1 Identification

GHS Product Identifier

HYDRAZINE 64%

Other means of identification

CAS:	302-01-2 7803-57-8
EC:	206-114-9
RTECS:	MU7175000
ICSC:	0281
UN:	2030
Composition:	mono-constituent substance
Origin:	Inorganic
Synonyms:	Diamine Diazane Levoxine Hydrazine base Nitrogen hydride Oxytreat 35 Hydrazin
Proper Shipping Name:	HYDRAZINE AQUEOUS SOLUTION, with >37% hydrazine, by mass
Chemical Formula:	H_4N_2

Recommended use of the chemical and restriction on use

It is used for corrosion control in boilers and to make other chemicals such as plastics, agricultural pesticides, plant growth regulators and medicines.

Supplier's details

AQUATRADE WATER TREATMENT CHEMICALS (PTY) LTD

4A Spanner Road
Spartan, Kempton Park
Gauteng, South Africa
1619
www.aquatradesa.co.za
sheq@aquatradesa.co.za

PO Box 357
Isando
Gauteng, South Africa
1600
Tel: +27 11 394 0752
Tel: +27 87 654 3326 (SDS Enquiries)

Emergency phone number

E le Sar: +27 82 921 0643 (Available Mon - Fri, GMT 5:00 to 20:00)
Spilltech: +27 861 000 366 (Available 24/7)

2 Hazard(s) identification

Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008

Flammable Liquid and Vapour (Category 3), H226
Acute Toxicity - Oral (Category 3), H301
Acute Toxicity - Dermal (Category 3), H311
Acute Toxicity - Inhalation (Category 2), H330
Skin Corrosion/Irritation (Category 1), H314
Skin Sensitization (Category 1), H317

Carcinogenicity - Inhalation - Respiratory: Nose (Category 1B), H350
Aquatic Toxicity - Acute (Category 1), H400
Aquatic Toxicity - Chronic (Category 1), H410

Full text of H statements : see section 16

GHS label elements

Danger

Flammable liquid and vapour

Toxic if swallowed

Toxic in contact with skin

Causes severe skin burns and eye damage

May cause an allergic skin reaction

Fatal if inhaled

May cause cancer

Very toxic to aquatic life

Very toxic to aquatic life with long lasting effects

Keep away from heat/sparks/open flames/hot surfaces. — No smoking.

Keep container tightly closed.

Take precautionary measures against static discharge.

Do not breathe dust/fume/gas/mist/vapours/spray.

Wash thoroughly after handling.

Do not eat, drink or smoke when using this product.

Contaminated work clothing should not be allowed out of the workplace.

Avoid release to the environment.

Wear protective gloves/protective clothing/eye protection/face protection.

IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.

IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.

IF ON SKIN: Wash with plenty of soap and water.

IF ON SKIN (or hair): Remove/Take off Immediately all contaminated clothing. Rinse SKIN with water/shower.

IF INHALED: Remove victim to fresh air and Keep at rest in a position comfortable for breathing.

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

IF exposed or concerned: Get medical advice/attention.

Specific treatment (see P330+P351+P352+P353 on this label).

If skin irritation or rash occurs: Get medical advice/attention.

Take off contaminated clothing and wash it before reuse.

Wash contaminated clothing before reuse.

In case of fire: Use alcohol-resistant foam, foam, water spray, dry powder, carbon dioxide to extinguish.

Collect spillage.

Store in a well-ventilated place. Keep cool.

Store locked up.

Dispose of contents and container in accordance with local, regional, national, international regulations.

Ground/bond container and receiving equipment. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools.

Obtain special instructions before use. Do not handle until all safety precautions have been read and understood.

Other hazards which do not result in classification

Hydrazine is an inorganic substance. According to REACH regulation Annex XIII, the PBT/vBvP assessment does not apply to inorganic chemicals.
Nevertheless, the properties of Hydrazine have been evaluated as far as possible.

P-criterion: As hydrazine is purely inorganic, it cannot be degraded in sewage treatment plants. Nevertheless, hydrazine will be degraded in aqueous media in the presence of metal ions, organic matter, etc, whereas the degradation rate is determined by the sum of all these factors, rather than by one factor alone. Several studies are available investigating the stability of hydrazine in aqueous media of a varying composition. They were not able to determine an exact half live, but they provide evidence that the environmental half life of hydrazine in aqueous media will be below 24 h. Concludingly, the environmental half life of hydrazine in the aquatic compartment will be smaller than 40 days not fulfilling the P criterion.
B-criterion: Only an estimated value is available accounting for 3.16. Furthermore, based on the physico-chemical properties of hydrazine (high water solubility, low logKow) and the rapid degradation in water, an accumulation of hydrazine in biota can be excluded. B-criterion not fulfilled.
T-criterion: The T criterion is fulfilled based on a NOEC(algae) =0.006 mg/l and Carc. Cat 1b according to EU Regulation No. 1272/2008 (GHS).

Justification: A substance is identified as a PBT substance if it fulfils all three PBT criteria described above. P and B criteria are not fulfilled.

Included in the Candidate List of Substances of Very High Concern (SVHC) according to Regulation (EC) No. 1907/2006 (REACH).

3 Composition/information on ingredients

Description	CAS Number	EINECS Number	%	Note
Hydrazine	302-01-2	206-114-9	0 - 99	Acute Tox. 3; Acute Tox. 2; Acute Tox. 3; Skin Corr. 1B; Skin Sens. 1; Carc. 1B; Aquatic Acute 1; Aquatic Chronic 1; H301, H330, H311, H314, H317, H350, H400, H410 Concentration limits: >= 10 %: Skin Corr. 1B, H314; 3 - < 10 %: Skin Irrit. 2, H315; 3 - < 10 %: Eye Irrit. 2, H319; M-Factor - Aquatic Acute: 10

4 First-aid measures

Description of necessary first-aid measures

Call 112 or 10177 or your local emergency help number immediately, for emergency assistance. Call the Poison Control Center at +27 21 931 6129 – Tygerberg or +27 21 658 5308 – Red Cross, Email: poisonsinformation@uct.ac.za, Website: https://www.afritox.co.za for further instructions. Provide them with information such as the compound taken, quantity and time of ingestion, age, weight and general health status of affected individual. Carefully remove the individual from the exposure area.

Inhalation

1. Move to fresh air.
2. Oxygen or artificial respiration if needed.
3. Victim to lie down in the recovery position, cover and keep him warm.
4. Call a physician immediately.

Skin

1. Take off contaminated clothing and shoes immediately.
2. Wash off immediately with plenty of water.
3. Keep warm and in a quiet place.
4. Call a physician or poison control centre immediately.
5. Wash contaminated clothing before re-use.

Eye Contact

1. Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes.
2. In the case of difficulty of opening the lids, administer an analgesic eye wash (oxybuprocaine).
3. Call a physician or poison control centre immediately.
4. Take victim immediately to hospital.

Ingestion

1. Call a physician or poison control centre immediately.
2. Take victim immediately to hospital.
3. In case of symptoms that indicate difficulty in swallowing including vomiting or decreased alertness, **DO NOT** give anything by way of mouth.
4. If swallowed, rinse mouth with water (only if the person is conscious).
5. Unless instructed by a healthcare professional, **DO NOT** induce vomiting in the affected individual. Following an ingestion of the substance, immediately give milk to drink
6. Artificial respiration and/or oxygen may be necessary.
7. Always try to take the compound bottle/container to the ER.

Emergency Life-Support Procedures

Acute exposure to hydrazine may require decontamination and life support for the victims. Emergency personnel should wear protective clothing appropriate to the type and degree of contamination. Air-purifying or supplied-air respiratory equipment should also be worn, as necessary. Rescue vehicles should carry supplies such as plastic sheeting and disposable plastic bags to assist in preventing spread of contamination.

Most important symptoms/effects, acute and delayed

Warning

Effects may be delayed for hours to days. Caution is advised.

Signs and Symptoms of Acute Hydrazine Exposure

Signs and symptoms of acute exposure to hydrazine may include severe eye irritation, facial numbness, facial swelling, and increased salivation. Hydrazine vapor may immediately irritate the nose and throat. Headache, twitching, seizures, convulsions, and coma may also occur. Gastrointestinal signs and symptoms include anorexia, nausea, and vomiting. Pulmonary edema and hypotension (low blood pressure) are common. Hydrazine is toxic to the liver, ruptures red blood cells, and may cause kidney damage. Dermal contact may result in irritation or severe burns.

Indication of immediate medical attention and special treatment needed, if necessary

Immediate first aid

Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand-valve resuscitator, bag-valve-mask device, or pocket mask, as trained. Perform CPR if necessary. Immediately flush contaminated eyes with gently flowing water. **DO NOT** induce vomiting. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature. Obtain medical attention.

Basic treatment

Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if necessary. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary. Monitor for shock and treat if necessary. Anticipate seizures and treat if necessary. For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport. **DO NOT** use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of water for dilution if the patient can swallow, has a strong gag reflex, and does not drool. Administer activated charcoal. Cover skin burns with dry, sterile dressings after decontamination.

Advanced treatment

Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag-valve-mask device may be beneficial. Consider drug therapy for pulmonary edema. Monitor cardiac rhythm and treat arrhythmias if necessary. Start IV administration of D5W /SRP: "To keep open", minimal flow rate/. Use 0.9% saline (NS) or lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Consider vasopressors if patient is hypotensive with a normal fluid volume. Watch for signs of fluid overload. Administer 1% solution methylene blue if patient is symptomatic with severe hypoxia, cyanosis, and cardiac compromise not

responding to oxygen. Treat seizures with diazepam (Valium) or lorazepam (Ativan). Monitor for signs of hypoglycemia (decreased level of consciousness, tachycardia, pallor, dilated pupils, diaphoresis, and/or a dextrose strip or glucometer reading less than 50 mg/dL) and administer 50% dextrose if necessary. Draw blood sample before administration. Use proparacaine hydrochloride to assist eye irrigation.

If this chemical gets into the eyes, remove any contact lenses at once and irrigate immediately for at least 15 min, occasionally lifting upper and lower lids. Seek medical attention immediately. If this chemical contacts the skin, remove contaminated clothing and wash immediately with soap and water. Seek medical attention immediately. If this chemical has been inhaled, remove from exposure, being rescue breathing (using universal precautions, including resuscitation mask) if breathing has stopped and CPR if heart action has stopped. Transfer promptly to a medical facility. When this chemical has been swallowed, get medical attention. Medical observation is recommended for 24-48 hr after breathing overexposure, as pulmonary edema may be delayed. As first aid for pulmonary edema, a doctor or authorized paramedic may consider administering a corticosteroid spray.

Prompt removal of the irritant and basic life support measures are key. Dermal exposure should be treated immediately with soap and water. Ocular exposure requires copious irrigation with tepid water.

Respiratory exposure should be treated with humidified supplemental oxygen and monitoring for respiratory distress. Chest radiographs, arterial blood gas determinations, and intubation may be clinically indicated.

Pyridoxine may be antidotal in hydrazine ingestions. Seizures are treated with routine medications, including diazepam, lorazepam, or phenytoin, and phenobarbital. Other routine laboratory studies include monitoring blood glucose, liver function tests, and hemoglobin measurement. If methemoglobinemia exists with a level greater than 30%, methylene blue should be used. Treatment is otherwise supportive and symptomatic.

5 Fire-fighting measures

Suitable extinguishing media

Excerpt from ERG Guide 153 [Substances - TOXIC and/or CORROSIVE (Combustible)]
FIRE
Small Fire

- Dry chemical, CO2 or water spray.

Large Fire

- Dry chemical, CO2, alcohol-resistant foam or water spray.
- Move containers from fire area if you can do it without risk.
- Dike fire-control water for later disposal; do not scatter the material.

Fire involving Tanks or Car/Trailer Loads

- Fight fire from maximum distance or use unmanned hose holders or monitor nozzles.
- Do not get water inside containers.
- Cool containers with flooding quantities of water until well after fire is out.
- Withdraw immediately in case of rising sound from venting safety devices or discoloration of tank.
- ALWAYS stay away from tanks engulfed in fire.

Specific hazards arising from the chemical

Decomposition products may include the following materials: nitrogen oxides. Vapours are heavier than air and will collect in low areas. Vapours may travel long distances to ignition sources and flashback. Vapours in confined areas may explode when exposed to fire. Containers may explode in fire. Storage containers and parts of containers may rocket great distances, in many directions. Closed containers may rupture violently when heated. Hydrazine can ignite spontaneously in air, when in contact with porous materials.

Special protective actions for fire-fighters

Use water spray to cool unopened containers.

Approach fire from upwind to avoid hazardous vapors and toxic decomposition products. Fight fire from protected location or maximum possible distance. Use water spray to keep fire-exposed containers cool. Use flooding quantities of water as fog or spray. Flooding quantities may be necessary to prevent reignition.

Small fires: Dry chemical, carbon dioxide, water spray, or foam. Large fires: Water spray, fog, or foam. Stay upwind; keep out of low areas. Wear positive pressure breathing apparatus and protective clothing. Isolate for one-half mile in all

directions if tank car or truck is involved in fire. Move container from fire area if you can do so without risk. Dike fire control water for later disposal, do not scatter material. Spray cooling water on containers that are exposed to flames until well after fire is out. If material or contaminated runoff enters waterways, notify downstream users of potentially contaminated waters. Notify local health and fire officials and pollution control agencies. From a secure, explosion-proof location, use water spray to cool exposed containers. If cooling streams are ineffective (venting sound increases in volume and pitch, tank discolors, or shows any signs of deforming), withdraw immediately to a secure position. The only respirators recommended for firefighting are self-contained breathing apparatuses that have full face-pieces and are operated in a pressure-demand or other positive-pressure mode.

If material on fire or involved in fire: Extinguish fire using agent suitable for type of surrounding fire. (Material itself does not burn or burns with difficulty.) Keep run-off water out of sewers and water sources.

If material on fire or involved in fire: Do not extinguish fire unless flow can be stopped. Use water in flooding quantities as fog. Solid streams of water may be ineffective. Cool all affected containers with flooding quantities of water. Apply water from as far a distance as possible. Use "alcohol" foam, dry chemical or carbon dioxide.

6 Accidental release measures

Personal precautions, protective equipment and emergency procedures

Isolation and Evacuation
Excerpt from ERG Guide 153 [Substances - TOXIC and/or CORROSIVE (Combustible)]
PUBLIC SAFETY

- CALL Emergency Response Telephone Number on Shipping Paper first. If Shipping Paper not available or no answer, refer to appropriate telephone number listed on the inside back cover.
- As an immediate precautionary measure, isolate spill or leak area in all directions for at least 50 meters (150 feet) for liquids and at least 25 meters (75 feet) for solids.
- Keep unauthorized personnel away.
- Stay upwind, uphill and/or upstream.
- Ventilate enclosed areas.

PROTECTIVE CLOTHING

- Wear positive pressure self-contained breathing apparatus (SCBA).
- Wear chemical protective clothing that is specifically recommended by the manufacturer. It may provide little or no thermal protection.
- Structural firefighters' protective clothing provides limited protection in fire situations ONLY; it is not effective in spill situations where direct contact with the substance is possible.

EVACUATION
Spill

- See Table 1 - Initial Isolation and Protective Action Distances for highlighted materials. For non-highlighted materials, increase, in the downwind direction, as necessary, the isolation distance shown under "PUBLIC SAFETY".

Fire

- If tank, rail car or tank truck is involved in a fire, ISOLATE for 800 meters (1/2 mile) in all directions; also, consider initial evacuation for 800 meters (1/2 mile) in all directions.
- [FLAG] In Canada, an Emergency Response Assistance Plan (ERAP) may be required for this product. Please consult the shipping document and/or the ERAP Program Section (page 391).

Advice for non-emergency personnel
Prevent further leakage or spillage if safe to do so. Keep away from Incompatible products.

Advice for emergency responders
Evacuate personnel to safe areas. Keep people away from and upwind of spill/leak. Ventilate the area. Wear suitable protective clothing.

Environmental precautions

Environmental considerations
Land Spill
Dig a pit, pond, lagoon, holding area to contain liquid or solid material. If time permits, pits, ponds, lagoons, soak holes, or holding areas should be sealed with an impermeable flexible membrane liner. Dike surface flow using soil, sand bags, foamed polyurethane, or foamed concrete. Absorb bulk liquid with fly ash, cement powder, or commercial sorbents.

Water spill
Use natural barriers or oil spill control booms to limit spill travel. Use natural deep water pockets, excavated lagoons, or sand bag barriers to trap material at bottom. Remove trapped material with suction hoses.

Air spill
Apply water spray or mist to knock down vapours.

Methods and materials for containment and cleaning up

Spillage Disposal
Evacuate danger area! Consult an expert! Personal protection: complete protective clothing including self-contained breathing apparatus. **DO NOT** let this chemical enter the environment. Collect leaking liquid in sealable non-metallic containers. Absorb remaining liquid in sand or inert absorbent. Then store and dispose of according to local regulations. **DO NOT** absorb in saw-dust or other combustible absorbents.

Cleanup Methods
ACCIDENTAL RELEASE MEASURES: Personal precautions, protective equipment and emergency procedures: Wear respiratory protection. **Avoid** breathing vapours, mist or gas. Ensure adequate ventilation. Remove all sources of ignition. Evacuate personnel to safe areas. Beware of vapours accumulating to form explosive concentrations. Vapours can accumulate in low areas. Environmental precautions: Prevent further leakage or spillage if safe to do so. **DO NOT** let product enter drains. Discharge into the environment must be avoided. Methods and materials for containment and cleaning up: Contain spillage, and then collect with an electrically protected vacuum cleaner or by wet-brushing and place in container for disposal according to local regulations.

Emergency response personal protective equipment: Wear special protective clothing and positive pressure self-contained breathing apparatus. Butyl rubber, Neoprene, nitrile rubber, polyvinyl chloride, Teflon, or Saranex barrier recommended.

Spill or leak procedures: Eliminate all ignition sources. Approach release from upwind. Use water spray to cool and disperse vapors, protect personnel, and dilute spills to form nonflammable mixtures. Control runoff and isolate discharged material for proper disposal.

Evacuate and restrict persons not wearing protective equipment from area of spill or leak until cleanup is complete. Remove all ignition sources. Stay upwind; keep out of low areas. In case of contact with material, immediately flush skin or eyes with running water for at least 15 min. Establish forced ventilation to keep levels below explosive limit. Absorb liquids in vermiculite, dry sand, earth, peat, carbon, or a similar material and deposit in sealed containers. Keep this chemical out of a confined space, such as a sewer, because of the possibility of an explosion, unless the sewer is designed to prevent the buildup of explosive concentrations. It may be necessary to contain and dispose of this chemical as a hazardous waste. If material or contaminated runoff enters waterways, notify downstream users of potentially contaminated waters.

