagenicity of hydrazine was positive.

As for mutagenicity of hydrazine, hydrazine and its sulfate induce methylation of guanine in hepatic DNA at a toxic dose and around, similar to other hepatotoxic compounds (ethanol, carbon tetrachloride, etc.). The liver has a physiological function to eliminate methyl base that is attached to guanine in hepatic DNA, however, hydrazine attaches more methyl bases to hepatic DNA than methyl bases removed and induces physiological unbalance, resulting in genotoxicity (Henscher, 1985, 1989).

There are some studies reporting that guanine of DNA changes into 7-methylguanine and O^6-methylguanine in DNA methylation (Barrows and Shank, 1981; Barrows et al., 1983; Becker et al., 1981; Bosan and Shank, 1983; Leakakos and Shank, 1994; Shank, 1987; TNO, 1990).

Many *in vitro* studies of hydrazine including reverse mutation, unscheduled DNA synthesis and

chromosomal aberration tests show positive results. Of *in vivo* studies, dominant lethal tests in mice and unscheduled DNA synthesis assays exhibited negative results, but mouse spot tests and gene mutation assay in *Drosophila* showed positive results. From overall evaluation of the results in *in vitro* and *in vivo* studies, hydrazine is considered to be genotoxic.

Table 7-8 Genotoxicity of hydrazine and its salts

Test system		Species (Organisms) /Strain	Concentration. / Dose μg/plate	Result [a)] S9-	Result [a)] S9+	Reference
in vitro	**Hydrazine**					
	Reverse gene mutation	*Salmonella typhimurium* TA 98, 1538	12-1,200	ND	-	Herbold, 1978
		TA100, 1535		ND	+	
		S. typhimurium TA 1536, 1537, 1538	120-12,000	ND	-	Herbold & Buselmaier, 1976
		TA1535		ND	+	
		G46		ND	+	
		S. typhimurium TA 100	0.1-1,000	-	+	McMahon et al., 1979
		TA 1535, 98, 1538		-	-	
		Escherichia coli WP2 / WP2uvrA$^-$	0.1-1,000	-	+	McMahon et al., 1979
		E. coli B/r / WP2uvrA	0-365	+	+	Noda et al., 1986
		Bacteriophage /hpt 203	160	+	ND	Chu et al., 1973
	Gene mutation	Yeast *Saccharomyces cerevisiae* XY726-7C(RAD),-7D(RAD), -7a(rad6-1),7842-(RAD)	6,400	+	ND	Lemontt & Lair, 1982
	Gene mutation	Mouse lymphoma L5178Y cells	3.2-160	+	ND	Rogers & Back, 1981
		Rat neonatal hepatocyte cells	40	+		Kumari et al., 1992
	Cell transformation	Human neonatal fibroblast cells	35	+	ND	Milo et al., 1981
	Alkaline elution	Isolated rat hapatocytes	0.96-96	+		Sina et al., 1983
	Micronucleus	Chinese hamster V79 cells	1.86-3.84	+	ND	Onfelt, 1987
	Hydrazine hydrate					
	Reverse gene mutation	*S. typhimurium* TA 98, 100, 1537,1538	50-500	-	^{w}+	De Flora, 1981
		TA1535		-	^{w}+	
		S. typhimurium TA 98, 100, 1537,1538	62.5-100	-	-	Parodi et al., 1981
		TA1535		+	+	
		S. typhimurium TA 100	10-500	-	-	Fraunhofer Institute, 1990a
		TA1535		+	+	
		S. typhimurium TA 100	6-384	-	ND	Bayer, 1989

