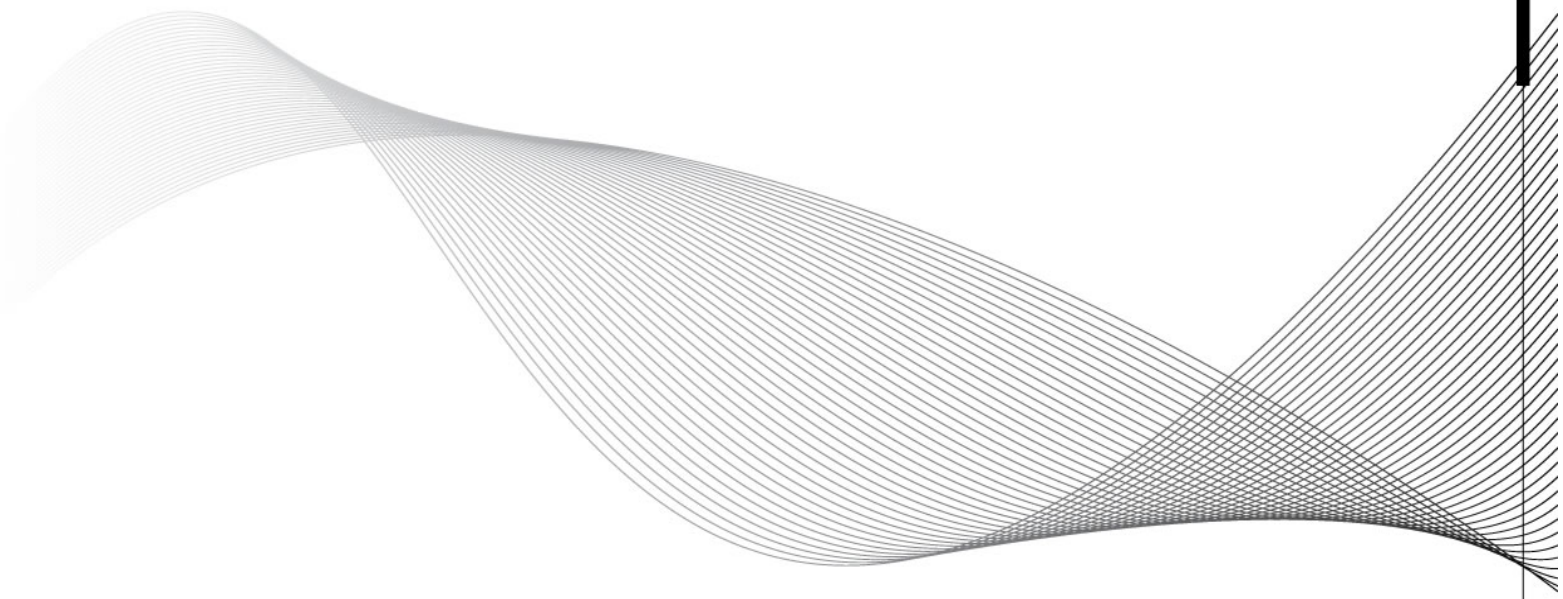
Social Europe



Recommendation from the Scientific Committee on Occupational Exposure Limits for hydrazine

SCOEL/SUM/164

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European Commission

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8-hour TWA:	not assigned *(see "Recommendation")*
STEL (15 min):	not assigned
Notation:	"skin"
BLV:	not assigned
SCOEL carcinogen group:	B *(genotoxic carcinogen, for which a threshold is not sufficiently supported)*

Substance identification:	Hydrazine
Synonyms:	Diamide
Structural formula:	$H_2N\text{-}NH_2$
CAS No.:	302-01-2
Molecular formula:	N_2H_4
Molecular weight:	32.05
Melting point:	1.5–2°C
Boiling point:	113.5°C

EU Classification:

Flam. Liq. 3	H226	Flammable liquid and vapour
Carc. 1B	H350	May cause cancer
Acute Tox. 3 *	H331	Toxic if inhaled
Acute Tox. 3 *	H311	Toxic in contact with skin
Acute Tox. 3 *	H301	Toxic if swallowed
Skin Corr. 1B	H314	Causes severe skin burns and eye damage
Skin Sens. 1	H317	May cause an allergic skin reaction
Aquatic Acute 1	H400	Very toxic to aquatic life
Aquatic Chronic 1	H410	Very toxic to aquatic life with long lasting effects

Conversion factor: 1 ppm = 1.332 mg/m^3; 1 mg/m^3 = 0.751 ppm

1. Occurrence/use and occupational exposure

According to IARC (1999), 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. The compound is used as an oxygen scavenger in boiler waters. Anhydrous hydrazine is used as an important component of high-energy fuels and rocket propellants (Lewis, 1993).

