HYDRAZINE

Data were reviewed in IARC (1974) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

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

Chem. Abstr. Name: Hydrazine

IUPAC Systematic Name: Hydrazine

1.1.2 *Structural and molecular formulae and relative molecular mass*

H_4N_2 Relative molecular mass: 32.05

1.1.3 *Chemical and physical properties of the pure substance*

(from American Conference of Governmental Industrial Hygienists (1992) unless otherwise noted)

(*a*) *Description*: Colourless, fuming, oily liquid with an ammonia-like odour

(*b*) *Boiling-point*: 113.5°C

(*c*) *Melting-point*: 2°C

(*d*) *Solubility*: Miscible with water and methyl, ethyl, propyl and isobutyl alcohols; insoluble in chloroform and diethyl ether

(*e*) *Vapour pressure*: 1.4 kPa at 20°C

(*f*) *Flash-point*: 37.8°C, closed cup

(*g*) *Explosive limits*: Upper, 100%; lower, 4.7% by volume in air

(*h*) *Conversion factor*: $mg/m^3 = 1.31 \times ppm$

1.2 Production and use

The world production capacity for hydrazine in 1981 was estimated to be about 36 thousand tonnes, not including countries with planned economies at that time (WHO, 1987). Production capacity estimates for hydrazine hydrate in 1988 were 25 thousand tonnes in the United States, 10 thousand tonnes in Germany, 10 thousand tonnes in France, 5 thousand tonnes in Japan and 3 thousand tonnes in the United Kingdom (Schirmann, 1989). Production capacity estimates for hydrazine solutions in 1992 were 16 500 tonnes in the United States, 6400 tonnes in Germany, 6100 tonnes in France,

6600 tonnes in Japan, 3600 tonnes in Korea, 3500 tonnes in Russia and 1400 in the People's Republic of China (Schiessl, 1995).

The principal applications of hydrazine solutions include chemical blowing agents, 40%; agricultural pesticides, 25%; and water treatment, 20%. The remaining 15% is used in a variety of fields including pharmaceuticals, explosives, polymers and polymer additives, antioxidants, metal reductants, hydrogenation of organic groups, photography, xerography and dyes (Schiessl, 1995). Anhydrous hydrazine is used as a component of high-energy fuels and rocket propellants (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

The National Occupational Exposure Survey (NOES, 1997) estimated that 59 147 workers (including 2840 females) in the United States were potentially exposed to hydrazine between 1981 and 1982.

National estimates on exposure were not available from other countries.

1.3.2 *Environmental occurrence*

Production of hydrazine and its use as a chemical intermediate, reducing agent, rocket fuel and boiler-water treatment agent may result in its release to the environment through various waste streams. Hydrazine is also naturally produced by *Azotobacter agile* during nitrogen fixation. It has been detected at low levels in wastewater samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 0.013 mg/m^3 as the threshold limit value for occupational exposures to hydrazine in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for hydrazine in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

Choroidal melanoma was observed in one man who had been exposed to hydrazine for six years. A study of men engaged in hydrazine manufacture comprised 423 men, with 64% ascertainment of vital status. None of the five cancers reported (three gastric, one prostatic and one neurogenic) occurred in the group with the highest exposure. A follow-up of this cohort extended the observations to 1982. Mortality from all causes was not elevated (49 observed, 61.5 expected) and the only excess was two lung cancer cases within the highest-exposure category, with a relative risk of 1.2 (95% confidence interval, 0.2–4.5) (IARC, 1987).

A cohort of 427 men who worked at a hydrazine plant in the United Kingdom for at least six months between 1945 and 1971 was followed up until 1992 (Morris *et al*., 1995). Follow-up was complete for 95%. Based on job history records, 78 of the workers were classified as having been exposed to high levels of hydrazine (estimated at about 1–10 ppm [1.3–13 mg/m^3]) and the remaining 375 to moderate or low exposure (< 1 ppm). There were 2145 person–years of follow-up in the latter group. Among the whole group, no increase was observed for all-cause mortality (86 deaths, standardized mortality ratio (SMR), 0.8), or for mortality from lung cancer (8 deaths; SMR, 0.7), cancer of the digestive tract (9 deaths; SMR, 1.0) or other cancers (8 deaths; SMR, 0.8), after comparison with the rates for England and Wales. Restricting attention to the high-risk group, the SMR for all-cause mortality was 0.7 (20 deaths) and that for lung cancer was 1.1 (3 deaths). No deaths from cancer of the digestive tract were observed. The SMR for other cancers was 0.8 (2 deaths). None of the SMRs was significantly different from 1.0. Of the three lung cancer cases in the high-exposure group, two occurred in workers with less than two years of occupational exposure to hydrazine.

3. Studies of Cancer in Experimental Animals

Hydrazine has been tested in mice by oral administration, producing liver and mammary tumours and lung tumours in both P and F_1 generations; after intraperitoneal administration to mice, it produced lung tumours, leukaemias and sarcomas. After oral administration to rats, it produced lung and liver tumours. When tested by inhalation, it produced benign and malignant nasal tumours in rats, benign nasal polyps, a few colon tumours and thyroid adenomas in hamsters, and a slight increase in the incidence of lung adenomas in mice (IARC, 1987).

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female NMRI mice, five to six weeks of age, were given hydrazine in the drinking-water at concentrations of 0, 2, 10 and 50 mg/L (ppm) for two years. The highest dose (50 ppm) was toxic, producing severely reduced weight gain and a lower survival; 10 ppm was the maximum tolerated dose (moderate body weight decrease). No increase in the incidence of tumours at any site or at any dose was observed (Steinhoff *et al*., 1990).