Test system	Species (Organisms) /Strain	Concentration. / Dose μg/plate	Result [a] S9-	Result [a] S9+	Reference
	TA 1535		+	ND	
Chromosome aberration	Human peripheral lymphocytes	15-90	-	-	Fraunhofer Institute, 1990b
DNA damage	*E. coli* WP2, WP67, CM871	75-800	+	-	De Flora et al., 1984
Unscheduled DNA synthesis	Primary cultured of isolated hepatocytes from ACI/N rats	0.005-50	-		Mori et al., 1988
	C3H/HeN mice		+		
Hydrazine hydrochloride					
Gene mutation	*Haemophilus influenzae*	210-105,000	+	ND	Kimball & Hirsch, 1975
	Yeast *S. cerevisiae* XY5054-18C,XY-222-1A, XY491-4B	10.5-21,000	+	ND	Lemontt & Lair, 1982
Sister chromatid exchange (SCE)	CHO cells [b]	6.6-105	+	ND	MacRae & Sitch, 1979
	Chinese hamster V79 cells	68.5-137	+	ND	Speit et al., 1984
Hydrazine sulfate					
Reverse gene mutation	*E. coli* 343/113/*uvr*B	200-4,000	ND	+	Mohn et al., 1981
	E. coli WP2	5-2,000	+	+	Mohn et al., 1981
	Yeast *S. cerevisiae* XV185-14C (polyploid)	133-266	+	ND	Mehta & von Borstel, 1981
Forward gene mutation	*S. typhimurium* TM677	-1,000	ND	+	Skopek et al., 1981
	Yeast *Schizosaccharomyces pombe*	0.05-5	+	+	Loprieno, 1981
DNA damage	*E. coli* WP2, WP67, CM871	ND	+	+	Green, 1981
	E. coli 343/636, -/591/	-2,834	+	-	Hellmer & Bolcsfoldi, 1992
Gene conversion	Yeast *S. cerevisiae* D7 (diploid)	385	+	-	Zimmermann & Scheel, 1981
	Yeast *S. cerevisiae* D3 (diploid)	-50,000	-	-	Simmon, 1979
	Yeast *S. cerevisiae* D4 (diploid)	0.33-333	-	+	Jagannath et al., 1981
Gene mutation	CHO cells [b]	0.04-500	-	-	Hsie et al., 1981
	Mouse lymphoma L5178Y cells	35.1-851	[w]+	ND	Amacher et al, 1980
	CHO AT3-2 cells	800-2,000	-	-	Carver et al., 1981
	Human lung fibroblast HSC172 cells	200-1,000	-	+	Gupta & Goldstein, 1981
Cell transformation	Syrian golden hamster embryo cells	1-150	ND	+	Pienta et al., 1978; Pienta, 1980
Unscheduled DNA synthesis	Human cancer cells HeLa	0.1-100	+	-	Martin & McDermid, 1981
	Human embryos fibroblast WI-38 cells	63-1,000	-	-	Robinson & Mitchell, 1981

Test system		Species (Organisms) /Strain	Concentration. / Dose μg/plate	Result [a)] S9-	Result [a)] S9+	Reference
	Alkaline elution	Mouse lymphoma L5178Y TK+/-cells	130-1,300	ND	-	Garberg et al., 1988
	Host-mediated gene mutation	*S. typhimurium* TA1950 (NMRI mouse)	150mg/kg Subcutaneous		+	Braun et al., 1976
		S. typhimurium G 46 (NMRI mouse)	10, 25, 50 mg/kg Subcutaneous		+	Rohrborn et al., 1972
		S. typhimurium TA1535 (Swiss-Webster mouse) intraperitoneal administration	420 mg/kg oral		+	Simmon et al., 1979
	Sister chromatid exchange (SCE)	DON cells [c)]	0.13-3	+	+	Baker et al., 1983
		CHO cells [b)]	32-1,667	-	-	Natarajan & van Kesteren-van Leuwen, 1981
		CHO cell [b)]	0.1-100	[w]+	[w]+	Perry & Thomson, 1981
in vivo	**Hydrazine**					
	Dominant lethal	Mouse ICR-Ha Swiss male	Intraperitoneal single, 42, 52 mg/kg		-	Epstein et al., 1972; Epstein & Shafner, 1968
	Gene mutation	*Drosophila* Oregon K	Oral (fed) 10 or 20 m mol/ND		+	Jain & Shukla, 1972
	Hydrazine hydrate					
	Spot	Mouse C57BL-6J female	Intraperitoneal single (gestation day 9) 40 mg.kg		+	Fraunhofer-Institute, 1989
	Alkaline elution	Mouse Swiss	Intraperitoneal single 78, 156 mg/kg or 52 mg/kg, 5 times		+	Parodi et al., 1981
	Hydrazine hydrochloride					
	Spot	Mouse C57BL female	Intraperitoneal single (gestation day 8-10) 40, 60, 80 mg/kg		+	Neuhauser-Klaus & Chauhan, 1987
	Unscheduled DNA synthesis	Mouse (101×C3H)F1 female	Intraperitoneal, single 10-120 mg/kg		-	Sotomayor et al., 1982
	Hydrazine sulfate					
	Sex-linked recessive lethal	*Drosophila melanogaster*	Oral (diet) ND 1st or 2nd half of larval stage		+	Narda & Migliani, 1972
		D. melanogaster Canton S	Oral (diet) 2,100 ppm injection 2,500 ppm/3-d		-	Yoon et al., 1985