Disposal Methods
Generators of waste (equal to or greater than 100 kg/mo) containing this contaminant, EPA hazardous waste number U133, must conform with USEPA regulations in storage, transportation, treatment and disposal of waste.

Product
Burn in a chemical incinerator equipped with an afterburner and scrubber but exert extra care in igniting as this material is highly flammable. Offer surplus and non-recyclable solutions to a licensed disposal company. Contact a licensed professional waste disposal service to dispose of this material; Contaminated packaging: Dispose of as unused product.

SRP
Wastewater from contaminant suppression, cleaning of protective clothing/equipment, or contaminated sites should be contained and evaluated for subject chemical or decomposition product concentrations. Concentrations shall be lower than applicable environmental discharge or disposal criteria. Alternatively, pretreatment and/or discharge to a permitted wastewater treatment facility is acceptable only after review by the governing authority and assurance that "pass through" violations will not occur. Due consideration shall be given to remediation worker exposure (inhalation, dermal and ingestion) as well as fate during treatment, transfer and disposal. If it is not practicable to manage the chemical in this fashion, it must be evaluated in accordance with EPA 40 CFR Part 261, specifically Subpart B, in order to determine the appropriate local, state and federal requirements for disposal.

Hydrazine is a waste chemical stream constituent which may be subjected to ultimate disposal by controlled incineration with facilities for effluent scrubbing to abate any ammonia formed in the combustion process.

Hydrazine is a potential candidate for liquid injection incineration with a temperature range of 650 to 1600 deg C and residence times of 0.1 to 2 seconds. Also a potential candidate for rotary kiln incineration with a temperature range of 820 to 1,600 deg C and residence times of seconds for liquids and gases; hours for solids. Also a potential candidate for fluidized bed incineration with a temperature range of 450 to 980 deg C and residence times of seconds for liquids and gases; longer for solids.

Controlled incineration with facilities for effluent scrubbing to abate any nitrogen compounds formed in the combustion process. Consult with environmental regulation agencies for guidance on acceptable disposal practices.

Recommendable method
Incineration. Peer-review: Dilute well with alcohol, hydrocarbon solvent before burning. Concentrated hydrazine may explode if heated. Hydrazine is a powerful reductant but should be well diluted prior to oxidizing. (Peer-review conclusions of an IRPTC Expert Consultation (May 1985))

Precautions for "Carcinogens"
There is no universal method of disposal that has been proved satisfactory for all carcinogenic compounds & specific methods of chemical destruction published have not been tested on all kinds of carcinogen containing waste. summary of avail methods & recommendations given must be treated as guide only.

Incineration may be only feasible method for disposal of contaminated laboratory waste from biological expt. However, not all incinerators are suitable for this purpose. The most efficient type is probably the gas fired type, in which a first stage combustion with a less than stoichiometric air:fuel ratio is followed by a second stage with excess air. Some are designed to accept aqueous & organic solvent solutions, otherwise it is necessary to absorb solution on to suitable combustible material, such as sawdust. Alternatively, chemical destruction may be used, especially when small quantities are to be destroyed in laboratory.

HEPA (high efficiency particulate arrestor) filters can be disposed of by incineration. For spent charcoal filters, the adsorbed material can be stripped off at high temp & carcinogenic wastes generated by this treatment conducted to & burned in an incinerator. LIQUID WASTE: Disposal should be carried out by incineration at temp that ensure complete combustion. SOLID WASTE: Carcasses of lab animals, cage litter, & misc solid wastes should be disposed of by incineration at temp high enough to ensure destruction of chemical carcinogens or their metabolites.

Small quantities of some carcinogens can be destroyed using chemical reactions but no general rules can be given. As a general technique treatment with sodium dichromate in strong sulfuric acid can be used. The time necessary for destruction is seldom known but 1-2 days is generally considered sufficient when freshly prepared reagent is used. Carcinogens that are easily oxidizable can be destroyed with milder oxidative agents, such as saturated solution of potassium permanganate in acetone, which appears to be a suitable agent for destruction of hydrazines or of compounds containing isolated carbon-carbon double bonds. Concentration or 50% aqueous sodium hypochlorite can also be used as an oxidizing agent.

Carcinogens that are alkylating, arylating or acylating agents per se can be destroyed by reaction with appropriate nucleophiles, such as water, hydroxyl ions, ammonia, thiols, & thiosulfate. The reactivity of various alkylating agents varies greatly & is also influenced by solution of agent in the reaction medium. To facilitate the complete reaction, it is suggested that the agents be dissolved in ethanol or similar solvents. No method should be applied until it has been thoroughly tested for its effectiveness & safety on material to be inactivated. For example, in case of destruction of alkylating agents, it is possible to detect residual compounds by reaction with 4-(4-nitrobenzyl)-pyridine.

Neutralization of hydrazine fuels with hypochlorite is a recommended procedure for the treatment of fuel spills prior to disposal. Previous research has shown that incomplete reaction of hypochlorite with the methylated hydrazine fuels monomethylhydrazine and unsymmetrical dimethylhydrazine leads to a wide variety of byproducts, including N-nitrosamines, which are believed to be highly carcinogenic. The results presented in this paper were obtained as part of a program to assess the environmental implications of using the hypochlorite method for the treatment and disposal of hydrazine fuel spills. The fuels examined were hydrazine, monomethylhydrazine, unsymmetrical dimethylhydrazine and Aerozine-50. The neutralization products were determined under experimental conditions comparable to those expected for actual spills. The effects of varying the temperature and the pH as well as of aging the final reaction mixture were determined. Quantitative measurements of nitrosamines produced are presented. Major and environmentally significant minor products were identified using gas chromatography /mass-spectrometry.

Liquid injection or fluidized bed incineration methods are acceptable disposal methods.

7 Handling and storage

Precautions for safe handling

Avoid exposure - obtain special instructions before use. Put on appropriate personal protective equipment. Eating, drinking and smoking should be prohibited in areas where this material is handled, stored and processed. Workers should wash hands and face before eating, drinking and smoking. Persons with a history of skin sensitization problems should not be employed in any process in which this product is used. **DO NOT** get in eyes or on skin or clothing. **DO NOT** breathe vapour or mist. **DO NOT** ingest. **Avoid** release to the environment. Use only with adequate ventilation. Wear appropriate respirator when ventilation is inadequate. **DO NOT** enter storage areas and confined spaces unless adequately ventilated. Keep in the original container or an approved alternative made from a compatible material, kept tightly closed when not in use. Store and use away from heat, sparks, open flame or any other ignition source. Use explosion-proof electrical (ventilating, lighting and material handling) equipment. Use non-sparking tools. Take precautionary measures against electrostatic discharges. To avoid fire or explosion, dissipate static electricity during transfer by earthing and bonding containers and equipment before transferring material. Keep away from acids. Empty containers retain product residue and can be hazardous.

Conditions for safe storage, including any incompatibilities

Storage
Store in accordance with local regulations. Store in a segregated and approved area. Store in original container protected from direct sunlight in a dry, cool and well-ventilated area, away from incompatible materials (see section 10) and food and drink. Eliminate all ignition sources. Separate from acids. Separate from oxidizing materials. Keep container tightly closed and sealed until ready for use. Containers that have been opened must be carefully resealed and kept upright to prevent leakage. **DO NOT** store in unlabelled containers. Use appropriate containment to avoid environmental contamination.

Fireproof. Separated from acids, metals, oxidants and food and feedstuffs. Keep under inert gas. Provision to contain effluent from fire extinguishing. Store in an area without drain or sewer access.

Storage Conditions
Keep container tightly closed in a dry and well-ventilated place. Containers which are opened must be carefully resealed and kept upright to prevent leakage.

It should be stored in glass containers in a cool, dark place. It is usually stored under nitrogen to reduce the flammability hazard and to maintain purity.

Detached storage is preferred. Inside storage should be in a standard flammable liquids storage warehouse, room, or cabinet. Provide water for flushing spills or leaks. Tanks should be located in water-filled dikes. Separate from acids, oxidizing materials, metal oxides. Normally stored under nitrogen.

DO NOT store in the same area as other flammable materials. Store in a secure poison location. Store separately in a corrosion-resistant location. Prior to working with this chemical you should be trained on its proper handling and storage. Before entering confined space where hydrazine may be present, check to make sure that an explosive concentration does not exist. Hydrazine must be stored to avoid contact with oxidizers (such as perchlorates, peroxides, permanganates, chlorates, and nitrates), strong acids (such as hydrochloric, sulfuric, and nitric); hydrogen peroxide, and metal oxides since violent reactions occur. Store in tightly closed containers in a cool, well-ventilated area away from heat. Sources of ignition, such as smoking and open flames, are prohibited where hydrazine is used, handled, or stored in a manner that could create a potential fire or explosion hazard. Wherever hydrazine is used, handled, manufactured, or stored, use explosion-proof electrical equipment and fittings. A regulated, marked area should be established where this chemical is handled, used, or stored in compliance with OSHA Standard 1910.1045.

SANS 10263-0 Warehousing
8.4.3.2 Where flammable or **corrosive** substances are stored, the floor shall slope away from the storage area (primary collection area) to a secondary catch basin or sump of capacity at least 10 % of the total available storage volume of the fire section concerned. The secondary catch basin shall be within the fire section, and shall be such that it can be well ventilated. Care shall be taken in the design of such areas to prevent contamination of the soil or ground water.

Storage

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Detached storage is preferred. Inside storage should be in a standard flammable liquids storage warehouse, room, or cabinet. Provide water for flushing spills or leaks. Tanks should be located in water-filled dikes. Separate from acids, oxidizing materials, metal oxides. Normally stored under nitrogen.

DO NOT store in the same area as other flammable materials. Store in a secure poison location. Store separately in a corrosion-resistant location. Prior to working with this chemical you should be trained on its proper handling and storage. Before entering confined space where hydrazine may be present, check to make sure that an explosive concentration does not exist. Hydrazine must be stored to avoid contact with oxidizers (such as perchlorates, peroxides, permanganates, chlorates, and nitrates), strong acids (such as hydrochloric, sulfuric, and nitric); hydrogen peroxide, and metal oxides since violent reactions occur. Store in tightly closed containers in a cool, well-ventilated area away from heat. Sources of ignition, such as smoking and open flames, are prohibited where hydrazine is used, handled, or stored in a manner that could create a potential fire or explosion hazard. Wherever hydrazine is used, handled, manufactured, or stored, use explosion-proof electrical equipment and fittings. A regulated, marked area should be established where this chemical is handled, used, or stored in compliance with OSHA Standard 1910.1045.

SANS 10263-0 Warehousing
8.4.3.2 Where **flammable** or **corrosive** substances are stored, the floor shall slope away from the storage area (primary collection area) to a secondary catch basin or sump of capacity at least 10 % of the total available storage volume of the fire section concerned. The secondary catch basin shall be within the fire section, and shall be such that it can be well ventilated. Care shall be taken in the design of such areas to prevent contamination of the soil or ground water.

8.4.3.9 A flame propagation inhibitor shall be installed at overflow points when **flammable** gases or **flammable** liquids are stored.

8.4.4.3 Outdoor secondary and tertiary basins may be connected by means of open gutters or closed pipelines. Where **flammable** liquids are stored, however, closed pipelines shall be connected by means such as siphons or flame-arrestor gauzes, which prevent "flashback" of burning liquid.

8.6.2 In areas where **flammable** or explosive substances are stored, appropriate measures shall be taken to prevent the accumulation of electrostatic charges or to discharge these under controlled circumstances. The relevant provisions of SANS 10123 shall apply (see also 5.1.2)

8.8.1 Ventilation
8.8.1.1 General
Every covered storage area shall be provided with either adequate natural ventilation or forced draught ventilation in accordance with Part 0 of SANS 10400:1990 that ensures at least five changes of air per hour. In general, poor ventilation occurs if vents are positioned near the floor, and good general ventilation occurs where vents are positioned both near the floor and near or in the roof. It shall be possible to shut off a forced draught ventilation system by means of a main switch in the event of a fire or the escape of poisonous or **corrosive** gases. Where highly **flammable** gases or **flammable** liquids are stored, effective extraction shall be provided, at or near floor level, and the ventilation shall be so efficient as to prevent the formation of an explosive atmosphere. A ventilation rate of up to 12 air changes per hour could be required in certain cases. Appropriate monitoring using an explosimeter is recommended. Where forced draught ventilation is applied,

it shall operate continuously during periods of normal operation, and might even need to operate during periods when the warehouse is unmanned.

8.8.2.1 Air conditioning shall preferably be of the ducted air type, with the air-conditioning plant situated well away from the storage area. Individual electric air conditioners shall not be used in areas where **flammable** materials are stored. Where it is necessary to humidify the storage area, this shall be done by direct spraying of steam or water vapour. Dehumidification could be required where a large quantity of substances that react violently with water are stored. Where room humidity is critical, appropriate monitoring shall be carried out

8.8.3 Where room heating is required to ensure product integrity, it shall be so designed as to ensure that the temperature in the warehouse does not fall below 5 °C. Heating systems shall preferably be based on hot water or steam, with the heat source and pipes, radiators or similar equipment that are likely to become hot, so positioned as to prevent direct heating of the stored product. Direct electrical room heating equipment, or portable gas-fired or oil-fired room heaters shall not be used in areas where **flammable** materials are stored. Where a maximum allowable temperature applies, appropriate monitoring systems shall be used. Facilities for heating a circulating medium shall be located outside the storage area or in a separate room. Where building insulation is used, it shall be of a non-combustible material such as mineral wool or glass fibre.

8.10.4 Where electric lighting is installed in a warehouse that is to be used for **flammable** or explosive products, it shall be protected in accordance with the relevant provisions of SANS 10108 for the class and division of hazardous location that the warehouse represents.

8.10.5 No switches may be installed inside a stock warehouse that is to be used for **flammable** or explosive products. Main switches shall be positioned outside the warehouse and shall be protected against the weather.

8.11.3 Wherever practicable, electrical equipment other than for permanent lighting, such as power points, power tools or hand lights, shall not be installed in a warehouse that is used for **flammable** or explosive products. Where such electrical equipment is used, it shall be protected in accordance with the provisions of SANS 10108 for the appropriate class and division of hazardous location that the warehouse represents.

9.7.2 Every type of storage area inside a warehouse shall be clearly demarcated, for example separate storage areas for poisons, **flammables** and **corrosives** shall display the relevant hazard class diamond (see table 1). The dimensions of the hazard class diamonds shall be at least 250 mm x 250 mm.

10.2.1.2 A warehouse in which any one of the following storage limits is exceeded shall be equipped with a hydrant system in addition to portable or mobile extinguishers:

a) 30 t of **flammable** toxic or combustible toxic materials;
b) 100 t of **flammable** materials; and
c) 250 t of combustible materials.

10.2.1.3 The firefighting water supply shall be such as to ensure an adequate response to all conceivable fires, and shall have a continuous flow rate of at least 1 200 L/min per hydrant in small warehouses. In larger warehouses in which highly **flammable** substances are stored and that are equipped with automatic sprinkler facilities, a capacity in the range 3 200 L/min to 6 000 L/min is likely to be required. Where it is necessary to achieve the required capacity, existing water supply systems shall be supplemented by water from a reservoir or firefighting pond. In all cases, the water supply shall be capable of being maintained for at least 120 min.

12.8.5 Storage of **flammable** liquids of class 3, **toxic** substances of division 6.1 and **corrosives** of class 8

Nitro-methane class 3, UN No. 1261, shall be separated from substances of class 6.1, and cyanides of division 6.1 shall be separated from acids of class 8. Concentrated acids and bases shall be segregated by at least 1 m. Packaged **flammable** liquids of class 3, **toxic** substances of division 6.1 and **corrosives** of class 8 that are of category 3 can be stored in the same area, provided that

a) they are kept above floor level, and
b) liquid dangerous goods of one class are not stored above dangerous goods of another class.

12.8.8.1 **Flammable** materials (see division 2.1, and classes 3 and 4 in SANS 10228) will greatly increase the risk of a

toxicant fire if stored in the same area as toxicants, therefore:

a) **Flammable** non-toxic materials shall be separated from **flammable** toxicants and from aerosols.
b) **Flammable** toxicants shall be separated from non-**flammable** toxicants.
c) **Flammable** materials shall be segregated from oxidizing substances and **corrosives**.

12.8.8.2 Oxidizing substances and organic peroxides (see class 5 in SANS 10228) can react violently with other products, and in particular with reducing substances and certain organic substances.
Oxidizing substances and organic peroxides shall be segregated from reducing substances, **toxic** substances and infectious substances, and from aerosol dispensers, **flammables** and **corrosives**.

12.8.8.3 **Toxic** and infectious substances (see class 6 in SANS 10228) can contaminate firefighting water in the event of a fire, therefore:

a) **Toxic** and infectious substances shall be separated from other **flammable** products and aerosols.
b) **Toxic** and infectious substances shall be segregated from oxidizing substances, organic peroxides and **corrosives**.
c) **Flammable toxic** and infectious substances shall be separated from non-flammable toxic and infectious substances (see 12.8.8.1).

12.8.8.4 **Corrosives** (see class 8 in SANS 10228) that leak or spill from their packaging can cause serious damage to other packages, with potentially hazardous consequences.

Corrosives shall be segregated from **toxic** substances, infectious substances, aerosols, **flammables**, oxidizing substances and organic peroxides.

12.13.8.4 No work that requires hot cutting or welding, or that is likely to generate heat or sparks, shall be carried out within 10 m of any **flammable** or combustible material or packaging. If such work can only be carried out in a place where products are stored, all **flammable** or combustible items shall be removed to a distance of at least 10 m from the working area and the site shall be inspected to ensure that there is no possibility of fire, explosion or contamination from leaks, vapours, dust, rags or other materials. Work shall not start unless the atmosphere has been tested for the presence of **flammable** vapours and a satisfactory result of the test has been noted on the work permit. A shield shall be created around the work area. Fire-proof blankets shall be so arranged as to prevent sparks from falling to the ground, particularly if welding is being done overhead. Care shall be taken that drains in the area are covered to prevent the entry of weld splatter or the ignition of vapours. During welding or cutting operations, at least one person shall stand by with a fire extinguisher.

12.14.1.5 Paints, **flammable** liquids and polishes for use on the premises shall, when not in use, be kept in metal containers, preferably outside the building. A separate metal container shall be provided for rags or cotton waste used in connection with polishes and cleaning fluids.

The provisions of above apply to the storage of the following quantities of dangerous goods.

