

HYDRAZINE

Hydrazine was considered by the *IARC Monographs Working Group* in 1973, 1987, and 1998 ([IARC, 1974, 1987, 1999](#)). New data have since become available and these have been taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 302-01-2

Chem. Abstr. Serv. Name: Hydrazine

IUPAC Systematic Name: Hydrazine

Synonyms: Levoxine, nitrogen hydride, diamide, diamine, anhydrous hydrazine, hydrazine base.

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: H_4N_2

Relative molecular mass: 32.05

1.1.3 Chemical and physical properties of the pure substance

From [IPCS \(1987a\)](#), [ECHA \(2011\)](#), [NIOSH \(2014\)](#), [HSDB \(2010\)](#)

Description: Colourless, fuming, oily liquid with a penetrating ammonia-like odour; odour threshold, 3–9 mg/m³

Note: Anhydrous hydrazine contains less than 37% water by mass; hydrazine hydrate [CAS No.: 7803-57-8] corresponds to a 64% or less aqueous solution of hydrazine ([HSDB, 2010](#))

Boiling point: 113.5 °C

Melting point: 2 °C

Vapour density: 1.1 (air = 1)

Solubility: 282.0 g/100 g in water at 25 °C; miscible with methyl, ethyl, propyl, and isobutyl alcohols; insoluble in chloroform and diethyl ether

Volatility: Vapour pressure, 14.4 mm Hg at 25 °C

Octanol/water partition coefficient (P): log K_{ow} , -2.07 at 25 °C

Flash point: 52 °C

Explosive limits: Upper, 100%; lower, 1.8% by volume in air

Stability: Hydrazine is stable when stored, but may cause hazardous reactions when in contact with strong oxidizing agents or acids. Contact with cellulose or cotton textiles, especially at elevated temperatures, may

result in ignition. Vapours may form explosive mixtures with air when the substance is heated above its flash point.

Decomposition: Forms nitrogen oxides, ammonia, and hydrogen

Conversion factor: 1 ppm = 1.31 mg/m³ at 25 °C

1.2 Production and use

1.2.1 Production

(a) Production process

Most hydrazine is produced by a variation of the Raschig process, where ammonia is oxidized using alkaline hypochlorite with or without the presence of a ketone such as acetone or butanone. It can also be made by the oxidation of ammonia by hydrogen peroxide in the presence of butanone and an oxygen-transfer agent (Schuessl, 2003).

Anhydrous hydrazine is made by breaking the hydrazine–water azeotrope with aniline. The aniline–water vapour condenses and phase separates. The water layer, contaminated with a small amount of aniline and hydrazine, flows to a biological treatment pond. The aniline and anhydrous hydrazine are separated in a final column (Schuessl, 1995).

(b) Production volume

(i) Anhydrous hydrazine

In 2009, hydrazine was produced by three manufacturers worldwide (SRI, 2009; as cited in NTP, 2014). Hydrazine was then available from 27 suppliers (ChemSources, 2009; as cited in NTP, 2014). USA imports of “hydrazine and hydroxylamine and their salts” generally increased between 1989 and 2008, to a maximum of 235 000 tonnes in 1999 (USITC, 2009 as cited in NTP, 2014).

Anhydrous hydrazine was not manufactured in the European Union in 2011, and less than 10 tonnes per year was imported to the European

Union (ECHA, 2011). The following suppliers of hydrazine in 2016 were identified: 27 suppliers in China, 26 in the USA, 5 in the United Kingdom, 3 in Germany, 2 in Japan, and 1 in each of 5 other countries; production volumes were not reported (ChemicalBook, 2016).

(ii) Hydrazine hydrate

Production capacity estimates for hydrazine hydrate in 1988 were: USA, 25 000 tonnes; France, 10 000 tonnes; Germany, 10 000 tonnes; Japan, 5000 tonnes; and United Kingdom, 3000 tonnes (Schirmann, 1989).

By 2011, hydrazine hydrate was manufactured in China, France, Germany, Japan, and the Republic of Korea, and possibly in the Russian Federation and the USA. The worldwide market demand for hydrazine hydrate was then about 80 000–90 000 tonnes per year (ECHA, 2011).

The following suppliers of hydrazine hydrate in 2016 were identified: 178 suppliers in China, 27 in the USA, 11 in the United Kingdom, 6 in Japan, 4 in Germany, and 1 in each of 5 other countries; production volumes were not reported (ChemicalBook, 2016).

1.2.2 Use

In its hydrated form, hydrazine (solutions with concentrations ranging from 0.01% to 100%) is used in multiple applications. It is used to synthesize pharmaceuticals, agrochemicals, and chemical blowing agents; as a stabilizing agent of aromatic amines for manufacture of paints, inks, and organic dyes; and as a reagent for the treatment of nuclear reactor waste. Hydrazine is used as a monomer in polymerizations, mostly for polyurethane coatings and adhesives; as a corrosion inhibitor in water treatment, mainly for the removal of dissolved oxygen; for pH adjustment in the feed water of boilers; and for the removal of solids from steam generators, notably in nuclear and thermal power-generation plants. Oxygen scavenging of steam by hydrazine may

also be carried out in paper mills, steel manufacture, and chemical production. It is also used as a reducing agent in the deposition of metals (e.g. nickel, chromium, tin, and precious metals); in plastics and glass manufacture; for recovery of precious and basic metals from metallic salt solutions; and as effluent sand in the purification of chemical reagents. Hydrazine is also a laboratory chemical reagent ([ECHA, 2011](#)).

The anhydrous form (at high purity levels, > 90%) is used as a propellant for aerospace vehicles (e.g. satellite propulsion and upper stages of satellite launchers); as a fuel in military power units for the F-16 fighter jet aircraft; and in gas generators for submarine rescue systems ([ECHA, 2011](#)).

1.3 Measurement and analysis

Hydrazine compounds are highly soluble in water and can be measured by spectrophotometry ([HSDB, 2010](#)).

Sampling and analysis methods for hydrazine in a variety of matrices are listed in [Table 1.1](#). Other hydrazines, such as 1,1- and 1,2-dimethylhydrazine, may interfere with these methods.

In addition, direct-reading papers or indicating tubes, based on colorimetric methods, are available commercially, with reported limits of detection of 65 µg/m³ for tapes and 330 µg/m³ for tubes ([IPCS, 1987a](#)).

More recently, an optical probe for hydrazine in air has been described. It uses colorimetric, fluorescent, and chemiluminescent outputs, and has a limit of detection of 3.2 ppb (0.1 µM) ([Cui et al., 2014](#)).

1.4 Occurrence and exposure

1.4.1 Natural occurrence

Hydrazine is naturally produced by the algae *Azotobacter agile* as a result of nitrogen fixation ([ATSDR, 1997](#)), and in tobacco plants ([Choudhary & Hansen, 1998](#)).

1.4.2 Environmental occurrence

Production and use of hydrazine may result in its release to the environment. It has been detected at low levels in wastewater samples ([HSDB, 2010](#)).

1.4.3 Occupational exposure

The National Occupational Exposure Survey estimated that 60 490 workers (including 2841 women) in the USA were potentially exposed to hydrazine between 1981 and 1983 ([NIOSH, 1997](#)). National estimates on exposure were not available from other countries.

Hydrazine is usually handled in closed systems, but fugitive emissions may occur. [Table 1.2](#) presents data on occupational exposures for hydrazine.

Data suggested that open manual transfer of hydrazine hydrate results in exposure to hydrazine of < 0.02 mg/m³, and that exposure is lower when closed transfer is used ([HSE, 2006](#)). Exposures of 0.014–0.35 mg/m³ (maximum, 1.18 mg/m³) have been measured in hydrazine hydrate production, and 0.29–2.59 mg/m³ in a rocket propellant facility where hydrazine was handled ([Cook et al., 1979](#); [IPCS, 1987a](#)). Refilling F-16 aircraft with hydrazine resulted in exposures as high as 10.5 mg/m³, but they were usually < 0.13 mg/m³ ([Christensen, 1978](#); [IPCS, 1987a](#)). Exposure during a spillage of hydrazine was measured as 800 mg/m³ ([Suggs et al., 1980](#)).

Hydrazine hydrate and acetylhydrazine were separately measured, as a result combined at 0.8660 µmol/g creatinine (range, not detected to 14.20 µmol/g creatinine) in the urine of production workers in five factories who had been exposed to hydrazine at 0.014 mg/m³ (range, not detected to 0.262 mg/m³) ([Nomiyama et al., 1998a](#)).

1.4.4 Exposure of the general population

No data were available to the Working Group.

Table 1.1 Selected methods of analysis of hydrazine in various matrices

Sample matrix	Sample preparation	Assay method	Limit of detection	Reference
Air	Collect in bubbler with hydrochloric acid; neutralize with sodium hydroxide; derivatize with dimethyl-aminobenzaldehyde; dilute with glacial acetic acid [NIOSH method 3503]	SP	0.9 µg/sample	NIOSH (1984)^a
Air	Adsorb on sulfuric acid-coated silica gel; elute with water; derivatize with 2-furaldehyde; extract with ethyl acetate [NIOSH method 248]	GC/FID	0.002 mg/m ³	NIOSH (1977a)^a
Air	Collect in bubbler with hydrochloric acid; derivatize with phosphomolybdic acid [NIOSH method S143]	SP	0.02 mg/m ³	NIOSH (1977b)^a
Air	Collect in micro-impinger containing acetone and glacial acetic acid	GC/NSD	5 µg/m ³	Holtzclaw et al. (1984)^a
Air	Collect on sulfuric acid coated Gas Chrom R; desorption with water [Method ORG-20]	HPLC	1.6 µg/m ³	OSHA (1980a)
Air	Collect on sulfuric acid-treated glass fibre filters; extract with buffered EDTA disodium solution; derivatize with benzaldehyde [Method ORG-108]	LC/UV	0.076 µg/m ³	OSHA (1980b)
Air	<i>Method 1</i> (filter sampling; recommended for personal sampling up to 2 hours): collect on filters treated with phosphoric acid in acetonitrile solution; extract in sulfuric acid; derivatize in benzaldehyde in methanol; add sodium tetraborate buffer solution	HPLC/UV	0.002 ppm	HSE (2014)
Air	<i>Method 2</i> (impinge sampling; recommended for long-term static sampling): collect in midjet impinger containing dilute sulfuric acid; derivatize in benzaldehyde in methanol; add sodium tetraborate buffer solution	HPLC/UV	0.002 ppm	HSE (2014)
Water	Acidify with hydrochloric acid; derivatize with <i>p</i> -dimethyl-aminobenzaldehyde	SP	5 µg/L	ASTM (1991)^a
Water	Derivatize with vanillin in ethanol; acidify with sulfuric acid	SP	0.065 ppm	Amlathe & Gupta (1988)^a
Water	Derivatize with 5-chlorosalicylaldehyde in acidified aqueous solution (ethanol/water/acetic acid = 30/66/4)	Fl at 570 nm	0.08 µM	Chen et al. (2008)
Water	Derivatize with acetone; extract with dichloromethane; dry with anhydrous sodium sulfate; concentrate by evaporation	GC/MS	0.70 ng/L	Davis & Li (2008)
Water	Derivatize with propyl chloroformate and pyridine; solid-phase microextraction	GC/MS	4.4 ng/L	Gionfriddo et al. (2014)
Water	Derivatize with <i>ortho</i> -phthalaldehyde, extract with methylene chloride	GC/MS	Surface water, 0.002 µg/L; drinking-water, 0.007 µg/L	Oh et al. (2013)
Soil	Extract with sulfuric acid; derivatize with 2,4-pentanedione	GC/TID	0.1 ppm	Leasure & Miller (1988)^a
Food	Extract with L-ascorbic acid; derivatize with 2-nitrobenzaldehyde; clean-up on alumina column	GC/ECD	10 ppb	Wright (1987)^a

Table 1.1 (continued)

Sample matrix	Sample preparation	Assay method	Limit of detection	Reference
Food	Derivatize with pentafluorobenzoyl chloride; extract with methylene chloride	GC/MS	0.01 ppm	Rutschmann & Buser (1991)^a
Tobacco & tobacco smoke	Derivatize with pentafluorobenzaldehyde; enrich with thin-layer chromatography; extract with ether	GC/ECD	0.1 ng/cigarette	Liu et al. (1974)^a
Smokeless tobacco	Derivatize with pentafluorobenzaldehyde; extract with hexane	GC/MS	10 ng/g smokeless tobacco	McAdam et al. (2015)
Urine	Precipitate protein with hydrochloric acid and ammonium sulfate, extract lipids with methylene chloride, derivatize aqueous fraction with pentafluorobenzaldehyde, extract with ethyl acetate	GC/NPD	8 µmol	Preece et al. (1992b)^a
Urine	Extract with methylene chloride, discard extract; derivatize aqueous fraction with <i>p</i> -chlorobenzaldehyde; extract with methylene chloride; dry and dissolve in ethyl acetate	GC/NPD	0.05 µg/mL	Timbrell & Harland (1979)^a
Urine	Deproteinate with trichloroacetic acid; derivatize with vanillin in ethanol; acidify with sulfuric acid	SP	0.065 µg/mL	Amlathe & Gupta (1988)^a
Plasma/Urine	None/Dilute with deionized water	Ion-exchange HPLC/ECD	8 ng/sample	Fiala & Kulakus (1981)^a
Plasma, liver tissue	Precipitate residual protein with hydrochloric acid and ammonium sulfate, extract lipids with methylene chloride, derivatize aqueous fraction with pentafluorobenzaldehyde, extract with chloroform	GC/MS	~20 nmol/mL	Preece et al. (1992b)^a
Serum, liver/brain tissue	Acidify; derivatize with <i>p</i> -dimethylaminobenzaldehyde in ethanol	SP	0.025 µg/sample	Alvarez de Laviada et al. (1987)^a
Serum	Treat with trichloroacetic acid; centrifuge; derivatize supernatant with <i>p</i> -dimethylaminobenzaldehyde in ethanol	SP	0.05 µg/mL	Reynolds & Thomas (1965)^a
Living cells	Probe was synthesized from <i>n</i> -(3-dimethylaminopropyl)- <i>N</i> -ethylcarbodiimide hydrochloride added to resorufin and 4-bromobutyric acid in dichloromethane; evaporated; purified and added to buffered cells	NMR/MS	~2 µM	Qian et al. (2014)

^a As cited in [ATSDR \(1997\)](#)

ECD, electrochemical detection; EDTA, ethylenediaminetetraacetic acid; FID, flame ionization detector; FI, fluorescence; GC, gas chromatography; HPLC, high-performance liquid chromatography; LC, liquid chromatography; MS, mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; NPD, nitrogen-phosphorus detector; NSD, nitrogen selective detection; SP, spectrophotometry; TTD, thermionic ionization detector; UV, ultraviolet

Table 1.2 Occupational exposures to hydrazine

Country	Job/process	Numbers of people exposed	Air concentration (mg/m ³)		Reference
			Typical	Exceptional	
USA	F-16 fighter jet refilling including nitrogen depressurization, catalyst purge, poppet valve replacement	NR	< 0.13	6.6–10.5	Christensen (1978)
USA	F-16 fighter jet applications	32		0.04–0.05	IPCS (1987a)
USA	Production	100–800	< 0.13	0.13–0.26 ^a	IPCS (1987a)
USA	Production	≤ 1100	< 0.35	< 1.18	IPCS (1987a)
USA	Derivative manufacture	< 25	< 0.13	~0.13	IPCS (1987a)
NR	Evaporation from liquid spill	NR	4		IPCS (1987b)
NR	At site of leakage	NR		800	Suggs et al. (1980)
USA	Rocket propellant-handling facility	NR	0.29–2.59 0.013 (inside RPE)		Cook et al. (1979)
USA	Rocket testing	10–100	0.01–0.02	0.14 ^b	IPCS (1987a)
NR	Process stream sampling	NR	0.05–0.35	1.19	ATSDR (1997)
Japan ^c	Production in 5 factories	NR	0.014	ND–0.262	Nomiya et al. (1998b)
United Kingdom ^c	Manual processing and distributing hydrazine hydrate solutions, open transfer (45–60 min)	NR		0.0045	HSE (2006)
	Manual processing and distributing hydrazine hydrate solutions, open transfer (41 min)	NR		0.0096	
	Manual processing and distributing hydrazine hydrate solutions, open transfer (41 min)	NR		0.013	
	Manual processing and distributing hydrazine hydrate solutions, closed transfer (15 min)	NR		0.002	
	Manual processing and distributing hydrazine hydrate solutions, closed transfer (15 min)	NR		0.003	

^a Short-term samples during specific operations

^b Level measured during aeration of the wastewater holding period

^c The data from Japan and the United Kingdom are for hydrazine hydrate, the others for hydrazine; note that exposures are all measured as hydrazine, but the processes involved handling of hydrazine hydrate
 ND, not detected; NR, not reported; RPE, respiratory protection equipment
 Compiled by the Working Group with data reported by [ECHA \(2011\)](#)

1.4.5 Exposure assessment in epidemiological studies

Workers were commonly also exposed to other carcinogens, which made it difficult to attribute identified risks specifically to hydrazine ([Camarano et al., 1984](#); [Wald et al., 1984](#); [Zhao et al., 2005](#); [Krishnadasan et al., 2007](#)). In a nested case–control study of 6107 aerospace workers and 4607 workers enrolled in a radiation monitoring programme, 87% of those exposed to hydrazine were also exposed to trichloroethylene, while levels of radiation were not reported ([Krishnadasan et al., 2007](#)).