2. Health significance

Hydrazine (liquid or vapour) is a strong irritant of skin and mucous membranes. In addition hydrazine causes skin sensitization (chapter 2.4.1). Symptoms of systemic intoxications reported are vomiting, muscle tremor, convulsions, paresthesia, anorexia, weight loss, kidney damage and centrolobular fatty changes of the liver (Jakobsen & Jensen, 1985; DFG, 1991).

2.1 Toxicokinetics

2.1.1 Human data

No data have been reported (IARC 1999).

2.1.2 Animal data

Kaneo et al. (1984) examined the tissue distribution of [15N]hydrazine in rats after a subcutaneous dose of 10 mg/kg 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 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 diacetyl-hydrazine. 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. The plasma and liver areas under the concentration-time curves for hydrazine increased linearly with doses of up to 27 mg/kg bw but were lower than expected at 81 mg/kg. 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 and 5.7 at 80 mg/kg. The urinary recovery of hydrazine and acetylhydrazine feil 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.

Hydrazine is also metabolized by rat liver microsomal enzymes to unknown products, ultimately yielding molecular nitrogen (Timbrell et al., 1982; Jenner & Timbrell, 1995). This is dependent upon oxygen and NADPH and 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 was also metabolized by rat liver mitochondria, but the monoamine oxidase inhibitors clorgyline and pargyline did not significantly decrease this activity (Jenner & Timbrell, 1995).

2.1.3 Biological monitoring

Although analytical methods for the detection of hydrazines are available, there are no valid industrial field studies on biological monitoring (Choudhary & Hansen, 1998).

2.2 Acute toxicity

2.2.1 Human data

The sharp ammoniacal smell of hydrazine vapour is noticeable. The odour threshold is about 3-4 ppm so that the danger of acute intoxication is small but chronic intoxication can readily occur (DFG, 1991).

Ingested liquid hydrazine produces local irritation which leads to protracted vomiting. The main symptoms in humans are of central nervous origin - somnolence, ataxia, restlessness, incoordination and paresthesia. With medical treatment these symptoms regress within a few days. Transient respiratory and cardiac rhythm disorders are also likely to be of central nervous origin (Drews et al., 1960; Reid, 1965).

Exposure to hydrazine vapour causes, sometimes after a latent period of several hours, nausea and vomiting as well as local eye irritation, especially of the conjunctiva, irritation of the mucous membranes of the upper respiratory tract - with respiratory distress - and of exposed skin areas (Byrkit, 1950; Sutton, 1963). One investigator found liver enzyme values in exposed persons to be increased (DFG, 1991).

One case of 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/m3 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, an d 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).

A number of systemic CNS symptoms of acute hydrazine intoxication, e.g. seizures, have been attributed to a hyperammonemic state resulting from the metabolism of hydrazine (Zelnick et al., 2003).

2.2.2 Animal data

The results of studies on acute toxicity of hydrazine have been compiled in detail by DFG (1991). In essence, main symptoms include hypopnea followed by increased excitability and tonicoclonic convulsions, drop in blood pressure, nerve conduction disturbances and, after oral administration, vomiting (as a result of irritation of the mucous membranes of the stomach). Histopathological changes included fatty metamorphosis of the liver and kidney changes.
LC50 values calculated for 4 h inhalation in rats and mice were given as 570 and 252 ppm, respectively (Jacobsen et al., 1955).

2.3 Irritation and corrosivity

2.3.1 Human data

Skin lesions caused by direct contact with hydrazine have often been described. Particularly frequent are reports of inflammatory skin conditions in persons involved in the production of hydrazine or its derivatives. Even workers whose uncovered skin was splashed with soldering fluid containing hydrazine hydrobromide, or who handled metal components which had been soldered using this fluid, developed dermatitis on the exposed skin areas (for details, see DFG, 1991).
Based on an extensive literature survey the Nordic Expert Group concluded that pure hydrazine is highly corrosive, and that also diluted solutions of hydrazine and its salts are irritating to the skin and mucous membranes (Jakobsen & Jensen, 1985).