Flammable liquids Class 3	
Category 1: closed-cup flashpoint < 23 °C and initial boiling point 35 °C	> 100 l
Category 2: closed-cup flash point < 23 °C and initial boiling point > 35 °C	> 500 l
Category 3: closed-cup flash point 23 °C and 60 °C	> 1 000 l
Toxic and infectious substances	
Class 6.1	
Category 1	> 5 kg
Category 2	> 50 kg
Category 3	> 500 kg
Class 6.2	
All quantities	
Corrosives (acids and bases) Class 8	
Category 1	> 50 kg
Category 2	> 200 kg

Category 3	> 1 000 kg

Special Provisions SANS 10263-0
E.2.6.1 Toxic substances of division 6.1 shall not be stored together with foodstuffs or stock feeds.

8 Exposure controls/personal protection

Control parameters

Recommended Exposure Limit (REL)
REL Ca C 0.03 ppm (0.04 mg/m3) [2-hour]

Permissible Exposure Limit (PEL)
PEL-TWA 1 ppm (1.3 mg/m³)
REL-C 0.03 ppm (0.04 mg/m³) [120 minutes]

Immediately Dangerous to Life or Health (IDLH)
IDLH 50 ppm ; A potential occupational carcinogen. (NIOSH, 2016)
NIOSH considers hydrazine to be a potential occupational carcinogen. [50 ppm]

Threshold Limit Values (TLV)
Threshold Limit Values 8 hr Time Weighted Avg (TWA): 0.01 ppm, skin

Threshold Limit Values
Peak Exposure Recommendation: Transient increases in workers' exposure levels may exceed 3 times the value of the TLV-TWA level for no more than 15 minutes at a time, on no more than 4 occasions spaced 1 hour apart during a workday, and under no circumstances should they exceed 5 times the value of the TLV-TWA level. In addition, the 8-hour TWA is not to be exceeded for an 8-hour work period.

0.01 ppm as TWA; (skin); A3 (confirmed animal carcinogen with unknown relevance to humans).

skin absorption (H); sensitization of skin (SH); carcinogen category: 2

Emergency Response Planning Guidelines

ERPG / LEL	Airborne Concentration
ERPG-1: The maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing more than mild, transient adverse health effects or without perceiving a clearly defined objectionable odour.	0.5 ppm
ERPG-2: The maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.	5 ppm
ERPG-3: The maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects.	30 ppm
LEL (Lower Explosive Limit): The minimum concentration in air of a flammable gas or vapour at which ignition can occur.	None

Acute Exposure Guideline Levels (AEGLs)

Exposure Time	AEGL 1 (Discomfort)	AEGL 2 (Impaired Escape)	AEGL 3 (Life Threatening/Death)

10 minutes	0.1	23	64
30 minutes	0.1	16	45
1 hour	0.1	13	35
4 hours	0.1	3.1	8.9
8 hours	0.1	1.6	4.4

Appropriate engineering controls

Eyewash fountains should be provided in areas where there is any possibility that workers could be exposed to the substance; this is irrespective of the recommendation involving the wearing of eye protection. Facilities for quickly drenching the body should be provided within the immediate work area for emergency use where there is a possibility of exposure.

> [Note: It is intended that these facilities provide a sufficient quantity or flow of water to quickly remove the substance from any body areas likely to be exposed. The actual determination of what constitutes an adequate quick drench facility depends on the specific circumstances. In certain instances, a deluge shower should be readily available, whereas in others, the availability of water from a sink or hose could be considered adequate.]

- Skin: Wear appropriate personal protective clothing to prevent skin contact.
- Eyes: Wear appropriate eye protection to prevent eye contact.
- Wash skin: The worker should immediately wash the skin when it becomes contaminated.
- Remove: Work clothing that becomes wet should be immediately removed due to its flammability hazard(i.e. for liquids with flash point Change: No recommendation is made specifying the need for the worker to change clothing after the work shift.

Individual protection measures

The selection of PPE is dependent on a detailed risk assessment. The risk assessment should consider the work situation, the physical form of the chemical, the handling methods, and environmental factors. Recommendations below is advisory only and must be evaluated by an industrial hygienist and safety officer familiar with the specific situation of anticipated use by our customers. It should not be construed as offering an approval for any specific use scenario.

Eye/face protection

Face shield (8 inch minimum) and safety glasses or safety goggles. Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166 (EU). Contact lenses should not be worn; they may contribute to severe eye injury.

Skin protection

Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands. The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.

Full contact

Material:	Nature latex/chloroprene
Minimum layer thickness:	0.6 mm
Break through time:	480 min
Material tested:	Lapren® (KCL 706 / Aldrich Z677558, Size M)

Splash contact

Material:	Nitrile rubber
Minimum layer thickness:	0.11 mm
Break through time:	30 min
Material tested:	Dermatril® (KCL 740 / Aldrich Z677272, Size M)

data source: KCL GmbH, D-36124 Eichenzell, phone +49 (0)6659 87300, e-mail sales@kcl.de, test method: EN374

If used in solution, or mixed with other substances, and under conditions which differ from EN 374, contact the supplier of the CE approved gloves.

Body Protection

Chemical spray smock and long sleeve flame retardant antistatic protective clothing suit composed of Nitrile, Silvershield, PVC, Neoprene, and butyl rubber fabric is highly recommended, having break through times greater than one hour. The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection

Where risk assessment shows air-purifying respirators are appropriate use a full-face respirator with multipurpose combination (US) or type ABEK (EN 14387) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Respirator Recommendations: At concentrations above the NIOSH REL, or where there is no REL, at any detectable concentration

Assigned Protection Factor (APF)	Respirator Recommendations
APF = 10,000	Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode.
APF = 10,000	Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained positive-pressure breathing apparatus.

Hygiene measures

Eye wash bottles or eye wash stations in compliance with applicable standards. Take off contaminated clothing and shoes immediately. Handle in accordance with good industrial hygiene and safety practice.

9 Physical and chemical properties

Physical and chemical properties

Appearance / physical state / colour @ at 20 °C and 1013 hPa:	Inorganic, colourless, oily liquid, which fumes at air and has a penetrating odor resembling that of ammonia
Melting point / freezing point @ 101 325 Pa:	-51.7 °C
Boiling point @ 101 325 Pa:	At ambient pressure (1013 hPa) hydrazine hydrate has a boiling point of 120 °C
Density @ 25 °C:	1.03 g/cm³
Particle size distribution (Granulometry):	study scientifically not necessary
Vapour pressure @ 25 °C:	12 hPa

Partition coefficient @ 20 °C:	logPow of -0.16
Water solubility:	completely miscible with water
Solubility in organic solvents / fat solubility:	Miscible with water as well as methyl, ethyl, propyl and isobutyl alcohols
Surface tension @ 25 °C:	74.0 mN/m
Flash point:	The flash point of hydrazine accounts for 38 °C (NIOSH, 1995). No exact flash point could be determined for hydrazine hydrate (Currenta, 2010).
Auto flammability @ 1 001 hPa:	290 °C
Flammability:	flammable
Explosiveness:	non explosive
Oxidising properties:	No
Oxidation reduction potential:	Not applicable
Stability in organic solvents and identity of relevant degradation products:	Not required. Substance is inorganic
Storage stability and reactivity towards container material:	No data
Stability: thermal, sunlight, metals:	Self Accelerating Decomposition Temperature of greater than 75 °C
pH:	12,75
Dissociation constant pKa @ 20 °C:	6.05
Viscosity @ 25 °C:	1.5 mPa*s
Ionization Potential:	8.93 eV
Odor Threshold:	160 mg/L
Refractive Index:	.46979 at 22.3 deg C/D 1.46444 at 35 deg C/D

NOTE: The physical data presented above are typical values and should not be construed as a specification.

10 Stability and reactivity

Reactivity

HYDRAZINE is a powerful reducing agent. May ignite spontaneously if mixed with hydrogen peroxide or with nitric acid. Decomposes with flame on contact with many metallic oxide surfaces [Haz. Chem. Data(1966)]. While boiling a piece of polyester fiber in hydrazine in a glass beaker, a technician put a somewhat rusty pair of metal tweezers into the hydrazine, which then ignited [MCA Case History 1893 (1973)]. Forms explosive metal hydrazides when mixed with alkali metals in presence of ammonia [Mellor 8, Supp. 2:95(1967)]. During the measurement of the shock sensitivity of a mixture containing hydrazine, a drop of the mixture fell on a tetryl explosive. The tetryl immediately burst into flames [ASESB 105]. Ignites spontaneously if mixed with nitrous oxide [Mellor 8, Supp. 2:214(1967)]. Reacts explosively with potassium and sodium dichromate [Mellor 11:234(1946-1947)].

HYDRAZINE, AQUEOUS SOLUTION, WITH NOT LESS THAN 37% BUT NOT MORE THAN 64% HYDRAZINE is a reducing agent (reacts with oxidizing agents) and a strong base. Dissolution in water moderates the reactivity of hydrazine. Neutralizes acids in exothermic reactions to give water and salts. Salts from neutralization of oxidizing acids are sometimes explosive when dried. Attacks glass (slowly) and rubber and cork [Merck]. A 64% solution of hydrazine in water corresponds to the chemical composition hydrazine hydrate ($N_2H_4.H_2O$).

AQUEOUS SOLUTIONS OF HYDRAZINE WITH NOT MORE THAN 37% HYDRAZINE are reducing agents (react with oxidizing agents) and chemical bases (react with acids to generate heat). Dissolution in water moderates the reactivity of hydrazine.

Chemical stability

Air and Water Reactions

Fumes in air. Highly flammable. Can self-ignite at low temperatures if in contact with a catalyst (example: autoignition temperature is 74°F in contact with rust). May ignite spontaneously while absorbed on porous materials such as earth, asbestos, cloth, or wood unless the heat of the continual hydrazine-air reaction has a chance to dissipate [Haz. Chem. Data(1966)]. Water soluble.

Reactive Group
Azo, Diazo, Azido, Hydrazine, and Azide Compounds. Bases, Strong

Reactivity Alerts
Highly Flammable. Strong Reducing Agent. Air-Reactive.

Possibility of hazardous reactions

Under normal conditions of storage and use, hazardous reactions will not occur.

Conditions to avoid

Contact with strong oxidising agents may cause hazardous reactions. Keep away from heavy metals, metals and their salts. Contact with cellulose or cotton textiles, especially at elevated temperatures, may result in ignition.

Incompatible materials

Reactive or incompatible with the following materials: acids.

Hazardous decomposition products

Ammonia, hydrogen. Under normal conditions of storage.

11 Toxicological information

Toxicological (health) effects

Test Type	Route	Dose	Effect	Reference
Rat				
LD_{50}	oral	60 mg/kg (60 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
LC_{50}	inhalation	570 ppm/4H (570 mg/kg)	SENSE ORGANS AND SPECIAL SENSES: OTHER: EYE	
LD_{50}	intraperitoneal	59 mg/kg (59 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
LD_{50}	intravenous	55 mg/kg (55 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
LD_{50}	intramuscular	53500 ug/kg (53.5 mg/kg)		Gigiena i Sanitariya. For English translation, see HYSAAV., 16(6)(53), 1972
Mouse				
LD_{50}	oral	59 mg/kg (59 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
LC_{50}	inhalation	252 ppm/4H (252 mg/kg)	SENSE ORGANS AND SPECIAL SENSES: OTHER: EYE	
LD_{50}	intraperitoneal	62 mg/kg (62 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
LD_{50}	intravenous	57 mg/kg (57 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
LD_{50}	unreported	200 mg/kg (200 mg/kg)		British Journal of Cancer., 6(160), 1952 [PMID:14954086]
Dog				
LDL_o	skin	96 mg/kg (96 mg/kg)		Toxicology and Applied Pharmacology., 21(186), 1972 [PMID:5023832]
LD_{50}	intravenous	25 mg/kg (25 mg/kg)		Medycyna Pracy. Industrial Medicine., 24(71), 1973
		16500 ug/kg		Gigiena i Sanitariya. For English translation, see HYSAAV.,

LD_{50}	intramuscular	(16.5 mg/kg)		16(6)(53), 1972
Rabbit				
LD_{50}	skin	91 mg/kg (91 mg/kg)		AMA Archives of Industrial Hygiene and Occupational Medicine., 9(199), 1954
LD_{50}	intravenous	20 mg/kg (20 mg/kg)		AMA Archives of Industrial Hygiene and Occupational Medicine., 9(199), 1954
LD_{50}	intramuscular	38500 ug/kg (38.5 mg/kg)		Gigiena i Sanitariya. For English translation, see HYSAAV., 16(6)(53), 1972
Guinea pig				
LD_{50}	skin	190 mg/kg (190 mg/kg)	BEHAVIORAL: CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD	U.S. Army Chemical Warfare Laboratories., CWL

Information on the likely routes of exposure

Workers - Hazard via inhalation route
Systemic effects
Long term exposure
Hazard assessment conclusion: high hazard (no threshold derived)
Acute/short term exposure
Hazard assessment conclusion: high hazard (no threshold derived)
Local effects
Long term exposure
Hazard assessment conclusion: high hazard (no threshold derived)
Acute/short term exposure
Hazard assessment conclusion: high hazard (no threshold derived)

Workers - Hazard via dermal route
Systemic effects
Long term exposure
Hazard assessment conclusion: high hazard (no threshold derived)
Acute/short term exposure
Hazard assessment conclusion: high hazard (no threshold derived)
Local effects
Long term exposure
Hazard assessment conclusion: high hazard (no threshold derived)
Acute/short term exposure
Hazard assessment conclusion: high hazard (no threshold derived)

Workers - Hazard for the eyes
Local effects
Hazard assessment conclusion: high hazard (no threshold derived)

Additional information - workers
Hydrazine (CAS 302-01-2)_Hazard assessment conclusion
WORKER
Actual EU Regulation:
According to DIRECTIVE (EU) 2017/2398 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2017 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work the binding limit value for occupational exposure is 0.013 mg/m³.

The Binding Limit Value is 0.013 mg/m³ whereas the LOAEC for irritation at the respiratory tract based on the available data is 0.066 mg/m³ (MacEwen 1981, Vernot 1985) and therefore higher than the Binding Limit Value. By that, even if there are uncertainties regarding the no effect level for irritation it is assumed that the Binding Limit Value covers also the aspect of non-neoplastic lesions including local irritation."

SCOEL 2016
Based on the assessment of SCOEL (2016), "the relevant toxicological endpoint for hydrazine is carcinogenicity. In addition, it is a potent contact sensitizer; allergic contact eczema caused by hydrazine has been described in numerous publications from different branches of industry. Evidence on respiratory sensitization is lacking".

Inhalation hazard:
"When tested by oral administration, it has produced mainly lung and liver tumors in rats, mice and hamsters. The most useful information comes from the long-term inhalation studies in rodents, 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 tumors in all groups. A subsequent inhalation study in rats, mice, dogs and hamsters (6h/d; 5d/wk at 0.05 ppm [rats, mice], 0.25, 1.0 ppm and 5 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 tumors at 1 and 5 ppm in rats. At 0.05 ppm, the incidence of nasal tumors in rats was slightly, but not significantly, higher than in 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.

While there is sufficient evidence of carcinogenicity in animals, the evidence of hydrazine carcinogenicity in humans has been recently evaluated as being limited. There are some data available on the carcinogenic effect in exposed aerospace workers, in particular to an increased risk of lung cancer. This would be compatible with the aforementioned experimental data from experimental animals.

Hydrazine has been characterised as genotoxic. 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.

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. 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. In this situation, the derivation of a health-based OEL is not possible at the present time. Therefore, SCOEL has decided to perform a dose-response analysis of the data on upper respiratory tract tumors from a long-term inhalation study of hydrazine in rats, mice, hamsters and dogs and derive risk numbers".

"Derived Limit Values/dose-response analysis (SCOEL 2016)
The long term inhalation study of hydrazine in rats, mice, hamsters and dogs demonstrated that the nasal epithelium of rats and hamsters was most sensitive to the tumorigenic activity of hydrazine following inhalation exposure. Especially the data on neoplastic lesions in male and female rats were suitable for dose-response modelling. BMD modeling of the neoplastic lesions observed in male and female rats revealed BMD10 values for malignant neoplasms which varied between 5.67 and 22.33 ppm. Based on these data it was concluded that a BMD10 of 5.67 ppm (corresponding to 7.6 mg/m^3), based on malignant thyroid tumors, would provide an adequate point of departure for definition of risk numbers.

Using this value the following risk numbers were derived:
A tumor risk of 1 : 10 at 7.6 mg/m3 (equal to 5.67 ppm)
A tumor risk of 1 : 1000 at 76 µg/m3 (equal to 0.057 ppm)
A tumor risk of 1 : 10 000 at 7.6 µg/m3 (equal to 0.0057 ppm)
A tumor risk of 1 : 106 at 0.08 µg/m3 (equal to 0.000057 ppm)

Skin notation
The available data on skin absorption and systemic effects seen in animals following dermal contact warrant a "skin notation"."

SCOEL 2016:
In the report of SCOEL (2016) (SCOEL/REC/164 – Hydrazine – Recommendation from the scientific committee on occupational Exposure limits (Sept. 2016) " 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. In this situation, the derivation of a health-based OEL is not possible at the present time".

"EXISTING OCCUPATIONAL EXPOSURE LIMITS (SCOEL 2016)
OEL's do exist in various EU Member States as well as outside the EU due to national regulations. These OEL's are

presented in the following table as examples and the list should not be considered as exhaustive (SCOEL/REC/164 – Hydrazine – Recommendation from the scientific committee on occupational Exposure limits (Sept. 2016)".

Overview of existing OELs for hydrazine

EU	TWA (8 hrs)		STEL (15 min)		Remarks	References
	ppm	mg/m³	ppm	mg/m³		
Austria	0.1	0.13	0.4	0.52	TRK, i.e. TMW and KZW, skin not.	AU GKV (2011)
Belgium	0.01	0.013			8 hrs TGG (TWA), skin not.	BE KB (2014)
Denmark	0.01	0.013	0.02	0.026		DK DWEA (2011)
Germany (AGS)	0.017$ 0.0017&	0.022$ 0.0022&			4:1000 risk number (draft) 4:10000 risk number (draft)	DE BAUA (2016)
Finland	0.1	0.13	0.3	0.4		FI MSAH 2012
France	0.1	0.1				FR INRF (2012)
Hungary				0.13		HU MHSFA (2000)
Ireland	0.01	0.01				IE HSA (2016)
Latvia		0.1				DE IFA (2015)
Norway	0.01	0.01				NO NLIA (2011)
Spain	0.01	0.13			inhalable aerosol	ES INSHT (2011)
UK	0.02	0.03	0.1	0.013	TWA	UK HSE (2011)

- STEL = Short Term Exposure Limit (usually 15 minutes average).
- TGG [TijdGewogen Gemiddelde] = TWA.
- TMW [Tagesmittelwer] = TWA; KZW [Kurzzeitwert] = STEL.
- TRK [Technische RichtKonzentration] = indicative concentration. Used when no 'safe' exposure level can be derived. Value based on technical feasibility.
- TWA = Time-Weighted Average (usually 8 hours average).
- TWAEV = Time-Weighted Average Exposure Value = TWA.
- VME [Valeur Moyenne d'Exposition] = TWA.
- $ Workplace exposure concentration corresponding to the proposed tolerable cancer risk.
- & Workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk.