3.1.2 *Rat*

Groups of 50 male and 50 female specific pathogen-free bred Wistar rats, six weeks of age, were given hydrazine in the drinking-water at concentrations of 0, 2, 10 and 50 mg/L (ppm) for 24 months. The concentration of 2 ppm was tolerated with little toxicity; 10 ppm proved to be the maximum tolerated dose and 50 ppm was clearly toxic, producing severely decreased body weight gain. An increase in tumour incidence was

observed in the liver: no tumour in the controls (0/100 both sexes combined); two tumours (2%) (1 hepatocellular adenoma, 1 haemangioma) in the 2-ppm group; three tumours (3%) (1 hepatocellular adenoma and 1 carcinoma, 1 cholangioma) in the 10-ppm group; and 14 tumours (14.6%) (8 hepatocellular adenomas, 3 carcinomas and 3 cholangiomas) in the 50-ppm group. In historical controls, the incidence of liver-cell tumours was 9/652 (1.4%) (Steinhoff & Mohr, 1988).

3.1.3 *Hamster*

Syrian hamsters were given hydrazine sulfate in the drinking-water at concentrations of 170, 340 and 510 mg/L (ppm) for two years (average doses, 4.6, 8.3 and 10 mg/kg bw hydrazine (free base)). Hepatocellular carcinomas were observed in hamsters treated with the highest dose of hydrazine sulfate after 78 weeks of exposure; the incidence of hepatocellular carcinomas in the three treated groups was 0/31 at 170 ppm, 4/34 at 340 ppm and 11/34 at 510 ppm (Bosan *et al.*, 1987).

3.2 Inhalation exposure

Rat: Groups of 100 male and 100 female Fischer 344 rats were exposed to 0 (control), 75 and 750 ppm [0, 98 and 980 mg/m^3] hydrazine (purity, 98.8%) by inhalation for 1 h once or once per week for 10 weeks. Animals were killed 24–30 months after exposure. In the 750-ppm hydrazine-treated group, polypoid adenomas were found in 4/99 males and 6/95 females. In addition, one nasal squamous-cell carcinoma and four cases of hyperplasia were noted in males and one case of hyperplasia in females (Latendresse *et al.*, 1995). [The Working Group noted that data were not presented for control tumour incidences, although the incidence of nasal adenomas in both sexes and that of nasal hyperplasia in males were significant.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

(a) In-vivo pharmacokinetics, tissue distribution and metabolism

Kaneo *et al.* (1984) examined the tissue distribution of [^{15}N]hydrazine in rats after a subcutaneous dose of 10 mg/kg bw by gas chromatography/mass spectrometry, using stable isotope internal standards. Maximal tissue levels of hydrazine were seen 30 min after dosing and it was eliminated from the liver, kidney, lung and plasma with half-lives of 3.3, 2.7, 3.0 and 2.3 h, respectively. At 8 h, levels in the kidney were notably higher

than those in other tissues. The levels of acetylhydrazine in the kidney were much higher than those in other tissues and peaked at 1 h, while the highest concentrations in other tissues occurred between 1 and 4 h after dosing. Only trace amounts of diacetylhydrazine were detected in the tissues. Within 48 h, a total of 30% of the dose was recovered in the urine, 24% as hydrazine and 3% each as acetyl- and diacetylhydrazine. The partial reversibility of hydrazine acetylation was shown after the administration of equimolar doses of acetylhydrazine. Tissue levels of hydrazine were between one quarter and one half of those of acetylhydrazine, while 6% of the dose was recovered in the urine as hydrazine compared with 19% as acetylhydrazine.

Preece *et al*. (1992) examined the influence of dose upon the disposition of hydrazine in rats using oral doses of 3, 9, 27 and 81 mg/kg bw. The plasma and liver areas under the curve (AUCs) for hydrazine increased linearly with doses of up to 27 mg/kg bw but were lower than expected at 81 mg/kg bw. At 3 and 9 mg/kg bw, plasma and liver levels were equivalent but, at higher doses, there was more compound in the plasma. At 24 h after dosing, the plasma:liver ratio was 4.4 at 60 mg/kg bw and 5.7 at 80 mg/kg bw. The urinary recovery of hydrazine and acetylhydrazine fell with increasing dose, from 38 to 17% of a dose for hydrazine and from 5 to 1% for acetylhydrazine. The extent of acetylation decreased, the hydrazine:acetylhydrazine ratio declining from 0.125 to 0.061.

(*b*) *In-vitro metabolic studies*

Hydrazine is metabolized by rat liver microsomal enzymes to unknown products, ultimately yielding molecular nitrogen (Timbrell *et al*., 1982; Jenner & Timbrell, 1995). This was dependent upon oxygen and NADPH and was increased by NADH in the presence of NADPH. Hydrazine metabolism was 20–70% lower in human microsomes prepared from three individuals compared with rats. Hydrazine is also metabolized by rat liver mitochondria, but the monoamine oxidase inhibitors clorgyline and pargyline do not significantly decrease this activity (Jenner & Timbrell, 1995).

(*c*) *Metabolic mechanisms of toxicity*

Studies with isolated rat hepatocytes have indicated that at least three CYP isoenzymes (2E1, 2B1 and 1A1/2) are involved in the detoxication of hydrazine, as inducers of these isoenzymes all reduce its cytotoxicity. Pretreatment of rats with diethyldithiocarbamate increased the cytotoxicity of hydrazine, this being associated with marked inhibition of CYP activities (Delaney & Timbrell, 1995).

Adult male Sprague-Dawley rats were treated with 0.9% saline vehicle (a single intraperitoneal dose) or hydrazine (100 mg/kg bw intraperitoneally), after which the CYP2E1 mRNA and protein levels were monitored by Northern and immunoblot analyses, respectively, and glutathione *S*-transferase-α (GST-α) Ya and Yc subunit levels were determined by immunoblot analysis. Hydrazine treatment produced an approximately 464% increase in renal CYP2E1 protein, but hepatic levels of CYP2E1 and of GST-α Ya and Yc subunits were not significantly altered. The observed increases in renal CYP2E1 protein levels were not accompanied by concomitant increases in

CYP2E1 mRNA, suggesting a post-transcriptional mechanism for the increase in renal CYP2E1 protein (Runge-Morris *et al*., 1996).