2.3.2 Animal data

Minimal irritation of the eyes was noted in monkeys during the first few weeks of inhalation exposure to 1 ppm hydrazine (Haun & Kinkead, 1973). This effect was not observed in monkeys exposed to 0.2 ppm hydrazine, or in mice exposed intermittently to 1 ppm hydrazine for 1 year (Haun & Kinkead, 1973, Vernot et al., 1985).

2.4 Sensitisation

2.4.1 Human data

Allergic contact eczema has been described described in numerous publications from different branches of industry (for details, see DFG 1999).
One publication reports about 150 notifications of allergic contact eczema from hydrazines between 1959 and 1983 (Pevny and Peter 1983). Noteworthy are the very low concentration of 0.08 mmol/l hydrazine sulfate in vaseline which was sufficient to cause sensitization in man in patch tests (Lepoittevin et al. 1995) and the extent of the eczema caused by the volatility of the substances. It is emphasized in some studies that, after sensitization has occurred, mere contamination of utensils with hydrazine and hydrazine in the ambient air (Brandt 1960, Wheeler et al. 1965, Wrangsjö and Martensson 1986) is sufficient to trigger eczema.

The sensitizing ability of hydrazine is further illustrated by the following observations. In a factory producing hydrazine sulfate, 5 employees developed contact allergy to the substance although only 4 of them had contact with the sulfate either during production or in the laboratory. One worker apparently became sensitized because he regularly had to walk through the production plant. The eczema recurred when the hydrazine sulfate was transported in plastic (Igelit) sacks (Brandt 1960).

In a soldering shop with 34 female workers, eczema developed in 12 of the women after a new soldering fluid containing a mixture of hydrazine monohydrochloride and tin chloride was introduced. In 6 of these women tests with 1 % hydrazine sulfate in water yielded positive results, in 30 controls negative results. One of these patients also reacted to the hydrazine derivatives hydralazine, phenylhydrazine and isonicotinic acid hydrazide (Frost and Hjorth 1959). Also in a soldering plant for tin cans in Sweden, 8 of 22 employees became ill a few weeks after the introduction of a new soldering fluid on a 4.5 % to 60 % hydrazine monohydrobromide basis (Misfeldt and Thormann 1984). In 35 of 70 solderers in a factory which produced relays, skin alterations developed within a period of 3 weeks to a few months after the first contact with a new soldering agent containing hydrazine. As also reported in other studies, eczema developed on the face, in particular on the eyelids and on parts of the arms not covered by protective clothes (Wheeler et al. 1965). In an explosives factory, 25 cases of eczema were recorded in 3 years despite various protective measures, although on average only 12 workers worked at these workplaces (Querangal des Essarts 1955).

The high capacity of hydrazine to cause sensitization is illustrated by an unusual case of eczema in a partner. A 30-year-old woman developed severe extensive contact eczema the first time she used a sun cream (active substance: dibenzalazine), which perhaps contained hydrazine or from which hydrazine was formed on the skin by rapid hydrolysis of the benzaldehyde hydrazone. The cause of the contact sensitization, which was confirmed by testing, finally proved to be the working clothes of her husband which also caused a reaction in epicutaneous tests and which she had frequently washed. As a boiler attendant the husband had regular contact with hydrazine (Ippen 1962).

Also to be mentioned is the treatment of nail mycosis with a 12.5 % aqueous hydrazine hydrate solution. Among 87 patients treated with the substance for 6 months, in 7 cases eczematous skin changes apparently occurred although application was supposed to be restricted to the body of the nail (Chen et al. 1991). Cross-reactions to hydrazine are apparently more frequent in cases in which the sensitization is caused by a hydrazide (e.g. isonicotinic acid hydrazide, hydralazine or dihydralazine) (Hövding 1967) than are reactions to hydrazides in those cases in which the primary sensitization is caused by hydrazine (Bandmann and Dohn 1967, Schultheiss 1959). In a re-exposure experiment, an auto-immune reaction which resembled systemic lupus erythematosus was observed in a laboratory technician after contact with hydrazine (Durant and Harris 1980). Such severe allergic reactions to hydrazine derivatives used as medicines, in particular the antihypertensives hydralazine (hydrazinophthalazine) and dihydralazine (dihydrazinophthalazine) have often been described (Malten 1962).

