HYDRAZINE

CAS: 302-01-2

Diamide; Diamine; Nitrogen hydride

N_2H_4

$H_2N–NH_2$

Skin

TLV–TWA, 0.01 ppm (0.013 mg/m^3)

A3 — Animal Carcinogen

1956–1962: TLV–TWA, 1 ppm

1961–present: Skin notation

1963: TLV–CEILING, 1 ppm

1964–1976: TLV–TWA, 1 ppm

1975: TLV–TWA, 0.1 ppm; A2, Suspected human carcinogen; proposed

1976: TLV–STEL, 0.3 ppm; proposed

1977: TLV–STEL proposal withdrawn

1977–1994: TLV–TWA, 0.1 ppm; A2

1989: TLV–TWA, 0.01 ppm; proposed

1994: A3, Animal carcinogen; proposed

1995: TLV–TWA, 0.01 ppm; Skin; A3

1996: Documentation revised

Chemical and Physical Properties

Hydrazine is a colorless, fuming, oily liquid with an ammonia-like or fishy odor characteristic of alkyl hydrazines. It should be stored in glass containers in a cool, dark place. Chemical and physical properties include:[1–3]

Molecular weight: 32.05
Specific gravity: 1.0036 at 25°C
Melting point: 2°C
Boiling point: 113.5°C at 760 torr
Vapor pressure: 10.4 torr at 20°C; 14.4 torr at 25°C
Flash point: 37.78°C, closed cup
Explosive limits: upper, 100%; lower, 4.7% by volume in air
Autoignition temperature: 270°C
Critical temperature: 380°C
Solubility: insoluble in chloroform and ether; miscible with water and methyl, ethyl, propyl, and isobutyl alcohols
Reactivity: incompatible with metal oxides (e.g., copper, iron, molybdenum); copper, lead, or manganese and their alloys; or oxidizing agents; exothermic, violent reaction may ensue when contact occurs
Decomposition products: toxic gases and vapors (e.g., carbon monoxide, oxides of nitrogen) may be released in a fire involving hydrazine
Conversion factors at 25°C: 1 ppm = 1.3 mg/m^3; 1 mg/m^3 = 0.76 ppm

Major Uses or Sources of Occupational Exposure

Hydrazine is used as a high-energy rocket fuel, a reducing agent, and for preparing organic hydrazine derivatives. It is also used as an oxygen scavenger for boiler waters.

Animal Studies

Acute

Hydrazine is rapidly and well absorbed by the skin, gastrointestinal tract, and lungs,[3] although its vapors are not absorbed significantly through the skin.[4]

Hydrazine is highly toxic after a single dose, with an oral LD_{50} of 60 mg/kg in rats.[5] In addition, skin exposure can result in severe irritation, burns, corrosion, sensitization, and lethality, with a dermal LD_{50} of 93 to 283 mg/kg in rabbits and guinea pigs.[6–8] Rabbit skin was treated with 3 ml of anhydrous hydrazine for 1 minute, followed by washing of the treated area; despite washing, mortality ensued 60 to 90 minutes after application.[9] Acute toxicity is characterized by liver damage consisting of fatty degeneration, red blood cell destruction and anemia, anorexia, weight loss, weakness, vomiting, excitability, hypoglycemia, and convulsions.[3] A concentration-dependent decrease in liver adenosin 5'-triphosphate (ATP) was seen in rats following intraperitoneal injection of 10 to 60 mg/kg, suggesting the ATP depletion is a cause of acute hydrazine toxicity.[10]

The 4-hour inhalation LC_{50} for hydrazine is 570 ppm for rats, with toxicity characterized by respiratory tract irritation and pathological damage to lung, liver, and kidneys.[3] The LC_{50} (1-hour) estimates for a 64% aqueous solution of aerosolized hydrazine (in terms of hydrazine) in rats was 5.8 mg/L for males and 3.4 mg/L for females. The only clinical sign seen during the exposure was exaggerated respiratory movements. Marked to moderate reductions in body weight and decreases in food and water consumption, lethargy, secretions from the eyes, and a poorly groomed appearance were reported following exposure which were no longer present 4 days post-treatment.[11]

Subchronic

In a 6-month inhalation study,[12] rats, mice, dogs, and monkeys were exposed continuously to hydrazine at 0.2 ppm or 1 ppm or were exposed 6 hours/day, 5 days/week at 1 ppm or 5 ppm. At 0.2 ppm, body weights of rats were lower than the controls, liver pathology was seen in mice, a decrease in the number of red blood cells was seen in dogs, and a minimal increase in fat deposition in the liver was seen in monkeys. In addition to these changes, there was increased mortality at 1 ppm with central nervous system (CNS) depression (primarily lethargy) in mice, body weight reductions in dogs, and ocular

irritation in monkeys. Along with the above changes, tonic convulsions were seen in one dog at 5 ppm.

Rats that were exposed 6 hours/day, 5 days/week for 5 to 40 days at 20, 53, or 224 ppm or for 6 months at 4.5 ppm or 14 ppm experienced increased mortality and decreased body weights in a dose-dependent fashion through all test groups.[13] Lethargy was seen during exposures, and lung and liver damage were detected in rats from all test groups.