In a retrospective cohort study in aerospace workers in southern California, USA, which used interviews, historical facility reports, and walkthrough surveys, job titles were discussed and classified into a time-dependent semi-quantitative job–exposure matrix (JEM) with respect to hydrazine compounds (e.g. hydrazine, 1-methylhydrazine, and 1,1-dimethylhydrazine) ([Morgenstern & Ritz, 2001](#); [Zhao et al., 2005](#); [Ritz et al., 2006](#)). The JEM was used to classify jobs held for at least 6 or 12 months (depending on the job) into low, medium, or high exposure. [Morgenstern & Ritz \(2001\)](#) stated that the categories reflect the probability, not the amount,

of hydrazine exposure, but this was not further clarified ([Morgenstern & Ritz, 2001](#)); however, subsequent reports referred to the classification in terms of intensity of exposure ([Zhao et al., 2005](#); [Ritz et al., 2006](#)); any employee involved in working hands-on with rocket engines or in fuel production and testing was assumed to have been exposed to hydrazine. For example, rocket test-stand mechanics were assigned to the highest intensities of exposure because they probably had the greatest contact with rocket engines ([Ritz et al., 2006](#)). Each job title was assigned to one of four categories of presumptive exposure (high, medium, low, or unexposed) for each chemical reflecting the relative intensity of that exposure in each of three periods: the 1950–1960s, the 1970s, and the 1980–1990s. A cumulative exposure score for each worker in the cohort was calculated by summing across all employment periods. Thus, each job received an intensity score (0 to 3, from unexposed to highly exposed) that was multiplied by the number of years in the job and then summed. In separate analyses, to take account of the fact that more hydrazine was used in the 1960s, scores of 1 for low, 4 for medium, and 9 for high intensities were used for that decade, retaining the original scores for all other decades ([Ritz et al., 2006](#)). In addition to hydrazine, there was exposure to other known carcinogens at the facility, including trichloroethylene, polyaromatic hydrocarbons, mineral oils, and benzene. In [Ritz et al. \(2006\)](#), a new JEM was derived assessing these exposures, and this information was used to adjust the hydrazine effect estimates for potential confounding by co-exposure to other chemicals ([Ritz et al., 2006](#)).

In a subsequent nested case–control study of cancer of the prostate identified through cancer registries, five controls per case were randomly selected, matched on age at start date of employment, and cohort (radiation or aerospace). For cases and controls, 69% had no identified exposure to hydrazine; 21% of cases and 24%

of controls were classified as having had low or moderate exposure; and 11% of cases and 7% of controls were classified as having had high exposure ([Krishnadasan et al., 2007](#)).

A separate and subsequent study at the same aerospace facility used company records to identify test-stand mechanics, including those monitored for radiation. These workers were paid hourly, unlike most of the test-stand workers (instrument mechanics, inspectors and engineers) who were salaried. The mechanics who were paid hourly were thought to be most likely to have been “hands-on” and hence to have had a higher probability of exposure to hydrazine and trichloroethylene. Hydrazine was present in rocket fuel at some but not all rocket-engine test stands. The electronic personnel files did not identify on which rocket stands the mechanics had worked, so the authors used company telephone numbers to identify a minority of the test-stand mechanics who were thought to have worked on stands that used hydrazine. The assignments were validated by “information gathered from walkthrough surveys at operating and closed test stands with knowledgeable personnel who were involved with engine tests over the years, discussions with over 100 long-term employees (both retired and active), and review of medical records of workers, which often identified the test stands and the chemicals used” ([Boice et al., 2006](#)).

[Ritz et al. \(1999\)](#) had been unable to link workers to specific test stands using company records, but former employees stated that many workers frequently changed work locations. In addition, leakage of fuel was thought to be a common source of exposure ([Ritz et al., 1999](#)).

In a separate study of a cohort of workers from a site in the east Midlands, United Kingdom, that manufactured hydrazine in open tanks and vessels, the exposure assessment was weaker. No measurements of the concentration of hydrazine in air had been made, exposure estimates were derived by the simulation of spillages and calculations using data on the saturated

vapour pressure of hydrazine. This suggested that maximum levels of 100 ppm were possible (Wald et al., 1984). Exposures were estimated to have been 1–10 ppm in the general plant area, and up to 100 ppm close to the hydrazine storage vessels (Wald et al., 1984; Morris et al., 1995). Those directly involved, for at least 6 months, in the manufacture of hydrazine or its derivatives, or its use as a raw material, were classified as having had high exposure. Moderate exposure was assigned to those with only an incidental presence in the hydrazine-manufacturing area for most of their career, e.g. fitters and engineers. Their exposure was estimated to have probably been “< 0.5 or 1 ppm for most of their employment”. The remainder of the cohort were thought to have had “little or no exposure”. In the risk analysis, the years at each exposure level were calculated on an individual basis (Morris et al., 1995).

1.5 Regulations and guidelines

Hydrazine is classified as a carcinogen in accordance with Article 57 (a) of the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations (EC-1907/2006; ECHA, 2011). Hydrazine is included in the list of harmonized classification and labelling of hazardous substances as carcinogen category 1B (ECHA, 2011).

According to the European Chemicals Agency (ECHA), the following Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements apply: H301 “toxic if swallowed”; H311 “toxic in contact with skin”; H314 “causes severe skin burns and eye damage”; H317 “may cause an allergic skin reaction”; H331 “toxic if inhaled”; H350 “may cause cancer”; H400 “very toxic to aquatic life”; H410 “very toxic to aquatic life with long lasting effects”; and H226 “flammable liquid and vapour” (ECHA, 2016).

Table 1.3 International limit values for occupational exposure to hydrazine

Country	Limit value, 8 hours		Limit value, short-term	
	ppm	mg/m ³	ppm	mg/m ³
Australia	0.01	0.013		
Austria	0.10	0.130	0.40	0.52
Belgium	0.01	0.013		
Canada, Ontario	0.01			
Canada, Quebec (Province)	0.10	0.130		
Denmark	0.01	0.013	0.02	0.026
Finland	0.01	0.013	0.05 ^a	0.07 ^a
France	0.10	0.100		
Germany (AGS)	0.017 ^b	0.022 ^b	0.034 ^{a,b}	0.044 ^{a,b}
	0.0017 ^c	0.0022 ^c		
Hungary				0.13
Ireland	0.01	0.01		
Latvia		0.10		
New Zealand	0.01	0.013		
People's Republic of China		0.06		0.13 ^a
Poland		0.05		0.10
Republic of Korea	0.05	0.06		
Singapore	0.10	0.13		
Spain ^d	0.10	0.13		
Switzerland	0.10	0.13		
USA, NIOSH			0.03 ^e	0.04 ^e
USA, OSHA	1.00	1.30		
United Kingdom	0.02	0.03	0.10	0.13

^a 15 minutes average value

^b Workplace exposure concentration corresponding to the proposed tolerable cancer risk

^c Workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk

^d Skin, sensitivity

^e Ceiling limit value

AGS, German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe); NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration
From the GESTIS Substance Database (IFA, 2015)

The United States Environmental Protection Agency (EPA) Integrated Risk Information System classifies hydrazine as a B2 carcinogen, a probable human carcinogen based on sufficient evidence of carcinogenicity in animals. The inhalation unit risk rate was stated as 4.9×10^{-3} per $\mu\text{g}/\text{m}^3$ based on a linearized multistage procedure

“extra risk model.” The oral cancer slope factor was stated as $3.0 \text{ (mg/kg per day)}^{-1}$ [these values are applicable to lifetime exposure] ([EPA, 2016](#)).

Hydrazine was listed as a chemical that may cause cancer in 1988, under California’s proposition 95, The Safe Drinking-water and Toxic Enforcement Act 1986 ([OEHHA, 2014](#)).

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended an 8-hour time-weighted average (TWA) of 0.013 mg/m^3 (0.01 ppm) as the threshold limit value for occupational exposures to hydrazine in workplace air, and have categorized it as an A2 “suspected human carcinogen” ([ACGIH, 1997](#)).

Other 8-hour TWA workplace limits vary from the proposed preliminary acceptable cancer risk value of 0.0017 ppm [0.0022 mg/m^3] in Germany, to the Occupational Safety and Health Administration (OSHA) value of 1.3 mg/m^3 ([IFA, 2015](#)) in the USA. Several countries have also set short-term exposure limits (STELs) varying between 0.02 and 0.4 ppm [$0.026\text{--}0.52 \text{ mg/m}^3$] ([IFA, 2015](#); [Table 1.3](#)).

The Agency for Toxic Substances and Disease Registry of the Centers for Disease Control and Prevention (CDC) in the USA has set a minimal risk level (MRL) of 0.004 ppm [0.00524 mg/m^3] for inhalation exposures of intermediate duration ([ATSDR, 2016](#)).

2. Cancer in Humans

See [Table 2.1](#)

[Wald et al. \(1984\)](#) studied 427 men in the east Midlands, United Kingdom, who were potentially exposed to hydrazine at a hydrazine-production plant between 1945 and 1971 (exposure at this plant ended in 1971), with at least 6 months of employment during this period. Workers were divided into presumed high, moderate, and low exposure groups. High exposure was estimated to be 1–10 ppm, moderate was < 1 ppm, and low

exposure was little or no exposure. Follow-up went to 1982 in this original report and was extended in subsequent reports by [Morris et al. \(1995, 2015\)](#). The most recent follow-up until 2012 identified 205 deaths ([Morris et al., 2015](#)). Mean length of exposure was 6.8 years and mean follow-up was 32 years. There was no statistically significant excess risk for any cancer. The relative risk (RR) of mortality for cancer of the lung was 0.72 (95% confidence interval, CI, 0.42–1.15; 17 deaths), and no significant or close to significant excess of lung cancer was seen at any exposure level or duration (RR for high exposure group, 1.22; 95% CI, 0.45–2.67). There was no marked excess of cancer of the digestive system for all men combined (RR, 1.02; 95% CI, 0.65–1.53; 23 deaths) nor for any exposure level or duration group (RR for high exposure, 0.44; 95% CI, 0.05–1.58). Few men were in the high exposure category, and there were only six lung cancers and two digestive cancers in this group. There was an overall deficit of all-cause mortality (standardized mortality ratio, SMR, 0.77), and the authors noted that these workers were not allowed to smoke at work due to the explosive nature of hydrazine.

[The Working Group noted that this cohort was of limited value for the evaluation of hydrazine since there were few deaths among men judged to have high exposure, while other exposure groups were exposed only incidentally or were judged not to have been exposed.]

[Ritz et al. \(1999\)](#) studied a cohort of 6107 male workers who worked at the Santa Susana Field Laboratory rocket testing facility (Rocketdyne) near Los Angeles, California, USA. Workers had to have been employed before 1980 and worked at least 2 years, and not to have been exposed to radiation (i.e. no evidence of monitoring). Mortality follow-up went until 1994; no data on cancer incidence were reported. The average length of follow-up was 29 years. Exposure assessment was based on job title, and a JEM was developed to estimate exposure depending on job title

Table 2.1 Cohort studies of cancer and exposure to hydrazine

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	No. of exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Morris et al. (2015) United Kingdom, east Midlands 1947–2012	427 male hydrazine-production workers employed for ≥ 6 mo Exposure assessment method: JEM; exposure divided into high (regular, 1–10 ppm), moderate (incidental, < 0.5–1 ppm), and little or no exposure; linkage to national mortality database	Lung Digestive system	All High All High	17 6 23 2	0.72 (0.42–1.15) 1.22 (0.45–2.67) 1.02 (0.65–1.53) 0.57 (0.07–2.08)	Age, sex, period	Mean employment, 6.8 yrs; mean follow-up, 32 yrs; English referent rates Strengths: well-defined cohort Limitations: limited number of men with high exposure
Ritz et al. (2006) USA, California 1960–2001	6044 for mortality; 5049 for incidence; employed for ≥ 2 yrs in 1960–1980 in a rocket-testing facility Exposure assessment method: JEM; 56% had no/low exposure, 26–28% had moderate exposure, 17% had high exposure; semi-quantitative ranking based on estimated intensity of exposure; high exposure defined as likely direct contact with hydrazine; linkage to state cancer registries and National Death Index	Lung, mortality Colorectum, mortality Lung, incidence Colorectum, incidence	Moderate High Trend-test <i>P</i> -value: 0.031 Moderate High Trend-test <i>P</i> -value: 0.481 Moderate High Trend-test <i>P</i> -value: 0.003 Moderate High Trend-test <i>P</i> -value: 0.041	37 36 12 10 22 26 28 19	1.24 (0.78–1.96) 1.67 (0.99–2.83) 0.83 (0.35–1.95) 1.55 (0.61–3.90) 1.18 (0.62–2.24) 2.49 (1.28–4.86) 1.75 (0.93–3.30) 2.16 (1.02–4.59)	Pay type (categorical), time since first employment (continuous), other possible carcinogens (TCE, PAHs, mineral oils)	Results presented for 20-yr lags; some overlap with Boice et al. (2006) , more rocket testing mechanics assumed exposed than in Boice et al., workers worked in earlier years than in Boice et al., during a time of likely higher exposure due to more rocket testing Strengths: long follow-up, semi-quantitative exposure assessment, cancer incidence data (California and eight adjoining states) as well as mortality Limitations: lack of direct measurement of hydrazine levels; some lack of cancer ascertainment expected

Table 2.1 (continued)

Reference, location, enrolment/ follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	No. of exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Boice et al. (2006) USA, California 1948–1999	8372; worked ≥ 6 mo at rocket-testing facility in 1948–1999 Exposure assessment method: JEM; analyses of subset of 1651 test-stand mechanics of whom 315 were judged to have had likely hydrazine exposure, with another 205 judged to have had possible but unlikely hydrazine exposure; linkage to state death registries and the national death index	Lung	Mortality: All workers Male test-stand mechanics Male test-stand mechanics with likely hydrazine exposure	215 63 15	0.89 (0.78–1.02) 1.07 (0.82–1.37) 1.45 (0.81–2.39)	Age, sex, period	Overlap with Ritz et al. (2006) , but many fewer rocket-testing mechanics classified as exposed; includes more recent workers than Ritz et al.; recent workers likely to have lower exposures Strengths: long follow-up; extensive exposure characterization based on assignment to categories Limitations: no cancer incidence data
		Colorectum	Mortality: All workers Male test-stand mechanics Male test-stand mechanics with likely hydrazine exposure	70 19 5	0.97 (0.75–1.22) 1.10 (0.66–1.71) 1.67 (0.54–3.89)		

CI, confidence interval; JEM, job-exposure matrix; PAHs, polycyclic aromatic hydrocarbons; TCE, trichloroethylene; TWA, time-weighted average

and year of employment. Work history records were available from the company. Inventories of hydrazine over time were also available for 1955–1994. Workers were assigned by expert judgment to categories of no, low, medium, and high probability of exposure to hydrazine, without reference to intensity of exposure; the low exposure group was small and results for this group were not reported. Hydrazine used in rocket fuel can exist as three variants: hydrazine itself, 1-methylhydrazine, and 1,1-dimethylhydrazine, but these could not be separated and exposure was analysed generically as “hydrazine” irrespective of the particular variant. Two sets of analyses were conducted, based on minimum length of duration of exposure (6 months or 24 months: HYD-6 or HYD-24, respectively). In some analyses, the exposure variable was high exposure by decade, as it was thought that intensity changed over time. No quantitative estimates of hydrazine exposure intensity were given. Exposure was analysed as a time-dependent variable, using highest exposure at any time, and retaining that highest exposure category if subsequent exposure was lower. Cancer of the lung was of primary interest in the analysis, but data for cancers of the lymphoid and haematopoietic tissues (ICD-9, 200–208), bladder and kidney, upper aerodigestive tract (ICD-9, 140–141 and 161) and pancreas were also reported. Covariates included in internal analyses were age, time since hire, and pay grade, and lags of 0, 10, and 15 years were used. Results shown were similar for both duration of exposure groups (HYD-6, $n = 1053$; HYD-24, $n = 827$). Relative risks for cancer of the lung for high exposure with a 15-year lag were 1.93 (95% CI, 1.27–2.93) or 2.10 (95% CI, 1.36–3.25) for high exposure within the HYD-6 and HYD-24 groups, respectively. No elevation in risk of cancer of the lung was seen for medium exposure. Analyses of high exposure (using the HYD-6 group) by decade showed that excesses of cancers of the lung, and lymphoid and haematopoietic tissues were greatest in 1960–1969. In the

high-exposure group, mortality from cancer of the lymphoid and haematopoietic tissues (RR for HYD-6, 2.83; 95% CI, 1.22–6.56; and RR for HYD-24, 1.42; 95% CI, 0.54–3.72; 15-year lag), and bladder and kidney cancer (RR for HYD-6, 1.65; 95% CI, 0.59–4.56; and RR for HYD-24, 1.80; 95% CI, 0.63–5.12) was also increased. Limited data on smoking for 295 workers showed no association between smoking and estimated occupational exposure to hydrazine. Furthermore, relative risks for a group of smoking related-cancers other than lung showed no positive trends with exposure.

[Ritz et al. \(2006\)](#) updated the earlier study ([Ritz et al., 1999](#)) on this cohort for mortality until 2001. A few workers from the previous cohort were found not to have been eligible, resulting in a cohort size of 6044. Cancer incidence between 1988 and 2000 was also ascertained in California and eight other states of the USA for 5049 workers who were alive as of the beginning of 1988. Death certificate information indicated that cancer incidence would have approximately 89% complete coverage using only these states during the follow-up. Exposure assessment was updated via walkthrough surveys, interviews with company personnel, and review of records. Each job title was assigned to one of four categories (no exposure, low, moderate, high) in three periods (1950–1969, 1970–1979, and 1980–1999). Employees with direct exposure to rocket engines or fuel production and testing were presumed to have been exposed to hydrazine. Exposure intensity was scored annually 0–3 for each job (3 being highest exposure), based on the four categories above, and then summed across employment years to derive a cumulative exposure score. Further details of exposure assessment are available in [Zhao et al. \(2005\)](#). Cox regression was conducted with calendar time as the time variable. Pay grade, age, time since hire, and exposures to trichloroethylene or mineral oils were included in all models. Cumulative exposure

scores were divided into three semiquantitative categories, low (≤ 3), medium (3 to ≤ 12), and high (> 12) for analyses; 56% (3401) of workers were judged to have had no/low exposure, 26% (1593) moderate exposure, and 17% (1050) high exposure.