Hazard assessment conclusion

Under Regulation No. 1272/2008 (GHS) the substance is classified in Carcinogenicity Class 1B; Hazard Statement H350: May cause cancer.

The derivation of a valid health-based DNEL /DMEL is not possible based on the available studies.

According to ECHA Guidance on information requirements and chemical safety assessment Part E: Risk characterization (May 2016) in cases 'when neither a DMEL nor a DNEL can be set for a carcinogen, because no suitable (semi-)quantitative animal or human data are available to establish relevant dose descriptors. In such circumstances, a qualitative assessment should be performed. Carcinogens classified in Category 1A and 1B, are allocated to the high hazard band on the basis that exposure to such substances should be strictly contained because they may cause serious health effects based on sufficient evidence of carcinogenicity derived from human or animal data and for which a dose threshold is not usually identifiable for many of these carcinogens. Non-genotoxic carcinogens which are classified in Category 2 in CLP are in principle allocated to the moderate hazard band, because they are regarded to represent a lower concern than Category 1A and 1B carcinogens according to CLP as there may be only limited evidence of carcinogenicity based on human or animal data. On the other hand, if the mode of action or carcinogenic potency remains unclear then these Category 2 carcinogens according to CLP could be assigned to the high hazard band, on a case by case basis'.

Due to the classification as Carc. 1B (H350) under Regulation No. 1272/2008 (GHS) an allocation of hydrazine to the high

hazard band for the hazard via inhalation and dermal route (systemic and local effects for long term and short term exposure) seems justified.

'With the strict control needed for mutagens (Cat 1A, 1B or 2 in CLP) and carcinogens classified in Category 1A, 1B or in Category 2 if potent, according to CLP, the RMMs/OCs aimed at avoidance of exposure will likely be sufficient to also cover for other relevant effects for which DNELs can be derived, for all routes of exposure. In that case, a qualitative risk characterisation will suffice, and there is no need to conduct a quantitative risk characterisation' (ECHA Guidance on information requirements and chemical safety assessment Part E: Risk characterization (May 2016).

Overall Conclusion:
The derivation of a valid health-based DNEL /DMEL is not possible based on the available studies. Based on the assessment of SCOEL (2016), the relevant systemic toxicological endpoint for hydrazine is carcinogenicity. Under Regulation No. 1272/2008 (GHS) the substance is classified in Carcinogenicity Class 1B; Hazard Statement H350: May cause cancer.

According to ECHA Guidance on information requirements and chemical safety assessment Part E: Risk characterization (May 2016) in cases 'when neither a DMEL nor a DNEL can be set for a carcinogen, a qualitative assessment should be performed. Carcinogens classified in Category 1A and 1B, are allocated to the high hazard band.

According to DIRECTIVE (EU) 2017/2398 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2017 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work the binding limit value for occupational exposure is 0.013 mg/m³.

Dermal hazard:
DNEL (short term)
Hydrazine is a caustic, fuming hygroscopic liquid at ordinary temperature and pressure (WHO1987).

There is no repeated dose toxicity study available using the dermal route.

According to SCOEL 2016 absorption via the skin is likely "Skin notation: The available data on skin absorption and systemic effects seen in animals following dermal contact warrant a "skin notation"."

According to ECHA Guidance on information requirements and chemical safety assessment Part E: Risk characterization (May 2016) in cases 'when neither a DMEL nor a DNEL can be set for a carcinogen, a qualitative assessment should be performed. Carcinogens classified in Category 1A and 1B, are allocated to the high hazard band.

Reproduction Toxicity
Fertility
There is no 2-generation toxicity study available.

For estimation the likelihood of the impairment of fertility the available Screening Reproductive Toxicity study can be taken as surrogate. After oral intake the resulting NOAEL (male fertility) is 11.52 mg/kg bw/day, NOAEL (female fertility) is 3.84 mg/kg bw/day, calculated in terms of hydrazine unaqueous.

In a subacute toxicity study according to OECD TG 407 hydrazine monohydrate was administered to male and female Crj:CD(SD)IGS rats by gavage at dose levels of 0, 1, 3, 10, 30 mg/kg bw/day. The NOAEL is 3 mg hydrazine monohydrate/kg bw/day for male and female rats based on changes in hematology, blood chemistry and absolute and relative weight increase in liver, spleen and kidneys and histopathologically fatty change of hepatocytes starting at 10 mg/kg.

Since these NOAELs are higher than the NOAEL for the oral repeated dose toxicity, it can be assumed that hydrazine is not a reproductive toxicant.

Developmental toxicity
Considering the available study on developmental toxicity in rats (i.p.: 2.5-10 mg/kg bw, gd 9-16) developmental toxicity occurs only in the presence of maternal toxicity NOAEL (maternal) 2.5 mg/kg bw/day and it can be concluded that hydrazine is not a reproductive toxicant.

General Population - Hazard via inhalation route
Systemic effects
Long term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Acute/short term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Explanation for the modification of the dose descriptor starting point:

Hazard described in the worker section. No exposure to general population.

Local effects

Long term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Acute/short term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

General Population - Hazard via dermal route

Systemic effects

Long term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Explanation for the modification of the dose descriptor starting point:

Hazard described in the worker section. No exposure to general population.

Acute/short term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Local effects

Long term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Acute/short term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

General Population - Hazard via oral route

Systemic effects

Long term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Acute/short term exposure

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

General Population - Hazard for the eyes

Local effects

Hazard assessment conclusion: hazard unknown but no further hazard information necessary as no exposure expected

Additional information - General Population

The substance is not used in the public domain and exposure of consumers is thus not to be expected.

Symptoms related to the physical, chemical and toxicological characteristics

Symptoms

Irritation eyes, skin, nose, throat; temporary blindness; dizziness, nausea; dermatitis; eye, skin burns; In Animals: bronchitis, pulmonary edema; liver, kidney damage; convulsions; [potential occupational carcinogen]

Inhalation Symptoms

Cough. Burning sensation. Headache. Confusion. Drowsiness. Nausea. Shortness of breath. Convulsions. Unconsciousness.

Skin Symptoms

MAY BE ABSORBED! Redness. Pain. Skin burns.

Eye Symptoms
Redness. Pain. Blurred vision. Severe burns.

Ingestion Symptoms
Burns in mouth and throat. Abdominal pain. Diarrhoea. Vomiting. Shock or collapse. Further see Inhalation.

Target Organs
Hepatic (Liver), Respiratory (From the Nose to the Lungs). Eyes, skin, respiratory system, central nervous system, liver, kidneys

Cancer Sites
In animals: tumors of the lungs, liver, blood vessels & intestine.

Delayed and immediate effects and also chronic effects from short and long term exposure

HUMAN STUDIES
Skin contact with anhydrous hydrazine leads to caustic-like burns and dissolves hair. Allergic contact dermatitis has been reported. Exposure to the eyes can produce temporary blindness. Liquid splashes to the eyes can produce corneal injury and burns. In cases of acute human poisoning, vomiting, severe irritation of the respiratory tract with the development of pulmonary edema, central nervous system depression, and hepatic and renal damage have been reported. Allergic contact dermatitis has been reported. Exposure to hydrazine increases the risk of incident lung cancers and colon cancers, based on a study in a cohort of aerospace workers.

ANIMAL STUDIES
Hydrazine hydrate produced moderately severe irritation when 3 to 5 mL was applied to rabbit cornea, whereas 1 mL was much less irritating. Rabbit skin that was treated with 3 mL of anhydrous hydrazine for 1 min, followed by washing the treated area. Despite washing, mortality ensued 60 to 90 min after application. Acute toxicity has been characterized by liver damage consisting of fatty degeneration, red blood cell destruction and anemia, anorexia, weight loss, weakness, vomiting, excitability, hypoglycemia, and convulsions. Groups of dogs, monkeys, rats, and mice were exposed either 24 hr/day, 7 days/wk to 6.2 or 1 ppm, or 6 hr/day, 5 days/wk to 1 or 5 ppm hydrazine for 6 months. Mortality was seen in mice and dogs, but not in monkeys or rats. Dogs showed hematologic deficits and increased numbers of reticulocytes. Liver changes that consisted of moderate to severe fatty infiltration were marked in mice and dogs, were slight to moderate in monkeys, and were absent in the rat. Groups of rats were exposed orally during gestation to 8 mg/kg bw hydrazine. 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. An increase in the number of lung tumors was observed in several strains of mice, but hydrazine did not increase the tumor yield in rats following either sc injection or intratracheal application. Hydrazine is positive in most standard assays for genetic toxicity endpoints.

ECOTOXICITY STUDIES
Eggs of fathead minnows (Pimephales promelas) at the mid-cleavage stage were exposed to hydrazine for 24 or 48 hr. Embryos, exposed for 24 hr, to 0.1 mg/L, showed several defects, such as slightly or moderately subnormal heart beat, hemoglobin levels, body movement, and amount of eye pigment. Embryos exposed to a hydrazine concentration of 1.0 mg/L for 48 hr appeared to have little chance of survival. Surviving embryos showed severe deformities and larvae exhibited reduced growth.

Human Toxicity Excerpts
Signs and Symptoms
Skin contact with anhydrous hydrazine leads to caustic-like burns and dissolves hair.

In cases of acute human poisoning, vomiting, severe irritation of the respiratory tract with the development of pulmonary edema, central nervous system depression, and hepatic and renal damage have been reported.

Toxic effects of hydrazine routes not specified include conjunctivitis, pulmonary edema, anemia (hemolytic), ataxia, convulsions, kidney toxicity, and liver toxicity.

Skin and eye irritation has occurred in humans, and allergic contact dermatitis has been reported. 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.

Exposure to the eyes can produce temporary blindness. Acutely breathing the vapors will cause intense irritation of the mucous membranes and lungs and can cause nausea, vomiting, and dizziness. Higher vapor concentrations can produce tremors, seizures, and comas with hemolysis. Liquid splashes to the eyes can produce corneal injury and burns, whereas splashes to the skin can produce severe burns, dermatitis, and skin sensitization.

Vomiting, weakness, and irregular breathing, with recovery in 5 days, occurred following ingestion of 20-30 mL of a 6% aqueous solution.

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.

Case Reports

Hydrazine (N(2)H(4)) is a clear, inorganic colourless liquid. It is known to be a skin sensitizer, a corrosive agent and it causes dermatitis on contact. Hydrazine is employed in chemical plants, used as a corrosion inhibitor for feed waters and may be added to rocket fuels. The authors report the case of a 68-year-old man with multiple basal cell carcinomas (BCCs) covering his arms and face. The patient worked in a steam power plant with extensive exposure to hydrazine for a period of over 10 years.

Hydrazine is a hazardous chemical commonly used as a reactant in rocket and jet fuel cells. Animal studies have demonstrated hepatic changes after hydrazine inhalation. Human case reports of hydrazine inhalation hepatotoxicity are rare. We report a case of mild hepatotoxicity following brief hydrazine vapor inhalation in a healthy young man, which resolved completely on expectant management.

A case of residual neurobehavioral impairment possibly related to occupational exposure to hydrazine was described. A 38 year old Israeli male was treated for repeated complaints of sore throat and colds. His wife noticed that he had difficulties remembering things that she had asked him to do. He became impotent. He had similar difficulties at work in performing tasks that he had previously done effortlessly. He had been employed as a water technician at a hospital for 7 years. His job activities involved monitoring water quality, adding hydrazine mixtures when necessary, and overseeing the workings of the hospital pumping system. He had intense intermittent inhalation and skin exposure to hydrazine while mixing and pouring hydrazine preparations, and almost constant inhalation exposure to hydrazine vapors in his workplace. He developed thrombocytopenia which was treated with steroids. He returned briefly to work, but had to be discharged because of recurring episodes of colds and malaise. His memory and concentration problems persisted and he became unable to work or understand and remember material he had read. Neuropsychological testing revealed deficits in specific task performance, memory, concentration, learning, judgment, and abstraction and mood problems. A computed tomographic examination showed no signs of brain damage. Over the next 4 years the patient showed a gradual improvement in his general well being, mood status, and ability to carry out some tasks. He was unable to hold down jobs or perform tasks commensurate with his previous level of technical and organizational skills. He eventually found work as a part time gardener. It was concluded that exposure to hydrazine during his work as a water technician is the most likely explanation for the neurobehavioral impairment. The case illustrates the need to be aware that exposure to hydrazine can cause neurobehavioral problems as sequelae.

A case of an epithelioid sarcoma developing in the thumb of a patient after repeated exposure to hydrazine fuel is presented. The authors hypothesize that the epithelioid sarcoma is a consequence of cutaneous exposure to hydrazine fuel.

Choroidal melanoma was observed in one man who had been exposed to hydrazine for six years.

After a laboratory technician had drunk 20-30 mL of a 6% aqueous solution of hydrazine (free base), he immediately vomited. Four hours later, weakness, somnolence, and arrhythmia were observed. Laboratory findings showed a slight but persistent leukocytosis. The serum-albumin fraction was decreased with an increase in the urine noted, while the patient showed irregular breathing. Five days after exposure, the patient had recovered.

The case of a 24-yr-old man who accidentally ingested a mouthful of hydrazine successfully treated with megadoses of intravenous pyridoxine hydrochloride (vitamin B6) injection, 10 g over a few hr, who subsequently developed sensory polyneuropathy, is reported. The neuropathy spontaneously resolved over the next 6 months. It was concluded that although part of the peripheral neuropathy could have been due to hydrazine toxicity, the predominantly sensory

neuropathy with axonal degeneration and spontaneous recovery is due to pyridoxine hydrochloride (vitamin B6) induced peripheral neuropathy.

Contact dermatitis caused by hydrazine was reported in two patients who worked in a gold plating factory. The workers wore gloves when carrying baskets between the different plating baths, but they had frequent spills over their hands and arms and were exposed to the vapor. The first case was a 54 year old man who worked for 20 years in the plating industry. After three weeks in the gold plating department the worker developed a recurrent hand eczema. It was located on the dorsal side of the hands and spread to the forearms. The patient recovered completely after changing his work responsibilities. The second case was a 23 year old worker in the same gold plating department who developed periorbital eczema four months after starting work in the gold plating department. The worker recovered completely after changing the working environment. The standard ICORG test procedures was used in performing the patch testing. In both workers, 1% hydrazine sulfate, and 1 and 10% gold plating stabilizer gave positive epicutaneous test reactions and potassium dicyanoaurate gave a negative reaction. Observations indicated that there was evidence that hydrazine in the gold plating baths caused the dermatitis.

A man sustained severe chemical burns (involving 22% of the body surface) following a hydrazine explosion. After a comatose period and with biochemical indicators of liver malfunction, recovery was seen in 5 weeks.

Epidemiology Studies

Animal studies suggest that hydrazine is a lung carcinogen, but human studies have been rare, rather small, and limited to cancer mortality. We examined cancer mortality and incidence in a cohort of aerospace workers with varying exposure to hydrazine contained in rocket fuels-extending previous mortality follow-up from 1994 to 2001 and investigating cancer incidence for the period 1988-2000 using population-registry data. We newly estimated hydrazine effects adjusting for occupational exposures to other carcinogens 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. Exposure to hydrazine was 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 small numbers rendering our analyses uninformative, and patterns considering exposure levels and lags were inconsistent. Use of random-effect models did not change our results. The findings reported here are consistent with our previous results for lung cancer mortality; our new results suggest that exposure to hydrazine increases the risk of incident lung cancers. We also found an increased risk of colon cancers. Results for other cancer sites are inconclusive.

Hydrazine is carcinogenic in animals, but there is inadequate evidence to determine if it is carcinogenic in humans. This study aimed to evaluate the association between hydrazine exposure and the risk of lung cancer. The cause specific mortality rates of a cohort of 427 men who were employed at an English factory that produced hydrazine between 1945 and 1971 were compared with national mortality rates. By the end of December 2012 205 deaths had occurred. For men in the highest exposure category with greater than two years exposure and after more than ten years since first exposure the relative risks compared with national rates were: 0.85 (95% CI: 0.18-2.48) for lung cancer, 0.61 (95% CI: 0.07-2.21) for cancers of the digestive system, and 0.44 (95% CI: 0.05-1.57) for other cancers. After 50 years of follow up, the results provide no evidence of an increased risk of death from lung cancer or death from any other cause.

Hydrazine was produced at a factory in the East Midlands of the United Kingdom between 1945 and 1971. The cohort of all 427 men who were employed there for at least six months with varying degrees of occupational exposure to hydrazine was followed up until the end of January 1992. By the end of July 1982 49 deaths had occurred and the observed mortality was close to that expected at each level of exposure. By the end of January 1992 a further 37 deaths had occurred. Again the observed mortality was close to that expected for all causes and also for lung cancer, cancers of the digestive system, other cancers, and all other causes, respective of the level of exposure. The results weigh against their having been any material hazard of occupational exposure to hydrazine. The small number of men studied means, however, that a relative risk as high as 3.5 for lung cancer cannot confidently be excluded.

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).

Non-Human Toxicity Excerpts

Laboratory Animals Acute Exposure

Hydrazine is a model toxin that induces both hepatotoxic and neurotoxic effects in experimental animals. The direct biochemical effects of hydrazine in kidney, liver, and brain tissue were assessed in male Sprague-Dawley rats using magic angle spinning nuclear magnetic resonance (NMR) spectroscopy. A single dose of hydrazine (90 mg/kg) resulted in changes to the biochemical composition of the liver after 24 hr including an increase in triglycerides and beta-alanine, together with a decrease in hepatic glycogen, glucose, choline, taurine, and trimethylamine-N-oxide (TMAO). From histopathology measurements of liver tissue, minimal to mild hepatocyte alteration was observed in all animals at 24 hr. The NMR spectra of the renal cortex at 24 hr after dosing were dominated by a marked increase in the tissue concentration of 2-aminoadipate (2-AA) and beta-alanine, concomitant with depletions in TMAO, myo-inositol, choline, taurine, glutamate, and lysine. No alteration to the NMR spectral profile of the substantia nigra was observed after hydrazine administration, but perturbations to the relative concentrations of creatine, aspartate, myo-inositol, and N-acetyl aspartate were apparent in the hippocampus of hydrazine-treated animals at 24 hr postdose. No overt signs of histopathological toxicity were observed in either the kidney or the brain regions examined. Elevated alanine levels were observed in all tissues indicative of a general inhibition of alanine transaminase activity. By 168 hr postdose, NMR spectral profiles of treated rats appeared similar to those of matched controls for all tissue types indicative of recovery from toxic insult.