4.2 Toxic effects

Toxic responses to hydrazine exposure have been reviewed (WHO, 1987).

4.2.1 *Humans*

One fatal poisoning was reported of a man who had handled hydrazine (hydrazine hydrate) once a week for an unknown number of hours over a period of six months. In simulated conditions, only 0.071 mg hydrazine/m^3 was measured, but probably skin exposure had also occurred. The man experienced conjunctivitis, tremor and lethargy after each exposure. Following the last exposure, he developed fever, diarrhoea and vomited. In hospital, six days later, many disorders were noted: conjunctivitis, stomatitis, arrhythmia, upper abdominal pain, enlarged abdomen, icterus, a tender and palpable liver, black faeces, incoherence and oliguria. X-ray examinations showed pleural effusion and lung shadowing. Laboratory findings comprised elevated blood bilirubin and creatinine levels, and protein and red blood cells in urine. Treatments administered included haemodialysis and B vitamins, which brought only temporary relief. The man died 21 days after the last exposure. Autopsy revealed pneumonia, severe renal tubular necrosis and nephritis and mild hepatocellular damage (Sotaniemi *et al*., 1971).

In two individuals working in gold plating, contact dermatitis against hydrazine was found (Wrangsjö & Mårtensson, 1986).

4.2.2 *Experimental systems*

Megamitochondria were induced in male Wistar rats placed for three or seven days on a diet containing 1% hydrazine (Wakabayashi *et al*., 1987). From biochemical analysis, the authors concluded that the formation of megamitochondria was due to fusion of adjacent mitochondria rather than to mitochondrial swelling.

In four-week-old male Wistar rats, 1% hydrazine in the diet resulted in the formation of megamitochondria, increased lipid peroxidation and decreased levels of reduced glutathione in the liver (Adachi *et al*., 1995).

Timbrell *et al*. (1996) reported that much higher hydrazine concentrations were required in rat hepatocyte cultures in comparison to plasma concentrations in male Sprague-Dawley rats to elicit the following hepatic/hepatocellular effects: lactate dehydrogenase leakage, ATP and GST depletion, increase in citrulline level, protein synthesis inhibition, taurine leakage and triglyceride accumulation.

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Hydrazine was mutagenic to yeast and bacteria and induced DNA damage in bacteria. Hydrazine induced somatic mutations in *Drosophila*. It induced DNA strand breaks in rat hepatocytes and unscheduled DNA synthesis in mouse hepatocytes *in vitro*. Conflicting results were obtained for induction of gene mutations in mouse lymphoma L5178Y cells. It did not induce chromosomal aberrations in rat liver cell line *in vitro* but did induce sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. In single studies *in vivo* in mice, hydrazine induced DNA strand breaks in liver and lungs. It did not induce sister chromatid exchanges in bone marrow or liver of mouse treated *in vivo* in one study. It weakly induced micronuclei in bone-marrow cells of mice treated *in vivo* in one of three studies. Hydrazine induced the formation of DNA adducts *in vitro* and of *N*7-methylguanine and O^6-methylguanine in liver of mice, rats and hamsters treated *in vivo*. In in-vivo studies with mice, hydrazine did not induce dominant lethal mutations in a single study or sperm abnormalities in two studies.

In the experiment described in Section 3.1.3, in which Syrian hamsters were given hydrazine sulfate in the drinking-water for two years, the levels of methylation of DNA guanine in liver, kidney and lung were measured. Both *N*7- and O^6-methylguanine were readily detectable at six months of exposure, but only trace amounts of these bases were detected after 12 months of exposure; these bases were again detected in liver DNA at exposure times of 18 and 24 months (Bosan *et al.*, 1987).

4.4.3 *Mechanistic considerations*

Administration of hydrazine to rodents results in the formation of *N*7-methylguanine and O^6-methylguanine in liver DNA. Co-administration of L-[*methyl*-^{14}C]methionine or [^{14}C]formate with the hydrazine led to labelling of the methylguanines, suggesting involvement of the one-carbon pool in the methylation process (Quintero-Ruiz *et al.*, 1981). It has been proposed that the methylation mechanism involves reaction of hydrazine with endogenous formaldehyde to yield formaldehyde hydrazone, which could be metabolized to the potent methylating agent diazomethane. In experiments using postmitochondrial (S9), microsomal, cytosolic or mitochondrial cell fractions from rat liver *in vitro*, methylation of DNA guanine occurred, S9 being the most active fraction. Neither the P450 monooxygenase nor flavin monooxygenase systems appeared to be important in hydrazine/formaldehyde-induced methylation of DNA. However, sodium azide, cyanamide and carbon monoxide all inhibited S9-supported DNA methylation. Bovine liver catalase, a haem-containing cytochrome, readily transformed hydrazine/formaldehyde to a methylating agent. The data support the proposal that formaldehyde hydrazone is the condensation product of hydrazine and formaldehyde, which is rapidly transformed in various liver cell fractions to a DNA-methylating agent (Lambert & Shank, 1988).