Chronic/Carcinogenicity

In a variety of studies, hydrazine has been shown to cause a tumorigenic response. Chronic oral administration to mice resulted in multiple types of tumors, including pulmonary adenomas or carcinomas, hepatocarcinomas, myeloid leukemia, reticulum cell sarcoma of the mediastinum, and lymphomas.[14–27] In contrast, two studies in which hydrazine was given orally to mice did not produce an increase in tumors.[28,29] Chronic oral administration of hydrazine to rats also resulted in lung adenomas and carcinomas and in liver tumors;[15,29,30] however, hamsters failed to show an increase in tumors following oral administration of hydrazine.[14,31] Studies in which hydrazine was tested for tumorigenic activity by unusual routes of administration, frequently for the purpose of examining the mechanism of action, have been reported. Hydrazine produced tumors in the mouse following intraperitoneal injection[18,23] but did not increase the tumor yield in rats following either subcutaneous injection or intratracheal application.[29]

The most useful information comes from long-term inhalation studies in which animals were exposed to hydrazine vapors. In mice, exposed for 6 months at 0.2, 1, or 5 ppm, there was an increased incidence of pulmonary tumors in all groups.[12,32] Another inhalation study was conducted in which rats, mice, dogs, and hamsters were exposed 6 hours/day, 5 days/week at vapor concentrations of 0.05 ppm (rats and mice), 0.25 or 1.0 ppm (rats, mice, hamsters, and dogs), or 5 ppm (rats, hamsters, and dogs) for 1 year and subsequently followed for their life span or 38 months.[33,34] An increased incidence of benign and malignant nasal tumors were observed at 1 and 5 ppm in rats. At 0.05 ppm, the incidence of nasal tumors in rats was slightly increased, but not significantly, above 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 changes characteristic of degenerative disease, including amyloidosis. Thyroid tumors and colon tumors were only slightly increased in hamsters exposed at 5 ppm. An increased incidence of pulmonary adenomas was observed at 1 ppm in mice. No increase in tumors was observed in mice exposed below 1 ppm. No compound-related neoplastic or non-neoplastic effects were observed in dogs at any dose level.[34]

Hydrazine was proven to be carcinogenic following lifetime administration in the majority of the rodent studies. The primary tissues are the liver, the lungs, and following inhalation, the epithelium of the nasal cavity. Steinhoff and Mohr[29] point out that these effects occur generally under conditions in which frank signs of toxicity (irritation, tissue damage) are occurring. Furthermore, the mechanism of action appears to be through indirect alkylation of DNA, which itself is closely connected to the toxic action of hydrazine (i.e., through reacting with a cellular substance that is an intermediate in the carcinogenic process).

Reproductive/Developmental

Groups of rats were exposed orally during gestation to 8 mg hydrazine (as the monohydrochloride)/kg body weight.[35] Maternal toxicity, including mortality and body weight loss, was seen, along with fetal toxicity that included reduced fetal weight and viability. Although some fetuses were pale and edematous, no major congenital malformations occurred.

A second developmental toxicity study tested rats at oral doses of 0, 2.5, 5, or 10 mg hydrazine (free base)/kg from days 6 to 15 of gestation.[36] The study also included a group treated with 10 mg/kg on days 7 to 9. Maternal toxicity and fetal toxicity occurred at the 5- and 10-mg dose levels with 2.5 mg/kg being an apparent no-observed-effect level (NOEL). Developmental delays, but no terata, were seen in the fetuses.

Mice were treated intraperitoneally with 0, 4, 12, 20, 30, or 40 mg hydrazine (free base)/kg body weight from day 8 through day 9 of gestation.[37] The following effects were observed: maternal mortality at 40 mg/kg; increased fetal deaths at 30 and 40 mg/kg; and reduced fetal weights and increased numbers of litters with malformed young (exencephaly, hydronephrosis, supernumerary ribs) at 12 and 20 mg/kg. In a gavage study,[38] no evidence of developmental toxicity was seen in rats treated with 13 mg/kg daily for 30 days prior to mating. In a study where rats were exposed to hydrazine in drinking water (0.00016–0.16 mg/kg doses),[39] no effects were seen in either maternal or fetal animals. It appears that the fetus is no more sensitive to the effects of hydrazine exposure than is the maternal animal.