During follow-up, 2117 workers had died (35%) and 691 incident cancers were found. Mean duration of employment was 16 years. Rate ratios for cancer of the lung with no lag for mortality (194 deaths) were 1.00, 1.46 (95% CI, 0.96–2.22), and 1.49 (95% CI, 0.94–2.35) for no/low, moderate, and high exposures, respectively (P for trend, 0.065), and for incidence (92 cases) the RRs were 1.00, 1.15 (95% CI, 0.60–2.20), and 2.31 (95% CI, 1.21–4.43) for the same exposure categories (P for trend, 0.007). With 20 years lag, these were respectively 1.00, 1.24 (95% CI, 0.78–1.96), and 1.67 (95% CI, 0.99–2.83) (P for trend, 0.031) for mortality, and 1.00, 1.18, (95% CI, 0.62–2.24), and 2.49 (95% CI, 1.28–4.86) (P for trend, 0.003) for incidence. For cancer of the colorectum, the relative risks for incidence (90 cases) were 1.00, 1.64 (95% CI, 0.86–3.11), and 2.09 (95% CI, 1.02–4.31) (P for trend, 0.043) for no lag, and 1.00, 1.75 (95% CI, 0.93–3.30), and 2.16 (95% CI, 1.02–4.59) (P for trend, 0.041) for 20 years lag. There was evidence for positive trends for cancer of the kidney (17 deaths, 16 incident cases) and pancreas (39 deaths, 21 cases), but these did not attain statistical significance. No trends were seen with “NHL and leukaemia” for either mortality or incidence (0 and 20-year lags), in contrast to the earlier mortality follow-up. Limited data on smoking for 200 workers showed no association between smoking and estimated occupational exposure to hydrazine. Furthermore, relative risks for all smoking related-cancers other than lung showed no positive trends with exposure. [The Working Group noted that this cohort was particularly informative because it is relatively large, with semi-quantitative exposure

assessment, and included cancer incidence as well as mortality.]

[Krishnadasan et al. \(2007\)](#) conducted a nested case-control study of 362 cases of cancer of the prostate and 1805 controls, matched on date of first employment and age at diagnosis. The study was nested within two cohorts, 4607 radiation-exposed Rocketdyne workers and the same 6107 rocket-testing Rocketdyne workers studied by [Ritz et al. \(2006\)](#). Exposures to hydrazine, trichloroethylene, polycyclic aromatic hydrocarbons, benzene, and mineral oil were evaluated. Incident cases of prostate cancer were ascertained in California and eight other states of the USA, as in [Ritz et al. \(2006\)](#). Based on a JEM, odds ratios (20-year lag) for those with high and low exposure to hydrazine, versus no exposure, were 0.84 (95% CI, 0.48–1.5) and 0.75 (95% CI, 0.50–1.1), respectively (P for trend, 0.30). [This study was largely uninformative, given the earlier data from [Ritz et al. \(2006\)](#), where no trends for prostate cancer were observed for hydrazine exposure among the rocket-testing workers.]

[Boice et al. \(2006\)](#) studied a group of 8372 Rocketdyne workers who worked for 6 months or more at the Santa Susana Field Laboratory rocket-testing facility from 1948 onward, and had potential exposure to hydrazine. Women were included among the rocket-testing facility workers, representing 15% of the cohort. Also included were 182 test-stand mechanics who were exposed to radiation. Analyses were limited to mortality, with no incidence data. Mortality comparisons were made using California referent rates, as well as referent rates based on 32 979 other Rocketdyne workers who did not do rocket testing and had no potential exposure to hydrazine. Internal comparisons were also conducted. Follow-up of test facility workers was conducted until 1999 and identified 2251 deaths (27% of the cohort). Among the 8372 rocket-testing workers, 1651 (20%) were test-stand mechanics, judged to have potential exposure to hydrazine. Of these however, [Boice et al. \(2006\)](#) estimated that only

315 (30%) were likely to have been exposed to hydrazine, while 205 others were judged to have possible but unlikely exposure to hydrazine, and the remainder were judged to have had no exposure to hydrazine. These definitions were based on job title and other company records. Some test-stand mechanics were also classified as being exposed to trichloroethylene, with 121 of these thought to have been exposed to both hydrazine and trichloroethylene.

Cancer mortality analyses of all rocket-testing workers compared with California population rates were unremarkable and not significantly different from the null for any specific type of cancer analysed, including lung (SMR, 0.89; 95% CI, 0.78–1.02). All-cause mortality was also decreased (SMR, 0.83; 95% CI, 0.80–0.86). Analyses by duration of employment also showed no significant excesses for any type of cancer for workers with longest duration of employment. Analyses of male test-stand mechanics paid hourly also did not show significant excesses for any cancer type, nor were there any significant excesses for those with > 5 years employment. The standardized mortality ratio for lung cancer was 1.07 (95% CI, 0.82–1.37) based on California referent data; the standardized mortality ratio for lung cancer for > 5 years employment was 1.06 (95% CI, 0.66–1.60). For the 315 test-stand workers estimated to have likely hydrazine exposure, the standardized mortality ratio for all cancers was 1.09 (95% CI, 0.75–1.52). The standardized mortality ratio for lung cancer in this group was 1.45 (95% CI, 0.81–2.39). Findings for deaths for other specific cancers were unremarkable and based on small numbers. Internal analyses of likely exposed, possibly exposed, versus not exposed to hydrazine for test-stand workers showed no evidence of a positive trend with increasing likelihood of exposure (analyses controlled for pay grade, hourly vs salaried). Analyses of test-stand mechanics by decade of exposure, comparing those with 3 or more years employment with those with less than 3 years

employment, showed the highest lung cancer mortality risk (RR, 1.40; 95% CI, 0.80–2.47) in the group exposed 1960–1969 ($n = 1454$), with an excess (RR, 1.29; 95% CI, 0.70–2.40) also seen in those exposed before 1960 ($n = 984$). Some internal analyses using Cox regression were also conducted among test-stand mechanics by length of employment and likelihood of hydrazine exposure (likely, possible, none). These analyses, in which follow-up time was the time variable, and which controlled for year of birth, year of hire, pay grade (hourly or salaried), and exposure to trichloroethylene, did not show any significant trends for either lung cancer or colon cancer. A smoking survey carried out among about 75 hourly-paid and 75 salaried test-facility workers, found that about 60% of hourly workers had ever smoked versus 40% salaried workers, suggesting the importance of controlling for pay grade. [The Working Group noted that [Boice et al. \(2006\)](#) is an informative study with relatively large number of deaths and extensive exposure characterization by assigned categories. The Working Group further noted that while the two cohorts of Rocketdyne workers ([Boice et al., 2006](#); [Ritz et al., 2006](#)) had important overlap, they were different populations. As noted above, the cohort studied by [Boice et al. \(2006\)](#) had a shorter minimum employment period and included women and workers hired in both earlier and later years. Furthermore, [Ritz et al. \(2006\)](#) considered all test-stand mechanics to have been exposed, while [Boice et al. \(2006\)](#) considered only a minority to have had likely or possible exposures based on presumed test-stand assignment. However, as pointed out in [Zhao et al. \(2005\)](#), test-stand mechanics frequently rotated among different test stands, making the classification used by [Boice et al. \(2006\)](#) imprecise. Furthermore, [Ritz et al. \(2006\)](#) included incidence data, while [Boice et al. \(2006\)](#) included only mortality data. Hence, few results in the two studies are directly comparable. It is of note that test-stand mechanics exposed before 1960

(RR for lung cancer, 1.29) and during the 1960s (RR, 1.40), with ≥ 3 years employment versus < 3 years employment in [Boice et al. \(2006\)](#) may be roughly comparable to the workers with high and moderate exposure with a 20-year lag in [Ritz et al. \(2006\)](#) (lung cancer mortality for those with moderate and high exposure, lung cancer RR, 1.24 and 1.67, respectively). These groups, across the two studies, showed a moderate excess of lung cancer. It should also be noted that in [Boice et al. \(2006\)](#), the group with likely or possible exposure had a lung cancer rate ratio of 1.45 versus the non-exposed. Finally, there was a notable increase in incidence of lung cancer in the [Ritz et al. \(2006\)](#) study in the group with high exposure and a 20-year lag (RR, 2.49).]

3. Cancer in Experimental Animals

Hydrazine or hydrazine salts were previously reviewed by the *IARC Monographs Working Group* (Volume 4, [IARC, 1974](#); Supplement 7, [IARC, 1987](#); and Volume 71, [IARC, 1999](#)). The Working Group concluded that there was *sufficient evidence* in experimental animals for the carcinogenicity of hydrazine ([IARC, 1999](#)). In the present *Monograph*, the Working Group evaluated the studies of carcinogenesis in experimental animals that had been reviewed previously, and also reviewed any new studies published since the earlier review.

Hydrazine was found to cause tumours of the lung in mice with an incidence of 100% ([Biancifiiori & Ribacchi, 1962](#)), and was then subsequently used in the laboratory to study formation of tumours of the lung in mice, rats, and hamsters. Most of the studies in mice in the present *Monograph* were single-dose studies designed to investigate possible mitigating agents for hydrazine, or mechanisms of lung-tumour induction by hydrazine.

See [Table 3.1](#)

3.1 Mouse

3.1.1 Gavage

A group of 22 female BALB/c mice (age, 8 weeks) was given hydrazine sulfate in water as 251 daily gavage doses at 1.13 mg per mouse during 46 weeks. By the end of the experiment (46 weeks), the mice had 100% incidence [$P < 0.0001$] of pulmonary adenoma [the majority] or carcinoma. A group of 216 untreated control female mice allowed to live their full lifespan (up to 121 weeks) had no pulmonary tumours ([Biancifiiori & Ribacchi, 1962](#)). [While a high incidence of pulmonary tumours was reported in treated mice versus controls, the study lacked experimental details and had a poor experimental design. For example, the initial number of treated mice was not given and no vehicle controls were included.]

In a follow-up study, [Biancifiiori et al. \(1963\)](#) treated a group of 84 female BALB/c mice (age, ~50 days) with hydrazine sulfate at 1.13 mg per day in water by gavage for up to 310 days. About three mice were killed every 10th day. The incidence of pulmonary tumours for the groups killed between day 200 and 240 was 15/15 (100%), between day 250 and 290 was 13/15 (87%), between day 300 and 340 was 14/14 (100%), and between day 350 and 380 was 8/8 (100%). [No information was provided if controls were used. While high incidences of pulmonary tumours were reported in treated mice, this study lacked experimental details and had a limited experimental design. The study was inadequate for the evaluation.]

Groups of 21 male and 21 female CBA/Cb/Se mice (age, 8 weeks) were treated daily with hydrazine sulfate at a total dose of 283 mg in water by gavage for 36 weeks, and then maintained for their lifetime ([Biancifiiori et al., 1964](#)). Groups of 37 male and 47 female CBA/Cb/Se mice served as untreated controls. Groups of 10 male and 10 female BALB/c mice (age, 8 weeks) were treated daily with hydrazine sulfate at a total

Table 3.1 Studies of carcinogenicity with hydrazine in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, BALB/c (F) 8 wks 46 wks Biancifiiori & Ribacchi (1962)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 1.13 mg/dose 251 treatments over 46 wks 216, NR 166, 22	<i>Lung</i> Adenoma or carcinoma (combined): 0/166, 22/22*	*[<i>P</i> < 0.0001]	Control animals were held for their lifetime While a high incidence (100%) of pulmonary tumours [mainly adenoma] was reported in treated mice vs “controls” (0%), the lack of experimental detail and poor experimental design (e.g. failure to report number of mice in treated group, single dose used, no discussion of pathology) made the study difficult to evaluate
Full carcinogenicity Mouse, CBA/Cb/Se (M) 8 wks Lifetime Biancifiiori et al. (1964)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 283 mg of total dose “Daily” gavage for 36 wks 37, 21 NA	<i>Lung</i> Pulmonary adenoma or carcinoma (combined): Incidence: 1/37, 16/21* Multiplicity: 1, 3 <i>Liver</i> Hepatoma [hepatocellular tumours]: Incidence: 4/37, 13/21* *[<i>P</i> < 0.0001]	*[<i>P</i> < 0.0001]	Principal limitations: poor description of experimental details; single dose used; small number of animals in exposure group; exposed for only 36 wks; no discussion of clinical signs
Full carcinogenicity Mouse, CBA/Cb/Se (F) 8 wks Lifetime Biancifiiori et al. (1964)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 283 mg of total dose “Daily” gavage for 36 wks 47, 21 NA	<i>Lung</i> Pulmonary adenoma or carcinoma (combined): Incidence: 4/47, 19/21* Multiplicity: 1, 6 <i>Liver</i> Hepatoma [hepatocellular tumours]; 2/47, 15/21*	*[<i>P</i> < 0.0001]	Principal limitations: poor description of experimental details; single dose used; small number of animals in exposure group; exposed for only 36 wks; no discussion of clinical signs
Full carcinogenicity Mouse, BALB/c (M) 8 wks Lifetime Biancifiiori et al. (1964)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 32 mg – total dose “Daily” gavage for 4 wks 22, 10 NA	<i>Lung</i> Pulmonary adenoma: Incidence: 6/22, 7/8* Multiplicity: 1.0, 2.4	*[<i>P</i> < 0.006]	Principal limitations: poor description of experimental details; single dose used for very short time; small number of animals in exposure and control groups; exposed for only 4 wks; no discussion of clinical signs

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, BALB/c (F) 8 wks Lifetime Biancifiiori et al. (1964)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 32 mg – total dose “Daily” gavage for 4 wks 23, 10 NA	<i>Lung</i> Pulmonary adenoma: Incidence: 5/23, 8/10* Multiplicity: 1.0, 2.9	*[$P < 0.0003$]	Principal limitations: poor description of experimental details; single dose used for very short time; small number of animals in exposure and control groups; exposed for only 4 wks; no discussion of clinical signs
Full carcinogenicity Mouse, CBA/Cb/Se (M) 8 wks Lifetime Severi & Biancifiiori (1968)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 1.13 mg/dose 1 × /day for 36 wks 37, 21 NA	<i>Liver</i> Hepatocellular adenoma or carcinoma (combined): 4/37, 13/21* <i>Lung</i> Adenoma or carcinoma (combined): 1/37, 16/21*	*[$P < 0.0001$] * [$P < 0.0001$]	Principal limitations: use of single dose; short duration of exposure Same data reported in Biancifiiori et al. (1964)
Full carcinogenicity Mouse, CBA/Cb/Se (F) 8 wks Lifetime Severi & Biancifiiori (1968)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 1.13 mg/dose 1 × /day for 36 wks 47, 21 NA	<i>Lung</i> Adenoma or carcinoma (combined): 4/47, 19/21* <i>Liver</i> Hepatocellular adenoma or carcinoma (combined): 2/47, 15/21*	*[$P < 0.0001$] * [$P < 0.0001$]	Principal limitations: use of single dose; short duration of exposure Same data reported in Biancifiiori et al. (1964)
Full carcinogenicity Mouse, BALB/c/Cb/Se (M+F, combined) Newborn Up to 425 days Milia et al. (1965)	Gavage Hydrazine sulfate, “pure” Water buffered with sodium bicarbonate 0, 17 mg – total dose 1 × /day for 60 days 20, 20 NR, NR	<i>Lung</i> Adenoma or carcinoma (combined): Incidence: 3/20, 20/20* Multiplicity: 1, 10 Total tumours: 3, 200	*[$P < 0.0001$]	Principal limitations: poor description of experimental design; small number of animals; no discussion of clinical signs, survival or body weights

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, Swiss (F) Age NR Up to 40 wks Roe et al. (1967)	Gavage Hydrazine sulfate (purity, NR) Distilled water 0 (untreated), 0.25 mg/dose 1 × /day, 5 days/wk for 40 wks 85, 25 42, 4	<i>Lung</i> Adenoma or carcinoma (combined): 8/79, 6/13*	* <i>P</i> < 0.001	Principal limitations: experimental details poorly described; single sex; short duration of exposure; poor survival in treated group
Full carcinogenicity Mouse, CBA/Cb/Se (M) Age NR Lifetime Biancifiiori (1969)	Gavage Hydrazine sulfate (purity, NR) Water 0.14 (intact virgin), 0.14 (gonadectomized), 0.28 (intact virgin), 0.28 (gonadectomized), 0.56 (intact virgin), 0.56 (gonadectomized) mg 1 × /day for a total of 150 doses (over 25 wks) 26, 25, 25, 26, 25, 23 NA	<i>Lung</i> Pulmonary tumours: 2/26, 3/25, 4/25, 3/26, 5/25, 5/23	NA	Principal limitations: poor description of experimental details; no discussion of pathology or clinical observations and no concurrent controls Study to investigate a possible hormonal effect on the formation of tumours by hydrazine sulfate
Full carcinogenicity Mouse, CBA/Cb/Se (F) Age NR Lifetime Biancifiiori (1969)	Gavage Hydrazine sulfate (purity, NR) Water 0.14 (intact virgin), 0.14 (gonadectomized), 0.28 (intact virgin), 0.28 (gonadectomized), 0.56 (intact virgin), 0.56 (gonadectomized) mg 1 × /day for a total of 150 doses (over 25 wks) 25, 25, 25, 25, 24, 25 NA	<i>Lung</i> Pulmonary tumours: 10/25, 2/25, 16/25, 6/25, 21/24, 7/25	NA	Principal limitations: poor description of experimental details; no discussion of pathology or clinical observations, and no concurrent controls Study to investigate a possible hormonal effect on the formation of tumours by hydrazine sulfate

Table 3.1 (continued)