A single dose of hydrazine (3 mg/kg ip) caused hepatic accumulation of triglycerides and depletion of ATP in rats after 9 hr.

Hydrazine hydrate produced moderately severe irritation when 3 to 5 mL was applied to rabbit cornea; 1 mL was much less irritating.

Rabbit skin that was treated with 3 mL of anhydrous hydrazine for 1 min, followed by washing the treated area; despite washing, mortality ensued 60 to 90 min after application. Acute toxicity has been characterized by liver damage consisting of fatty degeneration, red blood cell destruction and anemia, anorexia, weight loss, weakness, vomiting, excitability, hypoglycemia, and convulsions.

In rats, a dose of 20 mg/kg caused accumulation of lipid, swelling of mitochondria and appearance of microbodies in periportal and midzonal hepatocytes and in proximal tubular cells of kidney. Pretreatment with phenobarbital or piperonyl butoxide, respectively, reduced and increased severity of fatty liver.

The systemic biochemical effects of oral hydrazine administration (dosed at 75, 90, and 120 mg/kg) have been investigated in male Han Wistar rats using metabonomic analysis of (1)H NMR spectra of urine and plasma, conventional clinical chemistry, and liver histopathology. Plasma samples were collected both pre- and 24 h postdose, while urine was collected predose and daily over a 7 day postdose period. (1)H NMR spectra of the biofluids were analyzed visually and via pattern recognition using principal component analysis. The latter showed that there was a dose-dependent biochemical effect of hydrazine treatment on the levels of a range of low molecular weight compounds in urine and plasma, which was correlated with the severity of the hydrazine induced liver lesions. In plasma, increases in the levels of free glycine, alanine, isoleucine, valine, lysine, arginine, tyrosine, citrulline, 3-D-hydroxybutyrate, creatine, histidine, and threonine were observed. Urinary excretion of hippurate, citrate, succinate, 2-oxoglutarate, trimethylamine-N-oxide, fumarate and creatinine were decreased following hydrazine dosing, whereas taurine, creatine, threonine, N-methylnicotinic acid, tyrosine, beta-alanine, citrulline, N alpha-acetylcitrulline and argininosuccinate excretion was increased. Moreover, the most notable effect was the appearance in urine and plasma of 2-aminoadipate, which has previously been shown to lead to neurological effects in rats. High urinary levels of 2-aminoadipate may explain the hitherto poorly understood neurological effects of hydrazine. Metabonomic analysis of high-resolution (1)H NMR spectra of biofluids has provided a means of monitoring the progression of toxicity and recovery, while also allowing the identification of novel biomarkers of development and regression of the lesion.

The disposition and metabolism of hydrazine was studied in Sprague-Dawley-rats. Rats were treated with 3, 9, 27, or 81 mg/kg hydrazine-hydrate in water. Livers were removed for determination of toxicity and hydrazine levels after 4 days. After 4 days, animals treated with 81 mg/kg hydrazine lost more weight and drank less water overall, than controls. Histological examination of livers from animals treated with 27 and 81 mg/kg hydrazine demonstrated vacuolation, and intracellular fat droplets were identified in animals treated with the higher dose.

Injection of hydrazine (0.7 mmole/kg) in male fasting rats caused an increase in phosphatidate phosphohydrolase activity in the soluble fraction of the liver. The increased phosphatidate phosphohydrolase activity was parallel with a rise in hepatic triacylglycerol (3.5-fold) and in the catecholamine concentration (3.4-fold) in adrenal glands. Hydrazine also increased serum glucose. The hydrazine-induced increases in phosphatidate phosphohydrolase activity and triacylglycerol accumulation was completely prevented by adrenalectomy. The data suggest that increased phosphatidate

phosphohydrolase activity is at least partly responsible for hydrazine-induced fatty liver and that adrenal hormones may take part in the mechanism by which hydrazine exerts its effects on the liver.

LABORATORY ANIMALS: Subchronic Or Prechronic Exposure
Golden hamsters were administered hydrazine by gavage (60 and 100 daily doses, equivalent to 0.74 and 0.68 mg hydrazine over 15 and 20 weeks). Toxic effects in animals consisted of liver lesions, reticuloendothelial cell proliferation, cirrhosis, bile-duct proliferation, degenerative fibrous cells in hyalinized tissue.

In a 6-mo inhalation study, rats, mice, dogs, and monkeys were exposed continuously to hydrazine at 0.2 or 1 ppm or were exposed 6 hr/day, 5 days/wk at 1 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 mortalty 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/wk 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. Lethargy was seen during exposures, and lung and liver damage were detected in rats from all test groups.

Repeated oral exposure of rats to hydrazine (approximately equal to 2.5 mg/kg/day) for 10 days resulted in depletion of hepatic reduced glutathione and triglycerides. Repeated exposure to hydrazine also caused a significant (time dependent) induction of p-nitrophenol hydroxylase activity together with changes in other hepatic microsomal enzymes. These included 7-pentoxyresorufin O-deethylase and 7-ethoxyresorufin O-deethylase activity, total cytochrome p450, cytochrome b5 and cytochrome p450 reductase activity. Repeated exposure to lower levels of hydrazine (approximately equal to 0.250 mg/kg/day) caused no significant hepatic biochemical or microsomal changes after 5 or 10 days except for an increase in p-nitrophenol hydroxylase activity (17%) and liver ATP (15%) after 5 days.

LABORATORY ANIMALS: Chronic Exposure or Carcinogenicity
30 male and 30 female white mice were injected ip with 0.5 mg hydrazine in physiological saline. A total dose of 400 mg/kg body wt was given in 16 separate doses over 46 days. Of 13/34 survivors, 4 mice developed reticulum cell sarcomas of mediastinum and 9 developed myeloid leukemias within 100-313 days. Thymic lymphoma was observed in 1/60 control mice. An increase in the number of lung tumors was also observed in other strains of mice namely (BALB/c x DBA/2)F1 hybrid, C57Bl, SWR & BALB/C/CB/SE (newborn).

The carcinogenicity and chronic toxicity of hydrazine monohydrate was examined by administrating hydrazine monohydrate in drinking water to groups of 50 F344/DuCrj rats and 50 Crj:BDF1 mice of both sexes for two years. The drinking water concentration of hydrazine monohydrate was 0, 20, 40 or 80 ppm (wt/wt) for male and female rats and male mice; and 0, 40, 80 or 160 ppm for female mice. Survival rates of each group of males and females rats and mice were similar to the respective controls, except female rats administered 80 ppm. Two-year administration of hydrazine monohydrate produced an increase in the incidences of hepatocellular adenomas and carcinomas in rats of both sexes along with hepatic foci. In mice, the incidences of hepatocellular adenomas and carcinomas were increased in females, and significantly increased incidences of hepatocellular adenomas in females administered 160 ppm were observed. Thus, hydrazine monohydrate is carcinogenic in two species, rats and mice. Additionally, non-neoplastic renal lesions in rats and mice and non-neoplastic nasal lesions in mice were observed.

Hydrazine produced tumors in the mouse following ip injection but did not increase the tumor yield in rats following either sc injection or intratracheal application.

In mice exposed to hydrazine vapors for 6 months at 0.2, 1, or 5 ppm, there was an increased incidence of pulmonary tumors in all groups. 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 (rats and mice), 0.25 or 1.0 ppm (rats, mice, hamsters, and dogs), or 5.0 ppm (rats, hamsters, and dogs) for 1 yr and subsequently followed for their lifespan or 38 months. 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 at 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 effects or non-neoplastic effects were observed in dogs at any dose level.

A two phase study was conducted to assess the oncogenic potential of hydrazine in rats and hamsters exposed to hydrazine for repeated short or lifetime exposures and to investigate the acute and subchronic effects of hydrazine in relation to nasal tumorigenesis. Groups of male and female Fischer-344 rats and male Syrian Golden hamsters were exposed by inhalation to 750 ppm hydrazine for one (acute) or ten (subchronic) 1 hour weekly sessions, or to 75 ppm hydrazine in a lifetime exposure. The animals were killed at the end of the designated exposure period for a complete necropsy, histopathological evaluation, and morphological diagnosis of apoptosis. The regions of the nasal passages most severely affected by acute and subchronic hydrazine exposures included the lateral aspects of the naso and maxilloturbinates and the lateral wall in the anterior part of the nasal cavity. Degeneration and necrosis of the transitional, respiratory, and olfactory epithelia in the anterior nose were revealed by histopathologic examination after acute and subchronic exposures. Morphological diagnosis showed apoptosis in the olfactory and squamous metaplastic transitional epithelium. The squamous metaplastic transitional epithelium reverted back to normal seeming transitional epithelium by the end of 24 months. Low incidences of hyperplasia (2.6%) and neoplasia (5.7%) were detected after 24 months in rats exposed to 750 ppm hydrazine, and a similar trend was seen in hamsters. Because the distribution and severity of the lesion observed in the nasal mucosa of rats and hamsters in this study correlated well with reported inspiratory air flow patterns in the rat nasal passages, the authors suggest that hydrazine uptake as well as mucosal injury in these regions of the anterior nose was most likely enhanced by airflow patterns. The hyperplasias and polypoid adenomas seen in the hydrazine exposed groups appeared to be derived from the transitional epithelium of both rats and hamsters. Site specificity of these proliferative lesions correlated precisely with regions most severely affected by hydrazine in both acute and subchronic exposures.

Oral route

In the long-term drinking water study in rats under this particular severe experimental condition of exposure during the total lifetime, hydrazine induced increased liver tumours, at the highest the toxic - concentration of about 3 mg/kg bw/day (no effect at the next lower dose of 0.7 mg/kg bw/day). The majority of the liver tumours were benign thus demonstrating that hydrazine showed only a weak carcinogenic effect (Steinhoff 1988). In contrast, the 2 year drinking water study in mice revealed no increase in tumour incidence up to the highest dose tested (Steinhoff et al. 1990).
There are several publications discussing the mechanism of action of hydrazine in rat and mouse suggesting a dose-dependent increase in liver DNA methylation after single and repeated oral administration. In this context it is discussed that treatment with hydrazine disturb the balance of methylation and demethylation on N-7 and O-6 of guanine by inhibiting the demethylation which would result in accumulation of the methylated purines in the liver DNA (see also DFG 1989). Dose-response studies in rats revealed a single oral dose of 0.1 mg/kg as a starting dose for effects on liver DNA methylation (borderline effect, clear effects with 10 mg/kg; van Delft 1997; clear effect at 30 mg/kg; Becker et al. 1981). After the third of four oral doses of 3 mg/kg increase of 7-methylguanine was observed as trace and readily detectable after 4 treatments (Becker et al. 1981). Evidence of liver toxicity was shown at 2.5 mg/kg (exposure for 1-10 days; decrease of GSH, increase of triglycerides; Jenner & Timbrell 1992) and 3 mg/kg (3-4 doses; Becker et al. 1981). Therefore it is plausible that the liver tumours after long-term high dose exposure are secondary to liver toxicity and alteration of the balance of methylation and demethylation.

Inhalation route

In the above described inhalation study the local irritant, hydrazine, induced in hamsters and in rats, but not in mice, tumours only of the epithelium of the nasal cavity starting at 1.3 mg/m³. In contrast, the LOAEC in rats based on irritational effects in the nose, the larynx and trachea was much lower (0.066 mg/m³).As it is known that this tissue is highly sensitive to the local effects of carcinogens in rodents, it is difficult to extrapolate the results of this study to the human situation. It seems to provide evidence for a low carcinogenic potential of hydrazine (DFG 1989).

Dermal route

There are no data available using the dermal route.

Human information

There are epidemiological studies available investigating the association between hydrazine exposure and tumour development.(Cordier 1993, Ritz 1996). Although they are of limited validity (small numbers of participants, only estimated exposure information and the lack of discussion of confounding factors they did not reveal an indication of a causal association between human exposure to hydrazine and the development of cancer. Recently, Ritz (2006) published the results of an additional epidemiological study on the association between hydrazine exposure and lung cancer mortality in aerospace workers. Whereas this study of aerospace workers give some evidence of an association between hydrazine exposure and lung cancer mortality, a variety of limitations mentioned in the paper limits the overall evaluation and relevance for the assessment of hydrazine: at first, Ritz defined as "Hydrazine" a mixture of hydrazine, 1-methylhydrazine and 1,1 -dimethylhydrazine of unknown ratio. Most importantly, however, the exposure assessment is based on a job-

exposure matrix adjusted for other carcinogens e.g trichloroethylene but without specific measurements and potential confounding factors as e.g. smoking could only be partly included in the assessment. In the same cohort an association between mineral oil exposure and eg lung cancer risk was reported (Zhao et al (2005), Am J Indust Med 48, 249 -258). In contrast to this publication, in the meantime, data are available from the hydrazine producing industry (Arkema 2003) that show that under the circumstances of hydrazine production a limited epidemiological study do not reveal an indication of a carcinogenic response in humans under historic working conditons. These data are confirmed in a very recent follow-up study (Arkema 2014) which covers a longer follow-up period than the 2003 study and involves the integration of new workers into the cohort: no evidence of relationship between hydrazine exposure and cancer is observed.

Conclusion
Hydrazine is classified as animal carcinogen. Irrespective of this classification, the database is not fully conclusive regarding the mode of action that leads to the tumour response in animal studies, e.g. the carcinogenic effects of hydrazine have been shown only with maximally tolerated unambiguously toxic doses or locally irritating concentrations. Tumour responses are limited to the first site of contact in inhalation studies (nasal cavity) or the first organ of systemic availability after oral dosing (liver), respectively. Studies on the mode of action led to the conclusion that for the oral intake it is plausible that the liver tumours after long-term high dose exposure are secondary to liver toxicity and alteration of the balance of DNA methylation and demethylation. Regarding the local effects after inhalation exposure from the dose-response assessment (irritation threshold much lower than the concentration leading to tumours) it can be derived that that a direct cytotoxic mechanisms is most probably dominant.

Genotoxicity seems not to be a major cause for the tumour responses as for primary genotoxic carcinogens multiorgan tumour responses with a wide tissue distribution is typical, instead of a local first site of contact/first organ of systemic availability. Therefore, even if some role of genotoxicity at very high doses cannot be excluded, based on the available data the overall weight of evidence points to a non-genotoxic mechanism for the tumour responses in animal experiments. Local toxicity is regarded to be of main importance with tumour development as secondary response.

That reflection of the database led industry initially to propose to strengthen the database with a testing proposal to examine the irritation threshold after repeated inhalation with the aim to define the most sensitive level of the respiratory tract after repeated exposure, as well as the threshold for irritation after repeated exposure and on the respective dose-response relationship.

Based on responses received from the Competent Authorities that proposal was revised taking into consideration the following aspects:

- Within the activity of the EU Commission for an amendment of Directive 2004/37/EC on carcinogens and mutagens the proposal to set the 8hr TWA for Hydrazine (0.013 mg/m3) as a Binding Limit Value was agreed by the Advisory Committee on Safety and Health at Work (Opinion Doc. 2011/12).
- After implementation such a Binding Limit Value will be the corner stone for the risk management and it is expected that a more in depth knowledge on the Mode of Action most probably will not influence that Binding Limit Value.
- This view was supported by the responses from Member States to the testing proposal
- The scientific and regulatory value for further toxicological testing needs to be weighted with animal welfare considerations.

Based on these considerations the testing proposal for a short-term repeated dose toxicity study via the inhalation route was deleted."

Justification for selection of carcinogenicity via oral route endpoint:
Although individual animal data are not shown this is the only reliable study providing sufficient information to be worth to be mentioned

Justification for selection of carcinogenicity via inhalation route endpoint:
This is a reliable long term study using the most appropriate route of exposure and is therefore evaluated with Klimisch Score 2

Carcinogenicity: via inhalation route (target organ): respiratory: nose

LABORATORY ANIMALS: Developmental or Reproductive Toxicity
In rats and mice, hydrazine given orally produced adverse effects on fetuses and embryos at doses that were toxic for mothers. Adverse effects included increased resorptions, reduced fetal weight, increased perinatal mortality, increased

incidences of litters and fetuses with abnormalities in the 10 mg/kg bw group. In the offspring of Syrian golden hamsters subtle postnatal changes were observed after oral administration up to 170 mg hydrazine/kg bw on day 12 of gestation. Reproductive functions of rats (fertility of females, number of newborns, resorption of embryos) were not affected by administration of 13 mg hydrazine/kg bw for 30 days prior to mating.

Skeletal abnormalities were found in chicks after administration of 0.03 to 0.2 mg on the third day of incubation. Concentration of 0.002 mg/L was identified to be ineffective for reproduction /effects/ and teratogenicity in rats. Oral ingestion of hydrazine at a concentration of 0.82% in the diet resulted in marked embryotoxic and gonadotoxic effects in rats. Destruction of gonadal epithelium was observed in male rats.

A 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. 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 NOEL. Developmental delays, but no terata, were seen in the fetuses.

Mice were treated ip with 0, 4, 12, 20, 30, or 40 mg hydrazine (free base)/kg bw from day 6 though day 9 of gestation. 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, 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), no effects were seen in either maternal or fetal animals. The fetus appeared to be no more sensitive to the effects of hydrazine exposure than the maternal animal.

Use of murine spermatogenesis as a test system for hydrazine, monomethylhydrazine (MMH), and unsymmetrical dimethylhydrazine (UDMH) toxicities was investigated. BC3F1-mice were injected ip with 10% of the median lethal dose (LD50) of hydrazine, MMH, or UDMH for 5 days in time dependent studies. In dose dependent studies, mice were given UDMH at doses of 10, 25, 40, 55, or 70% of the LD50. At 0.8 and 3 weeks postexposure animals were sacrificed. The effects of 25 and 40% LD50 of MMH and 25% LD50 of hydrazine were determined 3.5 weeks after the insult. Body weight, testis to body weight ratios, hematocrits, histopathology of organs, and abnormal sperms were recorded. In the time studies, the percent of abnormally shaped sperm increased to a maximum of twice the control value for hydrazine and MMH. There was a 5 fold increase in abnormally shaped sperm with UDMH, followed by a rapid decrease to <1.5 times control values after 6 wk. Sperm number, testicular histology, and testis to body weight ratio did not change over the test period. For 5 weeks immediately after the end of exposure, mean body weight of each test group was less than controls. There was a clear response to increasing doses of UDMH in the percent of abnormally shaped sperm 3 weeks after exposure. There was no increase over the control percentages at 0.8 weeks. The percent of abnormally shaped sperm increased with increasing doses of MMH. The number of sperm produced with UDMH was reduced at the higher doses.