Test system		Species (Organisms) /Strain	Concentration. / Dose μg/plate	Result [a)] S9- S9+	Reference
	Chromosomal recombination	*D. melanogaster* Male and female	Oral (diet) 80 and 160 mg/L: Chronic exposure	^{w}+	Vogel & Nivard, 1993
	Cytogenetic	Mouse C57BL-6J male and female	Oral gavage Single 25, 50, 100 mg/kg	-	Wargovich et al., 1983
		D. melanogaster Oregon K	Oral (diet) ND 1st or 2nd half of larval stage	+	Narda & Migliani, 1972
	Micronucleus	Mouse ICR male	Intraperitoneal 11, 22, 44 (=1/2 LD_{50}) mg/kg	-	Kirkhart, 1981
		Mouse $B6C3F_1$ male	Intraperitoneal twice 24h interval 80% of LD_{50}	^{w}+	Salamone et al., 1981
		Mouse ICR male and female	Intraperitoneal 11, 22, 44 mg/kg (1/2 of LD_{50})	-	Tsuchimoto & Matter, 1981

a) ND: No data available, +: positive; -: negative; ^{w}+: weak positive,
b) CHO cells: Chinese hamster ovary cells.
c) DON cells: Chinese hamster lung cell-derived cell line.

Table 7-9 Genotoxicity of hydrazine and its salts (summary)

	DNA damage	Mutation	Chromosomal aberration	other
Bacteria	+	+	ND	ND
Mold / yeast / plant	ND	+	+	ND
Mold / yeast	ND	+/-	+/-	+
Culture cells	+	+/-	+	+/-
Mammals (*in vivo*)	+/-	+	+, -	-
Human	ND	ND	ND	ND

ND: No data available, +: positive; -: negative; +/-: either positive or negative.

7.3.7 Carcinogenicity

Studies on the carcinogenicity of hydrazine, hydrazine hydrate and hydrazine sulfate are summerized in Table 7-10.

a. Hydrazine

In an oral (drinking water) administration study, male and female Swiss mice were given drinking water containing 0 and 0.001% hydrazine (male: corresponding to 0 and 2.0 mg/kg/day; female: corresponding to 0 and 1.6 mg/kg/day: estimated by IPCS) in life-span of 113 weeks. The incidences of benign and

malignant lung tumors were increased in males and females, and the incidence of malignant lymphoma was increased in males but not in females (Toth, 1972). No statistical evaluation is reported in this study.

In inhalation exposure studies, female C57BL/6 mice, male and female F344 rats and male Syrian golden hamsters were exposed to hydrazine vapor for 12 months (6 hours/day, 5 days/week) and observed for further 15, 18 and 12 months, respectively. Exposure concentrations were 0, 0.05, 0.25 and 1 ppm (0, 0.066, 0.33 and 1.33 mg/m^3) for mice, 0, 0.05, 0.25, 1 and 5 ppm (0, 0.066, 0.33, 1.33 and 6.65 mg/m^3) for rats and 0, 0.25, 1 and 5 ppm (0, 0.33, 1.33 and 6.65 mg/m^3) for hamsters. In mice, the incidence of lung adenoma was slightly increased at 1 ppm. In rats, benign nasal epithelial tumors, mainly adenomatous polyps, were observed at 1 ppm and above, malignant nasal epithelial tumors at 5 ppm in both sexes, and thyroid gland adenocarcinoma in males at 5 ppm. In hamsters, benign nasal polyps were observed at 5 ppm. The tumor with the highest incidence was lung adenoma which was observed at 1 ppm (MacEwen et al., 1981 ; Vernot et al., 1985).