A maximization test was carried out in the U.S. with 23 healthy male prisoners (Kligman 1966). For induction, the test area on the forearm or lower leg was treated for 24 hours occlusively with a 5 % aqueous sodium dodecylsulfate solution and then for 48 hours occlusively with a 5 % hydrazine solution (no further details). This procedure was repeated several times and, after a pause of 10 days, provocation was carried out with a 48-hour epicutaneous test with a 0.5 % hydrazine solution on the back. As all 23 test persons were found to be sensitized, hydrazine was regarded as an extremely strong sensitizer.

Despite numerous descriptions of irritative reactions of the respiratory passages to hydrazine in the literature (Brooks et al. 1985, Keller 1988, Malo and Bernstein 1993, Vernot et al. 1985), there is no evidence that hydrazine causes allergic reactions of the respiratory tract.

2.4.2 Animal data

Reports of animal experiments on sensitization from hydrazine, hydrazine hydrate or hydrazine salts are not available (DFG, 1999).

2.5 Repeated dose toxicity

2.5.1 Human data

The primary endpoint of repeated exposure to hydrazine is cancer (see 2.8 or sensitisation (see 2.4.1). The experience concerning human intoxications is summarised under 2.2.1.

2.5.2 Animal data

Anorexia, vomiting, weight loss, lethargy and increased levels of transaminases and bilirubin were observed in Rhesus monkeys who received up to 20 injections of 20 mg/kg hydrazine. Pathological-anatomical investigations revealed fatty deposits in the liver, myocardium, kidneys and skeletal muscles (Patrick & Back, 1965).
Experimental studies on the toxicity of inhaled hydrazine were mostly performed at high concentrations. Main symptoms, at concentrations above 5 ppm, included hyperexcitability, locomotor disturbances, anorexia, vomiting, weight loss and dyspnoea. A comprehensive compilation has been provided by DFG (1991).
The experimental effects on specific organs/organ systems by repeated doses of hydrazine have been summarized by Choudhary and Hansen (1998) in the following way.

Oral dosing
In rats and mice, relatively mild effects on the liver such as megamitochondria formation, increased lipogenesis, and fatty changes occurred following daily dosings of 49-650 mg/kg (Marshall et al., 1983, Wakabayashi et al., 1983, Preece et al., 1992). Cirrhosis, reticuloendothelial cell proliferation, bile duct proliferation, and degenerative fibrous cells were observed in the livers of hamsters dosed with 4.9 mg/kg daily for 15-20 weeks (Biancifiori et al., 1966). No adverse effects were observed in the livers of mice receiving 9.5 mg/kg hydrazine daily for 2 years (Steinhoff et al., 1990).

Degeneration of the adrenals was noted in female mice given 9.3 mg/kg hydrazine daily for 25 weeks (Biancifiori et al. 1966). Similarly, no effects were observed in the thyroid or adrenals of hamsters given 5.3 mg/kg hydrazine daily for 15-20 weeks (Biancifiori et al., 1966).

Inhalation exposure
Several studies in animals have reported decreased body weight gain. Male and female hamsters experienced significantly decreased body weight gains compared with controls during a 10-week period of exposure to 750 ppm hydrazine (1 h per week; Latendresse et al., 1995). Weight gains returned to normal during the subsequent recovery period. Body weight gain was reduced in rats and dogs exposed continuously to 1 ppm hydrazine, or intermittently to 5 ppm (6 h/d; 5 d/week) for 6 months (Haun & Kinkead, 1973). No effects in body weight gain were observed in these species when exposed to 0.2 – 1.0 ppm hydrazine. In hamsters, however, exposure to 0.25 ppm hydrazine caused a 14% loss of body weight (Vernot et al., 1985).

Intermittent exposure to 5 ppm hydrazine for 1 year produced inflammation, hyperplasia, and metaplasia of the upper respiratory tract epithelium in rats and mice (Haun et al., 1984, Vernot et al., 1985). By contrast, no adverse effects were noted in the lungs of mice intermittently exposed to 1 ppm hydrazine. The tumour findings (nasal tumours) are summarised under 2.8.2.
No clinical or histopathological effects were noted on the cardiovascular system and the gastrointestinal tract of mice exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al., 1985).

In dogs exposed continuously to 1 ppm hydrazine for 6 months, haemoglobin, haematocrit, and red blood cell counts were all significantly reduced (by about 25-30%; Haun & Kinkead, 1973). These effects were not observed in dogs exposed to 0.2 ppm hydrazine in this study. No effects were reported on a large number of haematological parameters in rats and monkeys exposed to 1 ppm hydrazine continuously for 6 months (Haun & Kinkead, 1973).

