III. BIOLOGIC EFFECTS OF EXPOSURE

The biologic effects of hydrazines on humans and on animals discussed in this chapter include those of five compounds: hydrazine (H2NNH2), methylhydrazine (CH3NHNH2), 1,1-dimethylhydrazine ((CH3)2NNH2), 1,2-dimethylhydrazine (CH3NHNHCH3), and phenylhydrazine (C6H5NHNH2). All these hydrazines are at least slightly basic and polar, and they are strong reducing agents. The hydrazine bases are used in the production of salts and hydrazones that are used in surfactants, detergents, plasticizers, pharmaceuticals, insecticides, and herbicides [1]. Three of the hydrazines (hydrazine, methylhydrazine, and 1,1-dimethylhydrazine) have been used as rocket propellants [2]. Hydrazines are very reactive and have wide use, and they are capable of causing a variety of biologic effects.

The discussion of the toxic effects of the hydrazines includes the salts of hydrazines such as sulfate or hydrochloride since it is implicit that they differ in toxicity from the free base only when differences in pH, solubility, volatility, or mass (in expression of doses) are relevant to the development or expression of toxicity. Such salts are weakly bonded coordination compounds, and without regard to the form of the hydrazine compound administered, the salt or free base is formed according to the biologic medium. For example, the free base added to stomach contents will quickly form the hydrochloride salt, whereas in blood the free base form is more likely.

There has been a great deal of interest in the toxicologic implications of the hydrazines. As a result, there have been many animal studies conducted on the three hydrazines being used as rocket fuels.

Periodically, comprehensive reviews have been prepared by various groups, including the US Air Force [3,4] and the International Agency for Research on Cancer (IARC) [5]. The Committee on Toxicology of the National Academy of Sciences [6] also provided documentation on establishing guidelines for short-term community air exposures.

In addition, NIOSH has expressed concern about the possible tumorigenicity of a number of chemicals, including several hydrazines (Federal Register 40:26434, June 23, 1975). In the 1976 edition of NIOSH's Registry of Toxic Effects of Chemical Substances [7], several hydrazines were listed as animal carcinogens based, primarily, on the 1974 report of studies by IARC [5]. The most relevant studies cited by IARC, together with additional investigations of experimental carcinogenicity, will be reviewed and discussed.

Most of the hydrazines used in industrial processes are of technical grade and may contain trace amounts of contaminants either as decomposition products or as byproducts of the synthetic process. Contaminants found in propellant-grade hydrazine include 0.1-0.6% carbon dioxide, 0.3-1.0% water, 0.17-0.36% aniline, and trace amounts (0.3-4.6 ppm) of chloride [8]. Nitrosodimethylamine, a known hepatotoxin and carcinogen [9,10], is a starting compound in the synthesis of 1,1-dimethylhydrazine [11] and has been found in 1,1-dimethylhydrazine as a contaminant [12,13].

Little information is available on the decomposition of the hydrazines in air and water. Hydrazine is thermodynamically unstable and may decompose into hydrogen, ammonia, and nitrogen [11]. The reaction rate is reportedly slow at room temperatures but increases at elevated temperatures, particularly in the presence of metals such as copper [14].

1,1-Dimethylhydrazine decomposition was similar to that of hydrazine [15]. Ekshtat [16] observed that hydrazine hydrate decomposed almost completely in tap water in 15 days at an initial concentration of 5 mg/liter and in 25 days at 10 mg/liter. He indicated that phenylhydrazine behaved similarly, but he provided no supporting data.

Vapor-phase autoxidation of 1,1-dimethylhydrazine produces formaldehyde dimethylhydrazones, nitrogen, and water as major products and ammonia, dimethylamine, nitrosodimethylamine, diazomethane, nitrous oxide, methane, carbon dioxide, and formaldehyde as minor products [12]. This oxidation is accelerated when the substance is exposed to light and when it contacts metals and metal salts. Autoxidation of 1,2-dimethylhydrazine is rapid and complete, azomethane and water being its major products [12].