In an inhalation exposure study, male and female F344 rats and male Syrian golden hamsters were exposed to hydrazine at 0, 75 and 750 ppm (0, 100 and 1,000 mg/m^3) for 10 weeks (1 hour/week) and observed for further 28 and 22 months, respectively. Histopathological examination was limited in the nasal cavity. Benign nasal epithelial tumors were observed in males and females at 750 ppm. In male hamsters, both of benigh and malignant nasal epithelial tumors were observed at 750 ppm, but the incidence was not significant. The authors conclude that hydrazine develops nasal cavity epithelium tumors (Latendress et al., 1995).

b. Hydrazine hydrate

In an oral (via drinking water) administration study of hydrazine hydrate, the incidence of lung tumor was increased in mice, and the incidence of malignant uterine cancer was increased and liver tumors were developed in rats. These tumors were induced in rats and mice at 50 mg/L (Steinhoff and Mohr, 1988, 1990).

c. Hydrazine sulfate

No carcinogenicity study of hydrazine sulfate in compliance with the current guidelines was obtained (GDCh BUA, 1996). In many studies (some results are shown in Table 7-10), carcinogenicity of hydrazine sulfate was detected similar to carcinogenicity of hydrazine. In oral administration studies in mice, lung tumors (Biancifori, 1970b) were observed, and liver and lung tumors in rats (Biancifiori et al., 1966) and liver tumors in hamsters (Bosan et al., 1987).

As described above, carcinogenic responses were observed in experimental animals after oral administration and inhalation exposure. The most significant region of tumors after inhalation exposure to hydrazine was the respiratory system, and lung tumors developed in mice and tumors in the nasal cavity in rats and hamsters. These tumors were developed at a dose of 1.33 mg/m^3 with no significant differences in body weight and mortality compared to the control in mice, but at a toxic dose (death-inducing dose) of 6.65 mg/m^3 in rats and hamsters. Oral administration of hydrazine hydrate caused lung tumors in mice and liver and uterine tumors in rats, and oral administration of hydrazine sulfate resulted in liver and lung

tumors in mice and liver tumors in rats. From these results, hydrazine is considered to be carcinogenic.

The evaluations of carcinogenicity of hydrazine by the international and national organizations are shown in Table 7-11. The IARC has categorized hydrazine as Group 2B (the agent is possibly carcinogenic to humans). The U.S. EPA (2002) estimated the oral cancer slope factor for hydrazine as 3.0/(mg/kg/day) and the drinking water unit risk as 8.5×10^{-5}/(μg/L) based on the results of an oral administration (gavage) study of hydrazine sulfate in male CBA/Cb/Se mice (Biancifori, 1970b), and the inhalation unit risk as 4.9×10^{-3}/(μg/m^3) based on the results of an inhalation exposure study of hydrazine in F344 rats (MacEwen et al., 1981). Using the drinking water unit risk, the drinking water concentrations corresponding to the excess life-span cancer risk of 10^{-6} and 10^{-5} are 0.01 and 0.1 μg/L, respectively. Similarly, with the inhalation unit risk, the air concentrations corresponding to the excess lifespan cancer risk of 10^{-6} and 10^{-5} are 0.0002 and 0.002 μg/L, respectively.