Genotoxicity Studies

Hydrazine is positive in most standard assays for genetic endpoints. It is positive in producing forward mutation in *Bacillus subtilis*,[40,41] in plants,[42,43] and in mammalian cells.[44,45] Hydrazine produced a point mutation in the 61st codon column of H-*ras* gene in cultured newborn rat liver cells.[46] Hydrazine produced reverse mutation in *B. subtilis*,[47–49] fungi,[50] and in the host-mediated assay in mice.[51] It produced sex-linked recessive lethals in *Drosophila*[52] and chromosomal breaks or ab-

errations in plant cells[53,54] and animal cells.[55–58] Although positive in one micronucleus test,[59] hydrazine was inactive in two other assays for clastogenesis,[60,61] in the production of nuclear aberrations following oral exposure to mice,[62] or in increasing the yield of dominant lethals following intraperitoneal injection in mice.[63]

Human Studies

Skin and eye irritation has occurred in humans,[64–67] and allergic contact dermatitis has been reported.[68–73] No systemic responses were described in any of these reported exposures. Several incidents of systemic poisoning have been reported, mainly showing effects on the CNS, respiratory system, and stomach. Vomiting, weakness, and irregular breathing, with recovery in 5 days, occurred following ingestion of 20 to 30 ml of a 6% aqueous solution.[74] A second ingestion incident reported vomiting, unconsciousness, and sporadic, violent behavior with paraesthesia; the outcome was not described.[75] An accidental swallowing of a mouthful of hydrazine led to confusion, lethargy, and restlessness in a 24-year-old man; liver damage was detected clinically, but other signs of systemic toxicity appear to have been masked by the aggressive therapy program.[76] Another man sustained severe chemical burns (involving 22% of the body surface) following a hydrazine explosion. After a comatose period with biochemical indicators of liver malfunction, recovery was seen in 5 weeks.[77] Inhalation of vapors has produced pulmonary edema (six cases discussed) and has been treated successfully with pyridoxine.[78] An occupational exposure (both skin contact and inhalation) at an unknown concentration over a 6-month period produced conjunctivitis, tremor, and lethargy. Lung and liver damage occurred, and the individual died 21 days after the last exposure.[79]

The causes of death in a cohort of 427 male workers employed for at least 6 months in a hydrazine manufacturing plant failed to reveal any relationship between hydrazine exposure and cause of death.[80] A quantitative comparison of the rodent carcinogenicity data was applied to this human study to predict human cancer risk.[81] Under conditions of human exposure (1 to 10 ppm estimated), the animal data actually do predict that the human incidence of lung cancer would be indistinguishable from the background rate.[81] Cancer deaths among workers employed at nine hydrazine manufacturing facilities appeared no different than normal in a preliminary investigation.[82] A significant increase in cases of myocardial infarction was reported in a plant manufacturing hydrazine.[83] The author cautions that the conclusion is based on very small numbers, and no follow-up information is available.

TLV Recommendation

Based on the slightly higher incidence of nasal tumors observed in rats at 0.05 ppm[33,34] and by analogy with other hydrazines, specifically methyl hydrazine in which other signs of toxicity, including nasal irritation, were seen at 0.02 ppm in rats and mice,[84] the TLV Committee recommended a TLV–TWA for hydrazine of 0.01 ppm. A skin notation is recommended because of the systemic effects seen in animals following dermal contact.[6–9] Hydrazine does produce a carcinogenic response in rodents following a series of steps, many of which are amenable to modification; for example, the carcinogenic effect can be reduced or eliminated by such diverse factors as fiber in the diet, exposure to a second chemical or pesticides, and other factors. Until more information is available on activation pathways in animals compared to humans, the TLV Committee recommends an A3 classification, animal carcinogen.

Other Recommendations

OSHA PEL: In 1989, OSHA established an 8-hour PEL–TWA of 0.1 ppm, with a skin notation, for hydrazine.[85] OSHA concluded that this limit would significantly reduce the risks of cancer, liver disease, and hematopoietic effects clearly demonstrated in animals at exposure above the PEL. As a consequence of the 1992 decision by the U.S. Court of Appeals for the Eleventh Circuit vacating the PELs promulgated under the 1989 rulemaking,[86] hydrazine is regulated with a PEL–TWA of 1 ppm, and the skin notation was retained.[87]

NIOSH REL/IDLH: The NIOSH REL is a ceiling of 0.03 ppm (0.04 mg/m^3) as determined by a 2-hour air sample;[88] this level represented the lowest detectable concentration over this sampling period.[89] NIOSH did not concur with the 1989 OSHA PEL [Ex 8-47, Table N6B] citing studies demonstrating the carcinogenicity of hydrazine in rodents by a variety of dosing routes. NIOSH stated that hydrazine should be labeled a potential occupational carcinogen.[85] An IDLH value of 50 ppm has been established for hydrazine based on acute toxicity data in animals.[88] In addition, as part of the Institute's carcinogen policy, NIOSH recommends that the most protective respirators be worn when hydrazine concentrations exceed 0.03 ppm.

ACGIH Rationale for TLVs that Differ from the PEL or REL: The TLV is more protective (than the present PEL or REL) against the serious potential health risks for exposed workers, i.e., cancer, liver disease, and blood dyscrasias. The TLV of 0.01 ppm (0.013 mg/m^3) is based on a slightly higher incidence of nasal tumors observed in rats at 0.05 ppm. The skin notation was retained based on the substantiating evidence. The carcinogen designation was changed from A2 to A3 due to the lack of current information on activation pathways in animals compared to humans.

NTP Studies: NTP has not conducted chronic toxicologic and carcinogenicity studies of hydrazine. Genetic