Study design	Route	Incidence or multiplicity of tumours	Significance	Comments
Species, strain (sex) Age at start Duration Reference	Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals			
Full carcinogenicity Mouse, (BALB/c × DBA/2)F ₁ (CDF) (F) 7–8 wks 28–33 wks Kelly et al. (1969)	Gavage Hydrazine sulfate (purity, NR) 2% aqueous sodium bicarbonate 0, 41.6 mg total dose 1 × /wk for 8 wks 10, 28 10, 26	<i>Lung</i> Pulmonary tumours: 1/10, 13/28*	*[P < 0.05]	Principal limitations: experimental details poorly described; inadequate number of controls; no discussion of clinical observations or pathology
Full carcinogenicity Mouse, CBA/Cb/Se M 8 wks Lifetime Biancifiore (1970a)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 0.14, 0.28, 0.56, 1.13 mg/day 150 daily doses over 25 wks 30, 26, 25, 25, 25 NA	<i>Liver</i> Hepatoma [hepatocellular tumours]; 3/30, 1/26, 7/25, 12/25*, 15/25**	*[P < 0.003] **[P < 0.0001]	Principal limitations: short duration of exposure; lack of vehicle controls Hepatomas are mainly hepatocellular carcinomas
Full carcinogenicity Mouse, CBA/Cb/Se (F) 8 wks Lifetime Biancifiore (1970a)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 0.14, 0.28, 0.56, 1.13 mg/day 150 daily doses over 25 wks 29, 25, 25, 24, 24 NA	<i>Liver</i> Hepatoma [hepatocellular tumours]; 1/29, 0/25, 2/25, 16/24*, 15/24*	*[P < 0.0001]	Principal limitations: short duration of exposure; lack of vehicle controls Hepatomas are mainly hepatocellular carcinomas
Full carcinogenicity Mouse, BALB/c/Cb/ Se (M) 8 wks Lifetime Biancifiore (1970b)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 0.14 (21 mg total), 0.28 (42 mg total), 0.56 (84 mg total), 1.13 (170 mg total), 1.13 (32 mg total) mg/dose 28 or 150 doses over 4 or 25 wks 25, 24, 24, 26, 25, 20 NA	<i>Lung</i> Pulmonary adenoma or carcinoma (combined): 6/25, 13/24*, 15/24**, 17/26***, 20/22****, 17/20****	*[P < 0.05] **[P < 0.008] ***[P < 0.004] ****[P < 0.0001]	Principal limitations: no discussion of body-weight gain, or survival; lack of vehicle controls

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, BALB/c/Cb/ Se (F) 8 wks Lifetime Biancifiori (1970b)	Gavage Hydrazine sulfate (purity, NR) Water 0 (untreated), 0.14 (21 mg total), 0.28 (42 mg total), 0.56 (84 mg total), 1.13 (170 mg total), 1.13 (32 mg total) mg/ dose 28 or 150 doses over 4 or 25 wks 25, 25, 19, 25, 22, 20 NA	<i>Lung</i> Pulmonary adenoma or carcinoma (combined): 1/25, 8/25*, 17/19**, 19/25**, 20/22**, 15/20**	*[P < 0.02] **[P < 0.0001]	Principal limitations: no discussion of clinical signs, body-weight gain, or survival; lack of vehicle controls
Full carcinogenicity Mouse, BALB/c/Cb/ Se (F) 8 wks Lifetime Biancifiori (1970c)	Gavage Hydrazine sulfate (purity, NR) Water 0 mg (intact virgins), 1.13 mg (intact virgins), 0 mg (breeders), 1.13 mg (breeders), 0 mg (gonadectomized), 1.13 mg (gonadectomized) 150 daily doses of 1.13 mg/dose 25, 22, 25, 25, 26, 25 NA	<i>Lung</i> Adenoma or carcinoma (combined) Incidence: 1/25, 20/22*, 2/25, 25/25*, 7/26, 15/25** Multiplicity: 1, 3, 1, 14, 1, 5 Total tumours: 1, 60, 1, 201, 1, 50	*[P < 0.0001] **[P < 0.05]	Principal limitations: poor description of experimental details including duration of actual exposure; single dose used; no discussion of body-weight gain, or survival; lack of vehicle controls Study to test the effect of ovarian stimulation on pulmonary tumours induced by hydrazine sulfate in BALB/c/ Cb/Se (BALB/c) mice
Full carcinogenicity Mouse, C3Hb/Cb/Se (M) 8 wks Lifetime Biancifiori (1971)	Gavage Hydrazine sulfate (purity, NR) Water 0 mg (virgin), 1.13 mg (virgin), 0 mg (gonadectomized), 1.13 mg (gonadectomized) – total dose 150 daily doses of 1.13 mg/dose (170 mg total dose) 25, 27, 24, 25 NA	<i>Lung</i> Adenoma or carcinoma (combined): 0/25, 7/27*, 1/24, 1/25	*[P < 0.01]	Principal limitations: poor description of experimental details including duration of actual exposure; single dose used; no discussion of body-weight gain, or survival; lack of vehicle controls Tumours were mainly lung adenomas

Table 3.1 (continued)

Study design	Route	Incidence or multiplicity of tumours	Significance	Comments
Species, strain (sex)	Agent tested (purity)			
Age at start	Vehicle			
Duration	Dose regimen			
Reference	No. of animals at start			
	No. of surviving animals			
Full carcinogenicity	Gavage	<i>Lung</i>		Principal limitations: poor description of experimental details including duration of actual exposure; single dose used; no discussion of body-weight gain, or survival; lack of vehicle controls
Mouse, C3Hb/Cb/Se (F)	Hydrazine sulfate (purity, NR)	Adenoma or carcinoma (combined): 1/25, 13/27*, 3/25, 5/26, 3/23, 12/31**	*[P < 0.0004] **[P < 0.01]	
8 wks	Water			
Lifetime	0 mg (virgin), 1.13 mg (virgin), 0 mg (gonadectomized), 1.13 mg (gonadectomized), 0 mg (breeders), 1.13 mg (breeders) – total dose			
Biancifiore (1971)	150 daily doses of 1.13 mg/dose (170 mg total dose)			
	25, 27, 25, 26, 23, 31			
	NA			
Carcinogenicity with other modifying factors	Gavage	<i>Lung</i>		Principal limitations: no histological description of tumours; used only one dose; reported combined tumour incidence for males and females; no clinical signs, body weights or mortality information reported
Mouse, Swiss (M+F, combined)	Hydrazine sulfate, “analytical grade”	Incidence: 1/47, 22/29*, 11/18*, 26/33*, 17/31*, 13/18*, 16/21*	*[P < 0.0001]	Study on the effect of antioxidants on the formation of lung tumours in mice by hydrazine sulfate
10 wks	Water			
Up to 15 mo	0, 1.1 mg; 1.1 mg+1.1 mg L-arginine; 1.1 mg+1.1 mg pyridoxine hydrochloride; 1.1 mg+1.1 mg folic acid, 1.1 mg+1.1 mg L-arginine+L-sodium glutamate; 1.1 mg+1.1 mg L-sodium glutamate+pyridoxine hydrochloride mg/mouse/day			
Maru & Bhide (1982)	1 × /day, 5 days/wk for up to 15 mo			
	60, 60, 60, 60, 60, 60, 60			
	47, 29, 18, 33, 31, 18, 21			
Full carcinogenicity	Drinking-water	<i>Lung</i>		Principal limitations: use of a single dose
Mouse, Swiss (M)	Hydrazine sulfate, Fisher certified ACS	Adenoma or adenocarcinoma (combined): 11/110, 25/50*	*[P < 0.0001]	
6 wks	Water			
Lifetime	0 mg, 0.74 mg average daily consumption			
Toth (1969)	Daily/ad libitum in drinking-water			
	110, 50			
	NA			

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, Swiss (F) 6 wks Lifetime Toth (1969)	Drinking-water Hydrazine sulfate, Fisher certified ACS Water 0 mg, 0.65 mg average daily consumption Daily/ad libitum in drinking-water 110, 50 NA	<i>Lung</i> Adenoma or adenocarcinoma (combined): 14/110, 24/50*	*[$P < 0.0001$]	Principal limitations: use of a single dose
Full carcinogenicity Mouse, A/1 (M) 6 wks Up to 48 wks Yamamoto & Weisburger (1970)	Drinking-water Hydrazine sulfate (purity, NR) Water 0 mg/L, 0 mg/L + 1% L-arginine-L- glutamate (in the diet), 325 mg/L, 325 mg/L + 1% L-arginine-L-glutamate (in the diet), ad libitum in drinking- water 20, 20, 38, 37 NR	<i>Lung</i> Adenoma or adenocarcinoma (combined): 12/20, 11/20, 38/38*, 34/37**	*[$P < 0.0001$] **[$P < 0.005$]	Principal limitations: use of a single dose
Full carcinogenicity Mouse, NMRI (M) 5–6 wks 2 yrs Steinhoff et al. (1990)	Drinking-water Hydrazine hydrate (purity, 99.3%) Water 0, 2, 10, 50 ppm ad libitum 50, 50, 50, 50 NR	<i>Haematopoietic and lymphoid tissues</i> Malignant lymphoma: 4/50, 13/50, 6/50, 4/50	NS	Principal limitations: limited description of histopathology
Full carcinogenicity Mouse, NMRI (F) 5–6 wks 2 yrs Steinhoff et al. (1990)	Drinking-water Hydrazine hydrate, 99.3% Water 0, 2, 10, 50 ppm ad libitum 50, 50, 50, 50 NR	<i>Lung</i> Lung tumours (benign): 6/50, 6/50, 9/50, 15/50* <i>Haematopoietic and lymphoid tissues</i> Malignant lymphoma: 19/50, 31/50, 20/50, 19/50	* $P < 0.05$ NS	Principal limitations: limited description of histopathology

Table 3.1 (continued)

Study design	Route	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, Crj:BDF ₁ (M)	Drinking-water Hydrazine monohydrate (purity, 100%)	Liver Haemangioma or haemangiosarcoma	NS	Principal strengths: GLP study
6 wks	Deionized water	(combined): 3/50, 1/50, 6/50, 0/50		
2 yrs Matsumoto et al. (2016)	0, 20, 40, 80 ppm ad libitum, 7 days/wk 50, 50, 50, 50 31, 30, 36, 40	Hepatocellular adenoma or carcinoma (combined): 34/50, 24/50, 15/50, 10/50 Hepatocellular adenoma: 17/50, 12/50, 8/50, 6/50 Hepatocellular carcinoma: 21/50, 14/50, 9/50, 4/50	NS (increase) NS (increase) NS (increase)	
Full carcinogenicity Mouse, Crj:BDF ₁ (F)	Drinking-water Hydrazine monohydrate (purity, 100%)	Liver Haemangioma or haemangiosarcoma	$P < 0.05$ by Peto trend test	Principal strengths: GLP study Authors reported that hepatic haemangiomas in female mice were observed in three animals in the laboratory historical control data, which consisted of 899 female Crj:BDF ₁ mice (3/899, 0.3%)
6 wks	Deionized water	(combined): 1/50, 2/50, 1/50, 4/50		
2 yrs Matsumoto et al. (2016)	0, 40, 80, 160 ppm ad libitum, 7 days/wk 50, 50, 50, 50 26, 37, 29, 23	Haemangioma: 0/50, 0/50, 1/50, 3/50 Haemangiosarcoma: 1/50, 2/50, 0/50, 1/50 Hepatocellular adenoma or carcinoma (combined): 7/50, 8/50, 3/50, 17/50* Hepatocellular adenoma: 5/50, 6/50, 2/50, 14/50*	$P < 0.01$ by Peto trend test NS $P < 0.01$ by Peto trend test, * $P < 0.05$ by Fisher's exact test	
		Hepatocellular carcinoma: 2/50, 2/50, 1/50, 4/50	$P < 0.01$ by Peto trend test, * $P < 0.05$ by Fisher's exact test $P < 0.01$ by Peto trend test	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, BALB/c/Cb/Se (M+F, combined) Newborn Up to 270 days Milia et al. (1965)	Intraperitoneally Hydrazine sulfate ("pure") Water 0, 19 mg – total dose 1 × /day for 90 days 20, 20 NR, NR	<i>Lung</i> Adenoma or carcinoma (combined): Incidence: 2/20, 20/20* Multiplicity: 1, 5 Total tumours: 2, 100	*[<i>P</i> < 0.0001]	Principal limitations: poor description of experimental design; small number of animals per group, use of a single dose; no discussion of clinical signs, survival or body weights
Full carcinogenicity Mouse, (BALB/c × DBA/2)F ₁ (CDF ₁) (M) 7–8 wks 28–33 wks Kelly et al. (1969)	Intraperitoneally Hydrazine sulfate (purity, NR) 2% aqueous sodium bicarbonate 0, 20.8 mg total dose 1 × /wk for 8 wks 9, 30 8, 30	<i>Lung</i> Pulmonary tumours: 1/9, 6/30	NS	Principal limitations: experimental details poorly described, inadequate number of controls, no discussion of clinical observations or pathology
Full carcinogenicity Mouse, strain NR (M+F, combined) Age NR 313 days Juhász et al. (1966)	Intraperitoneally Hydrazine (purity, NR) Physiological saline 0, 400 mg/kg bw 16 injections over 46 days 60, 60 NR, 34	<i>Haematopoietic and lymphoid tissues</i> Reticular-cell sarcoma or myeloid leukaemia: 0/60, 13/34*	*[<i>P</i> < 0.0001]	Principal limitations: experimental details poorly described, use of a single dose, short exposure time, no discussion of clinical observations or pathology, poor description and discussion of tumour incidences
Carcinogenicity with other modifying factor Mouse, C57BL/6 (M+F, combined) 6–8 wk Up to 62 wks Mirvish et al. (1969)	Intraperitoneally Hydrazine sulfate (purity, NR) Water 0 (no irradiation), 0 (irradiated), 95 (irradiated), 95 (no irradiation) mg/kg bw Single 400 R total-body irradiation followed by 10 weekly injections ≥ 75, 29, 40, 36 NR, NR, NR, NR	<i>Lung</i> Adenoma: 9/75, NR, NR, 5/18 <i>Haematopoietic and lymphoid tissues</i> Leukaemia: NR, 2/25, 4/29, 0/33	[NS]	Principal limitations: experimental details poorly described; no discussion of clinical observations or pathology

Table 3.1 (continued)

Study design	Route	Incidence or multiplicity of tumours	Significance	Comments
Species, strain (sex)	Agent tested (purity)			
Age at start	Vehicle			
Duration	Dose regimen			
Reference	No. of animals at start			
	No. of surviving animals			
Full carcinogenicity	Inhalation	<i>Lung</i>		Principal limitations: single sex and low doses used; tumour incidence for some exposure groups not reported
Mouse, C57BL/6 (F)	Hydrazine (purity, 99.8%)	Adenoma: 4/378, NR, NR, 12/379*	*[P < 0.05]	
7 wks	Air			
27 mo	0, 0.05, 0.25, 1.0 ppm			
Vernot et al. (1985)	6 h/day, 5 days/wk for 1 yr			
	400, 400, 400, 400			
	NR, NR, NR, NR			
Full carcinogenicity	Gavage	<i>Lung</i>		Principal limitations: use of single dose, short duration of exposures
Rat, Cb/Se (M)	Hydrazine sulfate (purity, NR)	Pulmonary adenoma or carcinoma (combined):		See also Biancifiiori et al. (1966)
8 wks	Water	0/28, 3/14*	*[P < 0.05]	
Lifetime	0, 18 mg/dose	<i>Liver</i>		
Severi & Biancifiiori (1968)	1 × /day for 68 wks	Malignant tumours:		
	28, 14	0/28, 4/13*	*[P < 0.01]	
	NA			
Full carcinogenicity	Gavage	<i>Lung</i>		Principal limitations: use of a single dose, short duration of exposures
Rat, Cb/Se (F)	Hydrazine sulfate (purity, NR)	Pulmonary adenoma or carcinoma (combined):		See also Biancifiiori et al. (1966)
8 wks	Water	0/22, 5/18*	*[P < 0.02]	
Lifetime	0, 12 mg/dose			
Severi & Biancifiiori (1968)	1 × /day for 68 wks			
	22, 18			
	NA			
Full carcinogenicity	Drinking-water	<i>Liver</i>		
Rat, Wistar (M)	Hydrazine hydrate (purity, 99.3%)	Hepatocellular adenoma:		
6 wks	Water	0/50, 1/49, 1/50, 4/49*	*P < 0.01	
Lifetime	0, 2, 10, 50 ppm	Hepatocellular carcinoma:		
Steinhoff & Mohr (1988)	ad libitum in the drinking-water	0/50, 0/49, 1/50, 0/49	NS	
	50, 50, 50, 50			
	NA			

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested (purity) Vehicle Dose regimen No. of animals at start No. of surviving animals	Incidence or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, Wistar (F) 6 wks Lifetime Steinhoff & Mohr (1988)	Drinking-water Hydrazine hydrate (purity, 99.3%) Water 0, 2, 10, 50 ppm ad libitum in the drinking-water 50, 50, 50, 50 NA	<i>Liver</i> Hepatocellular adenoma: 0/50, 0/50, 0/50, 4/47* Hepatocellular carcinoma: 0/50, 0/50, 0/50, 3/47*	* $P < 0.01$ * $P < 0.01$	One of the hepatocellular carcinoma may not have been a primary tumour
Full carcinogenicity Rat, F344/DuCrj (M) 6 wks 2 yrs Matsumoto et al. (2016)	Drinking-water Hydrazine monohydrate (purity, 100%) Deionized water 0, 20, 40, 80 ppm ad libitum, 7 days/wk 50, 50, 50, 50 37, 39, 44, 39	<i>Liver</i> Hepatocellular adenoma or carcinoma (combined): 0/50, 0/50, 0/50, 4/50 Hepatocellular adenoma 0/50, 0/50, 0/50, 3/50 Hepatocellular carcinoma 0/50, 0/50, 0/50, 1/50 <i>Testis</i> Interstitial cell tumours: 37/50, 45/50*, 43/50, 44/50	$P < 0.01$ by Peto trend test $P < 0.01$ by Peto trend test NS $P < 0.05$ by Peto trend test, * $P < 0.05$ by Fisher's exact test	Principal strengths: GLP study
Full carcinogenicity Rat, F344/DuCrj (F) 6 wks 2 yrs Matsumoto et al. (2016)	Drinking-water Hydrazine monohydrate (purity, 100%) Deionized water 0, 20, 40, 80 ppm ad libitum, 7 days/wk 50, 50, 50, 50 40, 39, 44, 29	<i>Liver</i> Hepatocellular adenoma or carcinoma (combined): 1/50, 0/50, 3/50, 6/50 Hepatocellular adenoma: 1/50, 0/50, 3/50, 4/50 Hepatocellular carcinoma: 0/50, 0/50, 0/50, 4/50	$P < 0.01$ by Peto trend test $P < 0.05$ by Peto trend test	Principal strengths: GLP study Authors reported that hepatocellular carcinoma was observed in only one animal in the laboratory historical control data, which consisted of 898 female F344/DuCrj rats (1/898, 0.1%)

Table 3.1 (continued)