Table 1. Genetic and related effects of hydrazine

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage induction in lysogenic *Escherichia coli*	(+)	NT	5	Heinemann (1971)
PRB, Prophage induction in *Escherichia coli*	+	NT	320	von Wright (1981)
PRB, Prophage induction in *Haemophilus influenzae*	–	NT	6420	Balganesh & Setlow (1984)
ERD, *Escherichia coli* WP2, WP67 *uvrApolA*, CM871 *uvrArecAlexA*, differential toxicity	+	–	20	Green (1981)
SAF, *Salmonella typhimurium*, forward mutation, 8-azaguanine resistance	NT	+	100	Skopek *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	10	Anderson & Styles (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500	Baker & Bonin (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	25	Brooks & Dean (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation, fluctuation test	–	+	10	Hubbard *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	MacDonald (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	NG	Martire *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	750	Nagao & Takahashi (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	320	Parodi *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	10	Richold & Jones (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	–	NG	Simmon & Shepherd (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	NT	250	Wade *et al.* (1981)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	+	NT	500	Tosk *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	+	1200	Herbold & Buselmaier (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	+	1250	Anderson & Styles (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	75	Cheh *et al.* (1980)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	45	Baker & Bonin (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	250	Martire *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	250	Garner *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	120	Parodi *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	0.01	Richold & Jones (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	250	Rowland & Severn (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	250	Simmon & Shepherd (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	NT	250	Wade *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	NT	–	12000	Herbold & Buselmaier (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Baker & Bonin (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	MacDonald (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Martire *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	320	Parodi *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	10	Richold & Jones (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Simmon & Shepherd (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	–	12000	Herbold & Buselmaier (1976)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	–	1250	Anderson & Styles (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500	Baker & Bonin (1981)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	320	Parodi *et al*. (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	10	Richold & Jones (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Simmon & Shepherd (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	+	10	Anderson & Styles (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	Baker & Bonin (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Brooks & Dean (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Garner *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation, fluctuation test	–	–	500	Hubbard *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	MacDonald (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Martire *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NG	Nagao & Takahashi (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	320	Parodi *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	10	Richold & Jones (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Rowland & Severn (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Simmon & Shepherd (1981)
SAS, *Salmonella typhimurium* G46, reverse mutation	NT	+	120	Herbold & Buselmaier (1976)
SAS, *Salmonella typhimurium* TA92, reverse mutation	–	–	1000	Brooks & Dean (1981)
ECK, *Escherichia coli* K-12/343/113, forward or reverse mutation	+	+	200	Mohn *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	NT	16	von Wright & Tikkanen (1980a)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	NT	16	von Wright & Tikkanen (1980b)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation, fluctuation test	+	+	1	Gatehouse (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	+	50	Matsushima *et al.* (1981)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	+	48	Noda *et al.* (1986)
EC2, *Escherichia coli* WP2, reverse mutation	+	NT	16	von Wright & Tikkanen (1980b)
EC2, *Escherichia coli* WP2 B/r, reverse mutation	–	+	110	Matsushima *et al.* (1981)
ECR, *Escherichia coli* CM871 *lexArecAuvrA*, reverse mutation	+	NT	16	von Wright & Tikkanen (1980b)
ECR, *Escherichia coli* WP2 *uvr*A pKM101, reverse mutation	+	+	11	Matsushima *et al.* (1981)
SCH, *Saccharomyces cerevisiae JD1*, homozygosis by mitotic gene conversion	+	+	10	Sharp & Parry (1981)
SCH, *Saccharomyces cerevisiae D7*, homozygosis by mitotic gene conversion	+	+	385 ppm	Zimmermann & Scheel (1981)
SCF, *Saccharomyces cerevisiae* rad2-1, forward mutation	+	NT	6420	Lemontt (1978)
SCF, *Saccharomyces cerevisiae* XY597 strains, forward mutation	+	NT	6420	McDougall & Lemontt (1979)
SCR, *Saccharomyces cerevisiae* XV 185-14C, reverse mutation,	+	NT	133	Mehta & von Borstel (1981)
SZF, *Schizosaccharomyces pombe*, forward mutation	+	+	0.5	Loprieno (1981)
SCN, *Saccharomyces cerevisiae* D6, mitotic aneuploidy,	+	+	50	Parry & Sharp (1981)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		321 feed	Jain *et al.* (1969)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		321 feed	Shukla (1972)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		642 feed	Vijaykumar & Jain (1979)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		2500 feed	Yoon *et al.* (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		321 feed	Shukla (1972)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	NT	96	Sina *et al.* (1983)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
URP, Unscheduled DNA synthesis, ACTIN rat primary hepatocytes *in vitro*	–	NT	32	*Mori* et al. *(1988)*
UIA, Unscheduled DNA synthesis, C3H/HeN mouse primary hepatocytes *in vitro*	+	NT	3.2	*Mori* et al. *(1988)*
GCO, Gene mutation, Chinese hamster ovary CHO cells, five loci *in vitro*	–	–	2000	Carver *et al.* (1981)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	–	–	500	Hsie *et al.* (1981)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	NT	852	Amacher *et al.* (1980)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	NT	3.2	Rogers & Back (1981)
G51, Gene mutation, mouse lymphoma L5178Y cells, ouabain, thioguanine or cytosine arabinoside resistance *in vitro*	–	NT	160	Rogers & Back (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	NT	8	MacRae & Stich (1979)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	1167	Natarajan & van Kesteren-van Leeuwen (1981)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	100	Perry & Thomson (1981)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	+	+	158	Natarajan & van Kesteren-van Leeuwen (1981)
CIR, Chromosomal aberrations, rat liver cell line (RL_1) *in vitro*	–	NT	100	Dean (1981)
GIH, Gene mutation, human fibroblasts, diphtheria toxin resistance (HF Dip^r), *in vitro*	–	+	200	Gupta & Goldstein (1981)
HMM, Repair assay in *Escherichia coli* K12/*uvrB/recA* in male NMRI mice *in vivo*	–		840 po	Hellmér & Bolcsfoldi (1992)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DVA, DNA strand breaks in Swiss albino mouse liver and lung *in vivo*	+		33 ip × 5	Parodi *et al.* (1981)
MST, Mouse spot test, (T×HT)F_1 mice *in utero*	+		80 ip	Neuhäuser-Klaus & Chauhan (1987)
SVA, Sister chromatid exchange, CBA/J mouse bone marrow *in vivo*	–		100 ip × 1	Paika *et al.* (1981)
SVA, Sister chromatid exchange, CBA/J mouse liver *in vivo*	–		100 ip × 1	Paika *et al.* (1981)
MVM, Micronucleus test, ICR mouse bone marrow *in vivo*	–		44 ip × 2	Kirkhart (1981)
MVM, Micronucleus test, B6C3F_1 mouse bone marrow *in vivo*	+		70 ip × 2	Salamone *et al.* (1981)
MVM, Micronucleus test, CDI mouse bone marrow *in vivo*	–		44 ip × 2	Tsuchimoto & Matter (1981)
DLM, Dominant lethal test, ICR/Ha Swiss mice *in vivo*	–		52 ip × 1	Epstein *et al.* (1972)
DNA strand scission, ϕ×174 RF DNA *in vitro* [with haemolysate]	NT	+	96	Runge-Morris *et al.* (1994)
BID, DNA-adduct formation in M13mp18 viral DNA *in vitro*	+	NT	NG	Premaratne *et al.* (1995)
BVD, Formation of *N*7-methylguanine and O^6-methylguanine in male Fischer 344 rat liver DNA *in vivo*	+		60 po × 1	Barrows & Shank (1981)
BVD, Formation of *N*7-methylguanine and O^6-methylguanine in male Fischer 344 and male Sprague-Dawley rat liver DNA *in vivo*	+		45 po × 1	Becker *et al.* (1981)
BVD, Formation of *N*7-methylguanine in male Fischer 344 and male Sprague-Dawley rat liver DNA *in vivo*	+		3 po × 4	Becker *et al.* (1981)
BVD, Formation of *N*7-methylguanine in CBA mouse liver DNA *in vivo*	+		64 ip × 1	Quintero-Ruiz *et al.* (1981)
BVD, Formation of *N*7-methylguanine and O^6-methylguanine in male Syrian golden hamster liver DNA *in vivo*	+		90 po × 1	Bosan *et al.* (1986)
BVD, Formation of *N*7-methylguanine and O^6-methylguanine in male Syrian golden hamster liver DNA *in vivo*	+		1.12 dw 6 m	Bosan *et al.* (1987)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVD, Formation of *N*7-methylguanine and O^6-methylguanine in neonatal Sprague-Dawley rat liver DNA *in vivo*	+		25 sc × 1	Leakakos & Shank (1994)
BVD, Formation of *N*7-methylguanine and O^6-methylguanine in Wistar rat liver DNA *in vivo*	+		0.2 po × 1	van Delft *et al.* (1997)
BVP, Formation of *N*7-methylguanine in CBA mouse liver RNA *in vivo*	+		64 ip × 1	Quintero-Ruiz *et al.* (1981)
SPM, Sperm morphology (CBA × BALB/c)F_1 mice *in vivo*	–		50 ip × 5	Topham (1981)
SPM, Sperm morphology, B6C3F_1/CRL mice *in vivo*	–		400 ip × 5	Wyrobek *et al.* (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; NG, not given; ip, intraperitoneal; po, oral; dw, drinking-water; sc, subcutaneous

