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GUIDES FOR SHORT-TERM EXPOSURES OF THE PUBLIC TO AIR POLLUTANTS. V. GUIDE FOR HYDRAZINE, MONOMETHYL-HYDRAZINE, AND 1, 1-DIMETHYLHYDRAZINE

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Guides for Short-Term Exposures of the Public to Air Pollutants

V. Guide for Hydrazine, Monomethylhydrazine, and 1, 1-Dimethylhydrazine

by

The Committee on Toxicology

of the

National Academy of Sciences - National Research Council

Washington, D. C.

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I. INTRODUCTION

The search for improved rocket fuels to expedite exploration of space led to the introduction of hydrazine, monomethylhydrazine (MMH) and unsymmetrical dimethylhydrazine (UDMH) as fuels in propellant systems. These compounds are all storable, non-cryogenic, high-energy fuels that may be used alone or in combination as mixed amine fuels. In addition, hydrazine and its derivatives are finding increasing commercial application as intermediates in the synthesis of other products. Because of these developments substantial amounts of hydrazine, MMH and UDMH are presently manufactured, stored, and shipped in the United States. These materials are all toxic and would present a hazard to the public if they should be accidentally released into the environment.

The Committee on Toxicology of the National Academy of Sciences - National Research Council (1971) has previously recommended Emergency Exposure Limits (EEL's) for exposures to the vapors of hydrazine, MMH and UDMH. These limits are applicable only to personnel directly involved in spacecraft operations. At the request of the Environmental Protection Agency the Committee has prepared this document, which includes recommended limits for short-term exposures of the public to these pollutants. The Committee and Panel members have been confronted with several difficulties in arriving at these recommendations. Data on the toxicity of the hydrazines from animal studies are not as complete or consistent as desired; their extrapolation to the human situation is complicated by the fact that there are marked differences in species response to these agents. Furthermore, it has not been possible to survey these compounds as a homogeneous group because their differing physical characteristics and physiologic actions give rise to wide variations in potential toxic effects.

Most accidental exposures to these liquids would probably occur from spills that may result in toxic effects from inhalation and/or extensive direct skin contact. UDMH has the highest vapor pressure of the three compounds and presents the greatest inhalation hazard. All three are absorbed through the skin but since UDMH vaporizes most readily it represents the lowest hazard from cutaneous exposures. Exposures to mixed amine fuels may also occur. Aerozine "50", a widely used mixed amine fuel, is a 1:1 mixture by weight of hydrazine and UDMH. Inhalation hazards from spills of this liquid arise mainly

from UDMH while systemic toxic effects from skin contact are those of hydrazine.

All these compounds are convulsants as well as irritants to the eyes, skin, and respiratory tract. The magnitude of these effects varies widely among the three, and two have unique toxic actions. Hydrazine can cause delayed death from liver damage following acute or repeated exposures. MMH can cause hemolytic effects in man and animals. Experimental studies have also shown that the convulsant action of UDMH and MMH may be alleviated by the use of pyridoxine but this agent does not protect against the convulsant effects of hydrazine.

At the present time there is not enough information to speculate on the mechanisms of the toxicities that have been described. It is evident that a great deal of additional information is needed before we can truly assess the hazards these compounds present to human health.

The toxicology of these compounds is discussed in separate chapters, with recommended exposure limits. These limits are summarized in Table 4. A separate chapter is devoted to analysis and monitoring.

There is a body of evidence from animal experiments that hydrazine and many of its derivatives, including MMH and UDMH, over a prolonged period of repeated or continuous exposure may increase the number of tumors appearing near the end of the life span of the animals. It is believed that the short-term exposures of the public as contemplated in this Guide do not constitute a tumorigenic risk under the conditions and limits described here.

The Committee and its ad hoc Panel urge that a careful examination be undertaken of the tumorigenic risk to those who are occupationally exposed to hydrazine and its derivatives. It is further recommended that a close surveillance of the literature be maintained for new data that might require the modification of the foregoing comments and a re-evaluation of the uses of these materials. Additional research on the potential carcinogenicity of these compounds should be conducted.

II. GUIDE FOR HYDRAZINE

Background

Hydrazine (H_2NNH_2) is an extremely reactive compound that ordinarily does not occur free in nature. Because of its many unusual properties, chemists have long been interested in isolating and characterizing hydrazine and its salts and derivatives. These experiments have produced a large literature dating back to 1875.

The status of hydrazine as an exotic chemical changed during World War II when Germany began using hydrazine as a rocket fuel and developed a process that produced the compound on a tonnage basis. These events stimulated commercial interest in hydrazine and subsequently the first plant for the production of anhydrous hydrazine in the United States commenced operation in 1953.

Commercial Uses of Hydrazine

At the present time somewhere between ten and twenty million pounds of hydrazine are produced annually in the United States. The largest proportion of current production, about seven million pounds annually, is used for the preparation of derivatives that are applied in the formulation of plastics, rubber products, photographic supplies, insecticides, dyes, textiles, pharmaceuticals, and other products. About 100,000 pounds a year of hydrazine salts, mainly the hydrochloride or hydrobromide, are prepared and shipped for use as a soldering flux. In addition, about 1,000,000 pounds annually are shipped in aqueous solution (35-44%) for use as an oxygen scavenger in boiler water. This amount will probably increase. Varying amounts of anhydrous hydrazine are shipped for use as a rocket fuel. In 1963-64 about 11,000,000 pounds of anhydrous hydrazine were used for this purpose, but current consumption is less than 1,000,000 pounds a year.

The Physical and Chemical Properties of Hydrazine

Anhydrous hydrazine is a colorless, oily, hygroscopic liquid at room temperature, fuming in air, with a penetrating odor resembling that of ammonia. Hydrazine can be distilled at temperatures about 113.5°C. It is an extremely irritating gas, exhibiting a great affinity for water and a marked tendency to condense or to be adsorbed onto surfaces including metallic interfaces, chamber walls, and the fur of animals. It is quite difficult to prepare anhydrous hydrazine from aqueous solution because of its great affinity for water. However, it has been shown that solutions containing 85% or more hydrazine behave essentially like anhydrous hydrazine.

Hydrazine is notable for its great reactivity with a wide variety of reagents including the halogens, alkali metals, and sulfur dioxide. It is a powerful reducing agent and serves as a solvent for many inorganic substances. It is miscible with water and lower aliphatic alcohols. In aqueous solution hydrazine is a slightly weaker base (pKa_1 of 8.07) than ammonia. The concentration of such solutions is conventionally specified as mole % hydrazine hydrate ($N_2H_4 . H_2O$; M.W. = 50). Hydrazine and water form an azeotropic mixture at 55 mole % (bp_{760} = 120.3°C). It should also be noted that aqueous solutions of hydrazine reduce molecular oxygen quite rapidly; therefore, dilute solutions of hydrazine will deteriorate appreciably on contact with the atmosphere. Autoxidation is a complex reaction that is affected by pH (Audrieth and Ogg, 1951; Moeller, 1952).

Hydrazine burns in air with the liberation of 148.6 kilocalories per mole. It may ignite spontaneously on contact with oxidants like hydrogen peroxide and nitric acid or porous materials such as earth, asbestos, wood, or cloth. Hydrazine is considered reasonably thermostable and Thienes et al: (1948) have shown that it is not particularly susceptible to detonation by impact. However, it will decompose explosively on sparking at 100°C or at temperatures above 350°C. Some of the pertinent physical constants of hydrazine are listed in Table 1. For more information the reader is referred to the comprehensive review by Audrieth and Ogg (1951)

Effects On Animals

Acute Toxicity

After exposure to hydrazine, animals may die within a few hours on convulsions, respiratory arrest, or cardiovascular collapse; or two to four days later of kidney or liver injury (Weir et al. 1964; Witkin, 1956). When this delayed death is taken into account, the single-dose LD_{50} of hydrazine is not markedly different regardless of the route of administration (Krop, 1954; Witkin, 1956). The acute toxicity of hydrazine by oral and parenteral routes is given in Table 2.

The 4-hour LC_{50} of hydrazine vapor is 254 ppm for mice and 580 ppm for rats according to Jacobson et al. (1955). Comstock et al. (1954) reported a one-hour LC_{50} of 640 ppm for rats, although this value is a "nominal" concentration and is probably higher than the actual concentration.

It is interesting to note that the lethal dose of hydrazine vapor calculated from LC_{50} (lethal concentration at constant time) or LT_{50} (lethal time at constant concentration) data does not differ appreciably from the LD_{50} obtained from oral or parenteral administration to rodents. Such "maximum inhaled doses" assume complete retention of inhaled material (Clark et al. 1968) and are calculated as the product of the concentration of hydrazine in the vapor, duration of exposure, and minute volume (average volume of air reaching the alveoli per minute) of the species divided by body weight. However, agreement with LD_{50} values is good only within a moderate range of vapor concentrations. The correlation fails at concentrations that are sufficiently irritating to cause a decrease in tidal volume (average volume of inspired air in a single breath) by shallow breathing, or which decrease the rate of respiration and minimize physical activity.

Repeated Dose Toxicity

The lethality of hydrazine is approximately the same whether it is given in a large single dose or in an equivalent amount supplied in small discontinuous doses, e.g., daily. Furthermore, the accumulated lethal dose appears to be similar for all routes of absorption, including inhalation.

Patrick and Back (1964) gave daily intraperitoneal injections of hydrazine to monkeys and rats for various periods of time on a 5 days/week schedule. Four monkeys received 20 doses of 5 mg/kg, 6 received 4-5 doses of 20 mg/kg, and 2 received 20 doses of 5 mg/kg followed by 8 doses of 10 mg/kg and 4-5 doses of 20 mg/kg. None of

the animals died, although weakness, lethargy, emesis and weight loss were noted. Twenty-five rats were given 10 mg/kg/day for 5 weeks, and an equal number received 20 mg/kg/day for the same period of time. All animals survived the lower dose, but at the higher dose 10/25 died between the eighth and twenty-first doses. When Comstock et al. (1954) exposed rats 6 hr/day, 5 days/week, to hydrazine vapor, 54 ppm killed 14/16 in 4 to 13 exposures; 20 ppm killed 11/13 in 13 to 30 exposures; 14 ppm killed 23/30 in 1 to 105 exposures; and 5 ppm killed 2/10 with deaths in the twenty-eighth week. Similar daily exposures of dogs at 5 ppm over a 6-month exposure produced no deaths and very little pathology. However, elevating the concentration to 14 ppm produced marked effects and some deaths.

House (1964) found a high mortality among monkeys, rats and mice exposed to a concentration of 1 ppm of hydrazine vapor continuously for 90 days. Although 8 of 10 monkeys lived, only 2 of 50 rats and 2 of 100 mice survived. Most of the mice died within 4 weeks, while about half of the rats died between the sixth and tenth weeks.

Kulagina (1962) has found that a single 2-hour exposure to very small concentrations of hydrazine vapor (19 ppm; 0.6 mole/liter) caused detectable changes in the conditioned reflex responses of rats and mice. There were no deaths among rats exposed to 0.74 - 4 ppm (0.03 - 0.16 mmole/l) hydrazine vapor 4 hr/day, 6 days/week, for 7 months, but these animals showed effects on kinds of behavior that require coordinated function of the nervous system. These functions returned to normal 3-4 weeks after the exposure.