Fatty changes were observed in the livers of mice, dogs and monkeys exposed continuously to 0.2-1 ppm hydrazine for 6 months (Haun & Kinkead, 1973). The hepatotoxic effects were notably more severe in mice than in dogs or monkeys and were responsible for the increased mortality observed in this species.

Mild *renal* effects including amyloidosis and mineralisation were observed in hamsters exposed intermittently to 0.25 ppm hydrazine for 1 year; however, no effects were noted in the kidneys of mice exposed intermittently to 1 ppm hydrazine for 1 year (Vernot et al., 1985).

Tonic convulsions were noted in one of 8 dogs exposed continuously to 1 ppm hydrazine for 6 months but were not seen in any dogs exposed to 0.2 ppm (Haun & Kinkead, 1973). As seizures were also produced by the chemically related 1,1-dimethylhydrazine, although at higher exposure concentrations, this was taken as a corroboration of observations in humans that the CNS system is a target of inhaled hydrazine (Choudhary & Hansen, 1998).

2.6 Genotoxicity

2.6.1 In *vitro*

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 (for as detailed synopsis of all studies, see IARC, 1999).

2.6.2 *In* vivo – Human data

No data have been reported (IARC, 1999).

2.6.3 *In vivo* – Animal data

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 N7-methylguanine and O6-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.
Syrian hamsters were given hydrazine sulphate in the drinking-water for two years, the levels of methylation of DNA guanine in liver, kidney and lung were measured. Both N7-and 06-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).

2.6.4 DNA *adduct* formation and mode of action

Administration of hydrazine to rodents results in the formation of N7-methylguanine and 06-methylguanine in liver DNA. Co-administration of L-[methyl-14C] methionine or [14C]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 (Bosan & Shank, 1983; Bosan et al., 1986; see Figure 1). According to data of Barrows et al. (1983), there was no increased direct incorporation of the tritium-labelled methyl group of methionine into 5-methyl-cytosine in hydrazine-treated rats. 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 supported the proposal that formaldehyde-hydrazone, the condensation product of hydrazine and formaldehyde, is rapidly transformed in various (liver) cell fractions to a DNA-methylating agent (Lambert & Shank, 1988). This metabolic concept is summarised in Figure 1.

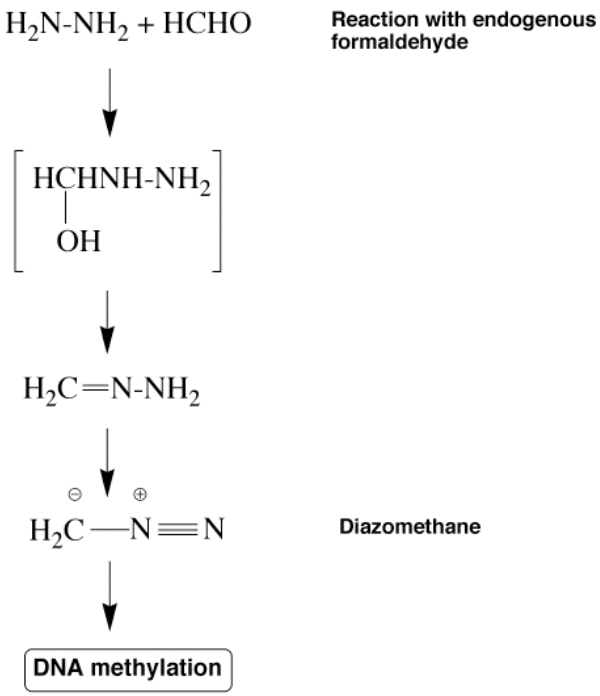

Figure 1: Metabolic concept of "indirect" methylation of DNA induced by hydrazine exposure: reaction of hydrazine with endodenous formaldehyde to the hydrazone, which is oxidised to the strong methylating agent diazomethane (Bosan & Shank, 1983)