Rats exposed to single doses (gavage) of hydrazine in the range 0.01–10 mg/kg bw showed an increase in *N*7- and *O*6-methylguanine above background levels in liver DNA only after doses greater than 0.1–0.2 mg/kg bw, doses which were still non-toxic or only weakly toxic (van Delft *et al.*, 1997).

5. Summary of Data Reported and Evaluation[1]

5.1 Exposure data

Exposure to hydrazine may occur in its production, and in the production of chemical blowing agents, agricultural chemicals and in water treatment. It has been detected at low levels in wastewater.

5.2 Human carcinogenicity data

The cancer risk of men exposed to hydrazine was investigated in two small cohort studies. In neither of these studies was an elevated risk observed for all cancers combined or for any specific cancer type.

5.3 Animal carcinogenicity data

Hydrazine was tested for carcinogenicity by oral administration to mice in several experiments, producing mammary and lung tumours. When tested by oral administration or inhalation exposure in rats, it produced lung, liver and nasal tumours and a few colon tumours. In hamsters, it produced liver tumours and thyroid adenomas following oral or inhalation exposure.

5.4 Other relevant data

Following subcutaneous administration of hydrazine to rats, maximum tissue concentrations were reached in about 30 min. Most urinary elimination was as unchanged hydrazine, with acetylhydrazine being the main metabolite but a minor elimination product. Tissue retention was longest in kidney, mainly due to the presence of acetylhydrazine. Hydrazine is metabolized and detoxified by at least three microsomal cytochrome P450 isoenzymes in rat liver (CYP2E1, CYP2B1 and CYP1A1/2), ultimately yielding molecular nitrogen.

Human exposure to hydrazine has resulted in severe effects upon the central nervous system, liver and kidneys. In rats, hydrazine is hepatotoxic, causing accumulation of triglycerides, inhibition of protein synthesis and the formation of macromitochondria.

Hydrazine induces gene mutations in bacteria, yeast and *Drosophila* and in-vivo treatment of mice, rats and Syrian hamsters results in the formation of *N*7-methylguanine and *O*6-methylguanine in liver DNA.

---

[1] Summary (but not the evaluation) prepared by the Secretariat after the meeting.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of hydrazine.