Weatherby and Yard (1955) have reported on exposures to small amounts of hydrazine vapor over an extended period of time. Guinea pigs exposed to 5-6 mg/m^3 (4-5 ppm) for 6 hr/day, 5 days a week for 47 days had no deaths, although at autopsy their lungs showed pneumonitis and diffuse atelectasis. Clark et al. (1968) have calculated the "maximum inhaled dose" for these exposures as 34-68 mg/kg/day. These same authors also gave young rats hydrazine in water at concentrations of 0.10, 0.20, 0.50, 1.00, and 2.00 mg/ml. Daily doses at these concentrations amounted to about 16, 26, 96, 128, and 192 mg/kg/day, respectively. The animals were reluctant to accept concentrations over 0.5 mg/ml and several animals receiving this amount or more died. Doses of 16 - 26 mg/kg/day did not produce any deaths or pathology after being ingested for 14 weeks. The stability of hydrazine

in water is a direct function of the dissolved oxygen, which raises some question regarding the significance of hydrazine administered in drinking water.

Tissue Pathology

In 1908 Underhill and Kleiner found that the liver is the chief site of structural damage after hydrazine intoxication of dogs (100 mg/kg s.c.). Wells (1908), reporting on the results of his histologic examinations of these dogs, emphasized the remarkably specific destruction of the cytoplasm of the parenchymatous cells of the liver, which began at the center of the lobule. The cell nuclei appeared intact but were surrounded by an overwhelming infiltration of fat. No other tissue appeared to be damaged. Amenta and Johnston (1962) reaffirmed these observations in rodents. Subcutaneous administration of 2×10^{-3} moles /kg hydrazine caused periportal and midzonal accumulation of liver fat and loss of liver glycogen, with recovery of all observed function within 3 to 4 days post-administration.

Single exposures of rodents to lethal (2,000 ppm) or sublethal (800 ppm) concentrations of hydrazine vapor for 1-2 hours did not produce liver damage (Thienes et al., 1948), but concentrations that caused death after one or more days did produce accumulation of fat in the liver. There were some deaths among rats and mice exposed to 6 mg/m^3 or 18 mg/m^3 hydrazine vapor for 6 hr/day for 30 weeks. (Comstock et al., 1954), but there was no evidence of liver pathology. Some pulmonary congestion, emphysema, and atelectasis were noted. In similar experiments rats were exposed to 6 mg/m^3 hydrazine vapor for 5 days a week for 18 weeks, Weatherby and Yard (1955) noted central-zone fatty changes in the liver and kidney congestion and areas of emphysema in the lungs. However, they found no pathology in animals that ingested 15-25 mg hydrazine daily in drinking water.

From the above it is apparent that hydrazine produces pathology in the lungs as well as the liver. While it is possible that these pulmonary effects are due to local irritation caused by inhalation, Thienes et al. (1948) have concluded that hydrazine has a direct effect on pulmonary tissue since they observed that toxic doses of hydrazine given by any route of administration affected the endothelium of blood vessels, particularly those in the lung.

Most of the pathology of hydrazine intoxication has been studied in rodents. However, Patrick and Back (1964) showed that fatty change in the liver takes place at much lower dosages in monkeys than in rats. Monkeys receiving 20 mg/kg daily for 7 days exhibited marked lipid accumulation in the liver, the kidneys, myocardium, and skeletal muscle. Massive liver necrosis was observed in one of the six animals.

Absorption, Distribution, and Excretion

Hydrazine is absorbed by many routes (Table 2). Recently, Smith and Clark (1972) have reported on the absorption of hydrazine through the intact skin of anaesthetized dogs. Topical application of high doses (3-15 mmoles/kg) (96-480 mg/kg) of hydrazine produced detectable amounts of hydrazine in plasma within thirty seconds. The kinetics of this process are not clear since dogs receiving the same dose of hydrazine attained different plasma concentrations of the compound and furthermore did not show any correlation between plasma and urinary concentrations of hydrazine. However, the authors believe that the rapidity of hydrazine absorption may be dose-related since the increase of the sixty-minute plasma concentration over the ten-minute value is a function of the amount of hydrazine applied.

Although the metabolic fate of hydrazine is unknown, it has been shown that some hydrazine is eliminated unchanged in the urine. McKennis et al. (1955) reported that 5-11% of an intravenous dose (50 mg/kg) of hydrazine sulfate was excreted by anaesthetized dogs after four hours. Within two days 50% of the dose of hydrazine sulfate was excreted by unanaesthetized dogs that received 15 mg/kg by intravenous injection. Evidence for a two-step in vivo acetylation of hydrazine following intraperitoneal injection of rabbits was reported by McKennis et al. (1959). This appears to be a detoxification mechanism. Dambrauskas and Cornish (1964) found that rats given 60 mg/kg of hydrazine s.c. excreted 8% and 27% after two and twenty hours, respectively.

Effects on Metabolism and Enzymes

Hydrazine produces a variety of metabolic effects, yet the bulk of investigative work has focused on the liver and the central nervous system. Hydrazine may cause a transient hyperglycemia followed by hypoglycemia. This sequence occurs during the first four hours following intravenous injection to dogs and has been associated with

depletion of glycogen stores in both liver and muscle (Taylor, 1966). Hydrazine has been found to inhibit the formation of carbohydrate from amino acid precursors (Lewis and Izume, 1926; Amenta and Johnston, 1963). Ray et al. (1970) have found that one site of inhibition is the conversion of oxaloacetate to phosphoenolpyruvate. Hydrazine also interferes with glycogen formation in the liver following glucose administration (Izume and Lewis, 1926; Amenta and Dominguez, 1965). The hypoglycemia in hydrazine-treated, fasted rats is associated with elevations in the concentration of free fatty acids in the plasma, the total fatty-acid content of the liver, and the hepatic secretion of triglycerides into the blood (Trout, 1966). If blood glucose is kept high by using nonfasted or carbohydrate fed rats, free fatty-acid levels in the plasma are not increased. Most of the work reporting accumulation of lipid in the liver and kidney following single or multiple doses of hydrazine has been done in the rat (Amenta and Johnston, 1962; Weatherby and Yard, 1955; Dominguez et al., 1962; Patrick and Back, 1965). It is not known how this deposition occurs but Clark et al. (1968) have speculated that lipid peroxidation may play an important role in the process. Some oxidative effects may be involved since Beyer (1943) has shown that vitamin C protects against the hepatic damage.

Hydrazine interference with carbohydrate, fat, and amino acid metabolism may be related to the fact that it produces a significant decline in serum concentration of insulin as well as glucose in 18-hour fasted rats (Potter et al., 1969). Hydrazine can also impede the secretion of insulin in response to an administered glucose load (Aleyassine and Lee, 1971). Aleyassine and Lee also have demonstrated that hydrazine inhibits the production of insulin from pancreatic tissue in vitro. They feel that this inhibition may result from the accumulation of certain biogenic amines in the beta cells of the pancreas following mono-amine oxidase inhibition.

Other authors have suggested that some interference with amine metabolism may also be responsible for the convulsant activity of hydrazine in the central nervous system. However, at the present time there are few reports of the effects of hydrazine on amine metabolism in intact animals. Reed et al. (1964) showed that hydrazine strongly inhibits the oxidation of putrescine and methylamine to CO_2 by intact rats. Hydrazine, unlike some of its derivatives, was not found to be a mono-amine oxidase inhibitor, in vivo, but it did appear to possess strong diamine oxidase suppressive activity. The

compound partially inhibited the metabolism of large doses of L-alanine-^{14}C to $^{14}CO_2$ and almost completely obstructed the conversion of gamma aminobutyric acid (GABA) -1-^{14}C to $^{14}CO_2$. Medina (1963) showed that rats injected with hydrazine had an inhibition of brain glutamic acid decarboxylase and GABA-transaminase and a concomitant rise in GABA. However, he could not establish a direct relationship between the convulsive action of hydrazine and the metabolism of GABA in whole rat brain.

Other investigators have attempted to relate hydrazine toxicity to the cofactors of GABA transaminase, (vitamin B_6 and its congeners). Unfortunately, neither pyridoxine nor pyridoxal phosphate protects against hydrazine convulsion in rats (Uchida and O'Brien, 1964) although vitamin B_6 does decrease the severity of convulsions initiated by some hydrazine derivatives. Although Roberts and co-workers have found that various mixtures of L-arginine, L-glutamate, L-alanine, alpha-ketoglutarate, and oxalacetate protect against hydrazine convulsions in the mouse, there is little evidence that liver changes or other metabolic effects are reduced (Roberts et al., 1963, 1964, 1965).

These metabolic effects, some of which are produced by very low doses, are transient and readily reversible. There is no evidence that they are related to any of the overt manifestations of hydrazine toxicity.

Cardiovascular Effects

The importance of cardiovascular toxicity from hydrazine remains speculative. Walton et al. (1954) could not produce a significant effect on heart contractile force in dogs at one-tenth to one-fourth the intravenous LD_{50} (LD_{50} = 25 mg/kg). They observed transient decreases in blood pressure and ectopic rhythms at two to eight times the LD_{50}, but death was produced by respiratory rather than cardiac arrest. Murtha and Wills (1953) demonstrated a gradual decrease in contractility of cat heart papillary muscle four to five hours after the addition of hydrazine to the muscle bath. They postulated that toxic cardiovascular manifestations would probably not be observed until some time after exposure.

Hayden and Murray (1965) studied the cardiopulmonary effects of subacute hydrazine toxicity by right and left heart catherization, expired-gas analysis, and necropsy. Seven rhesus monkeys were given

between 50 and 70 mg/kg i.p. over a three-day period. The animals were ill, but not moribund. The monkeys lost weight, and arterial blood pressure, cardiac and stroke index, systolic-ejection period, tension-time index, left-ventricular-work index, oxygen-consumption index, and arterial oxygen capacity decreased. Fatty myocardial alterations present in six of the seven monkeys were attributed to dehydration and secondary metabolic disturbances, but a direct action of hydrazine on the heart could not be excluded. Over all, doses required to produce marked changes in the cardiovascular system are far in excess of those that can be attained reasonably by inhalation.

Tumorigenesis

There have been reports that hydrazine is a tumorigenic agent and may possibly have some carcinogenic action in mice. Biancifiore and Ribacci (1962) and Biancifiore *et al.* (1964) gave 1.13 mg of hydrazine sulfate, by mouth, to mice twice daily for 46 weeks. All developed multiple pulmonary tumors. Juhasz *et al.* (1966) injected mice with 25 mg of hydrazine on sixteen occasions over a period of 46 days. At this time 34 of 60 mice survived and subsequently 13 of the survivors developed myeloid leukemia or tumors (reticulum-cell sarcomata) within 100 to 313 days. However, Toth (1972) observed no significant carcinogenesis when a 0.012% solution of hydrazine sulfate was the only drinking water ingested by randomly bred Syrian golden hamsters during their lifetime.

Mutagenesis

Hydrazine may react *in vitro* under rather severe conditions with the pyrimidine bases in nucleotides to form dihydro- or 4-hydrazino derivatives or to effect scission of the pyrimidine ring (Lingens and Schneider-Bernloehr, 1965). The occurrence of similar reactions *in vivo* could alter the base sequence in DNA or RNA and produce a mutagenic effect. Some mutagenic effects of hydrazine have been observed in bacteria but there have been no similar observations in animals (Lingens, 1961).

Effects On Plants

Hydrazine is poisonous to some plant seedlings. Heck et al. (1963) found that 1,000 ppm hydrazine in water decreased the number of peanut and corn seeds that would germinate. Hydrazine concentrations below 200 ppm reduced the germination of rice and peas but did not affect the germination of alfalfa or endive. The growth of all four was inhibited (Hoover et al., 1964).