Table 7-10 Carcinogenicity of hydrazine, hydrazine hydrate and hydrazine sulfate

Species sex/number of animals	Route	Dose/ Exposure Period (Post exposure observation period)/(purity)	Results	Reference
Hydrazine				
Mouse Swiss Male and female	Oral (via drinking water)	0, 0.001% (male: corresponding to 0, 2.0 mg/kg/day; female: corresponding to 0, 1.6 mg/kg/day: estimated by IPCS) 113 weeks (>95%)	Male: 0 / 0.001% Lung tumor (benign & malignant) 14/110 / 27/50 Malignant lymphoma 2/110 / 7/50 Female: 0 / 0.001% Lung tumor (benign & malignant) 11/110 / 24/50 Malignant lymphoma 16/110 / 9/50	Toth, 1969, 1972
Mouse C57BL-6 Female	Inhalation exposure	0, 0.05, 0.25, 1 ppm (0, 0.066, 0.33, 1.33 mg/m^3) 6 hours/day, 5 days/week, 12 months (Obs. 15 months) (99.8%)	Lung adenoma 0 / 0.066 / 0.33 / 1.33 mg/m^3 Female 4/373 / 3/364 / 5/382 / 12/379*	MacEwen et al., 1981; Vernot et al., 1985
Rat F344 Male and female	Inhalation exposure	0, 0.05, 0.25, 1, 5 ppm (0, 0.066, 0.33, 1.33, 6.65 mg/m^3) 6 hours/day, 5 days/week, 12 months (Obs. 18 months) (99.8%)	Nasal cavity epithelium benign tumor 0 / 0.066 / 0.33 / 1.33 / 6.65 mg/m^3 Male 0/149 / 2/99 / 2/99 / 10/98* / 66/99* Female 0/147 / 1/99 / 0/100 / 4/97* / 31/98* Nasal cavity epithelium malignant tumor Male 0/149 / 1/99 / 0/99 / 1/98 / 5/99* Female 0/147 / 0/99 / 0/100 / 0/97 / 5/98* Thyroid adenocarcinoma Male 7/149 / 6/99 / 5/99 / 9/98 / 13/99*	

Species sex/number of animals	Route	Dose/ Exposure Period (Post exposure observation period)/(purity)	Results	Reference
Rat F344 Male and female	Inhalation exposure	0, 75, 750 ppm (0, 100, 1,000 mg/m^3) 1 hour/week 10 weeks (Obs. 28 months) (98.8%)	Nasal cavity epithelium benign tumor 0 100 1,000 mg/m^3 Male 0/98 0/93 4/99* Female 0/98 0/ 100 6/95*	Latendresse et al., 1995
Hamster Syrian golden Male	Inhalation exposure	0, 0.25, 1, 5 ppm (0, 0.33, 1.33, 6.65 mg/m^3) 6 hours/day, 5 days/week, 12 months (Obs. 12 months) (99.8%)	Nasal mucosa polyp 0 0.33 1.33 6.65 mg/m^3 1/181 0/154 1/146 16/160*	MacEwen et al., 1981; Vernot et al., 1985
Hamster Syrian golden Male	Inhalation exposure	0, 75, 750 ppm (0, 100, 1,000 mg/m^3) 1 hour/week 10 weeks (Obs. 22 months) (98.8%)	Nasal epithelium tumor (benign and malignant) 0 100 1,000 mg/m^3 Male 0/100 1/93 5/94[a)]	Latendresse et al., 1995
Hydrazine hydrate				
Mouse NMRI Male and female	Oral (via drinking water)	0, 2, 10, 50 mg/L, life-span (99.3%)	Lung benign tumor (only female) 0 2 10 50 mg/L Female 6/50, 6/50, 9/50, 15/47*	Steinhoff & Mohr, 1990
Rat Wistar Male and female	Oral (via drinking water)	0, 2, 10, 50 mg/L, life-span (99.3%)	0 2 10 50 mg/L Male 0/50 1/49 1/50 4/49* Female 0/50 0/50 0/50 4/47* Liver tumor malignant Female 0/50 0/50 0/50 3/47* Uterine tumor malignant Female 7/50 9/50 8/50 14/47*	Steinhoff & Mohr, 1988
Hydrazine sulfate				
Mouse Swiss Male and female	Oral (via drinking water)	0, 0.012% 25 weeks (Life-span observation) (purity unknown)	Lung tumor 0 0.012% Male 11/110 25/50[a)] Female 14/110 24/50[a)]	Toth, 1969
Mouse CBA/Cb/Se Male and female	Oral gavage	0, 0.14, 0.28, 0.56, 1.13 mg/animal/day 25 weeks (total 150 times) (Life-span observation) (purity unknown)	Liver tumor 0 0.14 0.28 0.56 1.13 mg /day Male 3/30 1/26 7/25 12/25 15/25 [a)] Female 1/29 0/25 2/25 16/24 15/24 [a)]	Biancifiori, 1970b
Rat CBRI-Se Male and female	Oral gavage	Male: 0, 18 mg/animal /day Female: 0, 12 mg/animal/day 68 weeks (life-span observation) (purity unknown)	Lung tumor (benign and malignant) 0 18(12) mg/ day Male 0/28 3/14[a)] Female 0/22 5/18 [a)]	Biancifiori et al., 1966