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

Overall evaluation

Hydrazine is *possibly carcinogenic to humans (Group 2B).*

6. References

Adachi, K., Matsuhashi, T., Nishizawa, Y., Usukura, J., Popinigis, J. & Wakabayashi, T. (1995) Suppression of the hydrazine-induced formation of megamitochondria in the rat liver by co-enzyme Q_{10}. *Toxicol. Pathol.*, **23**, 667–676

Amacher, D.E., Paillet, S.C., Turner, G.N., Ray, V.A. & Salsburg, D.S. (1980) Point mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells. II. Test validation and interpretation. *Mutat. Res.*, **72**, 447–474

American Conference of Governmental Industrial Hygienists (1992) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Vol. 2, Cincinnati, OH, pp. 761–765

American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs® and BEIs®*, Cincinnati, OH, p. 26

Anderson, D. & Styles, J.A. (1978) The bacterial mutation test. Six tests for carcinogenicity. *Br. J. Cancer*, **37**, 924–930

Baker, R.S.U. & Bonin, A.M. (1981) Study of 42 coded compounds with the *Salmonella*/mammalian microsome assay. In: de Serres, F. J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 249–260

Balganesh, M. & Setlow, J.K. (1984) Prophage induction in *Haemophilus influenzae* and its relationship to mutation by chemical and physical agents. *Mutat. Res.*, **125**, 15–22

Barrows, L.R. & Shank, R.C. (1981) Aberrant methylation of liver DNA in rats during hepatotoxicity. *Toxicol. appl. Pharmacol.*, **60**, 334–345

Becker, R.A., Barrows, L.R. & Shank, R.C. (1981) Methylation of liver DNA guanine in hydrazine hepatotoxicity: dose–response and kinetic characteristics of 7-methylguanine and O^6-methylguanine formation and persistence in rats. *Carcinogenesis*, **2**, 1181–1188

Bosan, W.S., Lambert, C.E. & Shank, R.C. (1986) The role of formaldehyde in hydrazine-induced methylation of liver DNA guanine. *Carcinogenesis*, **7**, 413–418

Bosan, S.W., Shank, R.C., MacEwen, J.D., Gaworski, C.L. & Newberne, P.M. (1987) Methylation of DNA guanine during the course of induction of liver cancer in hamsters by hydrazine or dimethylnitrosamine. *Carcinogenesis*, **8**, 439–444

Brooks, T.M. & Dean, B.J. (1981) Mutagenic activity of 42 coded compounds in the *Salmonella/*mammalian microsome assay with preincubation. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 261–270

Carver, J.H., Salazar, E.P., Knize, M.G. & Wandres, D.L. (1981) Mutation induction at multiple gene loci in Chinese hamster ovary cells: the genetic activity of 15 coded carcinogens and non-carcinogens. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 594–601

Cheh, A.M., Hooper, A.B., Skochdopole, J., Henke, C.A. & McKinnell, R.G. (1980) A comparison of the ability of frog and rat S-9 to activate promutagens in the Ames test. *Environ. Mutag.*, **2**, 487–508

Dean, B.J. (1981) Activity of 27 coded compounds in the RL_1 chromosome assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 570–579

Delaney, J. & Timbrell, J.A. (1995) Role of cytochrome P450 in hydrazine toxicity in isolated hepatocytes *in vitro*. *Xenobiotica*, **25**, 1399–1410

van Delft, J.H., Steenwinkel, M.-J.S.T., de Groot, A.J.L., van Zeeland, A.A., Eberle-Adamkiewicz, G., Rajewsky, M.F., Thomale, J. & Baan, R.A. (1997) Determination of *N*7- and O^6-methylguanine in rat liver DNA after oral exposure to hydrazine by use of immunochemical and electrochemical detection methods. *Fundam. appl. Toxicol.*, **35**, 131–137

Epstein, S.S., Arnold, E., Andrea, J., Bass, W. & Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol. appl. Pharmacol.*, **23**, 288–325

Garner, R.C., Welch, A. & Pickering, C. (1981) Mutagenic activity of 42 coded compounds in the *Salmonella/*microsome assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 280–284

Gatehouse, D. (1981) Mutagenic activity of 42 coded compounds in the 'Microtiter' fluctuation test. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 376–386

Green, M.H.L. (1981) *A Differential Killing Test Using an Improved Repair-Deficient Strain of* Escherichia coli, Brighton, MRC Cell Mutation Unit

Gupta, R.S. & Goldstein, S. (1981) Mutagen testing in the human fibroblast diphtheria toxin toxin resistance (HF Dip^r) system. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 614–625

Heinemann, B. (1971) Prophage induction in lysogenic *Escherichia coli* with simple hydroxylamine and hydrazine compounds. *Appl. Microbiol.*, **21**, 726–731

Hellmér, L. & Bolcsfoldi, G. (1992) An evaluation of the *E. coli* K-12 *uvrB/recA* DNA repair host-mediated assay. II. In vivo results for 36 compounds tested in the mouse. *Mutat. Res.*, **272**, 161–173

Herbold, B. & Buselmaier, W. (1976) Induction of point mutations by different chemical mechanisms in the liver microsomal assay. *Mutat. Res.*, **40**, 73–84

Hsie, A.W., O'Neill, J.P., Machanoff, R., Schenley, R.L. & Brimer, P.A. (1981) Screening for mutagenic response of four coded chemicals by the CHO/HGPRT system. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 602–607

Hubbard, S.A., Green, M.H.L., Bridges, B.A., Wain, A.J. & Bridges, J.W. (1981) Fluctuation test with S9 and hepatocyte activation. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 361–370

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1–42*, Lyon, pp. 223–224

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 222–223

Jain, H.K., Khamankar, Y.G. & Shukla, P.T. (1969) Studies on mutation rates and range with base-specific chemicals. In: International Atomic Energy Agency, ed., *Induced Mutations in Plants*, Lanham, MD, Bernan-Unipub, pp. 251–258

Jenner, A.M. & Timbrell, J.A. (1995) *In vitro* microsomal metabolism of hydrazine. *Xenobiotica*, **25**, 599–609

Kaneo, Y., Iguchi, S., Kubo, H., Iwagiri, N. & Matsuyama, K. (1984) Tissue distribution of hydrazine and its metabolites in rats. *J. Pharmacol. Dyn.*, **7**, 556–562

Kirkhart, B. (1981) Micronucleus test on 21 compounds. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 698–704

Lambert, C.E. & Shank, R.C. (1988) Role of formaldehyde hydrazone and catalase in hydrazine-induced methylation of DNA guanine. *Carcinogenesis*, **9**, 65–70