Pinto bean plants and cotton seedlings grown in water containing hydrazine showed inhibition of growth and dehydration of foliage. Water solutions containing 300 ppm caused the death of cotton seedlings in 48 hours and 600 to 1,000 ppm caused death in 30 hours (Heck et al., 1963).

Spraying of seedlings (cotton, pinto bean, soybean, endive, and squash) with 2,000 ppm hydrazine caused slight temporary injury. Concentrations of 6,000-10,000 ppm hydrazine caused increased injury and some plants died. Fumigation of these and alfalfa seedlings with 25-30 ppm hydrazine caused severe injury including wilting, dehydration, and defoliation (Heck et al., 1963).

Effects On Humans

Data from human exposures to hydrazine are rare, but as early as 1887 Curtius recognized that hydrazine vapors were extremely irritating to the eyes, nose, and throat. Comstock et al. (1954), citing a 1946 U.S. Naval Report, mention that exposure to hydrazine vapor produces immediate and violent irritation of the nose and throat. Over a period of hours itching, burning, and swelling of the eyes may develop. After severe exposure, blindness, which lasts for about a day, may ensue. Inhalation of hydrazine vapor causes dizziness and nausea, and dermal contact with concentrated solutions of hydrazine results in alkali-like burns (Krop, 1954).

Olin Corporation, which produces anhydrous hydrazine and hydrazine hydrate, has maintained records of its employees since 1953. During that time 57 persons worked in the plant; 22 are still employed in the hydrazine operation, 9 work somewhere else in the same plant, and 7 others are employed at other company locations. Only 4 deaths have occurred among the 57 employees and all were considered to be the result of natural causes. From 1953 through 1960 there were 21 exposures to hydrazine that required medical attention. The majority of these involved severe eye irritation from vapors; the remainder involved primary skin irritation. One employee required reassignment because of dermal sensitization.

There are a number of published reports on dermal sensitization arising from exposures to hydrazine hydrate (Evans, 1959; van Ketel, 1964; Hovding, 1967), or hydrazine hydrobromide (Cook, 1955; Wheeler et al., 1965). It should be noted that the development of an allergy to hydrazine or its salts may generate sensitivity to hydrazine derivatives, including the drugs isoniazid and hydralazine (Apresoline). Use of these drugs by sensitized persons produces extensive eczema.

Severe effects from human exposures to hydrazine hydrate also have been noted. In 1965 Reid reported that a machinist became unconscious after drinking some concentrated hydrazine solution. The victim remained unconscious for several days and experienced numerous seizures during this time. However, his condition gradually improved and he was discharged from the hospital after two weeks although he still had residual neurological defects. His subsequent fate is unknown. Sotaniemi et al. (1971) described another machinist who died, apparently from repeated exposures to hydrazine hydrate. Initially, the victim

had experienced nausea, tremor, and conjunctivitis every time he handled hydrazine. On these occasions the hydrazine vapor concentration was estimated at 0.071 mg/m^3, but no details on the handling or skin exposure were given. After six months of repeated exposures to hydrazine he was admitted to the hospital because of cough, fever, diarrhea, vomiting, icterus, and stupor. He was jaundiced and incoherent; his cardiac rhythm was irregular, his blood pressure was 100/70 mm Hg., his abdomen was enlarged, and his liver was tender. He died after 3 weeks and autopsy showed severe tracheitis and bronchitis, lobar pneumonia, severe tubular necrosis with interstitial hemorrhage and inflammation in the kidneys, small focal liver cell necroses, and areas of granular degeneration of heart muscle fibers.

Treatment of Hydrazine Toxicity

Any material on the skin should be washed off immediately. Hydrazine is absorbed into the bloodstream very rapidly. Unfortunately, there is no specific therapy.

Treatment is symptomatic, aimed at controlling convulsions, overcoming hypoglycemia, and maintaining fluid balance and urinary output. Clark et al. (1968) give a more detailed discussion of supportive measures.

Existing Air-Quality Standards

The Threshold Limit Value adopted by the ACGIH for 1973 is 1.0 ppm (1.3 mg/M^3) with a "skin" notation. This value was based on studies of Comstock et al. (1954) who found no deaths among dogs and rats exposed to 5 ppm hydrazine, 6 hours daily, 5 days per week for 6 months.

The Emergency Exposure Limits (EEL) recommended for spacecraft operations by the Committee on Toxicology of the NAS/NRC are 30 ppm for 10 minutes, 20 ppm for 30 minutes, and 10 ppm for 60 minutes. The 10-minute limit is less than 10% of the 4-hour LC_{50} for mice and rats found by Jacobson et al. (1955). These limits are deemed well below those necessary to produce significant metabolic or CNS effects.

Proposed Short-Term Limits

The rationale for recommending limits for short-term exposure of the public to air pollutants is detailed in the first document of this series: "Basis for Establishing Guides for Short-Term Exposures of the Public to Air Pollutants," (NAS-NRC, 1971). These limits include both Short-Term Public Limits and Public Emergency Limits.

Short-Term Public Limits (STPL's)

The limits for short-term exposure of the public to air pollutants are established with a view toward the possibility of occasional repeated events in the same locality. These events, such as intentional release of hydrazine to the atmosphere from firing of rocket motors, are assumed to be controllable so that the limit is not exceeded in any area occupied by the public.

The primary effects in animals from acute exposures to hydrazine are pulmonary irritation, liver damage, and , at high doses, central-nervous-system effects including convulsions. Similar effects have been observed in humans with the addition of contact dermatisis and dermal sensitization. None of the foregoing effects are anticipated at the STPL's recommended since they are well below the lowest acute-effect level observed in animals (19 ppm for 2 hours). These are all time-weighted averages within the periods given. As a further

precaution against pulmonary irritation the recommendation for 10 minutes has been restricted to one half the total dose recommended for 30 and 60 minutes.

STPL's

Time	Limit (25° C/760 mm Hg)
10 min	15 ppm (20 mg/m^3)
30 min	10 ppm (13 mg/m^3)
60 min	5 ppm (7 mg/m^3)

Public Emergency Limits (PEL's)

Public emergency limits are those for accidental, unpredictable or uncontrollable events. These exposures are expected to be single events in the lifetimes of the very few people who would be accidentally exposed. The PEL's assume that some temporary discomfort may occur from irritation of the eyes and upper respiratory tract, but that any effect resulting from the exposure is reversible and without residual damage. As a further precaution against pulmonary irritation the recommendation for 10 minutes has been restricted to one-half the total dose recommended for 30 and 60 minutes.

The PEL's for hydrazine are identical to the EEL's. They are time-weighted averages.

PEL's

Time	Limit (25° C/760 mm Hg)
10 min	30 ppm (40 mg/m^3)
30 min	20 ppm (25 mg/m^3)
60 min	10 ppm (13 mg/m^3)

III. GUIDE FOR MONOMETHYLHYDRAZINE

Background

Monomethylhydrazine (MMH) is an important reactant in high-energy propellant systems. It is used almost exclusively as a rocket fuel and its consumption fluctuates with its use in our space program. At the present time about 200,000 pounds of MMH are produced annually in the United States.

Physical and Chemical Properties

MMH is a vitriolic liquid that fumes in air and possesses a characteristic ammoniacal odor. The compound has a great affinity for water and mixes with it in all proportions to yield weakly basic solutions (pKa 8.0±.1). It is only partially miscible with hydrocarbons and low-molecular-weight alcohols. Chemically, MMH is notable for its strong reductive capacity. In this respect MMH vapor is extremely reactive and undergoes rapid autoxidation in air. Vernot et al. (1967) studied this reaction in some detail since the rate of autoxidation affects the stability of solutions of MMH exposed to air.

The autoxidation of MMH results in a variety of products including carbon monoxide, methanol, acetaldehyde, and various carbon or nitrogen heterocyclic compounds. It appears that molecular nitrogen is the main product of the reaction and some methane is also produced. Vernot et al. (1967) have shown that the reaction obeys first-order kinetics with respect to MMH and is probably surface catalyzed. They have reported the half life of MMH vapor to be 34 minutes in a 320-ml glass container at room temperature.

MMH has many properties that contribute to its desirability as a fuel. The compound is extremely flammable and will ignite spontaneously if it comes in contact with metallic oxides or other oxidizing agents, or even if it is exposed to air over a large surface area. Its decomposition is highly exothermic yet the liquid itself is reasonably easy to handle and store since it is stable up to its boiling point if kept out of contact with air and it is not sensitive to decomposition from shock or friction. Table 1 lists some of the physical constants of MMH.

Acute Toxicity

MMH is an extremely lethal compound that exercises acute toxic effects in the central nervous system. (CNS). The LD_{50} values that have been determined for MMH are summarized in Table 2 and LC_{50} values are shown in Table 3. MacEwen et al. (1969) conducted a series of experiments to establish Emergency Exposure Limits (EELs) for MMH vapor. They exposed dogs, monkeys, rats, and mice to MMH vapors for single periods of 15, 30, or 60 minutes at concentration that would yield concentration x time (CT) doses of 900 ppm-minutes. The 900 ppm-minute CT dose of MMH used in these experiments was calculated to be 25% of the maximum nonlethal concentrations for the most susceptible species tested, the squirrel monkey. This concentration is also below the lowest dose reported to cause marginal decrements in the performance of trained monkeys (Reynolds and Back, 1966) and cats (Sterman et al., 1969a). None of these exposures produced respiratory irritation, overt signs of toxicity, biochemical, hematological, or pathological abnormality in any of the four species tested.

The signs of MMH toxicity in mice, rats, dogs, and monkeys include irritation of nose and eyes, salivation, emesis, diarrhea, hyperactivity, tremors, and severe tonic-clonic convulsions, which cause death.

When Reynolds and Back (1966) injected 18 monkeys intraperitoneally with small amounts of MMH (2.5 - 5 mg/kg), 10 animals showed decrements in the performance of previously learned operant tasks before the appearance of clinical evidence of illness. Sterman et al. (1969b) have reported dose-related effects on the learned performance of cats given subconvulsive doses of MMH. Intraperitoneal injection of 1, 2, or 4 mg/kg MMH depressed the runway performance of all cats within thirty minutes. Those cats receiving 1 to 2 mg/kg showed small decrements in performance initially but, surprisingly, performance was actually facilitated 24 hours after injection. However, the performance of cats receiving 4 mg/kg was completely disrupted at the end of 2-5 hours and was still depressed after 24 hours. Convulsions were initiated in cats given 9 mg/kg, but it is interesting to note that the onset of convulsions was delayed in cats who had been trained to restrict their physical movements.

Even though subtle changes in behavior can be detected before the onset of convulsions, it has not yet been possible to identify a specific neural site of action for MMH. At the present time it can only be said that MMH acts somewhere in the ventral structures of the mid-brain (Weir et al., 1965). The evidence for this assumption arises from experiments of Witkin and Weatherby (1955), who showed that rats and mice exposed to MMH in excess of LD_{50} doses do not convulse caudal to a cord transection or after prior treatment with d-tubocurarine. It has also been shown that convulsions induced in mice and rats by MMH can be abolished by the administration of secobarbital (50 mg/kg), phenobarbital (100 mg/kg), or mesantoin (200 mg/kg). Pyridoxine counteracts convulsive effects in several species (Back et al., 1963b).