Eggs of the South African clawed toad in the cleavage were exposed to hydrazine until hatching. Survival and development into normal larvae occurred at exposures below 10 mg/L. At 10 mg/L, 35% of the embryos were malformed at hatching. The effect was dose-related. Additional studies revealed that teratogenic effects appeared during neurulation. When larvae of the South African clawed toad were exposed to 1.0 mg hydrazine/L water, for 120 hr, all died in 24-48 hr following exposure. No significant effects on survival and development were observed after exposure to 0.1 mg/L, the next lower concentration tested.

LABORATORY ANIMALS: GENOTOXICITY

Using mouse liver microsomal mutagenicity assay, hydrazine was mutagenic to 5 strains of Salmonella typhimurium.

Of the 10 chemicals tested for their abilities to produce novobiocin-resistant mutants in hemophilus influenzae, hydrazine was unique because it induced a high incidence of mutation without killing significant numbers of cells at concentrations tested. Hydrazine may be acting as both mutagen and antimutagen in this system.

Hydrazine is positive in most assays that evaluate genetic toxicity end points. The few negative studies reported generally involved in vivo tests, where the reactivity of the chemical may have prevented interaction with the active genetic component. Hydrazine-induced damage is not random in the DNA molecule and the neonate shows less DNA adduct formation at low doses, but higher levels of formation at high doses. Genetic activity of hydrazine was shown in Drosophila

mutagenicity assays.

Hydrazine is positive in most standard assays for genetic endpoints. It was positive in producing forward mutation in Bacillus subtilis, in plants, and in mammalian cells. Hydrazine produced a point mutation in the 61st codon column of H-ras gene in cultured newborn rat liver cells. Hydrazine produced reverse mutation in B. subtilis, fungi, and in the host-mediated assay in mice. It produced sex-linked recessive lethals in Drosophila and chromosomal breaks or aberrations in plant cells and animal cells. Although positive in one micronucleus test, hydrazine was inactive in two other assays for clastogenesis, in the production of nuclear aberrations following oral exposure to mice, or in increasing the yield of dominant lethals following ip injection in mice.

Previous work has demonstrated that hydrazine after formylation to its corresponding hydrazone may be activated both in vivo and in vitro to a methylating intermediate resulting in the formation of O6-methyl- and N7-methylguanines in DNA. The ability of 17 hydrazine derivatives to alkylate liver DNA was determined after single administration to young adult male Sprague-Dawley rats or C57BL6 mice. Quantifiable amounts of N7-methylguanine were measured in liver DNA from animals treated with 10 of the 17 compounds. In 3 of the 10 cases quantifiable amounts of O6-methylguanine were also measured. Methylation of liver DNA guanine was obtained with hydrazine, hydralazine, procarbazine, isoniazid, phenylhydrazine, nialamide, nitrofurazone, maleic hydrazide, sulfomethoxypyridazine, and sulfamethiazole and two hydrazine-formaldehyde polymerization products, formalazine and tetraformyltrisazine.

The genotoxicity of a variety of hydrazine derivatives was examined in the DNA repair test on rat or mouse hepatocytes. Out of 32 hydrazine derivatives, 6 chemicals, ie, N'-acetyl-4-(hydroxymethyl)phenylhydrazine, 1,2-dimethylhydrazine dihydrochloride, 1-hydrazinophthalazine hydrochloride, methylhydrazine.sulfate, p,p-oxybisbenzene disulfonylhydrazide and phenylhydrazine hydrochloride, elicited positive DNA repair responses in the test on rat hepatocytes. In the test on mouse hepatocytes, 4 more hydrazine derivatives, ie, 1,1-dimethylhydrazine, hydrazine hydrate, hydrazine sulfate and 2-methyl-4-chlorophenoxyacetic acid hydrazide hydrochloride also generated positive responses, in addition to the 6 positive compounds in the rat assay.

Administration of the hepatotoxin and carcinogen, inorganic hydrazine, to rodents results in the formation of 7-methylguanine and O6-methylguanine in liver DNA; co-administration of (methyl-(14)C)methionine or (14)C formate with the hydrazine labels the methylguanines, suggesting involvement of the 1-carbon pool in the methylation process.

Genotoxic activation of hydrazine (HZ) and two symmetrical dialkylhydrazines, namely, 1,2-dimethylhydrazine and 1,2-diethylhydrazine (SDMH and SDEH) have been evaluated by means of the w/w + somatic assay of Drosophila. Both low bioactivation insecticide-susceptible (IS) and high biotransformation insecticide-resistant (IR) strains were used. The combined application of insecticide-susceptible and insecticide-resistant strains should, in principle, detect somatic cell recombinagens in the Drosophila melanogaster in vivo w/w + assay. The IS strain was more susceptible to toxicity induced by the test chemicals than the IR stocks. Its performance in the biotransformation of the chemicals tested was rather poor. With the active compounds, spot frequencies increased approximately linearly with dose for each spot type. SDEH gave a strong positive result in all three female genotypes exposed. HZ, and SDMH were overall weakly positive in the IR strain Haag-79 (HG-R). A comparison of the recombinagenic potencies between the active and the weakly positive compounds, and among strains, showed pronounced genotype-dependent differences between the low and the high bioactivation strains.

GENOTOXICITY-DNA ADDUCTS

The neonatal rat, because of its relatively rapid rate of liver DNA replication without chemical or surgical induction, was used to assess the genotoxicity of the carcinogen hydrazine. Hydrazine is a more potent acute toxicant in the neonate than in the adult rat. Administration of hydrazine sc (1.5-50 mg/kg bw) to newborn rats during the period of rapid liver DNA synthesis, 72-96 hr after birth, resulted in the formation of 7-methylguanine and O6-methylguanine in hepatic DNA; O6-methylguanine was seen only in animals given near-lethal doses of the carcinogen. Methylguanines were detectable in liver DNA only when the dose of hydrazine was necrogenic, but lethal doses of hydrazine to neonates produced more methylguanines in liver DNA than in adult rats given equal doses. Southern analyses were performed on liver DNA from neonates treated with 25 or 50 mg hydrazine/kg, doses which were necrogenic to the liver. The results indicated that one or more MspI restriction sites (5'-C decreases CGG-3') were lost or blocked in liver DNA from hydrazine-treated animals and that these sites were located at or near the genes for gamma-glutamyl transpeptidase and cytochrome p450 IIBl. Restriction sites near albumin, H-ras, and cytochrome p450 IIEl genes cut by MspI, HpaII, or HhaI did not appear to be affected by hydrazine treatment. The results suggest that hydrazine-induced damage is not random in the DNA molecule. The neonate shows less DNA adduct formation at low doses of hydrazine, but higher levels at high doses.

The induction of liver DNA adducts by hydrazine was investigated in two mouse strains. Male Swiss Webster mice and

B6C3F1 mice were administered single intraperitoneal injections of 0, 5, 10, 20 or 40 mg/kg hydrazine and were sacrificed 24 hours later. Isolated liver DNA was analyzed for chemical adducts involving purine bases, using high performance liquid chromatography and fluorescence spectrophotometry. Dose dependent formation of 7-methylguanine (7MG) and O6-methylguanine (06MG) was observed in liver DNA of both strains of mice. The persistence of the methylguanines in mouse liver DNA was determined in Swiss Webster mice and B6C3F1 mice administered 20 mg/kg hydrazine and sacrificed at 24 hour intervals for up to 96 hours. The rates of formation of 7-methylguanine and O6-methylguanine and the rate of removal of 7-methylguanine were similar in the two strains of mice. However, the rate of disappearance of O6-methylguanine was considerably slower in B6C3F1 mice than in Swiss Webster mice, with estimated half lifes of 200 hours and 17 hours in the two strains, respectively. The results of this study were compared with those of a similar study in which levels of O6-methylguanine and 7-methylguanine in liver DNA were followed in Syrian golden hamsters administered hydrazine in their drinking water for a period of 2 years. Results indicate that hydrazine may be a hepatocarcinogen to which B6C3F1 mice may be particularly susceptible due to the persistence of O6-methylguanine in this mouse strain.

ALTERNATIVE and IN VITRO TESTS

The effects of short-term exposure (4 hr) of primary rat hepatocytes to hydrazine HzN were investigated with reference to viability, mitochondrial function, and biomarkers of oxidative stress. The viability data showed an increase in lactate dehydrogenase leakage and a decrease in mitochondrial activity with increasing concentration of HzN. The results of studies of oxidative stress biomarkers showed a depletion of reduced glutathione (GSH) and an increase in oxidized GSH, increased reactive oxygen species generation, lipid peroxidation, and reduced catalase activity. Furthermore, depletion of GSH and catalase activity in hepatocytes by buthionine sulfoximine and 3-amino triazole, respectively, prior to exposure to HzN, increased its toxicity. The results suggest that acute HzN-induced cytotoxicity in rat hepatocytes is likely to be mediated through oxidative stress.

Cultured rat hepatocytes were exposed to hydrazine for 4 hr, 17 hr or 4 hr followed by a 13-hr post-exposure period. Hydrazine was cytotoxic as measured by leakage of lactate dehydrogenase, caused depletion of ATP and inhibited protein synthesis. The cytotoxicity and depletion of ATP in cultures exposed to hydrazine for 4 hr was less than that previously reported in hepatocyte suspensions exposed for 4 hr. The threshold cytotoxic concentration (20 mM) was also higher in cells in culture than in cells in suspension (16 mM). Inhibition of protein synthesis was detected at a much lower concentration of hydrazine (0.5 mM) than was required to deplete ATP (16 mM) or cause cytotoxicity (20 mM). ATP depletion and inhibition of protein synthesis were similar after a 4-hr exposure with or without a 13-hr post-exposure period, but leakage of lactate dehydrogenase still occurred during this period. After the 17-hr exposure, the leakage of lactate dehydrogenase, ATP depletion and inhibition of protein synthesis were greater and the threshold concentration of hydrazine required for a significant effect on all three parameters was lower. This was so whether compared with a 4-hr exposure, or a 4-hr exposure plus a 13-hr post-exposure period.

The ability of hydrazine, acetylphenylhydrazine, methylhydrazine, and phenylhydrazine to stimulate proteolysis in red cells has been characterized. All four hydrazines effectively stimulated proteolysis in red cells and in hemolysate as evidenced by a two to threefold increase in the rate of tyrosine release. The rate of tyrosine release varied linearly with time, increased with increasing concentration of hydrazine, and also increased as a function of hematocrit. The rank order for stimulation of proteolysis in red cells was phenylhydrazine greater than methylhydrazine greater than hydrazine approximately equal to acetylphenylhydrazine. Inhibitors of glycolysis in red cells only minimally (13-27%) decreased the rate of tyrosine release stimulated by the different hydrazines. Agents which diminished electron transport decreased the rate of tyrosine release.

Treatment of animals with hydrazine causes the accumulation of triglycerides in the liver but the mechanism remains unclear. Therefore, the effect of hydrazine on hepatic triglyceride synthesis and subsequent transport was studied in a hepatocyte model, in vitro in order to isolate liver cells from extrahepatic influences. Hepatocytes were isolated and either incubated in suspension with [(14)C]palmitate in the presence of hydrazine (2-12 mM) or pre-incubated with [(14)C]palmitate, washed free of the fatty acid and then incubated with hydrazine (2-12 mM). Hydrazine resulted in a significant reduction in the incorporation of [(14)C]palmitate into triglycerides and reduction in the transportation of triglycerides out of cells. When [(14)C]palmitate was in the incubation medium, ATP levels were reduced by lower concentrations of hydrazine than have previously been reported. None of the concentrations of hydrazine used affected cell membrane integrity (viability) as measured by LDH leakage. The (14)CO2 produced by the beta-oxidation of [(14)C]palmitate was also measured in short term incubations (30 min) carried out in sealed vessels. There was a dose dependent increase in (14)CO2 produced by very low concentrations of hydrazine (0.01-0.1 mM) after which the effect was maximal and concentrations above 8 mM hydrazine decreased (14)CO2 production. The data suggest that the inhibition of transportation of triglycerides out of cells by hydrazine may have a more important role in the accumulation of triglycerides in the liver than has been previously recognised. However, the model was not able to mimic the

accumulation of triglycerides in hepatocytes seen in vivo.

Isoniazid is an anti-tuberculosis drug that can cause hepatotoxicity in 20% of patients that is usually associated with an inflammatory response. Hepatocytes when exposed to non-toxic levels of H2O2, to simulate H2O2 formation by inflammatory cells, became twice as sensitive to isoniazid toxicity. Isoniazid cytotoxicity was prevented by 1-aminobenzotriazole, a non-selective P450 inhibitor or by bis-p-nitrophenyl phosphate (BNPP), an esterase inhibitor. Moreover, the cytotoxicity of hydrazine, the metabolite formed by amidase-catalyzed hydrolysis of isoniazid, was increased 16-fold by a non-toxic H2O2-generating system. The acetylhydrazine metabolite was found to be much less cytotoxic than hydrazine in this hepatocyte inflammation model. Hydrazine, therefore, seems to be the isoniazid reactive metabolite in this inflammation model. The molecular mechanism of hydrazine-induced cytotoxicity was attributed to oxidative stress as reactive oxygen species (ROS) and protein carbonyl formation occurred before the onset of hepatocyte toxicity. Hydrazinetoxicity also involved significant production of endogenous H2O2 which resulted in lysosomal membrane damage and leads to a collapse in mitochondrial membrane potential. These results implicated H2O2, a cellular mediator of inflammation, as a potential risk factor for the manifestation of adverse drug reactions, particularly those caused by hydrazine containing drugs.

OTHER TOXICITY INFORMATION

Hydrazine (HD) and acetylhydrazine (AcHD) are metabolites of the antituberculosis drug isoniazid (INH) that have been implicated in INH-induced liver damage. The hepatotoxicity of AcHD and HD were compared in adult male C57Bl/6J mice by evaluating hepatic histopathology, plasma biochemistry, and hepatic gene expression. By all measures, HD had significantly greater effects than AcHD. There was no evidence of liver damage following exposure to AcHD (300 mg/kg, po). However, HD at this dose caused marked hepatic necrosis, macrovesicular degeneration, and steatosis. Lipid accumulation was initiated 2 hr after HD exposure, with hepatic macrovesicular degeneration evident after 4 hr, and severe necrosis by 36 hr. Gene expression profiles were compared 24 hr following 100 mg/kg po of HD or AcHD. HD changed the hepatic expression of more genes than AcHD, particularly lipid synthesis, transport, and metabolism genes that may be involved in steatosis. Hepatic expression of genes regulated by peroxisome proliferator activated receptors (PPAR) and sterol regulatory element binding protein (SREBP) transcription factors was increased only by HD. The hepatotoxicty and hepatic gene expression profile of HD, but not AcHD, indicate that exposure to HD initiates a process whereby the production and intracellular transport of hepatic lipids is favored over the removal of fatty acids and their metabolites.

Gas chromatography-mass spectrometry (GC-MS) has great advantages for analyzing organic/amino acids, which are often targets in efficacy and/or toxicity studies. Although GC-MS has been used for the detection of many metabolic disorders, applications of GC-MS-based metabolomics in pharmacology/toxicology are relatively underdeveloped. We intended to investigate applicability of a GC-MS-based metabolomics approach for toxicological evaluation, and tried to elucidate the mechanism of hydrazine-induced hepatotoxicity. Rats were administered hydrazine chloride orally (120 and 240 mg/kg), and urine, plasma and liver samples were collected at 24 or 48 hr post-dosing. Conventional clinical chemistry and liver histopathology were performed, urine and plasma were analyzed by GC-MS, and metabolic profiles were assessed using chemometric techniques. Principal component analysis score plots showed clear separation of the groups, indicating dose-dependent toxicity and recovery. The mechanism of toxicity was investigated based on semi-quantification data of identified metabolites. Amino acid precursors of glutathione (cystein, glutamate and glycine) and a product of glutathione metabolism (5-oxoproline) were elevated dose-dependently, accompanied with elevation of ascorbate levels. In addition, intermediates of the TCA cycle were decreased, whereas participants of the urea cycle and other amino acids were increased. These alterations were associated with histopathological changes such as fatty degeneration and glycogen accumulation. Application of GC-MS-based metabolomics revealed that oxidative stress and GSH consumption play important roles in the etiology of hydrazine-induced hepatotoxicity, demonstrating that this approach is a useful tool in pharmacology and toxicology for screening, elucidating mode of action and biomarker discovery.

Megamitochondria were induced (reversible process) in mouse and rat hepatocytes by feeding diet containing hydrazine.

The toxicity of monomethylhydrazine, hydrazine and unsymmetrical dimethylhydrazine was determined for mixed and uniculture cultures of nitrifying, denitrifying, and anaerobic methanogenic bacteria. Monomethylhydrazine was more toxic than hydrazine, which was more toxic than dimethylhydrazine. The toxicity levels were low enough to preclude biological waste treatment of these compounds.

Hydrazine is acutely neurotoxic, hepatotoxic and nephrotoxic; it is also carcinogenic to liver and lung in rodents. Administration of hydrazine results in formation of 7-methylquanine and O6-methylguanine in target organ DNA of rats, mice, hamsters and guinea pigs. It has been suggested that hydrazine reacts with endogenous formaldehyde to form a condensation product which could be metabolized to a methylating agent. Solutions of 0.50 mM hydrazine and

formaldehyde have, upon mixing, NMR spectra (300 mHz) consistent with the formation of formaldehyde hydrazone but not other possible condensation products such as tetraformyltriazine or formaldehyde azine. These same solutions evidencing hydrazone formation, when incubated in an in vitro system containing post-mitochondrial (S9), microsomal, cytosolic or mitochondrial cell fractions, resulted in the methylation of DNA guanine; S9 was 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 heme-containing cytochrome, readily transformed hydrazine/formaldehyde to a methylating agent. The data support formation of formaldehyde hydrazine as the condensation product of hydrazine and formaldehyde which is rapidly transformed in various liver cell fractions, perhaps by catalase and/or catalase-like enzyme, to a methylating agent.

Several mechanisms for accumulation of triglycerides in the liver of rats exposed to single doses of hydrazine via injection routes have been proposed: 1. Increased mobilization of free fatty acids from adipose tissue (particularly observed at low plasma-glucose levels) leading to an increased uptake of free fatty acids, followed by increased triglyceride synthesis in the liver. This mobilization of free fatty acids might be caused by the effects of hydrazine on the sympathetic nervous system and on levels of adrenal steroid hormone, possibly in response to the hypoglycemia induced by hydrazine. Elevated concentrations of circulating corticosterone and decreased concentrations of insulin were found in the serum of rats exposed to hydrazine. Decreased blood-insulin levels were also measured in rats by another study. 2. Increased synthesis of triglycerides caused by increased enzymatic activity of phosphatidate phosphohydrolase in hepatocytes both in vivo and in vitro was reported. It has been suggested that this was a result of increased corticosterone levels. In addition, increased fatty acid synthesis was found in the liver of rats after hydrazine administration. 3. Triglycerides could accumulate in hepatocytes as a result of a decreased secretion of lipoproteins from liver to plasma. This could be explained by a decreased lipid-binding capacity of lipoproteins following an observed alteration in the proportion of phospholipids and cholesterol or by increased lipid peroxidation. The protein moiety of lipoproteins could also be subject to change.