Study design	Route	Incidence or multiplicity of tumours	Significance	Comments
Species, strain (sex)	Agent tested (purity)			
Age at start	Vehicle			
Duration	Dose regimen			
Reference	No. of animals at start			
	No. of surviving animals			
Full carcinogenicity	Drinking-water	<i>Liver</i>		Principal limitations: study examined the liver only
Hamster, Syrian golden (M)	Hydrazine sulfate (purity, > 99%; ACS grade)	Hepatocellular adenoma: 0/25, 1/30, 4/43, 10/40*	*[$P < 0.005$]	Study designed to investigate methylation status of DNA cytosine during the course of induction by hydrazine of liver cancer in hamsters
Age NR	Water	Hepatocellular carcinoma: 0/25, 0/30, 1/43, 3/40	[Consequently, the incidence of hepatocellular adenoma or carcinoma (combined) is significantly increased ($P < 0.005$) in high-dose animals]	
21 mo	0, 170, 340, 510 mg/L			
FitzGerald & Shank (1996)	ad libitum			
	25, 30, 43, 40			
	NR, NR, NR, NR			
Full carcinogenicity	Inhalation	<i>Nose</i>		
Hamster, Syrian golden (M)	Hydrazine (purity, 99.8%)	Adenoma (adenomatous polyp): 1/181, 0/154, 1/148, 16/160*	* $P \leq 0.01$	
7 wks	Air	<i>Thyroid</i>		
24 mo	0, 0.25, 1.0, 5.0 ppm	Parafollicular cell adenoma: 0/145, 0/117, 0/127, 4/137	NS	
Vernot et al. (1985)	6 h/day, 5 days/wk for 1 yr	<i>Colon</i>		
	200, 200, 200, 200	Adenocarcinoma: 0/158, 0/146, 2/129, 3/139	NS	
	NR, NR, NR, NR			

bw, body weight; F, female; GLP, good laboratory practice; M, male; mo, month; NA, not applicable; NR, not reported; NS, not significant; ppm, parts per million; wk, week; yr, year

dose of 32 mg in water by gavage for 4 weeks and held for their lifetime. Groups of 22 male and 23 female BALB/c mice served as untreated controls. Exposure of male and female CBA/Cb/Se mice to hydrazine sulfate caused a significant increase in the incidence of pulmonary adenoma or carcinoma (combined) [mainly adenoma] (males: 16/21 (76%) [$P < 0.0001$] versus 1/37 (3%) controls; females: 19/21 (90%) [$P < 0.0001$] versus 4/47 (9%) controls) and hepatoma [hepatocellular tumours] (males: 13/21 (62%) [$P < 0.0001$] versus 4/37 (11%) controls; females: 15/21 (71%) [$P < 0.0001$] versus 2/47 (4%) controls) in exposed mice. Exposure of male and female BALB/c mice to hydrazine sulfate caused a significant increase in the incidence of pulmonary adenoma or carcinoma (combined) [mainly adenoma] (males: 7/8 (88%) [$P < 0.006$] versus 6/22 (27%) controls; females: 8/10 (80%) [$P < 0.003$] versus 5/23 (22%) controls). [The data for the CBA/Cb/Se mice experiment were also reported in [Severi & Biancifiori \(1968\)](#). While high incidences of pulmonary and liver tumours were reported in exposed CBA/Cb/Se mice, and a high incidence of pulmonary tumours was reported in exposed BALB/c mice, the Working Group noted the poor experimental design, lack of experimental details and vehicle controls, use of a single dose, and small number of mice in treated groups (especially for the BALB/c groups).]

A group of 20 male and female (combined) newborn BALB/c mice was given hydrazine sulfate in sodium bicarbonate (total dose of 17 mg) daily by gavage for 60 days and were then held for up to age 425 days. A group of 20 male and female (combined) mice served as vehicle controls. There was a 100% (20/20) [$P < 0.0001$] incidence of lung adenoma or carcinoma (combined) (carcinoma, 16%) in the treated group compared with a 15% incidence (3/20, adenoma only) in controls ([Milia et al., 1965](#)). [While a high incidence of pulmonary tumours was reported in treated mice versus controls, the Working Group noted the lack of experimental

details, limited experimental design, and use of a single dose level.]

A group of 25 female Swiss mice [age at start not reported] was given hydrazine sulfate at a dose of 0.25 mg per day by gavage in water on 5 days per week for up to 40 weeks. A group of 85 untreated female Swiss mice served as controls. The incidence of bronchiolo-alveolar adenoma or carcinoma (combined) was 6/13 (46%) ($P < 0.001$) in treated mice that survived for up to 60 weeks, versus 8/79 (10%) controls ([Roe et al., 1967](#)). [The Working Group noted that experimental details were poorly described, only one sex was used, the duration of exposure was short, and there was poor survival in the treated group.]

In a study to investigate a possible hormonal effect on the formation of tumours by hydrazine sulfate, [Biancifiori \(1969\)](#) treated groups of 23 to 26 intact virgin or gonadectomized male and female CBA/Cb/Se mice (age, 8 weeks) with hydrazine sulfate as 150 daily doses of 0.14, 0.28, or 0.56 mg (total doses of 21, 42, or 84 mg) by gavage over about 25 weeks. The mice were then held for their lifetime. No concurrent controls were reported. In the groups receiving the highest dose, the incidence of pulmonary tumours [histopathology not further specified] was 87% (21/24) in intact virgin females and 20% (5/25) in intact virgin males. In the groups receiving the intermediate dose, the incidence of pulmonary tumours was 56% (16/25) and 16% (4/25), respectively. In groups receiving the lowest dose, the incidence of pulmonary tumour was 40% (10/25) and 7% (2/26), respectively. In gonadectomized mice, the incidence of pulmonary tumours [mainly adenoma] was 28% (7/25) in females and 21% (5/23) in males at the highest dose, 24% (6/25) and 11% (3/26) at the intermediate dose, and 8% (2/25) and 12% (3/25) at the lowest dose. [The Working Group noted that the study had limited description of experimental details (including histopathology), and lacked concurrent controls.]

A group of 30 female (BALB/c × DBA/2) F₁ (CDF₁) mice (age, 7–8 weeks) was given hydrazine sulfate (total dose, 41.6 mg) in aqueous 2% sodium bicarbonate by gavage once per week for 8 weeks, and then held for up to 33 weeks. A group of 10 female mice served as vehicle controls. Pulmonary tumours [not further specified] were observed in 13/28 (46%) [$P < 0.05$] treated mice compared with 1/10 (10%) controls ([Kelly et al., 1969](#)). [While a high incidence of pulmonary tumours was reported in treated mice versus controls, the Working Group noted the lack of experimental details, limited description of the histopathology, and the limited experimental design including the use of one sex, only 10 control animals, and a single dose.]

Groups of 24–26 male and female CBA/Cb/Se mice (age, 8 weeks) were treated with hydrazine sulfate at a dose of 0.14, 0.28, 0.56, or 1.13 mg per day (total dose: 21, 42, 84, or 170 mg) by gavage in water 150 times over 25 weeks, and then held for their lifetime ([Biancifiori, 1970a](#)). Groups of 30 males and 29 females served as untreated controls. Exposure of male and female mice to hydrazine sulfate caused a dose-related significant increase in the incidence of hepatoma [mainly hepatocellular carcinoma] (males: 3/30 (10%), 1/26 (4%), 7/25 (28%), 12/25 (48%) [$P < 0.003$], 15/25 (60%) [$P < 0.0001$]; females: 1/29 (3%), 0/25, 2/25 (8%), 16/24 (66%) [$P < 0.0001$], 15/24 (62.5%) [$P < 0.0001$]; for untreated controls, and the groups at 21, 42, 84, and 170 mg, respectively). Multiple pulmonary tumours were reported to be present in many treated animals, but data on tumour incidence were not provided. [The Working Group noted the lack of vehicle controls.]

Groups of 20–26 male and 19–25 female BALB/c mice (age, 8 weeks) were treated with hydrazine sulfate at a dose of 0.14, 0.28, 0.56, or 1.13 mg per day (total dose, 21, 42, 84, or 170 mg) by gavage in water for 150 daily doses over 25 weeks, or at a dose of 1.13 mg per day (total dose, 32 mg) for 28 daily doses over 4 weeks, and then

held for their lifetime ([Biancifiori, 1970b](#)). Groups of 25 males and 25 females served as untreated controls. Hydrazine sulfate significantly increased the incidence of pulmonary adenoma or carcinoma (combined) [mainly adenoma] in all dosed groups compared with controls. Tumour incidence for males was: 6/25 (24%), 13/24 (54%) [$P < 0.05$], 15/24 (62.5%) [$P < 0.008$], 17/26 (65%) [$P < 0.004$], 17/20 (85%) [$P < 0.0001$], 20/22 (91%) [$P < 0.0001$]; and for females was: 1/25 (4%), 8/25 (32%) [$P < 0.02$], 17/19 (89%) [$P < 0.0001$], 19/25 (76%) [$P < 0.0001$], 15/20 (75%) [$P < 0.0001$] and 20/22 (91%) [$P < 0.0001$]; for untreated controls, and the groups treated with 21, 42, 84, 32, and 170 mg, respectively. [The Working Group noted the limited description of experimental details, including body-weight gain or survival, and the lack of vehicle controls.]

Groups of 22–25 intact virgin, breeders, or gonadectomized female BALB/c mice (age, 8 weeks) were treated with hydrazine sulfate at a dose of 1.13 mg (total dose, 170 mg) by gavage in water as 150 daily doses, and then held for their lifetime ([Biancifiori, 1970c](#)). Three groups of 25–26 intact virgin, breeders, or gonadectomized mice served as untreated controls. Hydrazine sulfate increased the incidence of pulmonary tumours to 90% (20/22) [$P < 0.0001$, mainly adenoma] in intact virgins versus 4% (1/25) in controls, 100% (25/25) [$P < 0.0001$; adenoma:carcinoma, about 1:1] in breeders versus 8% (2/25) in controls, and 60% (15/25) [$P < 0.05$, mainly adenoma] in gonadectomized mice versus 27% (7/26) in controls. [The Working Group noted the poor description of experimental details, including duration of actual exposure, body-weight gain or survival, and the lack of vehicle controls and use of a single dose.]

[Biancifiori \(1971\)](#) gave five groups of 25–31 8-week-old male and female intact virgin, gonadectomized, or breeder (female only) C3H/Cb/Se mice, 150 daily doses of 1.13 mg/dose (170 mg total dose) of hydrazine sulfate in water by gavage over 25 weeks. The animals were then held for

their lifetime. Five groups of 23–25 intact virgin, gonadectomized or breeder animals served as untreated controls. Hydrazine sulfate increased the incidence of pulmonary tumours to 26% (7/27) [$P < 0.01$, mainly adenoma] in intact virgin males versus 0% (0/25) in controls, and to 48% (13/27) [$P < 0.0004$, mainly adenoma] in intact virgin females versus 4% (1/25) in controls. The incidence of pulmonary tumours was 4% (1/25) [adenoma] in gonadectomized males versus 4% (1/24) in controls, and 19% (5/26) in gonadectomized females versus 12% (3/25) in controls. Hydrazine sulfate increased the incidence of pulmonary tumours to 39% (12/31) [$P < 0.01$; adenoma:carcinoma, about 2:1] in female breeders versus 13% (3/23) in controls. [The Working Group noted the limited description of experimental details, including body-weight gain or survival, and the lack of vehicle controls, and use of a single dose.]

In a study to investigate the effect of antioxidants on the formation of tumours of the lung in mice by hydrazine sulfate, groups of 30 male and 30 female Swiss mice (age, 10 weeks) were treated with hydrazine sulfate at daily doses of 0 (control) or 1.1 mg by gavage in water for 5 days per week for up to 15 months. Five groups of treated mice were also simultaneously treated with 1.1 mg per day of the following antioxidants: L-arginine, pyridoxine hydrochloride, folic acid, L-arginine + L-sodium glutamate, or L-sodium glutamate + pyridoxine hydrochloride. The experiment was terminated at 15 months, except for the control group, which was maintained for lifetime. In all of the six groups treated with hydrazine sulfate, the incidence of lung tumours [not further specified] in males and females (combined) was significantly increased and ranged from 17/31 (55%) to 26/33 (79%) [$P < 0.0001$, for all treated groups versus the control group], while the incidence in the control group was 1/47 (2%) (Maru & Bhide, 1982). [The Working Group noted that this study used a single dose, reported combined tumour incidence for males and females, and reported no

clinical signs, body weights, mortality information, or histological description of tumours.]

In a study of perinatal exposure in Swiss mice in which hydrazine sulfate was used to induce lung tumours, exposed groups of male and female Swiss mice (parental generation) and groups of 6 (unexposed F_1) or 22 males and females (combined) of their F_1 generation were treated with hydrazine sulfate (in distilled water) at 0 (unexposed F_1) or 1.1 mg per day, 5 days per week, by gavage, at age 10–11 weeks, for their lifetime, respectively (Menon & Bhide, 1983). Two groups of 10 (unexposed F_2) or 35 males and females (combined) of the F_2 generation, were also exposed or not (unexposed F_2) to hydrazine sulfate transplacentally and through lactation. A group of 20 males and females served as untreated controls. To raise the F_1 progeny of hydrazine-treated females, dams received hydrazine (1.1 mg per day) from day 1 of gestation, and continued to receive hydrazine treatment through lactation until death. To raise the exposed F_2 progeny, F_1 males and females (combined) were treated with hydrazine from the age of 11 weeks for a period of 4 weeks, and were then kept for mating; pregnant F_1 females continued to receive hydrazine from day 1 of gestation through lactation until death. To raise the unexposed F_2 progeny, F_1 parents were of the untreated F_1 generation.

The incidence of adenocarcinoma of the lung in the parental generation exposed to hydrazine sulfate was 72% (21/29; $P < 0.05$, X^2 test, versus 1/20 untreated controls) in females and 88% (30/34; $P < 0.05$, X^2 test, versus 1/20 untreated controls) in males. F_1 mice receiving hydrazine sulfate only during gestation and lactation, and subsequently given distilled water from a young adult age showed a 50% (3/6; $P < 0.05$, X^2 test, versus 1/20 untreated controls) incidence of adenocarcinoma of the lung, while F_1 mice raised from the same stock of parents and receiving hydrazine sulfate at 1.1 mg per day showed a 90% (20/22; $P < 0.05$, X^2 test, versus 1/20 untreated controls)

incidence of adenocarcinoma of the lung. The F₂ generation of mice, whose parents received distilled water during gestation and lactation, and then distilled water by gavage from a young adult age (unexposed F₂ generation controls), had a 10% (1/10) incidence of adenocarcinoma of the lung, while the F₂ generation of mice, whose parents received hydrazine sulfate by gavage for 4 weeks and which were themselves exposed to hydrazine sulfate during gestation and lactation, showed a 45% (16/35; $P < 0.05$, X² test, versus 1/10 unexposed F₂ generation controls) incidence of adenocarcinoma of the lung. [The Working Group noted that the study used only a single dose, reported combined tumour incidences for males and females, and did not report on clinical signs, body weights or mortality.]

3.1.2 Drinking-water

[Toth \(1969\)](#) reported on a study in three strains of mice treated with hydrazine sulfate. Groups of 110 (control) or 50 male and female Swiss mice (age, 6 weeks) were given drinking-water containing 0% or 0.012% [120 mg/L] hydrazine sulfate (average daily dose, 0.74 mg and 0.65 mg for males and females, respectively) for their lifetime. Exposure of male and female Swiss mice to hydrazine sulfate caused a significant increase in the incidence of adenoma or carcinoma (combined) of the lung: males, 25/50 (50%) [$P < 0.0001$] versus 11/110 (10%) controls; females, 24/50 (48%) [$P < 0.0001$] versus 14/110 (13%) controls. Additionally, groups of 30 (control) or 40 male and female AKR mice (age, 6 weeks) were given drinking-water containing 0% or 0.012% hydrazine sulfate (average daily dose, 0.63 mg for males and females) for their lifetime, and groups of 30 (control) or 41 male and 30 (control) or 40 female C3H mice (age, 6 weeks) were given drinking-water containing 0% or 0.012% hydrazine sulfate (average daily dose, 0.98 mg and 0.84 mg for males and females, respectively) for their lifetime. No significant

increase in tumour incidence was observed in male and female AKR or C3H mice exposed to hydrazine sulfate. [The Working Group noted the use of a single dose.]

In a study to see whether the formation of lung tumours by hydrazine could be inhibited by arginine glutamate, groups of 20 or 37–38 male A/J mice (age, 6 weeks) were given drinking-water containing hydrazine sulfate at a concentration of 0 or 325 mg/L and feed containing 0% or 1% arginine glutamate for up to 48 weeks ([Yamamoto & Weisburger, 1970](#)). Hydrazine sulfate caused a significant increase [$P < 0.0001$] in the incidence of lung adenoma or carcinoma (combined) (38/38; 100%) in exposed mice compared with control mice (12/20; 60%). Upon addition of arginine glutamate, the incidence of pulmonary tumours in hydrazine-treated mice was not significantly affected, and arginine glutamate did not change the incidence of pulmonary tumours in control mice. [The Working Group noted the use of a single dose.]

Groups of 50 male and 50 female NMRI mice (age, 5–6 weeks) were given drinking-water containing hydrazine hydrate at a concentration of 0, 2, 10, or 50 ppm ad libitum for up to 2 years. A significant reduction in body weight was observed in groups at the highest dose. There was no difference in survival in any of the treated groups or controls. There was a significant increase ($P < 0.05$) in the incidence of benign lung tumours in females at the highest dose (15/50) compared with controls (6/50). There was no other significant increase in tumour incidence in any of the treatment groups compared with controls ([Steinhoff et al., 1990](#)). [The Working Group noted the limited description of the pathology of the lesions observed in treated and control mice.]