Later, van Delft et al. (1997) further examined the pattern of DNA methylation. The induction of N7- and O6-methylguanine was studied in liver DNA of rats, 16 hr after treatment with various doses of hydrazine. After DNA isolation, the presence of N7-methylguanine in DNA was assessed with an immunochemical method and with a physicochemical technique (HPLC with electrochemical detection). Application of these two methods resulted in almost identical patterns of dose-dependent induction of guanine N7-methylation in rats dosed orally with 0.1 to 10 mg hydrazine per kilogram of body weight, increasing from 1.1-1.3 to 39-45 N7-methylguanine per 106 nucleotides. At lower dosages a constant adduct level was observed, equivalent to that in untreated rats (background level). The O6-MeGua level was analyzed by a combination of HPLC separation and competitive radioimmunoassay. A background level was observed for untreated rats and no increase was visible up to the 0.2 mg/kg dose group. After hydrazine doses from 0.2 to 10 mg/kg, O6-methylguanine increased from 0.29 to 134 per 109 nucleotides. The data were interpreted to show that even at dosages below the maximum tolerated dose (0.6 mg/kg/day), for which carcinogenic effects have not been described experimentally, methyl DNA adducts are formed. The authors also concluded that their results were consistent with the aforementioned mechanistic concept of hydrazine-induced DNA methylation (Figure 1).

Zheng and Shank (1996) conducted a study to follow changes in DNA maintenance methylation in selected genes in liver DNA during the 21-month induction of liver adenomas and hepatocellular carcinomas by demonstrating changes in restriction fragment length polymorphism. Male Syrian golden hamsters were exposed to hydrazine sulphate in the drinking water at three concentrations (170, 340 and 510 mg/l) shown previously to result in a dose-dependent induction of liver tumours. Liver DNA from animals exposed to the high concentration for 6, 12, 16, 20 and 21 months

and animals exposed to the low or mid concentration for 21 months was digested with the restriction enzymes EcoRI, MspI, HindIII or BamHI, or a combination of one of these endonucleases and a methyl-sensitive restriction enzyme, HpaII or HhaI. The DNA digests were subjected to Southern analysis using a c-DNA probe for one of the following genes: DNA methyltransferase, c-Ha-ras, c-jun, c-fos, and c-myc proto-oncogenes, p53 tumor suppressor gene or gamma-glutamyltranspeptidase. Alteration in DNA restriction by methyl-sensitive endonucleases was detected in four (DNA methyltransferase, c-Ha-ras, p53 and c-jun) of the seven genes examined and as early as 6 months in animals exposed to the highest concentration of hydrazine sulphate; alteration of recognition sites in c-Ha-ras was also detected in DNA from animals exposed for 21 months to the intermediate concentration of hydrazine sulphate. Early changes in recognition sites, presumed to indicate altered methylation status of DNA cytosine and/or guanine mutations, were seen using c-DNA probes for DNA methyltransferase, c-Ha-ras and c-jun; in the p53 tumor suppressor gene alteration of such sites was a late event relevant to appearance of liver adenomas and hepatocellular carcinomas. Evidence for hypomethylation in the p53 and c-jun genes and hypermethylation of the c-Ha-ras and DNA methyltransferase genes was provided, and the study was interpreted to support the induction of both site-specific hypomethylation and hypermethylation reactions during the course of hydrazine carcinogenesis.

2.7 Carcinogenicity

2.7.1 *Human* data

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 live 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 an job history records, 78 of the workers were classified as having been exposed to high levels of hydrazine (estimated at about 1-10 ppm) 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.

Ritz et al. (1999) conducted a retrospective cohort study of 6107 aerospace workers to examine whether exposure to chemicals (primarily hydrazine fuels) during rocket-

engine fueling and testing affected cancer mortality. When conditional logistic regression analysis was applied and adjusted for confounding variables, the estimated rate ratio for lung cancer mortality, comparing exposed to unexposed workers from the same facility, ranged from 1.68 (95% confidence interval, 1.12 to 2.52) to 2.10 (95% confidence interval, 1.36 to 3.25), depending on job-duration threshold (6 or 24 months) and lag time (0 to 15 years). Results for hemato- and lymphopoietic cancer and for bladder and kidney cancer mortality were considered imprecise.
The same group (Ritz et al. 2006) further extended this mortality study in a follow-up from 1994 to 2001 and investigated the cancer incidence for the period 1988-2000 using population-registry data. Estimated hydrazine effects were adjusted for occupational exposures to other carcinogens and assessed through a job-exposure matrix. Rate-ratio estimates were derived from Cox proportional hazards and random-effects models using time-dependent exposure measures for hydrazine adjusting for trichloroethylene, polycyclic aromatic hydrocarbons, benzene, and mineral oil exposures. Exposures to hydrazine were positively associated with lung cancer incidence (estimated rate ratio for high vs. low exposure with 20-year lag = 2.5; 95% confidence interval = 1.3-4.9) and with colorectal cancer incidence (2.2; 1.0-4.6). Dose-response associations were observed for both outcomes; similar associations were found for lung cancer mortality but not for colorectal cancer mortality. Effect estimates for cancers of the pancreas, blood and lymph system, and kidneys were based on only small numbers. The authors concluded that their findings were generally consistent with the previous results (Ritz et al. 1999) for lung cancer mortality, and that the total data suggested that exposure to hydrazine increased the risk of incident lung cancers. They also pointed to the possibility of induction of colon cancer by hydrazine.