It has been postulated that hydrazine inhibits glyconeogenesis. This could occur via inhibition of pyridoxal phosphate-dependent aminotransferases and decarboxylases. It has been shown that hydrazine interferes with pyridoxal phosphate synthesis in vitro and in vivo. Inhibition of transaminases would also explain the increase in free amino acids observed in the plasma, liver, brain, and muscle of rats and in the plasma and urine of dogs. It could further explain several observations in rats, such as the depressed conversion of amino acids to carbon dioxide, the depressed incorporation of amino acids in plasma-glucose, and the enhanced incorporation of amino-labelled acids in liver proteins, 24 hr following hydrazine exposure. Inhibition of protein synthesis was also observed in rat livers up to 8.5 hr after exposure.

A proteomics approach combined with multivariate data analysis was used to examine the hepatotoxic effect of hydrazine in 30 male Sprague Dawley rats, assigned to four treatment groups and two control groups. Liver samples from the individual animals were resolved by two-dimensional differential gel electrophoresis (2-D DIGE) and protein patterns from the 2-D gels were analyzed by principal component analysis (PCA) and partial least squares regression (PLSR). The PCA plot was able to describe the variation in the protein expression related to dose and time, by separation or clustering of different animal groups. PLSR followed by variable selection (Jack-knifing) was used to select proteins that varied significantly in relation to the dose related response of the hydrazine treatment. The 10 up-regulated and 10 down-regulated proteins with highest rank in the PLSR model were identified by mass spectrometry. Hydrazine treatment induced altered expression of proteins related to lipid metabolism, Ca(2+) homeostasis, thyroid hormone pathways and stress response. Several of the identified proteins have not previously been implicated in hydrazine toxicity and may thus be regarded as new potential biomarkers of induced liver toxicity.

Numerical measures of toxicity (such as acute toxicity estimates)

Non-Human Toxicity Values

Test	Test Subject	Toxicity Value
Oral		
LD_{50}	Rat	60 mg/kg
	Mouse	59 mg/kg
	Rabbit	35 mg/kg bw
	Guinea pig	26 mg/kg bw
Dermal		
LD_{50}	Rabbit	91 mg/kg
	Guinea pig	190 mg/kg
Inhalation		
LC_{50}	Rat	570 ppm/4 hr

LC_{50}	Mouse	252 ppm/4 hr
IV		
LD_{50}	Rat	55 mg/kg
	Mouse	57 mg/kg
	Dog	25 mg/kg
	Rabbit	20 mg/kg
IP		
LD_{50}	Rat	59 mg/kg
	Mouse	62 mg/kg

Interactive effects

The influence of gut microbiota on the toxicity and metabolism of hydrazine has been investigated in germ-free and 'conventional' Sprague Dawley rats using (1)H NMR based metabonomic analysis of urine and plasma. Toxicity was more severe in germ-free rats compared with conventional rats for equivalent exposures indicating that bacterial presence altered the nature or extent of response to hydrazine and that the toxic response can vary markedly in the absence of a functional microbiome.

Pretreatment of Vicia faba root-tip meristems with a nontoxic dose of either hydrazine or N,N'-diformylhydrazine prior to the administration of maleic hydrazide, separated by 2 hr, resulted in a significant reduction of the yield of maleic hydrazide-induced chromatid aberrations compared to control treatments (maleic hydrazide only). This clastogenic adaptation was not observed when the alkylating agent triethylene melamine was used instead of maleic hydrazide. Thus, pretreatment with the hydrazines induces an error-free repair system which reduces maleic hydrazide-induced damage and both hydrazines and maleic hydrazide appear able to induce oxidative DNA lesions.

Administration of the hepatotoxin and carcinogen, inorganic hydrazine, to rodents results in the formation of 7-methylguanine and O6-methylguanine in liver DNA; co-administration of methyl-(14)C-methionine or (14)C-formate with the hydrazine labels the methylguanines, suggesting involvement of the 1-carbon pool in the methylation process. The present study investigates the proposal 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. Hamsters were pretreated with methanol, ethanol or cyanamide to alter the endogenous hepatic aldehyde levels prior to administration of hydrazine. Formaldehyde levels were refractory to the pretreatment; hepatic acetaldehyde levels were increased, but hydrazine administration under such conditions did not result in the formation of ethylated guanines in DNA. Methanol and ethanol inhibited hydrazine-induced methylaton of DNA. Hydrazine incubated with liver S9 fraction and calf thymus DNA induced the formation of 7-methylguanine and O6-methylguanine when formaldehyde was present in the incubation system; substitution of formaldehyde with acetaldehyde in the incubation medium did not result in any detectable alkylation of DNA. Both liver microsomal and cytosolic fractions demonstrated heat-labile activity in supporting the hydrazine-induced methylation process. Tetraformyltrisazine or a similar reaction product of hydrazine and formaldehyde, may be a more important intermediate than formaldehyde hydrazone in the hydrazine-induced methylation of DNA.

Hydrazine hepatotoxicity in vivo, as manifested by triglyceride accumulation, depletion of ATP and reduced glutathione (GSH) was shown to be dose related. The effect of pretreatment of rats with various inhibitors and inducers of cytochrome p450 on these dose-response relationships was investigated. Pretreatment with the inhibitor piperonyl butoxide increased triglyceride accumulation whereas pretreatment with the inducers phenobarbital and beta-naphthoflavone resulted in reduced triglyceride accumulation. Pretreatment with the inducers acetone and isoniazid also enhanced triglyceride accumulation. Only phenobarbital pretreatment also significantly reduced glutathione and ATP depletion. A linear correlation was found between hepatic glutathione and ATP levels in non-pretreated animals given various doses of hydrazine. However, exponential relationships were found between hepatic triglycerides and both hepatic ATP and glutathione. The results suggest that i) the hepatotoxicity of hydrazine can be modulated by inducing or inhibiting particular isoenzymes of cytochrome p450, ii) ATP and glutathione depletion may not be directly involved in the development of fatty liver.

The protective activity of melanin derived from tea (MDFT) was studied using hydrazine as a DNA-reactive chemical agent. Intra-peritoneal administration of MDFT at the doses of 5 or 20 mg/kg dose-dependently prevented liver toxicity induced by hydrazine in rats. It normalized rises in serum alanine transferase activity and a decrease in the glutathione level in the liver. It also reduced the hepatic malondialdehyde concentration. Monitoring the intensity of chemiluminescence showed that MDFT could prevent the production of free radicals that are generated owing to metabolic transformation of

hydrazine. It also prevented the formation 8-hydroxy-deoxyguanosine (8-OH-dG) DNA adducts. The results obtained in vivo and in vitro suggest that MDFT confers marked protection of the liver against hydrazine-induced oxidative toxicity.

Antituberculosis drug-induced hepatotoxicity (ATDH) complicates the treatment of 5-10% of patients treated for active tuberculosis (TB). Knowledge regarding the mechanism of toxicity is still incomplete. Metabolism and the formation of toxic metabolites of the TB drugs may play an important role in the development of ATDH. We studied hepatotoxicity and interactions between isoniazid (INH), its toxic metabolite hydrazine (HYD), rifampicin (RIF) and pyrazinamide (PZA) in human hepatoma cells (HepG2). After 24 hr pre-treatment with a non-toxic concentration of one of the four compounds, cells were exposed to increasing concentrations of INH, HYD, RIF or PZA. To determine whether pre-treatment increased toxicity, changes in the concentration at which 50% of cell growth was inhibited (IC50) were quantified using the WST-1 cytotoxicity assay. Pre-treatment with INH, HYD or RIF decreased the INH IC50 by 24%, 26% and 15%, respectively, meaning that INH toxicity was increased. INH and HYD pre-treatment decreased the PZA IC50 by 30% and 38%, respectively. HYD and RIF toxicity were not affected by the pre-treatments. The present study is the first to demonstrate that pre-treatment with INH or its toxic metabolite HYD increases the in vitro toxicity of PZA. In addition, pre-treatment with INH, HYD or RIF increases the in vitro toxicity of INH. These results give us greater insight into the development of ATDH.

The case of a 24-yr-old man who accidentally ingested a mouthful of hydrazine successfully treated with megadoses of intravenous pyridoxine hydrochloride (vitamin B6) injection, 10 g over a few hr, who subsequently developed sensory polyneuropathy, is reported. The neuropathy spontaneously resolved over the next 6 months. It was concluded that although part of the peripheral neuropathy could have been due to hydrazine toxicity, the predominantly sensory neuropathy with axonal degeneration and spontaneous recovery is due to pyridoxine hydrochloride (vitamin B6) induced peripheral neuropathy.

Where specific chemical data are not available

No further information available.

Mixtures

No further information available.

Mixture versus ingredient information

No further information available.

Other information

None.

12 Ecological information

Toxicity

Ecotoxicological Summary

Hazard for aquatic organisms

Freshwater

Hazard assessment conclusion:	PNEC aqua (freshwater)
PNEC value:	0.6 µg/L
Assessment factor:	10
Extrapolation method:	assessment factor
PNEC freshwater (intermittent releases):	0 mg/L

Marine water

Hazard assessment conclusion:	PNEC aqua (marine water)
PNEC value:	0.06 µg/L
Assessment factor:	100
Extrapolation method:	assessment factor

STP

Hazard assessment conclusion:	PNEC STP
PNEC value:	0.055 mg/L
Assessment factor:	100
Extrapolation method:	assessment factor

Sediment (freshwater)

Hazard assessment conclusion:	no hazard identified

Sediment (marine water)
Hazard assessment conclusion: no hazard identified

Hazard for air
Air
Hazard assessment conclusion: no hazard identified

Hazard for terrestrial organisms
Soil
Hazard assessment conclusion: no hazard identified

Hazard for predators
Secondary poisoning
Hazard assessment conclusion: no potential for bioaccumulation

Conclusion on classification
All effective concentrations describing acute effects of hydrazine towards aquatic organisms are below 1 mg/L. As hydrazine is purely inorganic, it is scored as not biodegradable. Hydrazine has only a very low potential to bioaccumulate in aquatic organisms.

Based on the available information, hydrazine has to be classified as:

- Dangerous for the environment; R50/53; very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment (Directive 67/548/EEC)
- Hazardous to the aquatic environment- H400, Acute Hazard, Category 1 and H 410, Chronic Hazard, Category 1 (Regulation EC 1272/2008)

Aquatic Toxicity
Endpoint Summary
The short-term toxicity of hydrazine towards fish (Lebsistes reticulatus) is characterized by an LC50(96 h) of 0.61 mg/L (Slonim, 1977). Exposure concentrations were proved indirectly through testing adverse effects of an altered test solution containing hydrazine towards the test animals.

For hydrazine an EC50(48 h) of 0.175 mg/L (mean of two separate tests) was observed with respect to the immobilization of daphnids (Velte, 1984), whereas exposure concentrations were proved by analytical measurements.

The long-term toxicity of hydrazine towards invertebrates was investigated yielding a NOEC(21 d) of 0.010 mg/L having reproduction as most sensitive end point (Currenta, 2010b). The test evaluation was based on time-weighted means of the measured concentrations.

The adverse effects hydrazine towards the growth of aquatic algae are characterized by an ErC_{50}(48 h) of 0.017 mg/L as well as a NOEC of 0.006 mg/L referring to the reduction of the growth rate (Currenta, 2009).

The toxicity of hydrazine towards microorganisms is characterized by an EC50(3 h) of 5.5 mg/L (nominal) testing the respiration rate of activated sludge (Currenta, 2010c).

Short-term toxicity to fish
LC_{50} for freshwater fish: 0.61 mg/L

Long-term toxicity to fish
According to the REACh Annex XI, Section 1, a test on long-term toxicity towards fish does not need to be conducted as it is scientifically not necessary. Vertebrate-animal testing can be avoided as fish are assumed to be not the most sensitive aquatic species.

Short-term toxicity to aquatic invertebrates
For hydrazine an EC_{50}(48 h) of 0.175 mg/L was observed with respect to the immobilization of daphnids (Velte, 1984).

Additional information
Since there is no significant differnce between the two obtained 48 h values, a mean EC50(48 h) of 0.175 mg/L was used

for the further assessment. Tests were conduced as a static renewal test, whereas initial hydrazine exposure concentrations were measured at 0 and 24 h, and the renewal concentrations were measure at 24 and 48 h by the means of a colorimetric method. The hydrazine loss was minor during the daphnid static exposures. Mean hydrazine loss was 2.7 % for the 24 h-period preceding and following renewal. Thus, the hydrazine concentration did not fall below 80 % of nominal concentrations justifying the use of nominal concentrations.

The study performance is comparable to current guidelines but having one minor drawback concerning the study documentation. No information is presented with respect to the mortality in control samples as an indication of stress or illness independent of the presence of the test item. Nevertheless, the results were used for the hazard assessment as the obtained results would rather overestimate the toxicity of the test item in the case that other factors contributed to the observed effects (stress, illness). Consequently, results would be more protective with respect to aquatic hazard assessment.

Long-term toxicity to aquatic invertebrates

EC_{10}, LC_{10} or NOEC for freshwater invertebrates: 0.01 mg/L

Additional information

As hydrazine is known to rapidly degrade in aqueous media, tests were conduced under semi-static conditions refreshing aqueous solutions each Monday, Wednesday and Friday to ensure a constant exposure of the test animals throughout the entire test duration. Furthermore, concentrations were measured on day 0, 7 and 14 in the freshly prepared media; and on day 2, 9 and 16 in the old media by the means of a photometric method to determine the effective exposure concentration. Effective concentrations ranged from 78.1 – 170 % of the nominal values in the freshly prepared media and from 17.0 – 110 % of the nominal values in the media after 48 hours, or 72 hours of exposure, respectively. Therefore, the test evaluation was based on time-weighted means of the measured concentrations.

Toxicity to aquatic algae and cyanobacteria

EC_{50} for freshwater algae: 0.017 mg/L

EC_{10} or NOEC for freshwater algae: 0.006 mg/L

Additional information

The results are expressed in terms of geometric mean measured concentrations as effective concentrations ranged from 93.8 % -99.2 % of nominal values at 0 hours, from 7.81 % - 12.5 % of nominal values at 24 hours and correspond to 3.13 % of nominal values at 48 hours, respectively.

The study was terminated after 48 h, because concentrations of the test item markedly decreased over time and thus the 48 h value reflects exposure better than the 72 h values. As cell numbers increased well above 16-fold over 48 h, and all other validity criteria are met, this is an option explicitly covered by OECD TG 201 (2006) and EU method C.3 (2009).

There are several other studies reporting lower effective concentrations (Bringmann, Scherfig, Dixon) than observed in the selected key study. But:

- no information is given whether concentrations were determined analytically. As the test item concentration was shown to be not constant over time, measure concentrations would be quite crucial for the study evaluation.
- according to the Guidance document R.7b (ECHA, 2008), a test duration of 72 h is recommended to ensure exponential growth over the entire test duration. Reported test durations are well above 72 h and no information is given concerning the algal growth.

Concluding, due to these drawbacks, the studies cannot be used for the hazard assessment of hydrazine as it cannot be ensured that the toxicity of hydrazine towards aquatic algae is adequately described.

Toxicity to microorganisms

EC_{50} for microorganisms: 5.5 mg/L

Additional information

According to the Guidance document R.7b (ECHA, 2008), preference is given to tests with a mixed inoculum that assess the functioning of the entire microbial community in a sewage treatment plant, rather than tests based on single species or even microbial sub-systems. Respirometry is generally considered as an approach that will integrate the functioning of all organisms in an STP. Concluding, Currenta (2010c) was chosen to represent the toxicity of the test item towards

microorganisms and thus the functioning of the sewage treatment plant, as all reported supporting studies performed by Bringmann et al. used single species as test organisms. These species represent only a minor part of microorganisms present in sewage treatment systems and should only be used for the risk assessment in the absence of other reliable data.

Persistence and degradability

Environmental fate & pathways

Hydrazine is mainly abiotically degraded through oxidative pathways when released in the aquatic, terrestrial and atmospheric compartment. Biotic degradation processes can be neglected as hydrazine is an inorganic compound and cannot serve as energy supply for microorganisms. Nevertheless, a test similar to a test on inherent biodegradability (OECD 302 B) showed a hydrazine elimination of 99 % after 24 hours when brought in contact with activated sludge. No distinction can be made between biotic, abiotic or physico-chemical elimination processes, but the results provide evidence that hydrazine will be removed to a significant extent subjecting hydrazine containing waste waters to a sewage treatment. A refined description of the environmental behaviour of hydrazine will thus be possible.

Dissipation of hydrazine in aqueous media is influenced by a multitude of factors, but there is evidence that hydrazine will be rapidly degraded in an aqueous media mainly due to autooxidative processes. In the aqueous compartment between 10 % up to 99 % of the applied hydrazine degraded within 4 days in the presence of oxygen, organic matter, carbonate and metal ions, whereas the degradation rate is determined by the sum of all these factors, rather than by one factor alone. Furthermore, hydrazine was shown to be not stable when introduced into culture media of two biological test systems. Effective concentrations decreased to about 3.13 % and 17 %, respectively after 48 h of incubation. No correlation between test conditions, medium composition and degradation rate can be found. An investigation on the stability of hydrazine in natural surface waters yielded DT50 values of approximately 2.67 h and 24 h, respectively, whereas the degradation was faster in water with the lower hardness and DOC values. The results from the accompanying analytical monitoring of two biological assays and the stability tests in natural surface waters provide evidence that the environmental half-life of hydrazine in aqueous media will be below 24 h. Nitrogen and water are the primary degradation products, whereas the presence of catalysts like phosphate or cupric ions is paralleled by the formation of ammonia. The half-life of 24hours in natural media is taken as a key value for the calculation of the environmental exposure.

Furthermore, hydrazine will undergo a rapid abiotic degradation in the soil compartment in the presence of oxygen and exchangeable metal cations held by the clay. Based on one older study in soil it be concluded that a half-life of 12 hours in soil is a realistic worst-case assumption.

In the atmosphere, hydrazine was shown to degrade in the presence of hydroxyl radicals. Assuming an OH-concentration of 500000 molecules/cm³ the atmospheric half life of hydrazine accounts for 6.3 h yielding only a limited potential for a long range atmospheric transport. In the absence of light, the degradation of hydrazine in air is characterized by half lives smaller than 6 h strongly depending on the prevailing humidity. In the presence of ozone, the atmospheric half life decreases below 2 h.