Acute exposure to MMH produces effects other than those on the CNS. Sopher et al, (1967) have described toxicity in dogs that begins with an episode of severe intravascular hemolysis, hemoglobinemia, and hemoglobinuria. This is followed by nephrotoxicity, which may include a frank necrosis of proximal tubular epithelial cells. Marked erythrophagocytosis by the Kupffer cells of the liver also occurs after 12 to 24 hours. Both the physical signs and pathology of the toxicity increase as the dose of MMH increases from 10 to 30 mg/kg.

Comparable dose levels do not produce severe effects in monkeys. The only renal effect these authors observed was swelling of the proximal tubular epithelium. Massive doses of MMH do not produce hemoglobinuria in monkeys and although erythrophagocytosis is seen it is not especially prominent. Back and Pinkerton (1967) have reported that intraperitoneal injections of MMH cause fatty infiltration of the liver in monkeys.

These hemolytic, renal, and hepatic effects are delayed and appear to be dissociated from CNS effects since they are not suppressed by pyridoxine (Sopher et al., 1967). They are not as pronounced when MMH is administered by inhalation rather than injection and in any event are not severe enough to cause death.

Repeated-Dose Toxicity

Back and Pinkerton (1967) investigated the effects of daily doses of MMH repeatedly injected intraperitoneally into monkeys. Their observations indicate that small increments of 2-5 mg/kg change "no-effect" doses of MMH to lethal doses. Twenty-three injections

of 2.5 mg/kg over a five-week period produced virtually no signs of illness in eight monkeys. However, successive daily injections of 5 mg/kg caused eight other monkeys to vomit on day two; four of the eight vomited and two convulsed on day three. The daily dose was then reduced to 2.5 mg/kg for eight days and none of these animals showed any adverse effects. Four received 12 more injections of 2.5 mg/kg MMH without effect. The dose for the other four was increased to 5 mg/kg/day and 12 such doses were tolerated with only occasional emesis. Finally three monkeys were placed on a regimen of 7 mg/kg/day alternating with 10 mg/kg/day; one died on day two, one on day three, and one on day four. These data also suggest that daily doses of 2.5 mg/kg or 5 mg/kg MMH do not have cumulative lethal effects since monkeys survived as many as 20 injections or a total dose of 65-95 mg/kg with no ill effects. However, the possibility that MMH build-up can occur at other times cannot be excluded.

Metabolic and morphologic data were collected on all the animals in these studies. The authors were not able to discover anatomical or biochemical pathology at any dose level. This finding is remarkable in view of the fact that extensive renal damage is seen in dogs given a single injection of 5-10 mg/kg MMH (Sopher et al., 1967).

Chronic exposures of dogs and monkeys to low concentrations of MMH vapor have been shown to produce a variety of hemolytic effects that are related to the reaction of MMH with circulating red blood cells (MacEwen and Haun, 1971). Groups of 8 beagle dogs and 4 rhesus monkeys were exposed to 0.2, 1.0, 2.0, and 5.0 ppm MMH vapor for six hours a day, five days a week for sic months. Half of the dogs were killed at the end of the experiment while the others were held for another 30 days to determine the reversibility of effects. A significant number of dogs showed a sharp increase in reticulocyte formation, serum bilirubin and alkaline phosphatase and a depression of red cell count, hematocrit, and total hemoglobin. In those exposed to 2 and 5 ppm the decrease in hemoglobin was accompanied by a dose-related increase in methemoglobin formation and the production of Heinz bodies. Hemolytic effects were not as pronounced in monkeys but red cell count, hematocrit, and total hemoglobin were decreased. The pattern of methemoglobin formation in monkeys is not clear but the appearance of Heinz bodies is taken as evidence that some reaction

occurs between MMH and hemoglobin. Few detrimental effects were observed during chronic exposures of groups of 50 Wistar rats and 40 ICR mice to 0.2, 1.0, 2.0, and 5 ppm, 6 hours a day, 5 days a week for 6 months. At concentrations of 2.0 and 5 ppm some mice died and some rats showed a dose-related depression of growth.

MacEwen and Haun (1971) concluded that chronic exposure of dogs to MMH produces a dose-related hemolytic anemia with Heinz body formation, which has no apparent threshold dose and which is reversible after removal from exposure, at least up to 5 ppm. Because of the similarity between dog and human blood, (Leahy, 1970) MacEwen et al. (1970) have recommended that the current Threshold Limit Value (TLV) of 0.2 ppm be re-examined to consider a safety factor for individuals with pre-existing blood dyscrasias or hemolytic traits.

Tissue Pathology

Pathologic findings in most species exposed to lethal concentrations of MMH include pulmonary congestion with some hemorrhage, hepatic congestion of varying degrees, and swelling of the renal tubular epithelium, which frequently appears glassy and eosinophilic (MacEwen et al., 1969). Sub-arachnoid hemorrhage and spleens that are bloodless with virtually empty sinusoids are frequently observed in dogs. Neither the hemorrhage nor the visceral congestion are extensive enough to cause death and they may be secondary to the severity of the convulsions that precede death (Jacobson et al., 1955).

Visceral congestion is also apparent in dogs and monkeys that survive near-lethal exposures to MMH but it is not as severe as that seen in animals that died during exposure. MacEwen et al. (1969) sacrificed dogs and monkeys serially for 60 days after exposure to high concentrations of MMH. During and after exposure the most common and persistent pathology occurs in the kidney and ranges from mild swelling of the tubular epithelium to vacuolization and coagulative necrosis of the epithelial cells. The renal changes observed in dogs were more extensive than those seen in monkeys.

Dogs exposed to subconvulsive doses of MMH exhibit hematuria, hemoglobinuria, methemoglobinuria, and urinary cast formation (Sopher et al., 1967). Histopathologic examination of their kidneys reveals proteinaceous precipitates in the proximal tubules with occasional hemoglobin casts and moderate to severe degeneration of

the proximal tubules frequently accompanied by tubular necrosis. Although renal function in monkeys does not appear to be greatly affected by exposure to MMH, George et al. (1968) have described some subcellular morphologic kidney changes after single injections of 7.5 mg/kg or repeated injections of 2.5 or 5 mg/kg MMH.

Kroe (1971) found renal tubular hemosiderosis in dogs and mice exposed intermittently to MMH vapor in concentrations greater than 1 ppm for six months. He also observed periportal cholestasis, bile-duct proliferation and hemosiderosis in the livers of both species. These effects were not seen in monkeys or rats.

Absorption, Distribution, and Elimination

MMH can be detected in plasma shortly after I.p. injection (Pinkerton et al., 1967) or cutaneous application (Smith and Clark, 1969); peak plasma levels generally occur after 2-4 hours. Distribution studies at 2 and 4 hours have shown that large amounts of MMH appear in muscle and that relatively high concentrations are found in the liver, kidney, bladder, pancreas, and serum of mice, rats, dogs, and monkeys. The elimination of MMH or its metabolites occurs via both urine and respiratory gases. Pinkerton et al. (1967) found that 25-40% of MMH or its metabolites was excreted in urine after 48 hours. In the mammalian kidney MMH is excreted by a combination of glomerular filtration, passive diffusion-mediated reabsorption and simultaneous tubular secretion, (Coe et al., 1967). Dost et al. (1966) showed that MMH is initially expired by rats as 4 parts methane and 1 part CO_2. The mechanisms involved in the production of CO_2 and CH_4 from MMH are not known but rate studies suggest that the two gases may be produced by different mechanisms.

The respiratory and urinary elimination of MMH appears to be subject to species variations and dose-related effects. The data of Pinkerton et al. (1967) indicate that mice, rats, dogs, and monkeys probably clear MMH in different ways. Dogs do not attain maximum excretory rates or tissue levels until four hours after injection, while monkeys, rats, and mice reach maximum levels within two hours. This difference may explain the renal side effects from administration of MMH that occur in dogs but not in other species. Dost et al. (1966) observed that the fraction of MMH converted to respiratory gases was dependent on the dose. After 27 hours 80% of a 0.46 mg/kg dose, 37% of a 5.5 mg/kg dose, 31.0% of an 11 mg/kg dose, and 24.0% of a 22 mg/kg dose were converted to methane and carbon dioxide. Similar

reductions in urinary elimination of increased doses of MMH also occurred. After 27 hours rats excreted 40% of a 5.5 or 11 mg/kg dose but only 20% of a 22 mg/kg dose. The lower rate of combined respiratory and urinary elimination of higher doses was accompanied by a greater retention of MMH in tissue. The authors speculated that there may be a limit to the rate at which the compound can be excreted. However, these effects could also arise from failure of excretory mechanisms due to intoxication.

Effects on Metabolism and Enzymes

Present evidence concerning the effects of alkylhydrazines on carbohydrate metabolism is inconsistent. However, attempts are being made to clarify this matter because these effects may be associated with some of the regulatory mechanisms that influence insulin secretion. The factors that mediate insulin release are not well understood but many effects of MMH toxicity appear to resemble those of insulin insufficiency.

In 1964 O'Brien *et al.* found that acute LD_{50} doses of MMH given to fed rats caused hyperglycemia, which occurred immediately and lasted several hours. Later Fortney and Clark (1967) reported the occurrence of transient hypoglycemia and glycogen depletion in anesthetized dogs given acute doses of MMH. Monkeys given acute doses of 30 mg/kg MMH also showed severely depressed glucose levels within an hour after injection (Back and Thomas, 1970).

Recently, Dost *et al.* (1973) have observed that it is difficult to distinguish specific effects of high doses of MMH from the general physiologic damage of massive intoxication. They conducted carefully controlled studies on rats by a method of continuous glucose infusion, which allowed observations of the early effects of lower doses, the increasing effect of accumulating material, the nature of acute toxic episodes and recovery, if it occurred. They found that subacute doses of MMH caused spectacular increases in the blood glucose of fasted animals given an adequate glucose supply and substantial increases in fasted rats given no glycogen or glucose. The administration of 0.05 mMole/kg/hr MMH to fasted rats who had been receiving a continuous infusion of 150 mg/hr glucose-6-^{14}C for 10 hours produced an increase in blood glucose that started three hours after MMH was added to the infusion. Blood glucose rose steadily thereafter from a concentration

of about 80 mg/100 cc to 170 mg/100 cc. The MMH infusion was stopped after 7 hours because of convulsions but blood glucose continued to rise for another hour, reaching a peak of 280-290 mg/100 ml and remaining elevated for four hours. Preconvulsive behavior was evident about two hours after blood glucose had obviously begun to rise and an hour before the onset of convulsions. Rats fasted for 36 hours were given a three-hour infusion of 0.1 mMole/kg/hr MMH with only trace amounts of added glucose. Blood glucose increased from about 75 mg/100 ml to 85 mg/100 ml blood. At this point convulsions ensued. The MMH infusion was stopped, but blood glucose rose sharply to about 130 mg/100 ml blood. The investigators also found that crystalline insulin added near the peak of increased blood glucose reversed the hyperglycemia. It caused a brief but precipitous drop in blood glucose, which recurred when the dose of insulin was repeated.

While blood glucose levels were increased by the administration of MMH the oxidation of glucose to CO_2 was depressed in both fasted rats and those with adequate glucose supply. It is interesting to note that the output of respiratory CO_2 returns to normal at the end of MMH administration when glucose infusion precedes the infusion of MMH but not when infusion of MMH precedes the administration of glucose.