Species sex/number of animals	Route	Dose/ Exposure Period (Post exposure observation period)/(purity)	Results	Reference
Hamster Syrian golden Male	Oral (via drinking water)	0, 170, 340, 510 mg/L 2 years (>99%)	Hepatocellular carcinoma 0 170 340 510 mg/L Male 0/31 0/31 4/34 11/34 a)	Bosan et al., 1987

a) No statistic evaluation available * Statistically significant difference

Table 7-11 Evaluations of carcinogenicity of hydrazine by the international and national organizations

Organization/ source	Classification	Classification criteria
IARC (2002)	Group 2B	The agent is possibly carcinogenic to humans.
ACGIH (2002)	A3	Confirmed animal carcinogen with unknown relevance to humans.
The Japan Society for Occupational Health (2002)	Group 2B	The substance with less evidence (possibly carcinogenic to humans).
U.S. EPA (2002)	Group B2	Agent for which there is "sufficient" evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies.
U.S. NTP (2001)	R	Reasonably anticipated to be human carcinogens.

7.4 Summary of effects on human health

Hydrazine is absorbed rapidly in any routes of exposure including oral, inhalation and dermal administration.

No major differences in distribution pattern of hydrazine in tissues were found among administration routes. Within 30 minutes after oral administration, the concentrations in the kidney, liver and lung reached the maximum, and especially the concentration in the kidney was high compared to other organs. Hydrazine was detected also in the brain in intravenous administration. In the liver, hydrazine is considered to have saturation effect. No difference was found in the order of organs by distribution concentrations up to 20 hours after treatment. The blood concentration was decreased biphasically.

It is considered that the metabolic process (mainly acetylation and free radical generation) and metabolites of hydrazine are same in all administration routes. In rat, hydrazine, monoacetylhydrazine, diacetylhydrazine, pyruvic acid hydrazone, urea and cyclic compound [1,4,5,6-tetrahydro-6-oxo-3-pyridazine-carboxyl acid (a reaction product of 2-oxoglutaric acid and hydrazine)] are detected in the urine, and hydrazine is eliminated in the expiration as nitrogen gas. It has been reported that in humans whose hydrazine metabolism (acetylation) is extremely slow due to acetylase enzyme deficiency, hydrazine absorbed might be accumulated in the plasma, and therefore, it is necessary to give special considerations to these individuals with high suseptibility to hydrazine.

In humans, coma and EEG hypoactivity were observed in a poisoning accident at the occasion of hydrazine explosion, and antidote treatment of pyridoxine recovered spontaneous motion impairment and

neuropathy. Hematuria, an increase in blood glucose level and hepatic dysfunction were observed also as hydrazine intoxication. Inhalation of hydrazine vapor induced neuropathy and pulmonary edema, however, the patient was improved by pyridoxine treatment. Oral intake of hydrazine or hydrazine hydrate in accidents induced vomiting, hepatotoxicity, neurologic and cardiovascular symptoms.

As hydrazine has ammonia- or amine-like odor and human olfactory threshold, which is 3 to 4 ppm, is low, acute exposure accidents at high concentrations rarely occur, but there is a possibility that long term exposures at low concentrations may cause poisoning.

Hydrazine sulfate does not induce irritation to the human skin, but hydrazine and its salts have skin sensitization. Therefore, the Japan Society for Occupational Health has classified hydrazine and its compounds into Group 2 of skin sensitizer.

In experimental animals, the acute toxicity values are as follows: oral LD_{50} values are 59 mg/kg in mice and 60 to 90 mg/kg in rats, inhalation LC_{50}s (4-hour exposure) are 330 mg/m^3 in mice and 350 to 760 mg/m^3 in rats, and dermal LD_{50} is 91 mg/kg in rabbits. Hydrazine hydrate showed similar acute toxicity values. Acute toxic symptoms are ataxia, hypoactivity, dyspnea, enhanced excitability, salivation, vomiting and convulsion. In acute inhalation exposure, pulmonary edema, lesion in bronchial mucosa, pulmonary congestion and nasal mucosa epithelium degeneration (necrosis, scale and inflammation) were observed and in intravenous administration, nephrotoxicity was found. In addition, acute administration of hydrazine induced hepatotoxicity.