Latendresse, J.R., Marit, G.B., Vernot, E.H., Haun, C.C. & Flemming, C.D. (1995) Oncogenic potential of inhaled hydrazine in the nose of rats and hamsters after 1 or 10 1-hr exposures. *Fundam. appl. Toxicol.*, **27**, 33–48

Leakakos, T. & Shank, R.C. (1994) Hydrazine genotoxicity in the neonatal rat. *Toxicol. appl. Pharmacol.*, **126**, 295–300

Lemontt, J.F. (1978) Loss of hydrazine-induced mutability in wild-type and excision-repair-defective yeast during post-treatment inhibition of cell division. *Mutat. Res.*, **50**, 57–66

Lewis, R.J., Jr (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold, pp. 610–611

Loprieno, N. (1981) Screening of coded carcinogenic/noncarcinogenic chemicals by a forward-mutation system with the yeast *Schizosaccharomyces pombe*. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 424–433

MacDonald, D.J. (1981) *Salmonella/*microsome tests on 42 coded chemicals. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 285–297

MacRae, W.D. & Stich, H.F. (1979) Induction of sister-chromatid exchanges in Chinese hamster ovary cells by thiol and hydrazine compounds. *Mutat. Res.*, **68**, 351–365

Martire, G., Vricella, G., Perfumo, A.M. & De Lorenzo, F. (1981) Evaluation of the mutagenic activity of coded compounds in the *Salmonella* test. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 271–279

Matsushima, T., Takamoto, Y., Shirai, A., Sawamura, M. & Sugimura, T. (1981) Reverse mutation test on 42 coded compounds with the *E. coli* WP2 system. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 387–395

McDougall, K.J. & Lemontt, J.F. (1979) Effects of spermine on the detection of induced forward mutation at the can1 locus in yeast: evidence for selection against canavanine-resistant mutants. *Mutat. Res.*, **63**, 21–34

Mehta, R.D. & von Borstel, R.C. (1981) Mutagenic activity of 42 encoded compounds in the haploid yeast reversion assay, strain XV185-14C. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 414–423

Mohn, G.R., Vogels-Bouter, S. & van der Horst-van der Zon, J. (1981) Studies on the mutagenic activity of 20 coded compounds in liquid tests using the multipurpose strain *Escherichia coli* K-12/343/113 and derivatives. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 396–413

Mori, H., Sugie, S., Yoshimi, N., Iwata, H., Nishikawa, A., Matsukubo, K., Shimizu, H. & Hirono, I. (1988) Genotoxicity of a variety of hydrazine derivatives in the hepatocyte primary culture/DNA repair test using rat and mouse hepatocytes. *Jpn. J. Cancer Res.*, **79**, 204–211

Morris, J., Densem, J.W., Wald, N.J. & Doll, R. (1995) Occupational exposure to hydrazine and subsequent risk of cancer. *Occup. environ. Med.*, **52**, 43–45

Nagao, M. & Takahashi, Y. (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 302–313

Natarajan, A.T. & van Kesteren-van Leeuwen, A.C. (1981) Mutagenic activity of 20 coded compounds in chromosome aberrations/sister chromatid exchanges assay using Chinese hamster ovary (CHO) cells. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 551–559

Neuhäuser-Klaus, A. & Chauhan, P. S. (1987) Studies on somatic mutation induction in the mouse with isoniazid and hydrazine. *Mutat. Res.*, **191**, 111–116

Noda, A., Ishizawa, M., Ohno, K., Sendo, T. & Noda, H. (1986) Relationship between oxidative metabolites of hydrazine and hydrazine- induced mutagenicity. *Toxicol. Lett.*, **31**, 131–137

NOES (1997) *National Occupational Exposure Survey 1981-83*, Unpublished data as of November 1997, Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health

Paika, I.J., Beauchesne, M.T., Randall, M., Schreck, R.R. & Latt, S.A. (1981) In vivo SCE analysis of 20 coded compounds. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 673–681

Parodi, S., De Flora, S., Cavanna, M., Pino, A., Robbiano, L., Bennicelli, C. & Brambilla, G. (1981) DNA-damaging activity in vivo and bacterial mutagenicity of sixteen hydrazine derivatives as related quantitatively to their carcinogenicity. *Cancer Res.*, **41**, 1469–1482

Parry, J.M. & Sharp, D.C. (1981) Induction of mitotic aneuploidy in the yeast strain D6 by 42 coded compounds. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 468–480

Perry, P.E. & Thomson, E.J. (1981) Evaluation of the sister chromatid exchange method in mammalian cells as a screening system for carcinogens. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 561–569

Preece, N.E., Ghatineh, S. & Timbrell, J.A. (1992) Studies on the disposition and metabolism of hydrazine in rats *in vivo*. *Hum. exp. Toxicol.*, **11**, 121–127

Premaratne, S., Mandel, M. & Mower, H.F. (1995) Detection of mutagen specific adduct formation in DNA using sequencing methodology. *Int. J. Biochem. Cell Biol.*, **27**, 789–794

Quintero-Ruiz, A., Paz-Neri, L.L. & Villa-Treviño, S. (1981) Indirect alkylation of CBA mouse liver DNA and RNA by hydrazine *in vivo*. A possible mechanism of action as a carcinogen. *J. natl Cancer Inst.*, **67**, 613–618

Richold, M. & Jones, E. (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 314–322

Rogers, A.M. & Back, K.C. (1981) Comparative mutagenicity of hydrazine and 3 methylated derivatives in L5178Y mouse lymphoma cells. *Mutat. Res.*, **89**, 321–328

Rowland, I. & Severn, B. (1981) Mutagenicity of carcinogens and noncarcinogens in the *Salmonella*/microsome test. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 323–332

Runge-Morris, M., Wu, N. & Novak, R. F. (1994) Hydrazine-mediated DNA damage: role of hemoprotein, electron transport, and organic free radicals. *Toxicol. appl. Pharmacol.*, **125**, 123–132