When pyridoxine is administered after MMH the oxidation of glucose to respiratory CO_2 is increased and blood glucose levels decline to normal (Dost et al., 1973). Pyridoxine also decreases MMH inhibition of glutamic and dihydroxyphenylalanine (DOPA)decarboxylases and glutamic-pyruvic transaminase in mouse brain (Furst et al., 1968). These findings lead to the speculation that the central nervous system effects of MMH may be related to these metabolic processes because they are all affected by the administration of pyridoxine. However, this cannot be established from the information that is available.

Cardiovascular and Renal Effects

The cardiovascular response to MMH in both conscious and unconscious dogs is characterized by depressor effects. Weir et al., (1965) measured changes in the cardiovascular function of two conscious dogs initially anesthetized with 25 mg/kg i. v. of sodium thiopental that received 25 and 50 mg/kg MMH, respectively, and four unconscious dogs (30 mg/kg sodium pentobarbital i. v.) that received 25 mg/kg (one dog), 50 mg/kg (two dogs) and 100 mg/kg (one dog). In all instances the MMH was given by intraperitoneal

injection. In all cases the MMH caused cardiac slowing accompanied by a minor fall in blood pressure in which the systolic pressure decreased about twenty minutes after injection and the diastolic pressure after ninety minutes. Recovery from these effects was still not complete after four hours. These authors also showed that MMH does not depress blood pressure or alter cardiac rate in animals in which ganglionic blockade had been produced with hexamethonium. Fifty mg/kg MMH administered in two dogs treated with 2 mg/kg hexamethonium produced a 25-30 mm rise in systolic and diastolic pressure and no alteration in cardiac rate. These findings support the conclusion that the cardiac slowing that usually occurs after the administration of MMH may be ascribed to medullary stimulation (Weir et al., 1965).

Experiments were also conducted to study the effect of MMH on the pressor activity of tyramine (Weir et al. 1965). When 50 mg/kg was given to two anesthetized dogs the pressor effect of tyramine increased 35% and the duration of the response doubled. These effects appeared within thirty (30) minutes and persisted for two hours. The pressor response to norepinephrine was unaltered by MMH. The prolongation and intensification of the cardiovascular effects of tyramine is generally accepted as evidence for monoamine oxidase inhibition; therefore, these experiments are consistent with other demonstrations that MMH is an inhibitor of this enzyme.

Carcinogenicity

Toth and Shimizu (1973) recently reported that significant numbers of Syrian golden hamsters developed malignant histiocytomas of the liver after ingesting 0.01% monomethylhydrazine in drinking water during their lifetime. Solutions were made up fresh on Monday, Wednesday, and Friday of each week; pH was not controlled (Toth, 1973). This Kupffer cell sarcoma occurred in 43 of 100 animals. The first tumors were observed after 46 weeks and the last developed after 103 weeks; the average latent period was 75 weeks. The average daily intake of MMH was 16 mg/kg based on a water consumption of 184 ml/kg/day. Convulsions and possibly anemia were noted at this dose level (Toth, 1973). No tumors were observed in control groups that ingested drinking water not treated with MMH.

Therapy of Intoxication

Some protection from the toxic manifestations of MMH can be attained. Mice and rats poisoned with 2 x LD_{50} of MMH may be kept free of seizures by repeated administration of mesantoin, phenobarbital,

or secobarbital but convulsions in dogs poisoned with MMH were not controlled by large doses (6 mg/kg) of mesantoin. Secobarbital did control convulsions in dogs, but 5-6 hours after the administration of MMH the dogs became comatose (Medical College of Virginia, 1954). Back et al. (1963b) and Geake et al. (1966) have shown that pyridoxine can counteract the convulsive effects of MMH in several species. However, pyridoxine does not fully prevent hypoglycemia, which may occur after the administration of large doses of MMH. Monkeys given 30 mg/kg MMH required additional glucose as well as pyridoxine to survive (Back and Thomas, 1970).

Effects on Humans

Reliable data on accidental human exposures to MMH are not available. Cases of eye irritation or skin irritation after repeated exposures to the chemicals have been reported from a plant where both MMH and UDMH are manufactured. In one instance dermal sensitization was severe enough to require job reassignment. The most accurate information on human exposures to vapor has been obtained from controlled studies done by MacEwen et al. (1970), who exposed seven volunteers to 90 ppm MMH for 10 minutes. Subjects found 90 ppm MMH more irritating to the eyes and nose than 30 ppm NH_3 but considerably less irritating than 50 ppm NH_3. Most experienced a slight moistening of the eyes but no overflow of tears. Several subjects reported a slight tickling sensation of the nose but none experienced coughing of bronchospasm. There were no changes in any of fourteen clinical chemistry tests that were followed for sixty days after exposure, but Heinz bodies amounting to 3-5% of the erythrocytes appeared in the exposed subjects by the seventh day. The Heinz bodies were not accompanied by any signs of anemia or reticulocytosis. Heinz body formation began to decline after two weeks and none were present at 60 days after exposure. Spirometric measurements of pulmonary function made over the 60 day period showed no changes in six subjects. One subject had decreased function but also displayed symptoms of respiratory infection. A chest X-ray showed acute bronchitis in the lower left lung field. This condition cleared in seven days and the pulmonary function measurements returned to baseline values.

Existing Air-Quality Values

Threshold Limit Value (TLV)

The American Conference of Governmental Industrial Hygienists (1973) has established a Threshold Limit Value (TLV) of 0.2 ppm by

volume of MMH vapor in air for industrial exposures. This is intended to be a concentration to which nearly all workers may be repeatedly exposed day after day without adverse effect.

Emergency Exposure Limits (EEL's)

The Committee on Toxicology of the National Academy of Sciences-National Research Council has recommended the following Emergency Exposure Limits for MMH for military and space personnel: 90 ppm for 10 minutes; 30 ppm for 30 minutes; and 15 ppm for 60 minutes.

Proposed Short-Term Limits

Experimental data and experience indicate that man is susceptible to irritation and possible injury from exposure to MMH. Concentrations up to 90 ppm cause some irritation of the eyes and respiratory tract but short exposures at this level are not incapacitating and would not interfere with self-rescue. Repeated exposures to low concentrations of MMH can result in chronic hemolytic anemia. Any exposure to high concentrations of MMH would probably result in convulsions. The short-term limits for the exposure of the public to air pollutants have been set as described in the first document of this series, "Basis for Establishing Guides for Short-Term Exposures of the Public to Air Pollutants", NAS-NRC (1971).

Short-Term Public Limits (STPL's)

The limits for short-term exposure of the public to air pollutants are established in view of occasional repeated events in the same locality. These events, such as the intentional release of MMH to the atmosphere, are assumed to be controllable with respect to concentration and duration of release so that the limit is not exceeded. The exposure limits selected for STPL's are one-tenth of the levels known to produce minimal effects in man which are fully reversible. No adverse effects to health are anticipated at these levels. The STPL's are time-weighted averages for the periods indicated.

STPL's

TIME	LIMIT ($25^{\circ}C/760$ MM. Hg)
10 min	9 ppm (16.9 mg/m^3)
30 min	3 ppm (5.6 mg/m^3)
60 min	1.5 ppm (2.8 mg/m^3)

Public Emergency Limits (PEL's)

Public Emergency Limits (PEL's) are applicable to accidental, unpredictable, or uncontrollable exposures of the public to toxic substances. These exposures are expected to be single events in the lifetimes of the very few people who would be accidentally exposed. The PEL assumes that some temporary discomfort may accrue to the public but that any effect resulting from the exposure is reversible and without residual damage. The limits recommended in this report are based on studies (MacEwen et al., 1969) that indicate no adverse effects on dogs, monkeys, rats, and mice exposed to a 900 ppm-minute CT dose of MMH. Exposure of humans to 90 ppm MMH for 10 minutes resulted in the formation of some Heinz bodies in the blood, but the effect was slight and reversible (MacEwen et al., 1970). This effect is considered acceptable in the rare event of an emergency. These values are considered to be time-weighted averages.

PEL's

TIME	LIMIT
10 min	90 ppm (169 mg/m^3)
30 min	30 ppm (56 mg/m^3)
60 min	15 ppm (28 mg/m^3)

IV. GUIDE FOR 1,1-DIMETHYLHYDRAZINE

Background

At the present time 1,1-dimethylhydrazine (unsymmetrical dimethylhydrazine, UDMH, Dimazine) is manufactured almost exclusively for rocket fuels, in which it is used either as the single high-energy component or as an ingredient in mixed amine fuels. About 1-2 million pounds are produced annually for this purpose. UDMH is assuming increased importance as a synthetic intermediate but the extent of this use is not known at the present time.

Physical and Chemical Properties

UDMH is a colorless, oily, hydroscopic liquid that fumes in air with an ammoniacal of "fishy" odor. The compound has a high vapor pressure and is extremely volatile. Its vapors are oxidized slowly and exothermically in air at room temperature. UDMH is a powerful reducing agent and reacts with a variety of reagents. It is completely miscible with water, alcohol, diethylenetriamine, hydrazine, and most hydrocarbons. It is a weak base (pK_a 7.21) that reacts exothermically with water to form weakly alkaline solutions which deteriorate on standing in air.

UDMH is not sensitive to shock or fraction and is thermally stable. However, the compound is flammable in air over a wide range of concentrations and is hypergolic with oxidants like hydrogen peroxide or nitrogen tetroxide. It will ignite spontaneously if it is adsorbed on materials with a large surface area or stored under conditions that prevent the dissipation of heat that accumulates during air oxidation. Table 1 lists some of its important physical properties.

Effects on Animals

Acute Toxicity

UDMH is primarily a convulsant and a respiratory irritant (Back et al., 1963a; Back and Thomas, 1963). Regardless of the route by which it is administered, lethal intoxication with UDMH in the mouse, rat, dog, and monkey usually progresses through tonic-clonic convulsions to respiratory arrest (Back and Thomas, 1963). Prior to convulsions animals other than rodents may salivate and vomit. All species show a time lapse between exposure to UDMH and the onset of seizures, but what occurs in this interval is not known. Back and Thomas (1963) have shown that the onset of seizures and death is hastened by pretreatment of mice with pentylenetetrazol (Metrazol®) but UDMH does not alter the pentobarbital sleep time of mice. Convulsive doses of UDMH produce significant dose-related alterations in brain electrical activity, sensory and motor excitability, and performance in a learned motor task (Fairchild and Sterman, 1964). Reynolds et al. (1963) have found that substantial decrements in performance appear soon after any exposure, which results in intoxication that can be clinically observed in monkeys. Delayed death from other than central nervous system effects has not been observed, but animals surviving acute exposures may be either highly irritable or depressed for several days.

LD_{50} data for all routes of administration except inhalation are presented in Table 2. Dogs and monkeys appear to be more susceptible to i. p. administration of UDMH than rodents. Witkin (1956) found the lethality of UDMH greater in rats than mice by i. p., i. v., and oral routes. However, other observations (Back and Thomas, 1963; O'Brien et al., 1964) indicate approximately the same LD_{50} values for both species by i. v. or i. p. administration. The lethality UDMH on cutaneous application is considerably reduced because a large percentage of the compound vaporizes before it is absorbed (Smith and Clark, 1971).

Jacobson et al. (1955) determined the 4-hour LC_{50} of UDMH vapor to be 172 ppm for mice, 252 ppm for rats, and 392 ppm for hamsters. Weeks et al. (1963) reported LC_{50} values for rats to be 1,410 ppm for one hour, 4,010 ppm for 30 minutes, 8,230 ppm for 15 minutes, and 24,500 ppm for five minutes. These authors made log-log plots of concentration vs. time for the LC_{50} values and concluded that within the span of their studies the lethality of UDMH was directly dependent on the total dose.