In application of 35% hydrazine and 55% hydrazine hydrate solutions to rabbit skins, irritation and corrosion were observed, respectively, and in application of 5% hydrazine hydrate solution to the rabbit eyes, no irritation was observed.

In the repeated administration of hydrazine, lesions were observed in the respiratory system, liver, kidney, central nervous and cardiovascular systems, especially marked in the respiratory system and liver. In the respiratory system, inhalation exposure induced proliferative changes including hyperplasia in the respiratory tract mucosa induced by chronic stimuli but not other administration routes. In oral administration, bile duct hyperplasia was found in male rats at the lowest dose. In inhalation exposure, hydrazine caused supression in body weight gain and inflammation in larynx and tracheal mucosa epithelium in rats at the lowest dose. As both in inhalation and oral administration, the toxicity is observed at the lowest doses, the LOAEL of hydrazine is 0.066 mg/m^3 in inhalation exposure and 0.13 mg/kg/day in oral administration.

In reproductive and developmental toxicity, oral administration of hydrazine via drinking water to male and female rats caused a decrease in the number of surviving embryos and an increase in resorption. Oral and inhalation administrations caused damage in the gonadal epithelial cells of male rats (parent). However, the original articles were not obtained and experimental conditions were unknown, and thus, these studies are considered as secondary information in this assessment. Intraperitoneal administration of hydrazine caused a reduction in fetal body weight, an increase in the number of resorption and an increase in the incidences of exencephalia, hydronephrosis and extra rib in mice and rats. These results show that hydrazine has reproductive and developmental toxicity including teratogenicity.

In genotoxicity, many *in vitro* studies of hydrazine including reverse mutation, unscheduled DNA

synthesis and chromosomal aberration tests show positive results. Of *in vivo* studies, the results of sister chromatid exchange test, dominant lethal tests in mice and unscheduled DNA synthesis assays exhibited negative results, but mouse spot tests and gene mutation assay in *Drosophila* showed positive results. The overall evaluation of these results indicate that hydrazine is genotoxic.

With regard to carcinogenicity, a retrospective cohort study (gender unknown) in humans reported that exposure to hydrazine did not increase a risk of cancer incidences. However, carcinogenic responses were observed in experimental animals after oral administration and inhalation exposure. The most significant region of tumors after inhalation exposure to hydrazine was the respiratory system, and lung tumors developed in mice and tumors in the nasal cavity in rats and hamsters. These tumors were developed at a dose of 1.33 mg/m^3 with no significant differences in body weight and mortality compared to the control in mice, but at a toxic dose (death-inducing dose) of 6.65 mg/m^3 in rats and hamsters. Oral administration of hydrazine hydrate caused lung tumors in mice and liver and uterine tumors in rats, and oral administration of hydrazine sulfate resulted in liver and lung tumors in mice and liver tumors in rats. From these results, hydrazine is considered to be carcinogenic. Hydrazine has been categorized as Group 2B (the agent is possibly carcinogenic to humans) by the IARC.