Runge-Morris, M., Feng, Y., Zangar, R.C. & Novak, R.F. (1996) Effects of hydrazine, phenelzine, and hydralazine treatment on rat hepatic and renal drug-metabolizing enzyme expression. *Drug Metab. Disp.*, **24**, 734–737

Salamone, M.F., Heddle, J.A. & Katz, M. (1981) Mutagenic activity of 41 compounds in the in vivo micronucleus assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 686–697

Schiessl, H.W. (1995) Hydrazine and its derivatives. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 13, New York, John Wiley, pp. 560–606

Schirmann, J.P. (1989) Hydrazine. In: Elvers, B., Hawkins, S., Ravenscroft, M. & Schulz, G., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th Ed., Vol. A13, New York, VCH Publishers, pp. 177–191

Sharp, D.C. & Parry, J.M. (1981) Induction of mitotic gene conversion by 41 coded compounds using the yeast culture *JD1*. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 491–501

Shukla, P.T. (1972) Analysis of mutagen specificity in *Drosophila melanogaster*. *Mutat. Res.*, **16**, 363–371

Simmon, V.F. & Shepherd, G.F. (1981) Mutagenic activity of 42 coded compounds in the *Salmonella*/microsome assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 333–342

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. & Bradley, M.O. (1983) Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res.*, **113**, 357–391

Skopek, T.R., Andon, B.M., Kaden, D.A. & Thilly, W.G. (1981) Mutagenic activity of 42 coded compounds using 8-azaguanine resistance as a genetic marker in *Salmonella typhimurium*. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 371–375

Sotaniemi, E., Hirvonen, J., Isomaki, H., Takkunen, J. & Kaila, J. (1971) Hydrazine toxicity in the human. Report of a fatal case. *Ann. clin. Res.*, **3**, 30–33

Steinhoff, D. & Mohr, U. (1988) The question of carcinogenic effects of hydrazine. *Exp. Pathol.*, **33**, 133–143

Steinhoff, D., Mohr, U. & Schmidt, W.M. (1990) On the question of the carcinogenic action of hydrazine—evaluation on the basis of new experimental results. *Exp. Pathol.*, **39**, 1–9

Timbrell, J.A., Scales, M.D.C. & Streeter, A.J. (1982) Studies on hydrazine hepatoxicity. 2: Biochemical findings. *J. Toxicol. environ. Health*, **10**, 955–968

Timbrell, J.A., Delaney, J. & Waterfield, C.J. (1996) Correlation between in vivo and in vitro toxic effects of foreign compounds. *Comp. Haematol. int.*, **6**, 232–236

Topham, J.C. (1981) Evaluation of some chemicals by the sperm morphology assay. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 718–720

Tosk, J., Schmeltz, I. & Hoffmann, D. (1979) Hydrazines as mutagens in a histidine-requiring auxotroph of *Salmonella typhimurium*. *Mutat. Res.*, **66**, 247–252

Tsuchimoto, T. & Matter, B.E. (1981) Activity of coded compounds in the micronucleus test. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 705–711

United States National Library of Medicine (1997*) Hazardous Substances Data Bank (HSDB)*, Bethesda, MD [Record No. 544]

Vijaykumar, N.K. & Jain, H.K. (1979) Comparative studies on induced mutations with physical & chemical mutagens in *Drosophila melanogaster*: Part I. Specificity and spectrum of mutations. *Indian J. exp. Biol.*, **17**, 61–65

Wade, D.R., Lohman, P.M.H., Mattern, I.E. & Berends, F. (1981) Mutagenicity of isoniazid in Salmonella and its effects on DNA repair and synthesis in human fibroblasts. *Mutat. Res.*, **89**, 9–20

Wakabayashi, T., Yamashita, K., Adachi, K., Kawai, K., Iijima, M., Gekko, K., Tsudzuki, T., Popinigis, J. & Momota, M. (1987) Changes in physicochemical properties of mitochondrial membranes during the formation process of megamitochondria induced by hydrazine. *Toxicol. appl. Pharmacol.*, **87**, 235–248

WHO (1987) *Hydrazine* (Environmental Health Criteria 68), Geneva, International Programme on Chemical Safety

WHO (1993) *Guidelines for Drinking-Water Quality*, 2nd Ed., Vol. 1, *Recommendations*, Geneva

Wrangsjö, K. & Mårtensson, A. (1986) Hydrazine contact dermatitis from gold plating. *Contact Derm.*, **15**, 244–245

von Wright, A. & Tikkanen, L. (1980a) The comparative mutagenicities of hydrazine and its mono- and di-methyl derivatives in bacterial test systems. *Mutat. Res.*, **78**, 17–23

von Wright, A. & Tikkanen, L. (1980b) Hydrazine and methylhydrazine as *recA*$^+$-independent mutagens in *Escherichia coli*. *Mutat. Res.*, **71**, 269–271

von Wright, A. (1981) Hydrazine and methylhydrazine as *rec*A+ independent mutagens in *Escherichia coli*. In: Seeberg, E. & Kleppe, K., eds, *Chromosome Damage and Repair* (NATO Adv. Study Inst. Ser. A, 40), New York, Plenum Press, pp. 517–520

Wyrobek, A., Gordon, L. & Watchmaker, G. (1981) Effect of 17 chemical agents including 6 carcinogen/noncarcinogen pairs on sperm shape abnormalities in mice. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 712–717

Yoon, J.S., Mason, J.M., Valencia, R., Woodruff, R.C. & Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. *Environ. Mutag.*, **7**, 349–367

Zimmermann, F.K. & Scheel, I. (1981) Induction of mitotic gene conversion in strain *D7* of *Saccharomyces cerevisiae* by 42 coded chemicals. In: de Serres, F.J. & Ashby, J., eds, *Evaluation of Short-Term Tests for Carcinogens. Report of the International Collaborative Program* (Progress in Mutation Research, Vol. 1), Amsterdam, Elsevier, pp. 481–490