[Matsumoto et al. \(2016\)](#) reported the results of a study that complied with good laboratory practice (GLP) in which groups of 50 male and 50 female Crj:BDF₁ mice (age, 6 weeks) were given drinking-water containing hydrazine

monohydrate at a concentration of 0, 20, 40, or 80 ppm (males), and 0, 40, 80, or 160 ppm (females) ad libitum for 2 years. Body weights of males at the intermediate and highest dose and of all groups of treated females were significantly decreased in a dose-related manner compared with controls. There was no significant difference in survival in any of the treated groups compared with controls, except in females at the lowest dose, in which survival was better than in controls. In females at the highest dose, hydrazine monohydrate caused a significant increase in the incidence of hepatocellular adenoma (14/50, 28%; $P < 0.05$) compared with controls (5/50, 10%), and a significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) (17/50, 34%; $P < 0.05$) compared with controls (7/50, 14%). There was a significant, dose-dependent positive trend ($P < 0.01$, Peto trend test) in the incidences of haemangioma of the liver, hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in treated female mice. There was also a significant, dose-dependent positive trend ($P < 0.05$, Peto trend test) for the incidence of haemangioma or haemangiosarcoma (combined) of the liver in females. There was no significant increase in the incidence of any tumours in males. [The strengths of this GLP study included the use of multiple doses, a high number of animals per group, and two sexes.]

3.1.3 Intraperitoneal injection

Two groups of 20 newborn male and female (combined) BALB/c/Cb/Se mice were treated by intraperitoneal injection of hydrazine sulfate (in water) once a day for 90 days (0 or 19 mg total dose/mouse) and then held for up to 270 days (Milia et al., 1965). There was a 100% incidence (20/20) [$P < 0.0001$] of lung adenoma or carcinoma (combined) (carcinomas, 27%) in the treated group compared with a 10% incidence (2/20, adenomas only) in controls. [The

Working Group noted the limited description of experimental design, small number of animals per group, use of only one dose, and absence of discussion of clinical signs, survival or body weights.]

Groups of 9 (control) or 30 male CDF₁ mice (age 7–8 weeks) were treated by intraperitoneal injection of saline (control) or hydrazine sulfate in 2% aqueous sodium bicarbonate once a week for 8 weeks (0 or 20.8 mg total dose/mouse) and then held for up to 33 weeks (Kelly et al., 1969). There was a non-significant increase in the incidence of pulmonary tumours [not further specified] in 6/30 treated animals (20%) versus 1/9 (10%) in controls. [The Working Group noted the poor description of experimental details, the use of a single dose, the small number of controls, the short exposure time, and absence of discussion of clinical observations or pathology.]

Groups of 30 male and 30 female (combined) white mice (strain and age not reported) [weight, ~20 g] were treated with hydrazine at a dose of 0 (control) or 400 mg/kg body weight (bw) in physiological saline in 16 intraperitoneal injections administered over 46 days, and were then held for up to 313 days (Juhász et al., 1966). It was reported that 13/34 (38%) mice surviving the treatment developed tumours of the haematopoietic and lymphoid tissues (reticulum cell sarcoma or myeloid leukaemia) [$P < 0.0001$] between days 100 and 313 of the experiment. No reticulum cell sarcoma or myeloid leukaemia was reported in the 60 controls after 1 year. [The Working Group noted the poor description of experimental details, the use of a single dose, the high mortality in treated animals, the reported combined tumour incidences, the short exposure time, the absence of discussion of clinical observations or pathology, and the poor description and discussion of tumour incidences.]

In a study of hydrazine and a modifying factor (irradiation), groups of 29 or 40 male and female C57BL/6 mice (equal numbers of each sex per group) (age, 6–8 weeks) were exposed once to

400 R total-body irradiation and, starting 1 week after irradiation, given intraperitoneal injections of aqueous hydrazine sulfate at a dose of 0 or 95 mg/kg bw once per week for 10 weeks, and then held for up to 62 weeks. A group of 36 mice received no irradiation and weekly injections of hydrazine sulfate, and were also held for up to 62 weeks. A fourth group of at least 75 animals served as untreated controls. In the non-irradiated groups, lung adenomas were observed in 5/18 (28%) [not significant] mice treated with hydrazine sulfate compared with 9/75 (12%) untreated controls. The incidence of leukaemia was not increased in the irradiated/hydrazine treated group (4/29) compared with irradiated-only controls (2/25) (Mirvish et al., 1969). [The Working Group noted the use of a single dose, the limited description of experimental details, the short exposure time, the lack of reporting of clinical signs, body weights, and mortality information or histological description of tumours.]

3.1.4 Inhalation

Groups of 400 female C57BL/6 mice (age, 7 weeks) were exposed to 0 (concurrent control), 0.05, 0.25, or 1.0 ppm [0, 0.04, 0.2, and 0.8 mg/m³] anhydrous hydrazine (purity, 99.8%) by inhalation for 6 hours per day, 5 days per week, for 1 year, and then held for an additional 15 months. Deaths during exposure were below 10% in all groups, and exposed mice demonstrated significantly higher mortality than controls at the end of the experiment, but without any dose–response relationship (controls, 72–79%; exposed, 84–87%). An increase in the incidence of lung adenoma was reported in mice at the highest dose (12/379, 3%) [$P < 0.05$] versus controls (4/378, 1%). No information on lung tumours was given for the other exposure groups (Vernot et al., 1985). [The Working Group noted the low doses used and the lack of tumour data for the groups receiving the lowest and intermediate doses.]

3.2 Rat

3.2.1 Gavage

Groups of 14–28 male and female CB/Se rats were given “pure” hydrazine sulfate as a daily gavage dose in water at 0, 12 (females only), or 18 (males only) mg/day for 68 weeks, and then held for their lifetime. Pulmonary adenoma or carcinoma was observed in 3/14 (21%) [$P < 0.05$] treated males and 5/18 (28%) [$P < 0.02$] treated females. Malignant liver tumours were observed in 4/13 (30%) [$P < 0.01$] treated males. No pulmonary or liver tumours were observed in control males (0/28) or females (0/22) (Biancifiori et al., 1966; Severi & Biancifiori 1968). [The Working Group noted the short duration of exposure, the small number of rats per exposure group, the use of a single dose, and the limited description of experimental design and results.]

3.2.2 Drinking-water

Groups of 50 male and 50 female Wistar rats were given drinking-water containing hydrazine hydrate (purity, 99.3%) at a concentration of 0, 2, 10, or 50 ppm ad libitum for their lifetime. A significant reduction in body weight was observed in males and females at the highest dose. There was no significant difference in survival in any of the treated groups or controls. There was a significant increase ($P < 0.01$) in the incidences of hepatocellular adenoma in males at the highest dose (4/49) and females at the highest dose (4/47), and of hepatocellular carcinoma in females at the highest dose (3/47; one of the tumours may not have been a primary tumour). The incidence of hepatocellular adenoma or carcinoma (combined) in females at the highest dose (7/47) was significantly increased [$P < 0.01$]. No hepatocellular tumours were observed in the 50 male and 50 female controls (Steinhoff & Mohr, 1988).

In a GLP study, groups of 50 male and 50 female F344/DuCrj rats (age, 6 weeks) were given drinking-water containing hydrazine

monohydrate at a concentration of 0, 20, 40, or 80 ppm ad libitum for 2 years ([Matsumoto et al., 2016](#)). Body weights of males and females at the intermediate and highest doses were significantly decreased in a dose-related manner compared with controls. Survival in females at the highest dose was significantly reduced compared with controls, while survival was similar to controls for all other groups of treated females and for all groups of treated males. Hydrazine monohydrate in male rats caused a significant positive trend in the incidence of hepatocellular adenoma (0/50, 0/50, 0/50, 3/50; $P < 0.01$ by Peto trend test) and hepatocellular adenoma or carcinoma (combined) (0/50, 0/50, 0/50, 4/50; $P < 0.01$ by Peto trend test). In female rats, hydrazine monohydrate caused a significant positive trend in the incidence of hepatocellular adenoma (1/50, 0/50, 3/50, 4/50; $P < 0.05$ by Peto trend test), hepatocellular carcinoma (0/50, 0/50, 0/50, 4/50; $P < 0.01$ by Peto trend test), and hepatocellular adenoma or carcinoma (combined) (1/50, 0/50, 3/50, 6/50; $P < 0.01$ by Peto trend test). There was also a significant increase and positive trend in the incidence of interstitial cell tumours of the testis (37/50, 45/50*, 43/50, 44/50; $*P < 0.05$; $P < 0.05$ by Peto trend test). [The strengths of this GLP study included the use of multiple doses, a high number of rats per group, and two sexes.]

3.2.3 Inhalation

Groups of 150 (controls) or 100 male and female F344 rats (age, 7 weeks) were exposed to anhydrous hydrazine (purity, 99%) at a concentration of 0 (control), 0.05, 0.25, 1.0, or 5.0 ppm [0, 0.04, 0.2, 0.8, or 4.0 mg/m³] by inhalation for 6 hours per day, 5 days per week for 1 year, and then held for an additional 18 months. Deaths during exposure were low in all groups (below 10%), and mortality was similar in all groups at the end of the study. A significant increase in the incidence of adenomatous polyps [adenoma] of the nose was reported in males exposed to

the higher two doses (0/146, 2/96, 1/94, 9/97*, 58/98*; $*P \leq 0.01$) and in females at the highest dose (0/145, 2/97, 0/98, 2/94, 28/95*; $*P \leq 0.01$). A significant increase in the incidence of thyroid carcinoma was also reported in males at the highest dose (7/146, 6/96, 5/94, 9/97, 13/98**; $**P \leq 0.05$) ([Vernot et al., 1985](#)).

Groups of 100 male and 100 female F344 rats (age, 9–11 weeks) were exposed to anhydrous hydrazine (purity, 98.8%) at a concentration of 0, 75, or 750 ppm [0, 98 and 980 mg/m³] by inhalation for 1 hour per day, 1 day per week, for 10 weeks, and then held for 24–30 months. Polypoid adenomas of the nose were found in 4/99 (4%, $P < 0.05$) males at the highest dose, and 6/95 (6%, $P < 0.05$) females at the highest dose. In addition, one nasal squamous cell carcinoma was reported in males. No nasal tumours were observed in 98 male and 98 female controls ([Latendresse et al., 1995](#)). [The Working Group noted that this study was inadequate for the evaluation because of inadequate exposure for a study of full carcinogenicity.]

3.3 Hamster

3.3.1 Gavage

Groups of 23–56 male and female (sex distribution not given) Syrian golden hamsters (age, 8 weeks) were treated with hydrazine sulfate (purity not reported) at a total dose of 0, 180, or 280 mg by gavage in water for 15 or 20 weeks, and then held for life ([Biancifiori, 1970a](#)). There was a significant decrease in survival in treated hamsters compared with controls. No information on body weight was provided. No significant increase in the incidence of tumours was reported. A significant increase in cirrhosis of the liver was reported in both treatment groups, but not in the controls. [The Working Group noted that the study used a short duration of exposure, and was considered inadequate for the evaluation because of inadequate reporting of results in controls.]

3.3.2 Drinking-water

Groups of 50 male and 50 female Syrian golden hamsters (age, 9 weeks) were given drinking-water containing hydrazine sulfate (purity not reported) at a concentration of 0.012% [120 mg/L] for life. The average daily intake of hydrazine sulfate was 2.3 mg for both sexes. There was a slight decrease in body weight, but no effect on survival in treated animals compared with controls. No significant increases in the number of tumours produced were reported in treated hamsters. A non-significant increase in the incidence of polypoid adenoma of the caecum was reported in treated males (3/49, 6%) and females (4/45, 9%) compared with controls, but statistics and tumour incidence in controls were not provided (Toth, 1972). [The Working Group considered that the study was inadequate for the evaluation because of the use of a single dose and because of the inadequate reporting of results in controls.]

Groups of 40 male Syrian golden hamsters (age at start not given; weight, 50–60 g at 1 week before exposure) were given drinking-water containing hydrazine sulfate (purity, > 99%) at a concentration of 0 (control), 170, 340, or 510 mg/L for 2 years (average doses, 0, 4.6, 8.3, and 10.3 mg/kg bw per day) (Bosan et al., 1987). There was a significant decrease in survival in all treated groups. Hepatocellular carcinomas were observed in hamsters treated with the two higher doses of hydrazine sulfate after 78 weeks of exposure. The incidences of hepatocellular carcinoma were 0/31 (controls), 0/31, 4/34 (12%), and 11/34 (32%; [$P < 0.0004$]).

Groups of 25–40 male Syrian golden hamsters (age at start not given; weight, 50–70 g at 1 week before exposure) were given drinking-water containing hydrazine sulfate (purity, > 99%) at a concentration of 0 (control), 170, 340, or 510 mg/L for up to 21 months (average doses calculated from consumption data: 0, 4.2, 6.7, and 9.8 mg/kg bw per day) (FitzGerald & Shank, 1996). There was

a significant decrease in survival in all treated groups. The incidence of hepatocellular adenoma was 0/25 (control), 1/30 (3%), 4/43 (9%), and 10/40 (25%) [$P < 0.005$], and the incidence of hepatocellular carcinoma was 0/25 (control), 0/30, 1/43 (2%) and 3/40 (8%), respectively. [The Working Group noted that the incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased [$P < 0.005$] in the group at the highest dose compared with controls.]

3.3.3 Inhalation

Groups of 200 male Syrian golden hamsters (age, 7 weeks) were exposed to anhydrous hydrazine (purity, 98.8%) at a concentration of 0 (control), 0.25, 1.0, or 5.0 ppm [0, 0.2, 0.8 or 4.0 mg/m³] by inhalation for 6 hours per day, 5 days per week, for 1 year, and then held for an additional 1 year (Vernot et al., 1985). Exposure to hydrazine had no effect on body weights of hamsters in any treated group compared with controls. Deaths during exposure were high in all exposure groups (32–33% versus 19% in controls), but mortality was similar in all groups at the end of the study (2 years). A significant increase in the incidence of nose adenomatous polyps [adenoma] was reported in the group at the highest dose: 1/181 (1%) controls; 0/154; 1/148 (1%); 16/160* (10%), * $P \leq 0.01$. A non-significant increase in the incidence of parafollicular cell adenoma of the thyroid gland was also reported in the group at the highest dose (4/137, 3%, versus 0/145 in controls), as was a non-significant increase in the incidence of adenocarcinoma of the colon in the groups at the intermediate and highest dose (2/129, 2% and 3/139, 2%, respectively, versus 0/158 in controls) (Vernot et al., 1985).

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

4.1.1 Absorption, distribution, excretion

(a) Humans

Organ toxicity after accidental or intentional exposure to hydrazine demonstrated absorption into the systemic circulation and distribution to target tissues (Nagappan & Riddell, 2000; Kao et al., 2007). After occupational exposure, hydrazine was absorbed and excreted in the urine (Nomiya et al., 1998a). Exposure to the therapeutic drug isoniazid, containing a hydrazine group, resulted in excretion of hydrazine and its metabolites in the urine (Timbrell et al., 1977; Blair et al., 1985; Donald et al., 1994; Preziosi, 2007).

(b) Experimental systems

Absorption of hydrazine was rapid after either oral or dermal administration in experimental animals. Hydrazine was detected in femoral blood within 30 seconds after application of a dose of 3–15 mmol/kg bw to an area of shaved chest skin of anaesthetized dogs. The serum concentration of hydrazine peaked within the first hour for most doses, followed by a slow decline over a 6-hour holding period. Unchanged hydrazine was excreted in the urine. Mortality was high across the dosing range (Smith & Clark, 1972). When hydrazine hydrate (corresponding to hydrazine free base at 3–81 mg/kg bw) was given orally (gavage) to rats, hydrazine was at its greatest concentration in the plasma and liver within 30 minutes after dosing, with the exception of a peak in plasma concentration 90 minutes after administration of the highest dose (Preece et al., 1992a). The liver to plasma ratio of hydrazine decreased with increasing dose, suggesting

saturation of uptake by the liver. An effect on dose elimination was also observed, with about 40% of the lowest dose but less than 20% of the highest dose being excreted in the urine within 24 hours after administration. Dambrauskas & Cornish (1964) investigated the fate of hydrazine in rats given hydrazine hydrate at a dose of 60 mg/kg bw by subcutaneous injection. The dose was well distributed, with hydrazine detected in adipose, blood, brain, kidney, liver, lung, muscle, skin, and other tissues within 2 hours after dosing. About 13% of the total administered dose was recovered in the assayed tissues as unchanged hydrazine, with the highest concentration present in the kidney (41–56 µg/g). Hydrazine (8% of the total administered dose) was excreted in the urine. Matsuyama et al. (1983) provided additional evidence that hydrazine crosses the blood–brain barrier in rats. After intravenous injection, hydrazine was detected in the brain accompanied by an increase in gamma-aminobutyric acid (GABA) over a period of 10 hours. Hydrazine was rapidly absorbed and distributed to tissues when administered as hydrazine sulfate at a dose of 0.31 mmol/kg bw by subcutaneous injection in rats (Kaneo et al., 1984). Springer et al. (1981) recovered up to 75% of [¹⁵N]-labelled hydrazine from single doses of 1 mmol/kg bw administered by various injection routes (intra-peritoneal, subcutaneous, intravenous) in rats. Up to 25% of the total administered dose was recovered as nitrogen (N₂) in expired air within 48 hours. An additional 50% was excreted in the urine as unchanged hydrazine and acid-labile metabolite(s). The disappearance of intravenously administered hydrazine from blood was described as biphasic, with calculated half-lives of 0.74 and 27 hours. In mice, intraperitoneal administration of [¹⁵N]-labelled hydrazine sulfate at 1 mmol/kg bw resulted in rapid distribution to tissues including blood, brain, liver, kidney, and lung (Nelson & Gordon, 1981). Clearance from tissues was extensive by 24 hours. About 30% of the administered dose was recovered as N₂ and

40% was recovered in the urine as hydrazine and metabolites within 48 hours after injection (Nelson & Gordon, 1981).

Mice excreted about 50% of an administered dose of either 40 or 60 mg/kg bw as unchanged hydrazine in the urine within 48 hours after a subcutaneous injection. Less than 1.5% of the administered hydrazine remained in each carcass at this time-point. The unrecovered dose was assumed to be metabolites (Dambrauskas & Cornish, 1964).