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ABBREVIATIONS

ACGIH : American Conference of Governmental Industrial Hygienists
ADH : alcohol dehydrogenase
ALDH : aldehyde dehydrogenase
ALP : alkaline phosphatase
ALT : alanine aminotransferase
ASAT : aspartate aminotransferase
AST : aspartate aminotransferase
ATSDR : Agency for Toxic Substances and Disease Registry
BCF : Bioconcentration Factor
BHK : Syrian hamster kidney culture cells
BOD : Biological Oxygen Demand
BUN : blood urea nitrogen
CAS : Chemical Abstract Services
CAS Online : Chemical Abstract Services Online
CEPA : Commonwealth Environment Protection Agency
CERHR : Center for the Evaluation of Risks to Human Reproduction
CERI : Chemicals Evaluation and Research Institute, Japan
CHL : Chinese hamster lung cells
CHO : Chinese hamster ovary cells
CICAD : Concise International Chemical Assessment Document
Cmax : the maximum concentration of a compound in the blood, etc.
COD : Chemical Oxygen Demand
CPK : Creatinine phosphokinase
DDT : dichlorodiphenyltrichloroethane
DOC : Dissolved Organic Carbon
EA : Environment Agency of Japan
EC : European Communities
EC_{10} : Effect Concentration measured as 10% effect
EC_{50} : median Effect Concentration
ECB : European Chemicals Bureau
ECETOC : European Centre for Ecotoxicology and Toxicology of Chemicals
EEC : European Economic Communities
EHC : Environmental Health Criteria
EHI : Estimated Human Intake
EPA : Environmental Protection Agency (USA)
EU : European Union
EUSES : Europian Union System for the Evaluation of Substances
FAD : flavin adenine dinucleotide
FAO : Food and Agriculture Organisation of the United Nations
GABA : g-aminobutyric acid
GC : gas chromatography
GGT : gamma-glutamyl transpeptidase
GLP : Good Laboratory Practice
hr : hour
HSDB : Hazardous Substances Data Bank
IARC : International Agency for Research on Cancer
IC : Industrial Category
IC_{50} : median Immobilisation Concentration or median Inhibitory Concentration
ILO : International Labour Organisation
IPCS : International Programme on Chemical Safety
IRIS : Integrated Risk Information System
IUCLID : International Uniform Chemical Information Database (existing substances)
Koc : Soil adsorption coefficient Koc
Kow : octanol/water partition coefficient
LC_{50} : median Lethal Concentration

LD_{50} : median Lethal Dose
LDH : lactate dehydrogenase
LLNA : Local Lymph Node Assay
LOAEL : Lowest Observed Adverse Effect Level
LOEC : Lowest Observed Effect Concentration
LOEL : Lowest Observed Effect Level
MAO : monoamineoxydase
MATC : Maximum Acceptable Toxic Concentration
MCH : mean corpuscular hemoglobin
MCV : mean corpuscular volume
METI : Ministry of Economy, Trade and Industry, Japan
MHLW : Ministry of Health, Labour and Welfare
min : minute
MITI : Ministry of International Trade and Industry, Japan
MNLD : maximum non lethal dose
MOE : Ministry of the Environment, Japan
MOF : Ministry of Finance, Japan
MOS : Margin of Safety
MTD : maximum tolerance dose
NAT2 : N-acetyltransferase
NCI : National Cancer Institute
NICNAS : Australia's National Industrial Chemicals Notification and Assessment Scheme
NIES : National Institute for Environmental Studies, Japan
NITE : National Institute of Technology and Evaluation, Japan
NMR : nuclear magnetic resonance analysis
NOAEL : No Observed Adverse Effect Level
NOEC : No Observed Effect Concentration
NOEL : No Observed Effect Level
NTE : neurotoxic esterase
NTP : National Toxicology Program (USA)
NZW : New Zealand White
OECD : Organisation for Economic Cooperation and Development
OPIDN : Organophosphate-induced delayed neuropathy
OR : odds ratios
ppm : parts per million
$polA^-$: DNA polymerase$^-$
$polA^+$: DNA polymerase$^+$
pKa : negative log of the acid dissociation constant
PRTR : Pollutant Release and Transfer Register
RBC : Radiation Biology Center
RAR : Risk Assessment Report
RC : Risk Characterisation
RfC : Reference Concentration
RfD : Reference Dose
RTECS : Registry of Toxic Effects of Chemical Substances
SCE : Sister chromatid exchange
SDH : sorbitol dehydrogenase
SER : smooth endoplasmic reticulum
SG : Syrian golden
SIDS : Screening Information Data Set
SLRL-test : sex-linked recessive lethal test
SOD : superoxide dismutase
TDI : Tolerable Daily Intake
TE : toxic equivalent
TLV : Threshold Limit Value
Tmax : time until a concentration reaches Cmax.
TOXLINE : Toxicology Literature Online
UV : ultraviolet

v/v : volume per volume ratio
w : week
w/w : weight per weight ratio
WHO : World Health Organization
γ-GTP : γ-glutamyl transpeptidase
δALS : δ-aminolevulinic acid synthetase