The potential to bioaccumulate in aquatic organisms is scored as very low due to low logKow of -0.16, the high water solubility and the rapid degradation of hydrazine in the aquatic environment.

A test on adsorption/ desorption cannot be conducted as it is technically not possible. Nevertheless, there are several studies available dealing with the behaviour of hydrazine in the presence of soil. Assessed individually, they all have several drawbacks. But combining the information of these studies, it can be concluded that hydrazine might sorb or degrade depending on the prevailing conditions. At low pH values, mainly sorption occurs, whereas at higher pHs, degradation is supported. Additionally, the soil composition might contribute to hydrazine degradation. No definite value for sorption on soil can be determined as a multitude of factors determine the behaviour of hydrazine in that environmental compartment.

Environment Canada (2011) supports these findings and concluded without knowledge of the latest studies performed at Currenta (2010): "There are several lines of evidence to suggest that the persistence of hydrazine in natural ecosystems is low to moderate: all four half-lives in air are less than 1 day; the 26 halflives in water range from 0.2 to 125 days; the three half-lives in soil are less than or equal to 3 days; the one estimated biodegradation half-life in aerobic sediment is 1.6 day. Ready biodegradability tests indicate that the degree of degradation depends on hydrazine loading. Tests on natural water samples indicate that biodegradability is also a function of bacterial abundance and species present. Decrease of water temperature can decrease degradation half-lives in this compartment but this effect is not established with certainty given the low level of detail provided by James (1989) and Jingqiu et al. (1994) for their experiments.

Stability
In the atmospheric compartment, hydrazine is rapidly degraded under the presence of hydroxyl radicals. Assuming an OH-concentration of 500,000 molecules/cm³, an atmospheric half-life of 6.3 h was derived.

According to the Guidance document R.11 (ECHA, 2008) atmospheric half-lifes smaller than 2 days indicate a limited potential for a long range atmospheric transport.

A test in 2 different surface waters yielded a degradation with half-lifes between 2.6 and 24 hours at 20°C.

Phototransformation in air
Hydrazine is rapidly degraded under the presence of hydroxyl radicals yielding a temperature independent rate constante of 6.1 E-11 cm³/(molecule * s) (T= 298 - 424 K) (Pitts et al., 1980). Based on these results an atmospheric half life of 6.3 h can be calculated assuming an OH concentration of 500000 molecules/cm³.

Hydrolysis
A guideline test was waived as the substance is marketed as aqueous dilution with varying concentrations of hydrazine, a hydrolytical reaction can be excluded. The disappearance of hydrazine is rather caused by the presence of various water constituents (for example organic matter, oxygen, carbonate, metal ions) than by the presence of water molecules itself. This has been shown by a study where natural surface water (pond water, river water) was spiked with hydrazine. The substance declined rapidly with half lives of 2.6 hours (pond water) and 24 hours (river water) (Sapers 2010). Another study (Slonim 1076) supports these finding, as half-lives for hydrazine in natural surface waters were a few hours, whereas clean tap waters showed higher stability to hydrazine.

Supporting evidence is given by a synopsis of the available literature (Canada hydrazine assessment 2011) where a melange of data is given assessing biodegradation and abiotic degradation.

Phototransformation in water
The presence of UV light has only a minor effect on hydrazine oxidation by ozone.

Biodegradation
Endpoint summary
In accordance with the guidance document on information requirement and chemical safety assessment (R.7b, ECHA, 2008) biodegradability studies are not required for inorganic substances as they cannot be tested for biodegrability. But a test similar to a test on inherent biodegradability (OECD 302 B) showed a hydrazine elimination of 99 % after 24 hours when brought in contact with activated sludge (Currenta, 2010a).

Biodegradation in water: screening tests
A test similar to a test on inherent biodegradability (OECD 302 B) perfomred with a domestic sewage sludge showed a hydrazine elimination of 99 % after 24 hours when brought in contact with activated sludge (Currenta, 2010a).

Biodegradation in water and sediment: simulation tests
In accordance with the guidance document on information requirement and chemical safety assessment (R.7b, ECHA, 2008) biodegradability studies are not required for inorganic substances as they cannot be tested for biodegradability.

Biodegradation in soil
Standard OECD test guidelines are not applicable to inorganic chemicals such as Hydrazine.

Bioaccumulative potential

Endpoint summary
In accordance with Section 1 of REACh annex XI, a bioaccumulation study is scientifically unjustified. Based on the low logKow (-0.16, MITI 2002), the high water solubility and the rapid degradation of hydrazine in the aquatic environment, an accumulation is not expected.

Bioaccumulation: aquatic / sediment
In accordance with Section 1 of REACh annex XI, a bioaccumulation study is scientifically unjustified. Based on the low logKow (-0.16, MITI 2002) and the rapid degradation of hydrazine in the aquatic environment, an accumulation is not expected.

Mobility in soil

Endpoint summary
In the absence of any reliable data to describe the adsorption/ desorption behaviour of hydrazine, a new study would become necessary. But in accordance with Section 2 of REACh annex XI, a test on adsorption/ desorption cannot be conducted as it is technically not possible. Furthermore, no reliable QSAR methods exist to estimate the Koc values of ionizable, inorganic compounds.

There are several studies available dealing with the behaviour of hydrazine in the presence of soil. Assessed individually, they all have several drawbacks hampering the determination of a partition coefficient as the documentation is insufficient. But summarizing the information, hydrazine might sorb or degrade when present in soil depending on the prevailing conditions. At low pH values, sorption mainly occurs, whereas at higher pHs, degradation is supported. Additionally, the soil composition might contribute to hydrazine degradation. No definite value for sorption on soil can be determined as a multitude of factors determine the behaviour of hydrazine in that environmental compartment.

Adsorption / desorption
In the absence of any reliable data to describe the adsorption/ desorption behaviour of hydrazine, a new study would become necessary. But in accordance with Section 2 of REACh annex XI, a test on adsorption/ desorption cannot be conducted as it is technically not possible. Furhtermore, no reliable QSAR models exist to estimate the Koc values for ionizable inorganic compounds.

Henry's Law constant
Henry's law constant (H) (in Pa m^3/mol): 0.06 @ 20 °C

Constant derived for this assessment using the value of vapour pressure 2100 hPa (Environment Canada 2011) and a solubility of 10E06 mg/L which is equivalent to completely miscible.

Other adverse effects

No additional data.

13 Disposal considerations

Disposal methods

Waste disposal recommendations
Dispose of waste and container in accordance with local and/or national regulations. Hazardous waste shall not be mixed together with other waste. Different types of hazardous waste shall not be mixed together if this may entail a risk of pollution or create problems for the further management of the waste. Hazardous waste shall be managed responsibly. All entities that store, transport or handle hazardous waste shall take the necessary measures to prevent risks of pollution or damage to people or animals. Recycle/reuse. Remove for physico-chemical/biological treatment. **DO NOT** discharge into drains or the environment.

Dilute with plenty of water. Solutions with high pH-value must be neutralized before discharge. Neutralise with acid. In accordance with local and national regulations.

Ecology - waste materials
DO NOT release to the environment.

Empty Container
Avoid reuse of empty container. Consider refilling. Rinse/Decontaminate thoroughly with water before disposal or return to supplier. Where possible recycling is preferred to disposal or incineration. Dispose of as unused product. In accordance with local and national regulations.

14 Transport information

UN Number

TRANSPORTATION CLASSIFICATION	ADR/RID	ADN(R)	IMDG	ICAO/IATA
Identification Number	2030	2030	2030	2030
Proper Shipping Name	HYDRAZINE AQUEOUS SOLUTION, with	HYDRAZINE AQUEOUS SOLUTION, with	HYDRAZINE AQUEOUS SOLUTION, with	HYDRAZINE AQUEOUS SOLUTION, with

	>37% hydrazine, by mass	>37% hydrazine, by mass	>37% hydrazine, by mass	>37% hydrazine, by mass
Transport Hazard Class(es)	8(6.1) 	8(6.1) 	8(6.1) 	8(6.1) 
Packing Group	II	II	II	II
Environmental Hazards	No	No	No	No
Emergency Response	ERG: 153	N/A	EMS: F-A, S-B	N/A
Special provisions Exempt Quantity Quantity Limitations	Road 50Kg F: 20 Passenger Rail - Forbidden	-	-	Passenger - Forbidden 30 L - Cargo

UN Proper Shipping Name

Refer above section 14.1

Transport hazard class(es)

Refer above section 14.1

Packing group, if applicable

Refer above section 14.1

Environmental hazards

Refer above section 14.1

Special precautions for user

DO NOT load with Classes 1, 4.1, 4.2 , 4.3, 5.1 and 5.2.
May be loaded with Classes 2.1 and 8A if kept at least 1 metre apart.
DO NOT transport Nitromethane (UN1261) with toxics (Class 6.1).
DO NOT load with foodstuffs or stockfeeds.
Cyanides **must not** be transported with acid.
Can be loaded with all other classes.
Goods of different classes **must be** segregated by an air space of at least 100mm or by an approved segregation device or non-dangerous goods.

P, B, L and O provisions as per SANS 10231:2006
L13
If any substance has leaked and spilt in a vehicle or container, the vehicle or container may not be re-used until after it has been thoroughly cleaned and, if necessary, disinfected or decontaminated. Any other goods and articles carried in the same vehicle or container shall be examined for possible contamination.

L28
Packages shall not be loaded together with packages known to contain foodstuffs, other articles of consumption or animal feeds.

Excerpt from ERG Guide 153 [Substances - TOXIC and/or CORROSIVE (Combustible)]
EMERGENCY RESPONSE
FIRE
Small Fire

- Dry chemical, CO2 or water spray.

Large Fire

- Dry chemical, CO2, alcohol-resistant foam or water spray.
- Move containers from fire area if you can do it without risk.
- Dike fire-control water for later disposal; do not scatter the material.

Fire involving Tanks or Car/Trailer Loads

- Fight fire from maximum distance or use unmanned hose holders or monitor nozzles.
- Do not get water inside containers.

- Cool containers with flooding quantities of water until well after fire is out.
- Withdraw immediately in case of rising sound from venting safety devices or discoloration of tank.
- ALWAYS stay away from tanks engulfed in fire.

SPILL OR LEAK

- ELIMINATE all ignition sources (no smoking, flares, sparks or flames in immediate area).
- Do not touch damaged containers or spilled material unless wearing appropriate protective clothing.
- Stop leak if you can do it without risk.
- Prevent entry into waterways, sewers, basements or confined areas.
- Absorb or cover with dry earth, sand or other non-combustible material and transfer to containers.
- DO NOT GET WATER INSIDE CONTAINERS.

FIRST AID

- Ensure that medical personnel are aware of the material(s) involved and take precautions to protect themselves.
- Move victim to fresh air.
- Call 911 or emergency medical service.
- Give artificial respiration if victim is not breathing.
- Do not use mouth-to-mouth method if victim ingested or inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device.
- Administer oxygen if breathing is difficult.
- Remove and isolate contaminated clothing and shoes.
- In case of contact with substance, immediately flush skin or eyes with running water for at least 20 minutes.
- For minor skin contact, avoid spreading material on unaffected skin.
- Keep victim calm and warm.
- Effects of exposure (inhalation, ingestion or skin contact) to substance may be delayed.

Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

Not applicable.

15 Regulatory information

Safety, health and environmental regulations specific for the product in question

SA NATIONAL LEGISLATION

Hazardous Substances Act 15 of 1973 and Regulations.
Occupational Health and Safety Act 85 of 1993 and Regulations.

SA NATIONAL STANDARDS

SANS 10228 : 2006 : Identification and Classification of Dangerous Goods for Transport by Road and Rail.
SANS 10231 : 2018 : Transport of dangerous goods - Operational requirements for road vehicles.
SANS 10234 : 2008 : Globally Harmonized System of classification and labelling of chemicals (GHS).
SANS 11014 : 2010 : Safety Data Sheets for chemical Products.

REACH Regulation (EC) No 1907/2006

This product contains only components that have been either pre-registered, registered, are exempt from registration, are regarded as registered or are not subject to registration according to Regulation (EC) No. 1907/2006 (REACH)., The aforementioned indications of the REACH registration status are provided in good faith and believed to be accurate as of the effective date shown above. However, no warranty, express or implied, is given. It is the buyer´s/user´s responsibility to ensure that his/her understanding of the regulatory status of this product is correct.

Seveso III: Directive 2012/18/EU

Listed in Regulation: Not applicable

Atmospheric Standards

Listed as a hazardous air pollutant (HAP) generally known or suspected to cause serious health problems. The Clean Air Act, as amended in 1990, directs EPA to set standards requiring major sources to sharply reduce routine emissions of toxic pollutants. EPA is required to establish and phase in specific performance based standards for all air emission sources that emit one or more of the listed pollutants. Hydrazine is included on this list.

Clean Air Act as amended in 1990, Sect. 112 (b) (1) Public Law 101-549 Nov. 15, 1990

CERCLA Reportable Quantities

Persons in charge of vessels or facilities are required to notify the National Response Center (NRC) immediately, when there is a release of this designated hazardous substance, in an amount equal to or greater than its reportable quantity of 1 lb or 0.454 kg. The toll free number of the NRC is (800) 424-8802. The rule for determining when notification is required is stated in 40 CFR 302.4 (section IV. D.3.b).

Releases of CERCLA hazardous substances are subject to the release reporting requirement of CERCLA section 103, codified at 40 CFR part 302, in addition to the requirements of 40 CFR part 355. Hydrazine is an extremely hazardous substance (EHS) subject to reporting requirements when stored in amounts in excess of its threshold planning quantity (TPQ) of 1,000 lbs.

RCRA Requirements

U133; As stipulated in 40 CFR 261.33, when hydrazine, as a commercial chemical product or manufacturing chemical intermediate or an off-specification commercial chemical product or a manufacturing chemical intermediate, becomes a waste, it must be managed according to Federal and/or State hazardous waste regulations. Also defined as a hazardous waste is any residue, contaminated soil, water, or other debris resulting from the cleanup of a spill, into water or on dry land, of this waste. Generators of small quantities of this waste may qualify for partial exclusion from hazardous waste regulations (40 CFR 261.5).

Chemical safety assessment

Performed for substance: Yes

16 Other information

Other information

Full text of H-Statements referred to under section 2

Hazard statements

H226	Flammable liquid and vapour.
H301	Toxic if swallowed.
H311	Toxic in contact with skin.
H314	Causes severe skin burns and eye damage.
H317	May cause an allergic skin reaction.
H330	Fatal if inhaled.
H350	May cause cancer.
H400	Very toxic to aquatic life.
H410	Very toxic to aquatic life with long lasting effects.

Precautionary statements

P201+P202	Obtain special instructions before use. Do not handle until all safety precautions have been read and understood.
P210	Keep away from heat/sparks/open flames/hot surfaces. — No smoking.
P233	Keep container tightly closed.
P240+P241+P242	Ground/bond container and receiving equipment. Use explosion-proof electrical/ventilating/lighting equipment. Use only non-sparking tools.
P243	Take precautionary measures against static discharge.
P260	Do not breathe dust/fume/gas/mist/vapours/spray.
P264	Wash thoroughly after handling.
P270	Do not eat, drink or smoke when using this product.
P272	Contaminated work clothing should not be allowed out of the workplace.
P273	Avoid release to the environment.
P280	Wear protective gloves/protective clothing/eye protection/face protection.
P301+P330+P331	IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P301+P310	IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician.
P302+P352	IF ON SKIN: Wash with plenty of soap and water.
P303+P361+P353	IF ON SKIN (or hair): Remove/Take off Immediately all contaminated clothing. Rinse SKIN with water/shower.
P304+P340	IF INHALED: Remove victim to fresh air and Keep at rest in a position comfortable for breathing.

P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308+P313	IF exposed or concerned: Get medical advice/attention.
P370+P378	In case of fire: Use alcohol-resistant foam, foam, water spray, dry powder, carbon dioxide to extinguish.
P321	Specific treatment (see P330+P351+P352+P353 on this label).
P333+P313	If skin irritation or rash occurs: Get medical advice/attention.
P362+P364	Take off contaminated clothing and wash it before reuse.
P363	Wash contaminated clothing before reuse.
P391	Collect spillage.
P403+P235	Store in a well-ventilated place. Keep cool.
P405	Store locked up.
P501	Dispose of contents and container in accordance with local, regional, national, international regulations.

Labelling REGULATION (EC) No 1272/2008

Signal Word

Danger

Pictograms Hazard to Human

GHS02	Flammable hazard
GHS05	Corrosive hazard
GHS06	Toxic hazard
GHS07	Health hazard
GHS08	Serios health hazard
GHS09	Environmental hazard

Pictogram Hazard during Transport

Class 6.1	Toxic substance
Class 8	Corrosive substance

Acronyms

ACGIH	American Conference of Governmental Industrial Hygienists
ATE	Acute Toxicity Estimate
CAS	Chemical Abstract Service
DOT	Department of Transport (USA)
EC50	median effective concentration
EINECS	European Inventory of Existing Commercial Chemical Substances
ICSC	International Chemical Safety Cards
IDLH	Immediately dangerous to life or health
im	intramuscular
ip	intraperitoneal
iv	intravenous
LC50	Median Lethal Concentration
LD50	median lethal dose
RTECS	Registry of Toxic Effects of Chemical Substances
NFPA	National Fire Protection Agency (USA)
NIOSH	National Institute for Occupational Safety and Health (USA)
OSHA	Occupational Safety and Health Administration (USA)
PEL	Permissible Exposure Limit
REL	Recommended Exposure Limit
TWA	Time-Weighted Average

Training advice

Provide adequate information, instruction and training for operators.

Information sources

1. European Chemicals Agency https://echa.europa.eu/es/registration-dossier/-/registered-dossier/14983/1
2. National Center for Biotechnology Information PubChem Database. Hydrazine, CID=9321, https://pubchem.ncbi.nlm.nih.gov/compound/9321 (accessed on May 14, 2019)

3. International Labour Organisation
   https://www.ilo.org/dyn/icsc/showcard.display?p_lang=en&p_card_id=0281&p_version=2
4. Cameo Chemicals https://cameochemicals.noaa.gov/unna/2030
5. Hazmat Tool https://www.hazmattool.com/emergencyguide.php?i=153

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MANUFACTURER/SUPPLIER DISCLAIMER:

IMPORTANT: This information is given without a warranty or guarantee. No suggestions for use are intended or shall be construed as a recommendation to infringe any existing patents or violate any national or local laws. Safe handling and use is the responsibility of the customer. Read the label before using this product. This information is true and accurate to the best of our knowledge.

Revision History

Revision	Date	Change
1.0	2019/05/15	Preparation of the safety data sheet according to SANS 11014:2010