4.1.2 Metabolism

(a) Humans

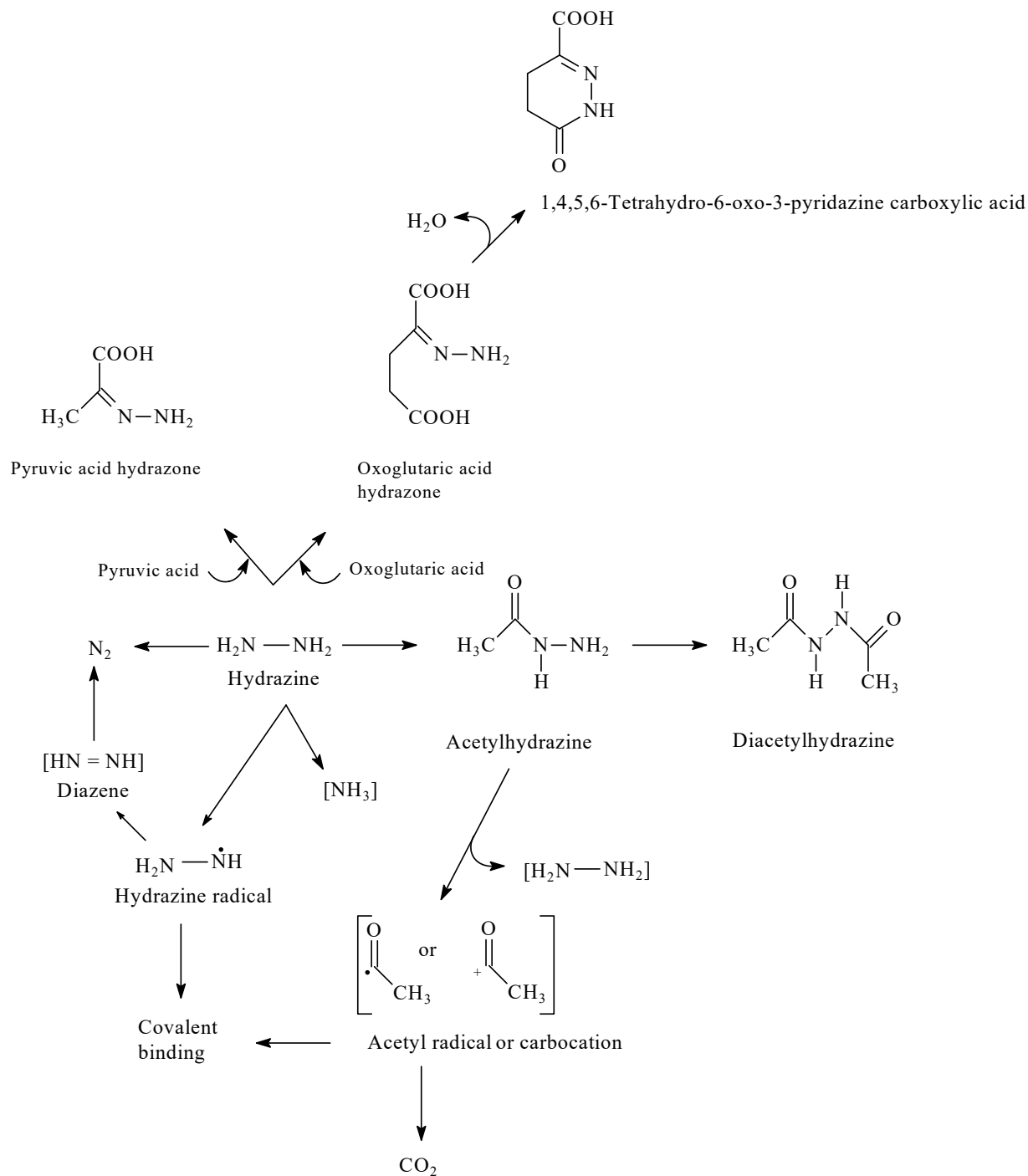
Hydrazine was metabolized to acetylhydrazine (monoacetylhydrazine) in exposed workers (Nomiya et al., 1998a). In male Japanese workers, the rate of acetylation was dependent on polymorphisms in *N*-acetyltransferase (NAT2), with half-lives of about 2 and 4 hours in rapid and slow acetylators, respectively (Koizumi et al., 1998). Acetylhydrazine and diacetylhydrazine have been detected in the urine of subjects receiving isoniazid (Ellard & Gammon, 1976; Timbrell et al., 1977). Oxidative metabolism of hydrazine was demonstrated in human microsomes based on disappearance of the chemical over time from the incubation mixture; however, the rate of metabolism was slower than in rat microsomes (Jenner & Timbrell, 1995). A review of isoniazid metabolism indicated that pathways of hydrazine biotransformation are similar in humans and other mammals (Preziosi, 2007). The metabolism of hydrazine is discussed in greater detail below.

(b) Experimental systems

Pathways of hydrazine metabolism in experimental animals include oxidation and acetylation (Colvin, 1969; Fig. 4.1). Acetylhydrazine and/or diacetylhydrazine have been observed in the urine of animals treated with hydrazine. The presence and/or relative abundance of these

acetylated metabolites are species-dependent. Bollard et al. (2005) detected diacetylhydrazine in the urine of rats and mice treated orally with hydrazine hydrochloride at a dose of 100 or 250 mg/kg bw. In contrast, acetylhydrazine was detected in the urine in rats, but not in mice. This result was attributed to higher activity of *N*-acetyltransferase in the mouse. Dogs, unlike rats and mice, have little to no capacity to acetylate hydrazine (McKennis et al., 1959). This limitation may have contributed to the prolonged elimination of hydrazine in dogs as reported by Smith & Clark (1972). Rabbits treated with hydrazine excreted diacetylhydrazine in the urine (McKennis et al., 1959). Kaneo et al. (1984) demonstrated that metabolism of hydrazine to acetylhydrazine in rats was reversible. Acetylhydrazine may give rise to a carbon-centred acetyl radical or carbocation, capable of binding to macromolecules or oxidation to carbon dioxide (CO₂) (Sinha, 1987; Mörike et al., 1996; Preziosi, 2007). Hydrazine may also give rise to hydrazones (Preziosi, 2007). The metabolite 1,4,5,6-tetrahydro-6-oxo-3-pyridazine carboxylic acid, a derivative of oxoglutarate hydrazone, was found in the urine of rats and mice treated with hydrazine (Nelson & Gordon, 1981; Delaney & Timbrell, 1995; Bollard et al., 2005). Hydrazine is oxidized to N₂ in rats and mice (Nelson & Gordon, 1981; Springer et al., 1981). Degradation of hydrazine to ammonia (NH₃) may be possible, especially in dogs (McKennis et al., 1959; Colvin, 1969; Preziosi, 2007). Oxidative metabolism of hydrazine was catalysed primarily by cytochrome P450s (CYPs) in rat microsomes (Noda et al., 1987; Jenner & Timbrell, 1995). Mixed function oxidases may also play a role (Jenner & Timbrell, 1995). Results from incubation in rat hepatocytes suggested the involvement of CYP2E1, CYP2B1, and CYP1A1/2 in the metabolism of hydrazine (Delaney & Timbrell, 1995). CYP activity was demonstrated in the metabolism of [¹⁵N₂]-[¹⁴C]-labelled acetylhydrazine to N₂ and CO₂ in the rat (Mörike et al., 1996). A hydrazine radical,

Fig. 4.1 Proposed metabolic scheme for hydrazine in mammals



Adapted from [Nelson & Gordon \(1981\)](#), [Noda et al. \(1985\)](#), [Delaney & Timbrell \(1995\)](#), and [Mörike et al. \(1996\)](#)

potentially giving rise to a diimide (diazene), was identified in microsomal incubations of hydrazine using a spin-trapping method ([Noda et al., 1985](#)).

4.2 Mechanisms of carcinogenesis

The evidence on the "key characteristics" of carcinogens ([Smith et al., 2016](#)) – concerning whether hydrazine is genotoxic, induces oxidative stress, alters cell proliferation, cell death or nutrient supply, and modulates receptor-mediated mechanisms – is summarized below.

4.2.1 Genetic and related effects

See [Table 4.1](#) and [Table 4.2](#)

(a) Humans

No data on exposed humans were available to the Working Group.

One study reported the induction of single-strand breaks and alkali-labile sites (comet assay) in human lung cells in vitro ([Robbiano et al., 2006](#)).

(b) Experimental systems

Considerable information was previously reviewed by the *IARC Monographs* Working Group regarding whether hydrazine is genotoxic in experimental systems ([IARC, 1999](#)). Multiple studies identified *N*7-methylguanine and *O*⁶-methylguanine in the livers of mice, rats (including neonates) and hamsters treated with hydrazine in vivo. The available data suggested that the DNA methylation mechanism involved reaction of hydrazine with endogenous formaldehyde, followed by metabolism of the resulting hydrazone to a methylating agent, most likely diazomethane. Other reports concerned the formation of DNA adducts (not characterized) in M13mp18 viral DNA in vitro.

One study found that hydrazine induced organ-specific genotoxicity in mice, and that the target organs for DNA damage (alkaline comet

assay) depended on the route of administration. DNA damage was found in the stomach, liver, and lungs of mice given hydrazine as a single intraperitoneal dose at 100 mg/kg bw. When the same dose was administered orally, DNA damage was also found in the colon and brain ([Sasaki et al., 1998](#)). More recently, another study reported the induction of single-strand breaks and alkali-labile sites (comet assay) in primary lung cells from male rats as well as in the lungs of rats given a single oral dose of hydrazine ([Robbiano et al., 2006](#)). Lack of induction of sister-chromatid exchanges in bone marrow or liver of mice, and conflicting results on induction of micronuclei in mouse bone-marrow cells (in one study out of three), were observed ([IARC, 1999](#)).

Hydrazine induced DNA strand breaks in rat hepatocytes and unscheduled DNA synthesis in mouse hepatocytes. There were conflicting results for the induction of gene mutations in mouse lymphoma L5178Y cells (one positive result and two negative, all in the absence of exogenous metabolic activation). Hydrazine induced sister-chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, but gave negative results for the induction of chromosomal aberrations in rat liver RL1 cells ([IARC, 1999](#)).

Hydrazine was mutagenic in yeast and bacteria, induced DNA damage in bacteria, and caused somatic mutations in *Drosophila* ([IARC, 1999](#)).

4.2.2 Oxidative stress

(a) Humans

No data in exposed humans were available to the Working Group.

In human hepatoma HepG2 cells, hydrazine (0.25–2.0 mM) depleted reduced glutathione in a concentration-dependent manner, whereas reactive oxygen species (ROS) were decreased, as assessed using the dye 2',7'-dichlorodihydrofluorescein diacetate ([Olthof et al., 2009](#)).

Table 4.1 Genetic and related effects of hydrazine in human and rodent cells in vitro

Species, strain	Tissue, cell line	End-point	Test	Results	Concentration (LEC or HIC)	Comments	Reference
Human	Lung	DNA damage	DNA strand breaks (comet assay)	+	Hydrazine, 0.5–4 mM	Cells from four donors, analysed independently; all had dose-dependent increases in single-strand breaks and alkali-labile sites	Robbiano et al. (2006)
Rat, Sprague-Dawley	Lung	DNA damage	DNA strand breaks (comet assay)	+	Hydrazine, 0.5–4 mM	Dose-dependent increases in single-strand breaks and alkali-labile sites	Robbiano et al. (2006)

+, positive; HIC, highest ineffective concentration; LEC, lowest effective concentration

Table 4.2 Genetic and related effects of hydrazine in experimental animals in vivo

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED/HID)	Comments	Reference
Rat, Sprague-Dawley, M	Lung, liver, and kidney	DNA damage	DNA strand breaks (alkaline comet assay)	+	Hydrazine, 30 mg/kg bw; i.p.; single dose	Purity, 98%; positive in all tissues tested	Robbiano et al. (2006)
Mouse, CD-1, M	Stomach, liver, lung	DNA damage	DNA strand breaks (alkaline comet assay)	+	Hydrazine, 100 mg/kg bw; i.p.; single dose	DNA damage was not increased in colon, kidney, bladder, brain, or bone marrow	Sasaki et al. (1998)
Mouse, CD-1, M	Stomach, colon, liver, lung, brain	DNA damage	DNA strand breaks (alkaline comet assay)	+	Hydrazine, 100 mg/kg bw; i.g.; single dose	DNA damage was not increased in kidney, bladder, or bone marrow	Sasaki et al. (1998)

+, positive; bw, body weight; HID, highest ineffective dose; i.g., gavage; i.p., intraperitoneal; LED, lowest effective dose; M, male

(b) *Experimental systems*(i) *Non-human mammals in vivo*

In Wistar rats fed diets containing 0.5% hydrazine dichloride for 7 days, there were significant increases in lipid-soluble fluorophores (lipofuscin) in the liver, heart, muscle, and spleen ([Antosiewicz et al., 2002](#)). This index of oxidative stress induction by hydrazine was diminished in the heart and skeletal muscle by the antioxidant α -tocopherol diacetate.

In Wistar rats, hydrazine (intraperitoneal dose of 80 mg/kg bw) decreased hepatic glutathione levels, increased levels of malondialdehyde (a measure of lipid peroxidation), and increased levels of 8-hydroxy-2'-deoxyguanosine DNA adducts (8-OHdG, a measure of oxidative DNA damage). These changes were prevented by tea melanin ([Hung et al., 2003](#)).

In Sprague-Dawley rats, hydrazine dihydrochloride (0, 120, or 240 mg/kg bw by gavage) increased levels of the precursor amino acids of glutathione biosynthesis in the urine and/or plasma and increased plasma 5-oxoproline (a product of glutathione metabolism) ([Bando et al., 2011](#)).

Several studies have reported suppression by antioxidants of the induction of megamitochondria (enlarged and abnormally shaped mitochondria that are thought to arise by membrane fusion) by hydrazine. For instance, in Wistar rat liver, hydrazine-induced formation of megamitochondria, and accompanying increases in lipid peroxidation were suppressed by co-treatment with coenzyme Q₁₀ (CoQ₁₀). CoQ₁₀ did not prevent the decrease in reduced glutathione that was observed in rats treated with hydrazine ([Adachi et al., 1995](#)). The formation of megamitochondria in the liver of Wistar rats fed diets containing 1.0% hydrazine for 7 days was also suppressed by α -tocopherol (intraperitoneal dose of 700 mg/kg bw). A marked increase in hepatic level of lipid-soluble fluorophores, an indicator of oxidative stress, was also observed in hydrazine-treated

rats; however, these increases were not prevented by α -tocopherol ([Antosiewicz et al., 1994](#)). The formation of megamitochondria in the livers of Wistar rats fed diets containing 0.5% hydrazine for 7 days was suppressed by various free radical scavengers including CoQ₁₀, α -tocopherol, 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (4-OH-TEMPO), and by allopurinol, a xanthine oxidase inhibitor ([Wakabayashi et al., 1997](#)). In addition, 4-OH-TEMPO lowered hepatic lipid peroxidation, assessed by measuring levels of thiobarbituric acid reactive substances (TBARS) and of lipid-soluble fluorophores. Allopurinol was less effective than 4-OH-TEMPO in preventing loss of mitochondrial phosphorylating ability and in preventing lipid peroxidation in liver ([Matsushashi et al., 1997](#); [Wakabayashi et al., 1997](#)). An increase in the rate of generation of hydrogen peroxide was also observed in isolated liver mitochondria obtained from Wistar rats that had been fed diets containing 1% hydrazine for 3 days ([Karbowski et al., 1999](#)). [The Working Group noted that induction of megamitochondria by hydrazine is probably due to free radicals generated by exposure to this agent, and that the hepatotoxicity of hydrazine is probably due to induction of oxidative stress.]

Perfusion of Sprague-Dawley rat livers with hydrazine, acetylhydrazine, or isoniazid at 5 mM in the presence of the spin-trapping agent α -phenyl-*tert*-butylnitron produced the carbon-centred radical that was shown to be the same acetyl radical ([Sinha, 1987](#)).

(ii) *Non-human mammalian cells in vitro*

During CYP-mediated oxidative metabolism of hydrazine by rat liver microsomes, the formation of a free radical intermediate was detected by electron spin resonance spectroscopy using α -phenyl-*tert*-butylnitron as the spin-trapping agent; the radical species trapped with α -phenyl-*tert*-butylnitron was identified as a hydrazine-derived metabolite by mass spectrometry ([Noda et al., 1985](#)). Inhibitors of CYP, and the

antioxidant ascorbic acid decreased the generation of hydrazine radical by rat liver microsomes ([Matsuki et al., 1991](#)).

Lipid peroxidation (TBARS) was increased significantly in rat liver slices incubated with hydrazine at 15 mM for 10 hours. This increase was associated with extensive hepatic necrosis ([Walubo et al., 1998](#)).

Exposure of primary rat hepatocytes (isolated from Fischer 344 rats) to hydrazine (at 25 mM and above) reduced catalase activity, depleted reduced glutathione, and increased oxidized glutathione and lipid peroxidation (TBARS), while ROS was increased at hydrazine concentrations of 100 mM and above ([Hussain & Frazier, 2002](#)).

Hydrazine (8 mM) increased the formation of hydrogen peroxide and ROS, and protein carbonylation in hepatocytes isolated from Sprague-Dawley rats. ROS formation and protein carbonylation were decreased by a ROS scavenger (4-OH-TEMPO) and by a CYP inhibitor (1-aminobenzotriazole) ([Tafazoli et al., 2008](#)).

[Hung et al. \(2003\)](#) showed that melanin derived from tea reduced hydrazine-induced free radical formation in rat hepatocytes isolated from Wistar rats, as assessed by measuring chemiluminescence intensity.

In hepatocytes isolated from Sprague-Dawley rats, the effects of hydrazine and isoniazid on lipid peroxidation and mitochondrial depolarization were significantly reduced by pre-treatment with *N*-acetylcysteine. Hydrazine (8 mM) significantly increased ROS whether or not glutathione was depleted, and also increased lipid peroxidation and mitochondrial membrane depolarization ([Heidari et al., 2013](#)).

Incubation of primary Wistar rat hepatocytes with hydrazine (2 mM) induced the formation of megamitochondria, decreased the mitochondrial membrane potential, and increased intracellular levels of ROS (assessed using 2',7'-dichlorodihydrofluorescein diacetate) ([Teranishi et al., 1999](#)).

These changes were suppressed by co-treatment of hepatocytes with the free radical scavenger CoQ₁₀ (1 μM).