2.7.2 *Animal* data

Oral dosing
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).

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).

Syrian hamsters were given hydrazine sulphate 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 hydrazine (free base)). Hepatocellular carcinomas were observed in hamsters treated with the highest dose of hydrazine sulphate 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).

Inhalation exposure
Year-long intermittent exposures of rats, mice, hamsters, and dogs to hydrazine were conducted using concentrations of 0.05, 0.25, 1.0, and 5.0 ppm. Rats were held 18 months postexposure; hamsters, 1 year postexposure; mice, 15 months postexposure; and dogs, 38 months postexposure. Male and female rats exhibited dose-dependent incidences of benign nasal adenomatous polyps and smaller numbers of malignant nasal epithelial tumours after 1 year of exposure to hydrazine and 18 months postexposure holding. Nasal tumours were often associated with chronic irritation and were most frequent in male rats, with an incidence of greater than 50% in the highest exposure group. Hamsters exposed to 0.25-ppm and higher concentrations showed pathologic changes characteristic of degenerative disease, including amyloidosis. After exposure to 0.5 ppm hydrazine, hamsters developed a 10% incidence of benign nasal polyps compared to 0.5% in controls. Small numbers of colon neoplasms and thyroid parafollicular cell adenomas were found in hamsters, but only in the highest concentrations tested. Lung adenomas appeared to be marginally increased in mice exposed to 1.0 ppm hydrazine, the highest concentration tested in this species. No consistent clinical or pathological effects were seen in dogs during or after exposure to hydrazine at any concentration. Using amyloidosis as a criterion, a no-effect level was not achieved in hamsters. In rats, there appeared to be a marginal production of nasal tumours at 0.05 ppm, while mice showed no effects at 0.25 ppm. This study demonstrated that the nasal respiratory epithelia of rats and hamsters are the most sensitive tissues to the tumorigenic action of hydrazine following inhalation exposures (Vernot et al., 1985).

In addition to this study, Latendresse et al. (1995) addressed the question of a carcinogenic potential of hydrazine in rats and male hamsters exposed to a high concentration of hydrazine for repeated short exposures, in order to investigate the relationships of acute and subchronic effects of hydrazine to nasal tumorigenesis. In Phase 1 (acute and subchronic) and Phase 2 (lifetime) experiments, groups of male and female Fischer 344 rats and male Syrian golden hamsters were exposed by inhalation to 0, 75 (Phase 2 only), or 750 ppm hydrazine for 1 (acute) or 10 (subchronic) 1-hr weekly exposures. Rodents were euthanized 24 hr after exposures 1 and 10 and 24 to 30 months poststudy initiation. Significant reductions in body weight were observed in hydrazine-treated rodents compared to controls during the exposure interval. No hydrazine-induced mortality was detected. Histopathologic examination after the acute and subchronic exposures revealed degeneration and necrosis of transitional, respiratory, and olfactory epithelia in the anterior nose and, in rats exposed subchronically, squamous metaplasia of the transitional epithelium. Minimal to mild rhinitis resulted from hydrazine exposures. Apoptosis was observed in olfactory and squamous metaplastic transitional epithelium. Lesions occurred at sites reportedly having high air-flow and generally appeared to be more severe in the anterior portion of the nose. By 24 months, the squamous metaplastic transitional epithelium reverted back to normal-appearing transitional epithelium. By 24+ months, low incidences (sexes combined) of hyperplasia (5/194, 2.6%) and neoplasia (11/194, 5.7%) were detected, principally in the transitional epithelium of the 750 ppm hydrazine-treated rats. A similar incidence of hyperplasia (2/94, 2%) and neoplasia (5/94, 5.3%) was detected in the high-exposure group of hamsters. The location and type of hydrazine-induced proliferative lesions were similar to those reported in a chronic N2H4-exposure study (5.0 ppm x 6 hr/day x 5 days/week for 1 year) conducted in our laboratory, but the chronic study had much higher incidences (rats, sexes combined: hyperplasia 15.5% vs 2.6% and polypoid adenoma 44.6% vs 5.2%).