The LC_{50}-values reported for dogs are 981 ppm for one hour, 3,578 ppm for 15 minutes, and 22,550 ppm at five minutes (Weeks et al., 1963). In the same study it was found that dogs showed minimal toxic responses (dullness, mild fasciculations, and slight tremors) after exposure to 1,200 ppm, 400 and 100 ppm for 5, 15, and 60 minutes respectively. No adverse effects were seen in dogs exposed to 50, 200 and 600 ppm UDMH vapor for 60, 15, and 5 minutes respectively. Jacobson et al. (1955) did not determine an LC_{50} for dogs but found that after exposure of 3 dogs for 192 minutes to 111 ppm, 2 dogs were dead and the third moribund. He also reported that exposure of another group to 24 ppm UDMH vapor for 4 hours had no effect on two of three dogs but the other vomited, convulsed, and subsequently recovered.

Toxicity of Repeated Doses

The lethality of UDMH may be increased by repeated exposures to the compound. The LD_{50} for single doses administered i.p. to rats is between 102-131 mg/kg (Table 2) yet Cornish and Hartung (1969) have found that repeated injections of 70, 50, or 30 mg/kg resulted in a high mortality rate among rats: 9 of 10 receiving 70 mg/kg/day died during the first two days; 6 of 10 receiving 50 mg/kg/day and 5 of 10 receiving 30 mg/kg/day died during days two and three. These findings suggest that UDMH is accumulated. However, this process is apparently limited in some manner since all deaths occurred during the first three days and the 10 of 30 rats that survived after three days also survived three weeks of repeated administration of UDMH.

Other studies of repeated exposures to UDMH vapor (Rinehart et al., 1960) also suggest some accumulation of the compound in rodents and dogs. The 4-hour LC_{50} for mice has been reported as 172 ppm (Jacobson et al., 1955) but after exposure to 140 ppm for 6 hours a day 29 of 30 mice died in a calculated median survival time of three days. Exposure to 75 ppm for five hours a day for seven weeks killed eight of 30 mice within five weeks. The mice showed intermittent tremors during exposure and all deaths resulted from clonic-tonic convulsions.

Although Jacobson et al. (1955) found no deaths in dogs exposed to 25 ppm UDMH vapor for four hours, Rinehart et al. (1960) observed severe toxic signs and death in one dog after exposure to 25 ppm six hours a day for three days. At this time he also reported severe toxic signs (depression, salivation, emesis, diarrhea, bradycardia, fever and convulsions) in one dog and minimal toxic signs (depression and salivation) in another. However, both of these dogs survived 13 weeks of daily exposure to 25 ppm. All three dogs, including the one that died, developed hemolytic anemia. Rinehart et al. (1960) observed

only mild anemia in dogs exposed to 5 ppm six hours a day, 5 days a week for 26 weeks.

On the other hand, it has been shown that repeated exposures to small amounts of UDMH can occur without toxicity. Weeks et al. (1963) observed no adverse effects in groups of four dogs exposed twice weekly for six weeks to 50, 200 and 600 ppm UDMH vapor for 60, 15, and 5 minutes respectively. Likewise House (1964) observed virtually no effects after the continuous exposure of monkeys, rats and mice to 0.56 ppm UDMH vapor for 90 days. Clinical chemistry determinations were within normal limits and functional evaluations disclosed only a decreased swimtime for rats and mice. However, some tissue pathology did occur.

Cornish and Hartung (1969) found no fatalities among rats receiving 10 mg/kg/day i.p. for three weeks. This last finding confirmed prior studies of Back and Thomas (1963) who found, in addition, no significant differences between the acute lethality (LD_{50}) of UDMH administered to rats previously treated with 10 mg/kg UDMH for 20 days and the LD_{50} for control animals.

Tissue Pathology

Neither Jacobson et al. (1955) nor Weeks et al. (1963) found any pathology attributable to UDMH vapor in rats and dogs after single lethal or non-lethal exposures. Rinehart et al. (1960) found no abnormal morphology in rats and mice sacrificed at intervals through a six-week series or exposures to 140 ppm or 75 ppm UDMH vapor. However, dogs exposed daily to 25 ppm vapor for several weeks had pigment deposits in the spleen and in the Kupffer cells of the liver; one dog developed alveolar hemorrhage, emphysema, and atelectasis. House (1964) exposed animals continuously to 0.56 ppm UDMH for 90 days and found that liver hemosiderosis appeared in mice; rats showed renal tubular vacuolization and necrotic areas in the heart while monkeys acquired some degenerative lesions in the liver, probably fatty changes. Repeated doses of 10 mg/kg UDMH i.p. produced no significant pathologic changes in rats (Back and Thomas, 1963; Cornish and Hartung, 1969). However, rats surviving 50 mg/kg or 70 mg/kg i.p. for 21 days had slight fatty changes in the renal tubular epithelium (Cornish and Hartung, 1969). Recently, it has been shown that turkeys given feed previously treated with UDMH developed fatty metamorphosis of hepatic cells. Ultrastructural studies showed that the lipid congregates in glycogen areas and is associated with a distended smooth endoplasmic reticulum (Simpson and Barrow, 1972).

Adsorption, Distribution, and Elimination

Regardless of the route of administration, UDMH is rapidly absorbed into the blood and excreted by the kidneys. UDMH was detected in the blood within 30 seconds after the application of 300 - 1,800 mg/kg to the shaved skin of dogs (Smith and Clark, 1971) but peak concentrations did not appear for 60 - 201 minutes. Back et al. (1963a) found that peak concentrations of UDMH in plasma occurred 15-60 minutes after the intraperitoneal administration of 50 mg/kg to hydrated rats, cats, dogs, and monkeys. UDMH could be detected in the urine of these animals three minutes after injection and both radiometric and colorimetric techniques indicated that 30-50% of the dose was excreted within five hours. Dost et al. (1966) also measured the urinary secretion of UDMH and found the amount of ^{14}C in the urine 53 hours after the intraperitoneal administration of UDMH-^{14}C to be equivalent to 56% of a 20 mg/kg dose, 53% of a 60 mg/kg dose, and 70% of an 80 mg/kg dose. In addition, these investigators showed that UDMH is metabolized to respiratory CO_2. The latter process is apparently influenced by the amount of the compound given; in ten hours 30% of an 0.88 mg/kg dose, 15.2% of a 20 mg/kg dose, and 7% of an 80 mg/kg dose were metabolized to CO_2.

Otherwise, very little is known about the metabolism of UDMH. Back et al. (1963a) have postulated that UDMH may undergo some complexing in plasma, but distribution studies do not show the preferential accumulation of the compound in any tissue or organ. Aldrich and Mitz (1963) found evidence for two metabolites of UDMH in urine. They recovered 20% of a 40 mg/kg dose of ^{14}C-UDMH from the urine of rats and dogs within four hours. Fifty percent of this was unreacted UDMH, 3-10% was identified as glucose dimethylhydrazone, and 20-25% was a single component that was not identified but thought to be a neutral hydrazone or hydrazide of higher molecular weight than pyruvic acid.

Effects on Metabolism and Enzymes

An extensive array of metabolic and biochemical parameters has been investigated in an effort to understand the toxic actions of UDMH. With regard to glucose metabolism, the injection of non-fasted rats with LD_{50} doses of UDMH caused marked hyperglycemia, which persisted for at least an hour (O'Brien et al., 1964). Similar hyperglycemia in

anaesthetized dogs did not result in depletion of liver or muscle glycogen (Clark et al., 1968) but Minard et al. (1965) have reported that convulsions induced by UDMH lowered brain glycogen levels in rats and they concluded this resulted from the convulsion rather than a direct action of UDMH. Amenta and Dominguez (1965) found that the injection of 1.25 mMole/kg UDMH inhibits the conversion of D-glucose-U-^{14}C to $^{14}CO_2$ but did not alter the production of respiratory CO_2 from acetate.

The pronounced central nervous system effects of UDMH intoxication have suggested some interference with amine metabolism. Reed et al. (1964) found that as little as 6 mg/kg UDMH administered intraperitoneally to rats inhibits the oxidation of methylamine-^{14}C and putrecine-1;4-^{14}C to $^{14}CO_2$. UDMH also suppresses monoamine and diamine oxidase activity (Reed et al., 1964) and produces severe inhibition of glutamic acid decarboxylase (GAD) activity but is only a weak inhibitor of Gamma aminobutyric acid (GABA) transaminase (Medina, 1963). Medina (1963) also observed that subcutaneous injection of 1.25 mMole/kg UDMH depresses the conversion of glycine-1-^{14}C to respiratory $^{14}CO_2$ in intact rats while Reed et al. (1964) found that intoxication of rats with 1.5 mMole/kg UDMH i.p. did not decrease the metabolism of sodium L-glutamate 1-^{14}C (4.4 mMole/kg i.p. or 20 mMole/kg, oral) to respiratory $^{14}CO_2$. At the present time it is difficult to assess the significance of these observations.

Cardiovascular and Renal Effects

The intravenous injection of 1 to 50 mg/kg UDMH did not produce any acute effect on the carotid blood pressure, respiration or ECG of anaesthetized dogs (Back and Thomas, 1963b; Britz, 1965). It did not alter responses caused by electrical stimulation of the peripheral end of the cut vagus, nor did it affect the action of acetylcholine, histamine, epinephrine, norepinephrine, or reserpine on blood pressure. All animals given 100 mg/kg or more UDMH died in cardiovascular collapse even though respiration was supported artificially (Back and Thomas, (1963b).

UDMH produces a marked diuresis in rats. A single i.p. injection of 80 mg/kg produced a three-fold increase in urine during a six-hour period (Cornish et al., 1965; Barth et al., 1967). During the first two hours after the injection the average urinary excretion of potassium and calcium was significantly less than normal (Barth et al., 1967). On the other hand Wong (1966) observed no appreciable effect on maximal tubular readsorption of glucose and only a slight increase in glomerular filtration rate after the injection of 45 mg/kg UDMH in dogs. Van Stee (1965) also found no significant impairment of glomerular filtration rate and did not see any alteration in p-amino-hippurate and inulin clearances in dogs. Repeated injections of 30-50 mg/kg daily for three weeks

produced a marked water diuresis in rats that was sustained for the entire period (Cornish and Hartung, 1969).

Carcinogenicity

Argus and Hoch-Ligeti (1961) reported no increase in incidence of tumors among 25 rats after gastric intubation of 0.325 mg of UDMH daily, 5 days per week, for 53 weeks. On the other hand, Roe et al. (1967) found a significant increase in pulmonary tumors among 9 female Swiss mice that survived more than 50 weeks of oral administration, 5 days per week, of 0.5 mg/kg of UDMH. The tumors were of a type that commonly arise spontaneously in mice.

Mutagenesis

UDMH reacts in vitro under severe conditions with the pyrimidine bases in nucleotides to form dihydro- or 4-hydrazino derivatives or to effect scission of the pyrimidine ring (Lingens and Schneider-Bernloehr, 1965). The occurrence of similar reactions in vivo could alter the base sequence in DNA or RNA and produce a mutagenic effect. Some mutagenic effects of UDMH have been observed in bacteria but there have been no similar observations in animals (Clark et al., 1968).