In primary cultures of Wistar rat hepatocytes, mitochondria were enlarged by hydrazine, and mitochondria were substantially larger in hepatocytes isolated from rats pre-treated with phenobarbital and then incubated with hydrazine. The effect of phenobarbital was attributed to the induction of CYP, which had been reported to metabolize hydrazine and generate free radicals ([Noda et al., 1987](#)). In addition, compared with controls, levels of malondialdehyde in homogenates of hepatocyte cultures treated with hydrazine at 2 mM were elevated (155%) after incubation for 4 hours and significantly increased (240%) after incubation for 22 hours ([Karbowski et al., 1997](#)).

(iii) Acellular systems

Hydrazine (0.5 mM) produced fragmentation of calf thymus DNA in a cell-free system containing manganese (Mn) or copper (Cu) ions. DNA damage induced by hydrazine plus Mn(II) or Mn(III) was inhibited by hydroxyl radical scavengers or superoxide dismutase, but not by catalase; while DNA damage caused by hydrazine plus Cu(II) was inhibited by catalase, but not by hydroxyl radical scavengers or superoxide dismutase. Electron spin trapping using 5,5-dimethyl-1-pyrroline *N*-oxide confirmed that hydrazine plus Mn(III) produced hydroxyl free radical via superoxide and not via hydrogen peroxide. Thus, ROS may also be produced by nonenzymatic activation of hydrazine ([Yamamoto & Kawanishi, 1991](#)).

4.2.3 Altered cell proliferation, death, or nutrient supply

(a) Humans

No data were available to the Working Group.

(b) *Experimental systems*

(i) *In vivo*

In Syrian golden hamsters given drinking-water containing hydrazine sulfate (170, 340, or 510 mg/L for up to 21 months), increases in megalocytosis, intranuclear inclusions, bile duct hyperplasia, and foci of cellular alteration were observed after 18 months in the groups receiving the intermediate and highest doses. However, incorporation into liver DNA of ¹⁴C-thymidine, administered before termination as an index of cell replication, was not different in any of the exposure groups compared with controls at any interim evaluation ([FitzGerald & Shank, 1996](#)).

No studies were identified that showed suppression of apoptosis by hydrazine. In an inhalation study, increases in the incidence of apoptosis based on histological criteria were reported in the nose of Fischer 344 rats exposed to hydrazine (750 ppm) for 1 or 10 hours. Increased incidences of proliferative nasal lesions, including epithelial hyperplasia and adenoma, were also observed in these rats held for up to 28 months after exposure ([Latendresse et al., 1995](#)).

Hepatic steatosis and hyperlipidaemia were induced in Wistar rats given hydrazine as a single intraperitoneal injection at 50 mg/kg bw. Compared with controls, exposed rats had increased levels of triglycerides, cholesterol, free fatty acids, and total lipids in plasma and liver tissue. Hydrazine also caused a decrease in levels of triglycerides and total lipids in adipose tissue ([Vivekanandan et al., 2007](#)). [The Working Group noted that increased mobilization of triglycerides from adipose tissue to the liver by hydrazine may contribute to the development of hepatic steatosis by this chemical.]

In C57Bl/6 mice, significant increases (more than twofold) in the hepatic expression of several genes involved in triglyceride and cholesterol synthesis, lipid transport, and fatty acid oxidation were detected 24 hours after administration of a

single oral dose of hydrazine sulfate (100 mg/kg bw). The gene expression profiles resulting from hydrazine exposure were consistent with production and intracellular transport of hepatic lipids being favoured over removal of fatty acids ([Richards et al., 2004](#)).

(ii) *In vitro*

In hepatocytes isolated from Wistar rats, pre-labelled with [¹⁴C]palmitate, and incubated with 2–12 mM hydrazine, the percentage of radio-labelled triglycerides appearing in the medium decreased with increasing concentrations of hydrazine [these results indicated that reduced secretion of triglycerides from liver cells might also be a factor in hydrazine-induced hepatic steatosis] ([Waterfield et al., 1997](#)). [Waterfield et al. \(1997\)](#) also reported the following hepatic or hepatocellular effects: lactate dehydrogenase leakage, adenosine triphosphate (ATP) and glutathione S-transferase depletion, increase in citrulline level, inhibition of protein synthesis, taurine leakage, and triglyceride accumulation.

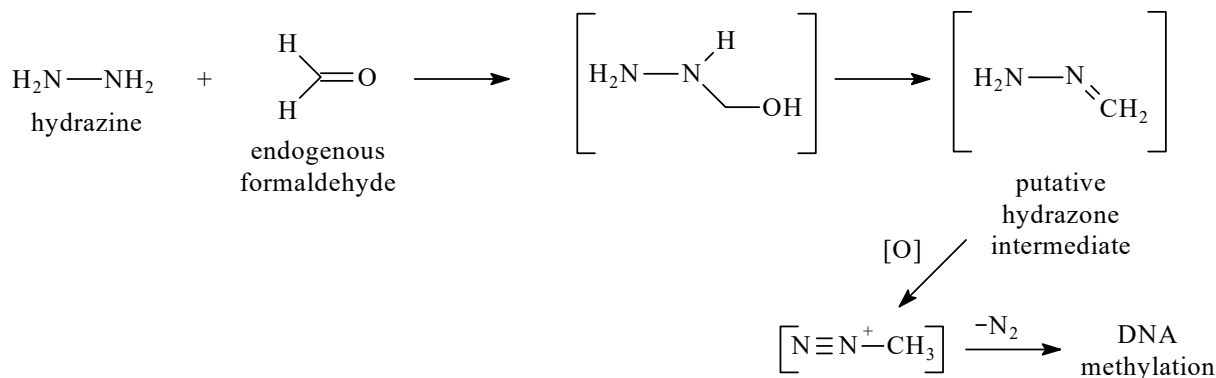
[Dilworth et al. \(2000\)](#), using metabolically competent rat liver spheroids, also showed ATP depletion after hydrazine treatment that required even higher concentrations than hepatocytes in primary culture. [Garrod et al. \(2005\)](#) observed an increase in triglycerides and β -alanine, combined with a decrease in hepatic glycogen, glucose, choline, taurine, and trimethylamine-*N*-oxide (TMAO) in the rat liver 24 hours after a dose of hydrazine of 90 mg/kg bw. In the renal cortex, 2-aminoadipate, and β -alanine increased, which concurred with a decrease in TMAO, *myo*-inositol, choline, taurine, glutamate, and lysine.

4.2.4 Receptor-mediated effects

(a) *Humans*

No data were available to the Working Group.

Fig. 4.2 Proposed pathway for the metabolic generation of a methylating electrophile from formaldehyde hydrazone, a condensation product of hydrazine and formaldehyde



Postulated metabolites are represented in square brackets
Adapted from [Lambert & Shank \(1988\)](#)

(b) Experimental systems

In C57Bl/6 mice, a single dose of hydrazine sulfate at 100 or 300 mg/kg bw increased hepatic gene expression by peroxisome proliferation-activated receptor (PPAR) and sterol regulatory element-binding protein transcription factors after 24 hours ([Richards et al., 2004](#))

To detect possible toxicity pathways with hydrazine in Sprague-Dawley rat liver, a combination of genomics, proteomics, and metabolomics was used to detect changes in mRNA, proteins, and endogenous metabolites after a single oral dose (30 or 90 mg/kg bw). The results of these combined techniques suggested that hydrazine can affect hepatic oxidative stress, Ca^{2+} concentration, and thyroid hormone homeostasis, glucose and lipid metabolism; several mechanistic pathways for toxicity in the rat liver were described ([Klenø et al., 2004a, b](#)).

In addition to hepatotoxicity, effects on the central nervous system in rodents have been associated with changes in GABA levels. Specifically, these changes were caused by depletion of pyridoxal phosphate, which requires gamma-aminobutyrate aminotransferase and glutamate decarboxylase ([IPCS, 1987a](#)).

4.2.5 Other mechanisms

No additional mechanistic data in exposed humans or human cells were available to the Working Group.

Concerning epigenetic effects, hydrazine increased the labelling of methylguanines upon co-administration of L-[methyl- ^{14}C]methionine or [^{14}C]formate in rodents ([Lambert & Shank, 1988](#)). In Syrian golden hamsters given drinking-water containing hydrazine sulfate (170–510 mg/L) for up to 21 months, hypomethylation of cytosines occurred at the highest exposure level ([FitzGerald & Shank, 1996](#)). In this 21-month study, [Zheng & Shank \(1996\)](#) reported hypomethylation in the *p53* tumour suppressor gene and in the *c-jun* proto-oncogene, and hypermethylation in the *c-Ha-ras* proto-oncogene and in the DNA methyltransferase gene. No changes were detected for *c-fos*, *c-myc*, and γ -glutamyltranspeptidase. [Lambert & Shank \(1988\)](#) proposed a pathway for the generation of a methylating electrophile from formaldehyde hydrazine, a condensation product of hydrazine and formaldehyde ([Fig. 4.2](#)).

Inflammatory infiltrates were only of minimal severity in animals killed after a single exposure or 10 exposures of 1 hour to hydrazine at 750 ppm, or at least 2 years after exposure ([Latendresse et al., 1995](#)).

4.3 Data relevant to comparisons across agents and end-points

For all compounds evaluated in the present volume of the *IARC Monographs*, including hydrazine, analyses of high-throughput screening data generated by the Tox21 and ToxCast™ research programmes of the government of the USA ([Kavlock et al., 2012](#); [Tice et al., 2013](#)) are presented in the *Monograph* on 1-bromopropane, in the present volume.

4.4 Cancer susceptibility

No data were available to Working Group.

4.5 Other adverse effects

4.5.1 Humans

Hydrazine is hepatotoxic, nephrotoxic, immunotoxic, and neurotoxic in humans. Hydrazine produces strong irritation of the skin, eye, and mucous membranes, and can also cause skin sensitization. After ingestion, reported systemic effects are vomiting, muscle tremor, convulsions, seizures, paresthesia, anorexia, weight loss, kidney damage, and centrilobular fatty changes of the liver ([SCOEL, 2010](#)). No data concerning reproductive toxicity in humans were available to the Working Group ([HSDB, 2010](#)).

4.5.2 Experimental systems

The toxicological effects of hydrazine in experimental animals were comparable to those seen in humans, with pronounced effects on the liver, kidneys and lungs. In the rat, liver accumulation of lipids, swelling of mitochondria, and formation of microbodies in the hepatocytes were observed. In general, similar hepatic lesions were observed in rat, mice, hamsters, dogs, and monkeys, but the intensity of the effects was species-dependent. In addition, effects in experimental animals have also been observed

on the proximal tubular kidney cells, lungs, central nervous system, haematological system, and ocular regions, while behavioural effects like lethargy and depression were also reported ([HSDB, 2010](#)).

Hydrazine and mono-acetyl hydrazine are formed as reactive metabolites of isoniazid, and may play a role in its toxicity (reviewed by [Hassan et al., 2015](#)). In the metabolism of isoniazid, NAT2 is responsible for the formation of acetyl hydrazine, which is further oxidized by CYP2E1 to *N*-hydroxy acetyl hydrazine that is eventually converted to acetyl diazine. The latter compound may be the toxic metabolite itself, or break down further to the reactive acetyl onium ion, acetyl radical, and ketene, which in turn can bind covalently to hepatic macromolecules, resulting in liver toxicity.

5. Summary of Data Reported

5.1 Exposure data

Hydrazine exists as anhydrous hydrazine (containing < 37% water by mass), or as hydrazine hydrate (an aqueous solution containing ≤ 64% hydrazine). Hydrazine is used in the manufacture of pharmaceuticals, agrochemicals, chemical blowing agents, paints, inks and organic dyes, polyurethane coatings, and adhesives. In addition, hydrazine has several direct applications as an oxygen scavenger, a corrosion inhibitor, a reducing agent, and a propellant. Exposure predominantly occurs in the workplace, with highest exposures in facilities where hydrazine is handled as rocket propellant and in the refilling of fighter aircrafts. No exposure of the general population has been identified.

5.2 Human carcinogenicity data

Associations between cancer and exposure to hydrazine have been studied in workers manufacturing hydrazine in the United Kingdom, and in workers testing rocket engines at a field laboratory in California, USA.

The manufacturing cohort study used a crude measure of exposure and had a small number of cancer deaths. This study was judged to be uninformative for the purposes of evaluation.

Two investigations featuring overlapping cohorts of rocket-testing workers at the same facility in California, USA, were considered to be more informative. One study was restricted to mortality with wider criteria for eligibility, including workers employed for shorter duration. This study also had a narrower definition of exposure, classifying a smaller proportion of workers as highly exposed. The other study at the California rocket-testing facility included incidence data and had a broader definition of exposure. Nevertheless, some subgroups in both studies were roughly comparable and these showed an excess of cancer of the lung. The study of incidence also showed a statistically significant positive exposure–response relationship for cancer of the lung. Taken together, the findings of these studies were suggestive of excesses of cancer of the lung attributable to exposure to hydrazine for workers with higher exposure and earlier exposure periods. Although analyses of these studies were not adjusted for tobacco smoking, internal analyses of exposure–response are unlikely to be confounded by smoking. Furthermore, in the study of incidence, smoking data for a subset of workers suggested that the proportion of smokers was similar in workers with or without exposure to hydrazine, and no excess of other smoking-related cancers was observed.

5.3 Animal carcinogenicity data

Hydrazine (usually administered as hydrazine sulfate) was tested in studies of carcinogenicity in mice treated by gavage, in the drinking-water, by intraperitoneal injection, or by inhalation. Hydrazine was tested in studies in rats and hamsters treated by gavage, in the drinking-water, or by inhalation.

In mice, hydrazine caused a significant increase in the incidence of adenoma and/or carcinoma of the lung in four different strains of males and/or females treated by gavage in 11 studies. Most of these studies were single-dose studies; tumour incidences usually ranged from 75% to 100%, and tumour multiplicity often ranged from 3 to 10 in the treated groups. A significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) was also observed in males and females in two of these gavage studies. In addition, hydrazine caused a significant increase in the incidence of adenoma or carcinoma of the lung in three different strains of male and/or female mice when administered in the drinking-water in three studies; a significant increase in the incidence of lung adenoma or carcinoma (combined) in males and females (combined) when administered by intraperitoneal injection in one study; and a significant increase in the incidence of tumours of the haematopoietic and lymphoid tissues (reticulum cell sarcoma or myeloid leukaemia) in males and females (combined) when administered by intraperitoneal injection in one study. In one study in female mice given drinking-water containing hydrazine, there was a significant increase (with a significant positive trend) in the incidence of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined); there was also a significant positive trend in the incidence of hepatocellular carcinoma, liver haemangioma, and liver haemangioma or haemangiosarcoma (combined). Hydrazine also caused a significant

increase in the incidence of lung adenoma in one study in female mice treated by inhalation.

In one study in rats, hydrazine caused a significant increase in the incidence of lung adenoma or carcinoma (combined) in males and females treated by gavage; a significant increase in the incidence of malignant liver tumours was also reported in males. Hydrazine caused a significant increase in the incidence of hepatocellular adenoma in two strains of male and female rats given drinking-water containing hydrazine in two studies, a significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) and of hepatocellular carcinoma in female rats in these two studies, and a significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) and of interstitial cell tumours of the testes in male rats in one of these studies. Hydrazine caused a significant increase in the incidence of nasal adenoma in male and female rats, and of thyroid carcinoma in male rats, treated by inhalation in one study.

In male hamsters given drinking-water containing hydrazine, there was a significant dose-related increase in the incidence of hepatocellular adenoma or carcinoma (combined) in one study, and a significant increase in the incidence of hepatocellular carcinoma in another study. Hydrazine also caused a significant dose-related increase in the incidence of nasal adenoma in male hamsters treated by inhalation in a third study.

5.4 Mechanistic and other relevant data

In humans and other mammals, hydrazine is absorbed rapidly.

With respect to the key characteristics of human carcinogens, there is *strong* evidence that hydrazine is electrophilic or can be metabolically activated. Acetylated metabolites as well as unchanged hydrazine have been detected in the

urine of exposed humans. Hydrazine is acetylated in rodents and rabbits. Oxidative metabolism of hydrazine via formation of nitrogen and carbon dioxide has been demonstrated in mammals. Reactive intermediates include nitrogen- and carbon-centred-radicals, as well as a postulated carbocation.

There is *strong* evidence that hydrazine is genotoxic, primarily from experimental systems. DNA single-strand breaks were observed in a single study of human lung cells exposed to hydrazine. The frequency of single-strand breaks was also increased in the lungs of exposed rats and in rat lung cell cultures. In mice, hydrazine induced formation of DNA strand breaks in the liver, lung, and stomach. DNA adducts from hydrazine, *N*7-methylguanine and *O*⁶-methylguanine, were detected in the liver of mice, rats, and hamsters exposed to hydrazine *in vivo*. Hydrazine was mutagenic in yeast and bacteria, and induced DNA damage in bacteria and somatic mutations in *Drosophila*.

There is *strong* evidence that hydrazine induces oxidative stress in experimental systems. Numerous studies have shown that exposure to hydrazine induces oxidative stress in mammalian systems, both *in vivo* and *in vitro*. In hepatocytes isolated from rats, hydrazine decreased levels of reduced glutathione, and increased various indicators of the formation of reactive oxygen species. In addition, most of these changes were prevented by co-treatment with antioxidants. The production of free-radical intermediates during cytochrome P450 mediated metabolism of hydrazine was demonstrated by electron spin resonance spectroscopy using a spin-trapping agent.

There is *strong* evidence that hydrazine alters cell proliferation, cell death, and nutrient supply in experimental systems. Hepatic steatosis was induced in rats, and reduced secretion of triglycerides was seen in isolated rat hepatocytes treated with hydrazine. In a study of exposure by

inhalation, apoptosis was increased in the nasal epithelium of rats.

There is *weak* evidence that hydrazine modulates receptor-mediated effects. Gene interactions with the peroxisome proliferator-activated receptors and sterol regulatory-element binding protein have been observed in mice. Hydrazine was considered marginally active in the Tox21 aryl hydrocarbon receptor reporter-gene assay.

There were few data on other key characteristics of carcinogens (alters DNA repair or causes genomic instability, induces epigenetic alterations, induces chronic inflammation, is immunosuppressive, or causes immortalization).

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of hydrazine. A positive association has been observed between exposure to hydrazine and cancer of the lung.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of hydrazine.

6.3 Overall evaluation

Hydrazine is *probably carcinogenic to humans* (Group 2A).

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