The product of concentration x time was the same (7500 ppm hours) for the high-dose groups for both studies, but the duration of exposure was 150x longer and the concentration was 150x lower in the chronic study. According to the authors, these comparisons suggested that the duration of exposure is a more significant factor than concentration in hydrazine-induced nasal tumorigenesis. [The IARC Working Group, when assessing this study, 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 (IARC, 1999)].

2.8 Reproductive toxicity

Data on reproductive toxicity of hydrazine are scarce. No histopathological lesions in the ovaries were noted of mice and hamsters given orally 9.3 and 5.3 mg/kg hydrazine daily for 15-25 weeks (Biancifiori et al., 1966).

In female rats exposed by inhalation intermittently to 5 ppm hydrazine for one year, atrophy of the ovaries and inflammation of the endometrium and Fallopian tubes were noted (Vernot et al., 1985). "Senile" testicular atrophy was observed in male hamsters exposed by inhalation to 1 ppm hydrazine for one year, but not in hamsters exposed to 0.25 ppm (Vernot et al. 1985). An absence of sperm production was observed in hamsters exposed to 5 ppm hydrazine. The authors concluded that testicular changes normally associated with ageing were accelerated by hydrazine.

Recommendation

The relevant toxicological endpoint for hydrazine is carcinogenicity. IARC (1999) has evaluated the evidence of carcinogenicity in experimental animals as being sufficient and summarised that the compound had been tested 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 (IARC 1999).

Among this body of data, the most useful information comes from the long-term inhalation studies and is related to the upper respiratory tract. In mice, exposed in a preliminary study for 6 months at 0.2, 1, or 5 ppm, there was an increased incidence of pulmonary tumours in all groups (Haun & Kinkead, 1972; MacEwen, 1974). A subsequent inhalation study in rats, mice, dogs and hamsters (6h/d; 5d/wk at 0.05 ppm [rats, mice], 0.25 and 1.0 ppm [rats, mice, hamsters, dogs] for 1 year with a follow-up for life span or 38 months revealed an increased incidence of benign and malignant nasal tumours at 1 and 5 ppm in rats. At 0.05 ppm, the incidence of nasal tumours in rats was slightly, but not significantly, over the controls. An increased incidence of benign nasal polyps was observed in hamsters at 5 ppm. In addition, hamsters exposed at 0.25 ppm showed pathological degenerative changes, including amyloidosis. An increased incidence of pulmonary adenomas was observed at 1 ppm in mice (MacEwen et al., 1979; Vernot et al., 1985).

The evidence of hydrazine carcinogenicity in humans was evaluated by IARC (1999) as being inadequate. In the meantime, however, the studies of Ritz et al. (1999, 2006) have pointed to the possibility of a carcinogenic effect in exposed areospace workers, in particular to an increased lung cancer mortality (see 2.8.1). This would be compatible with the aforementioned experimental data.
Hydrazine has been characterised as genotoxic (2.6.1). Studies into the mode of action have revealed an indirect mechanism of genotoxicity, involving reaction with

endogenous formaldehyde and ultimate formation of a DNA-methylating agent (for details, see 2.6.4).

In principle, the systemic genotoxicity of hydrazine, based on such an indirect mechanism, may be characterised by a threshold at low exposure levels (when hydrazine-induced DNA methylation becomes insignificant vs. the normal methylation background). However, the critical target upon occupational inhalation exposure is the respiratory tract, and specific studies into the local mode of carcinogenic action, as well as appropriate toxicokinetic modellings, are lacking.

There are considerable species differences regarding hydrazine carcinogenicity at the upper respiratory tract, and caution is warranted in view of the possibility of generation of human lung cancer. In this situation, the derivation of a health-based OEL, or a reasonable quantitative risk assessment based on experimental tumour data, is not possible at the present time.

Therefore, hydrazine is categorised into the SCOEL carcinogen group B, as a genotoxic carcinogen, for which the existence of a threshold cannot be sufficiently supported at present (Bolt & Huici-Montagud, 2007).

The systemic effects seen in animals following dermal contact warrant a „skin notation".

As there are no adequate data, a recommendation for biological monitoring cannot be given.

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