Therapy of Intoxication

UDMH is one of a group of carbonyl reagents, compounds characterized by their ability to condense with the oxygen of aldehydes and ketones, which may produce acute vitamin B_6 deficiency and convulsions. Experiments have shown that the convulsant activity of these agents can be blocked by the administration of B_6 vitamins (Reeves, 1961; Vilter, 1964). Subsequently, Back et al. (1963b) found that pyridoxine was more effective than pyridoxamine in preventing UDMH convulsions in mice and monkeys. On the basis of his data he suggested the administration of 25 mg/kg pyridoxine hydrochloride for the emergency treatment of human intoxication with UDMH. Half this amount would be given intravenously and the remainder injected intramuscularly in several sites.

Effects on Humans

Cases of human poisoning by UDMH have been rare. Shook and Cowart (1957) refer to one event in which two workers 750 yards from a spill of UDMH inhaled fumes and experienced initial choking and difficulty in breathing. Four hours later both men became nauseated and vomited but both recovered without further incidents. These authors also reviewed the history of five people who had repeated laboratory exposure to UDMH and six workmen engaged in storage and transfer of the compound. None of these subjects had any acute signs of toxicity. Evidence from other sources also lead these authors to suspect that hemolysis develops after repeated exposures to UDMH.

Frierson (1965) has reported on six men who inhaled Aerozine-50 (AZ50), a 1:1 mixture by weight of hydrazine and UDMH. Because the vapor pressure of UDMH is approximately 10 times that of hydrazine, Aerozine vapor is approximately 85% UDMH (Azar et al., 1970). Four men who had to work for two hours in an area contaminated with AZ50 suffered severe nausea and vomiting even though they were wearing air packs and acid suits. Two hundred mg of pyridoxine stopped emesis within 20 minutes. Two other men were exposed to large amounts of AZ50 vapor, one through a defective mask over a period of 90 minutes, the other by direct inhalation. They complained of headache, nausea, shakiness, burning sensation in facial skin, sore throat, and tightness in the chest. Examination showed paleness, sweating, wheezing, twitching of the extremities and clonic movements. Dyspnea and other symptoms abated after the administration of 600 mg pyridoxine, 200 mg i.v., and 400 i.m. at two sites. However, both patients developed pulmonary edema which subsided about six hours after the administration of steroids and oxygen. Follow-up studies over the next three weeks revealed no abnormality in blood, liver or kidney function. Chest X-rays taken four weeks later were normal.

Effects on Plants

UDMH has adverse effects on some seeds and plants. Heck et al. (1963) found that 1,000 ppm UDMH in water decreased the number of squash seeds that would germinate. Hoover et. al. (1964) found that concentration of UDMH less than 200 ppm did not affect the germination of rice, Alaska peas, alfalfa, or endive but did inhibit the growth of all plants except Alaska peas. Pinto beans and cotton seedlings grown in solution containing UDMH showed dehydration and defoliation. When UDMH concentrations reached 1,000 ppm cotton seedlings died in 48 hours. Seedlings (cotton, pinto bean, soybean, endive, squash) sprayed with 2,000 ppm UDMH suffered slight temporary injury; those sprayed with 6,000 to 10,000 ppm UDMH had increased injury and some died. Fumigation of the seedlings mentioned above and alfalfa with

25-30 ppm caused severe injury.

Existing Air Quality Values

Threshold Limit Value (TLV)

The American Conference of Governmental Industrial Hygienists (1973) has established a Threshold Limit Value of 0.5 ppm by volume of UDMH vapor in air for industrial exposures. This is intended to be a concentration to which nearly all workers may be exposed day after day without adverse effect.

Emergency Exposure Limits (EELs)

The Committee on Toxicology of the National Academy of Sciences-National Research Council has recommended the following Emergency Exposure Limits for UDMH for military and space personnel: 100 ppm for 10 minutes; 50 ppm for 30 minutes; and 30 ppm for 60 minutes.

Proposed Short-Term Limits

The philosophy underlying the recommendation of limits for short-term and emergency exposure of the public to air pollutants is detailed in the first document of this series: "Basis for Establishing Guides for Short-Term Exposures of the Public to Air Pollutants", NAS-NRC (1971).

The few human exposures to UDMH that have occurred have been accidental and to unknown concentrations. Such data are not adequate for setting exposure limits. However, there is a large amount of data from experimental exposure of animals and they suggest limits for human exposures. The recommended total accumulated dose has been reduced for both shorter exposure times in order to reduce the possibility of exceeding the body's detoxification capacity and to minimize any chance of respiratory irritation.

Short-Term Public Limits (STPL's)

The limits for short-term exposure of the public to air pollutants are established in anticipation of occasionally repeated events in the same locality. These events, involving intentional release of UDMH to the atmosphere, are assumed to be controllable with respect to

concentration and duration so that the limit is not exceeded. The exposure limits selected for STPL's are one-half the limits considered acceptable for emergencies and are well below the no-effect levels for dogs, the most sensitive species (Weeks et al., 1963). These are time-weighted averages.

STPL's

Time	Limit (25° C/760 mm Hg.)
10 min	50 ppm (127 mg/m^3)
30 min	25 ppm (63.5 mg/m^3)
60 min	15 ppm (38.2 mg/m^3)

Public Emergency Limits

Public Emergency Limits are those for accidental, unpredictable, or uncontrollable events. These exposures are expected to be single events in the lifetimes of the very few people who would be accidentally exposed. The PEL assumes that some temporary discomfort may be experienced by some individuals, but that any effect resulting from the exposure is reversible and without residual damage. The following time-concentration combinations have been selected because they are below by a factor of 3 to 5 those that cause a detectable effect in dogs, one of the most sensitive species. Weeks et al. (1963) found no adverse effects in dogs exposed to 200 ppm for 15 minutes or 50 ppm for 60 minutes. They are time-weighted averages.

PEL's

Time	Limit (25° C/760 mm Hg)
10 min	100 ppm (255 mg/m^3)
30 min	50 ppm (127 mg/m^3)
60 min	30 ppm (76.5 mg/m^3)

Analytical Methods

Analytical methods for hydrazine as well as for monomethylhydrazine and unsymmetrical dimethylhydrazine are based on (1) coupling to form colored compounds, (2) basicity of the compounds, (3) reductive capacity of the compounds, (4) liberation of gas on reduction. None of the methods is absolutely specific.

The coupling of hydrazine with p-dimethyl-aminobenzaldehyde to form a yellow to orange azine can be used for quantitative determination of hydrazine (Pesez and Petit, 1947). The procedure can be adapted for determination of hydrazine in air by drawing a known volume of air through an impinger containing two ml of concentrated hydrochloric acid in 10 ml of water and then adding the coupling reagent to the solution. Presumably, this reaction could also be employed to determine UDMH. A colorimetric method for UDMH using trisodium pentacyanoamino ferroate as a reagent is suitable for analysis of blood and urine (Pinkerton et al., 1961).

The quantitative method described by Geiger and Vernot (1967) for determining monomethylhydrazine in air could be calibrated for hydrazine and UDMH; this method measures the change in absorbance of an iodine-potassium iodide solution when air containing hydrazine is passed through it.

Hydrazine, MMH and UDMH can be measured quantitatively by trapping their vapors in 3-5N hydrochloric acid, and then reacting this solution with potassium iodate. Nitrogen gas is released stoichiometrically (McKennis et al., 1958).

The current flow between a reference electrode and a platinum electrode at which hydrazine is oxidized can be calibrated to quantitate concentrations of hydrazine vapor in air (Haller and Harshman, 1953). The same oxidation reaction should be suitable for measurement of other easily oxidizable hydrazine derivatives.

A detector kit for hydrazine and UDMH, for use with a hand-operated sampling pump, is manufactured by Mine Safety Appliances Company.

A personal dosimeter for estimating exposure to the vapors of hydrazine, MMH or UDMH can be made by impregnating a material such as silica gel with "bindane" (Δ 1, 2' -bindane-1"3, 3' -trione) and spreading a thin layer of the impregnated material on a supporting film base (Plantz et al., 1968). Ammonia and cigarette smoke interfere with this test system.

Table 1

PHYSICAL CHEMICAL PROPERTIES

Compound	Hydrazine	Monomethyl-Hydrazine	1, 1, -Dimethyl-Hydrazine
Molecular Formula	H_2NNH_2	CH_3HNNH_2	$(CH_3)_2NNH_2$
Molecular Weight	32.05	46.07	60.10
Boiling Point°C	113.5	87.5	63.3
Melting Point°C	2.0	-20.9	-58.0
Odor Threshold ppm.	3-4	1-3	0.3-1
Density (25/25) g/cc.	1.00	0.87	0.78
Vapor Density (air = 1)	1.1	1.6	2.0
Vapor Pressure, mmHg(25°C)	14.38	49.63	157.0
Flash Point, °F(TCC)	100	80	5
Flammability Range in Air % Vol., 1 atm.	4.7 - 100	2.5 - 98	2.5 - 95
1 ppm Vapor, 25°C/760 mm	0.001309 mg/1	0.001881 mg/1	0.002554 mg/1
1 mg/1 vapor, 25°C/760 mm	764 ppm	532 ppm	408 ppm

Table 2

Acute Toxicity of Hydrazine, MMH and UDMH

(LD_{50})

Species	Route	LD_{50} mg/kg			Reference
		Hydrazine	MMH	UDMH	
Mouse	Intravenous	57	33	250	Witkin, 1956
	Intraperitoneal	62	32	290	Witkin, 1956
				132	Weir et al., 1964
				125	Back and Thomas, 1963
	Oral	59	33	265	Witkin, 1956
Rat	Intravenous	55	33	119	Witkin, 1956
	Intraperitoneal	59	32	104	Witkin, 1956
				102	O'Brien et al., 1964
				131	Witkin, 1956
	Oral	60	33	122	Witkin, 1956
Guinea Pig	Cutaneous	192	49	1329	Rothberg and Cope, 1956
Rabbit	Intravenous	26	12	1060	Rothberg and Cope, 1956
	Cutaneous	94	96	60	Rothberg and Cope, 1956
				60	Witkin, 1956
Dog	Intravenous	25	12	1200	Witkin, 1956
Monkey	Intraperitoneal	> 20	-	60 - 100	Patrick and Back, 1965

Table 3
Acute Inhalation Toxicity of Hydrazine, MMH and UDMH
(LC_{50})

Species	Duration of Exposure(hrs)	LC_{50}(ppm)			Reference
		Hydrazine	MMH	UDMH	
Mouse	1		122		Haun et al., 1970
	4	254	56	172	Jacobsen et al., 1955
			65		Haun et al., 1970
Rat	1/12			24,500	Weeks et al., 1963
	1/4			8,230	Weeks et al., 1963
	1/2			4,010	Weeks et al., 1963
	1			1,410	Weeks et al., 1963
	1	640			Comstock et al., 1954
	1		244		Haun et al., 1970
	4	58	74	252	Jacobsen et al., 1955
			78		Haun et al., 1970
Hamster	4		392		Jacobsen et al., 1955
Dog	1/12			22,550	Weeks et al., 1963
	1/4			3,578	Weeks et al., 1963
	1		96		Haun et al., 1970
Monkey (squirrel)	1		82		Haun et al., 1970
Monkey (rhesus)	1		162		Haun et al., 1970

Table 4

RECOMMENDED LIMITS FOR EXPOSURE

Compound	STPL's (25°C/760mm. Hg.)			PEL's(25°C/760mm Hg.)		
	Time	Limit		Time	Limit	
	min	ppm	mg/m^3	min	ppm	mg/m^3
Hydrazine	10	15	20	10	30	39
	30	10	13	30	20	26
	60	5	7	60	10	13
Monomethylhydrazine	10	9	17	10	90	169
	30	3	6	30	30	56
	60	1.5	3	60	15	28
1,1, Dimethylhydrazine	10	50	127	10	100	255
	30	25	64	30	50	127
	60	15	38	60	30	77

References

Aldrich, F. L., and Mitz, M. A. (1963). Intermediary metabolic pathways of 1,1-dimethylhydrazine; Fed. Proc. 22:539.

Aleyassine, H., and Lee, S. H. (1971). Inhibition by hydrazine, phenelzine and pargyline of insulin release from rat pancreas; Endocrinology 89:125-129.

Amenta, J. S., and Dominguez, A. M. (1965). The effect of hydrazine and congeners on $C^{14}O_2$ respiratory pattern of various metabolic substrates; Toxicol. Appl. Pharmacol. 7:236-246.

Amenta, J. S., and Johnston, E. H. (1962). Hydrazine-induced alterations in rat liver; a correlation of the chemical and histologic changes in acute hydrazine intoxication; Lab. Invest. 11:956-961.

Amenta, J. S., and Johnston, E. H. (1963). The effects of hydrazine upon the metabolism of amino acids in the rat liver; Lab. Invest. 12:921-928.

American Conference of Governmental Industrial Hygienists (1973). TLVs® Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1973. Cincinnati, Ohio.

Argus, M. F., and Hoch-Ligeti, C. (1961). Comparative study of the carcinogenicity of nitrosamines; Natl. Cancer Inst., J. 27:695-709.

Audrieth, L. F., and Ogg, B. A. (1951). The Chemistry of Hydrazine. 1st ed. New York, Wiley and Sons.

Azar, A., Thomas, A. A., and Shillito, F. H. (1970). Pyridoxine and phenobarbital as treatment for Aerozine-50 toxicity; Aerospace Med. 41:1-4.

Back, K. C., and Pinkerton, M. K. (1967). Toxicology and pathology of repeated doses of monomethylhydrazine in monkeys. Wright-Patterson AFB, Ohio. AMRL-TR-66-199.

Back, K. C., and Thomas, A. A. (1963). Pharmacology and toxicology of 1,1-dimethylhydrazine (UDMH); Am. Ind. Hyg. Assoc. J. 24:23-27.

Back, K. C., and Thomas, A. A. (1970). Aerospace problems in pharmacology and toxicology; Ann. Rev. Pharmacol. 10:395-412.

Back, K.C., Pinkerton, M.K., Cooper, A.B., and Thomas, A.A. (1963a). Absorption, distribution, and excretion of 1,1-dimethylhydrazine (UDMH); Toxicol. Appl. Pharmacol. 5:401-413.

Back, K.C., Pinkerton, M.K., and Thomas, A.A. (1963b). Therapy of acute UDMH intoxication; Aerospace Med. 34:1001-1004.

Barth, M.L., Geake, C.L. and Cornish, H.H. (1967). 1,1-Dimethylhydrazine-induced diuresis; Toxicol. Appl. Pharmacol. 11:26-34.

Beyer, K.H. (1943). Protective action of vitamin C against experimental hepatic damage; Arch. Intern. Med. 71:315-324.

Biancifiori, C., Bucciarelli, E., Clayson, D.C., and Santilli, F.E. (1964). Induction of hepatomas in CBA/Cb/Se mice by hydrazine sulphate and the lack of effect of croton oil on tumor induction in BALB/c/Cb/Se mice; Brit. J. Cancer 18:543-550.

Biancifiori, C., and Ribacchi, R. (1962). Pulmonary tumors in mice induced by oral isoniazid and its metabolites; Nature 194:488-489.

Britz, W.E., Jr. (1965). Cardiovascular effects of 1,1-dimethylhydrazine in the anaesthetized dog. USAF School of Aerospace Medicine, Brooks AFB, Texas. SAM-TR-65-56.

Clark, D.A., Bairrington, J.D., Bitter, H.L., Coe, F.L., Medina, M.A., Merritt, J.H. and Scott, W.N. (1968). Pharmacology and toxicology of propellant hydrazines. USAF School of Aerospace Medicine, Brooks AFB, Texas. Aeromedical Review 11-68.

Coe, F.L., Howe, R.W., and Goetting, J.A. (1967). The effects of monomethylhydrazine upon renal function. USAF School of Aerospace Medicine, Brooks AFB, Texas. SAM-TR-67-61.

Comstock, C.C., Lawson, L.H., Greene, E.A. and Oberst, F.W. (1954). Inhalation toxicity of hydrazine vapor; A.M.A. Arch. Ind. Hyg. Occup. Med. 10:476-490.

Cook, W.A. (1955). Protection of workers against dermatitis on exposure to hydrazine hydrobromide soldering flux; Arch. Gewerbepathol. Gewerbehyg. 13:616-618.

Cornish, H. H., and Hartung, R. (1969). The subacute toxicity of 1,1-dimethylhydrazine; Toxicol. Appl. Pharmacol. 15:62-68.

Cornish, H. H., Geake, C. L., and Barth, M. L. (1965). Biological action of 1,1-dimethylhydrazine; Biochem. Pharmacol. 14:1901-1904.

Curtius, T. (1887). Ueber das Diamid (Hydrazin); Ber. Deut. Chem. Ges. 20:1632-1634.

Dambrauskas, T., and Cornish, H. H. (1964). The distribution, metabolism, and excretion of hydrazine in rat and mouse; Toxicol. Appl. Pharmacol. 6:653-663.

Dominguez, A. M., Amenta, J. S., Hill, C. S., and Domanski, T. J. (1967). Morphologic and biochemical alteration in the kidney of the hydrazine-treated rat; Aerospace Med. 33:1094-1097.

Dost, F. N., Johnson, D. E., and Wang, C. H. (1973). Metabolic effects of monomethyl hydrazine. Wright-Patterson AFB, Ohio. AMRL-TR-73-33.

Dost, F. N., Reed, D. J., and Wang, C. H. (1966). The metabolic fate of monomethylhydrazine and unsymmetrical dimethylhydrazine; Biochem. Pharmacol. 15:1325-1332.

Evans, D. M. (1959). Two cases of hydrazine hydrate dermatitis without systemic intoxication; Brit. J. Ind. Med. 16:126-127.

Fairchild, M. D., and Sterman M. B. (1964) Behavioral and Neurophysiological studies of UDMH in the cat. Wright-Patterson AFB, Ohio. AMRL-TDR-64-72.

Fortney, S. R., and Clark, D. A. (1967). Effect of monomethylhydrazine on methemoglobin production in vitro and in vivo; Aerospace Med. 38:239-242.

Frierson, W. B. (1965). Use of pyridoxine HCl in acute hydrazine and UDMH intoxication; Ind. Med. Surgery 34:650-651.

Furst, A., Gustavson, W. R., and deRopp, R. S. (1968). Biochemical pharmacology of hydrazines toxicity. Wright-Patterson AFB, Ohio. AMRL-TR-68-132.

Geake, C. L., Barth, M. L., and Cornish, H. H. (1966). Vitamin B_6 and the toxicity of 1,1-dimethylhydrazine; Biochem. Pharmacol. 15: 1614-1618.

Geiger, D. L., and Vernot, E. H. (Oct 4, 1967). The continuous analysis of monomethylhydrazine in toxicological exposure chambers. Presented at the Technicon Symposium, "Automation in Analytical Chemistry." p. 427-430.

George, M. E., Mautner, W., and Back, K. C. (1968). Nephrotoxic effects of monomethylhydrazine in monkeys. Wright-Patterson AFB, Ohio. AMRL-TR-68-110.

Haller, J. F., and Harshman, R. C. [Nov 12, 1953]. A sensitive hydrazine detector. Niagara Falls, N. Y. Mathieson Chemical Corporation. Unpublished report.

Haun, C. C., MacEwen, J. D., Vernot, E. H., and Eagan, G. F. (1970). Acute inhalation toxicity of monomethylhydrazine vapor; Am. Ind. Hyg. Assoc. J. 31:667-677.

Hayden, R. O., and Murray, R. H. (1965). Cardiopulmonary effects of sub-acute hydrazine poisoning in Rhesus monkeys; Ind. Med. Surgery 34: 925-933.

Heck, W. W., Bloodworth, M. E., Clark, W. J., Darling, D. R., and Hoover, W. (196). Environmental pollution by missile propellants. Wright-Patterson AFB, Ohio. AMRL-TDR-63-75.

Hoover, W. L., Bloodworth, M. E., Clark, W. J., Heck, W. W. and Hold, L. (1964). Environmental pollution by missile propellants. Wright-Patterson AFB, Ohio. AMRL-TDR-64-5.

House, W. B. (1964). Tolerance criteria for continuous inhalation exposure to toxic materials. III. Effects on animals of 90-day exposure to hydrazine, unsymmetrical dimethylhydrazine (UDMH), decaborane, and nitrogen dioxide. Wright-Patterson AFB, Ohio. ASD-TR-61-519 (III).

Høvding, G. (1967). Occupational dermatitis from hydrazine hydrate used in boiler protection; Acta Dermato-Venereol. 47:293-297.

Izume, S., and Lewis, H. B. (1926). The influence of hydrazine and its derivatives on metabolism. III. The mechanism of hydrazine hypoglycemia; J. Biol. Chem. 71:51-66.

Jacobson, K. H., Clem, J. H., Wheelwright, H. J., Jr., Rinehart, W. E., and Mayes, N. (1955). The acute toxicity of the vapors of some methylated hydrazine derivatives; A. M. A. Arch. Ind. Health 12:609-616.

Juhász, J., Baló, J , and Szende, B. (1966). Tumour-inducing effect of hydrazine in mice; Nature 210:1377.

Kroe, D. J. (1971). Animal pathology resulting from long-term exposure to low levels of monomethylhydrazine. Proc., 2nd Annual Conference on Environmental Toxicology. Wright-Patterson AFB, Ohio AMRL-TR-71-120, p. 271-276.

Krop, S. (1954). Toxicology of hydrazine: A review; A. M. A. Arch. Ind. Hyg. Occup. Med. 9:199-204.

Kulagina, N. K. (1962). The toxicological characteristic of hydrazine. Wright-Patterson AFB, Ohio. Foreign Technology Division. FTD-HT-66-306. Source: AMN SSSR. Toksikologiya Novykh Promyshlennykh Khimicheskikh Vishchestv, No. 4:65-81.

Leahy, H. F. (1970). Monomethylhydrazine effect on blood, in vitro. Proc., 1st Annual Conference on Environmental Toxicology. Wright-Patterson AFB, Ohio. AMRL-TR-70-102, p. 365-381.

Lewis, H. B., and Izume, S. (1926). The influence of hydrazine and its derivatives on metabolism. II. Changes in the non-protein nitrogenous constituents of the blood and in the metabolism of injected glycine in hydrazine intoxication; J. Biol. Chem. 71:33-49.

Lingens, F. (1961). Mutagene Wirkung von Hydrazin auf Escherichia coli-Zellen; Naturwissenschaften 48:480.

Lingens, F., and Schneider-Bernloehr, A. (1965). Reaction of naturally-occurring pyrimidine bases with hydrazine and methyl-substituted hydrazines; Ann. Chemie 686:134-144.

MacEwen, J. D., and Haun, C. C. (1971). Chronic exposure studies with monomethylhydrazine. Proc., 2nd Annual Conference on Environmental Toxicology. Wright-Patterson AFB, Ohio. AMRL-TR-71-120, p. 255-270.