Examining the oxidation of methylhydrazine in air, Vernot et al [17] found that methylhydrazine kept in a glass tube at a vapor concentration of 4.6% (v/v) decomposed to molecular nitrogen and methane according to first-order kinetics and had a half-life of 34 minutes at 22-24 C. The reaction appeared to be surface-catalyzed, since decomposition was essentially complete in 10 minutes when polyethylene containers were substituted for glass. In a similar study [18], the same major products were identified, in addition to minor products such as methanol, ammonia, azomethane, methyldiazine, dimethylamine, formaldehyde methylhydrazone, formaldehyde hydrazone, and dimethyl and trimethyl piperazines. The main products of thermal degradation of methylhydrazine and 1,1-dimethylhydrazine were hydrogen cyanide, nitrogen, and ammonia [19]. Decomposition of methylhydrazine increased rapidly at temperatures over 500 C; 1,1-dimethylhydrazine began to decompose at 200-300 C and completely decomposed at 800 C.

Extent of Exposure

Hydrazine, methylhydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine are characterized by a fishy, ammonia-like odor [5,9]. These four compounds are clear, colorless, flammable or combustible, hygroscopic liquids that are soluble in water, ethanol, and other polar solvents [9,11]. Phenylhydrazine has a faint aromatic odor and occurs as yellow monoclinic crystals or oil. It is miscible with alcohol, ether, chloroform, and benzene, but only sparingly soluble in water [10]. The chemical and physical properties of these hydrazines are presented in Tables XI-1 through XI-5 [5,9-11,20-22]. Occupations with potential exposure to hydrazines are listed in Table XI-6 [11,23].

(a) Hydrazine

Hydrazine is a highly polar, weakly basic, fuming liquid that occurs naturally as a product of nitrogen fixation by Azotobacter agile [11]. It has been identified in tobacco grown without the use of maleic hydrazide [24]. Hydrazine is presently produced commercially by the Raschig and the urea processes [11]. The Raschig method involves reacting sodium hypochlorite with excess ammonia and then flash-boiling to recover dilute hydrazine, which is then fractionated to produce the hydrate. The urea process oxidizes urea with hypochlorite to produce hydrazine hydrate [2,25]. In 1974, it was estimated that 17,000 metric tons of hydrazine were produced in the United States by four companies [25]. It is used as a rocket propellant, polymerization catalyst, a blowing agent, a reducing agent, an oxygen scavenger in boiler water treatment, in the synthesis of maleic hydrazide, and in the manufacture of drugs [5]. NIOSH estimates that approximately 9,000 workers are potentially exposed to hydrazine in

the United States. In addition, about 89,000 workers are potentially exposed to the dihydrochloride salt, 2,500 to the sulfate salt, 1,500 to the hydrobromide salt, and 1,700 to the hydrate.

(b) Methylhydrazine

Methylhydrazine is a flammable liquid and can absorb carbon dioxide and water from the air [2]. It has been found in a wild edible mushroom Gyromitia esculenta [24], and it is commercially prepared from the reaction of monochloramine and monomethylamine [26]. About 200,000 pounds of methylhydrazine are produced annually in the United States, where it is primarily used as a rocket fuel [6]. Small amounts are used as an intermediate in organic synthesis and as a solvent [22]. NIOSH estimates that approximately 1,000 workers in the United States are potentially exposed to methylhydrazine.

(c) 1,1-Dimethylhydrazine

1,1-Dimethylhydrazine is a colorless liquid that fumes in air and gradually turns yellow [5]. It is miscible with water, ethanol, ether, dimethylformamide, and hydrocarbons. Not found in nature, it is commercially produced by the reaction of dimethylamine with chloramine [10] or by the reduction of nitrosodimethylamine [10,11]. It is used in rocket fuels, in chemical synthesis, and in photographic chemicals and as a stabilizer for fuel additives, an absorbant for acid gases, and as a plant-growth control agent [22]. About 1-2 million pounds are produced annually for use in rocket propulsion. The extent of other uses is unknown. According to NIOSH estimates, 1,500 workers in the United States are potentially exposed to 1,1-dimethylhydrazine.

(d) 1,2-Dimethylhydrazine

1,2-Dimethylhydrazine, not found in nature, is a liquid produced in small quantities for laboratory use by reducing an azine with lithium aluminum hydride, by hydrolyzing alkyl-substituted diazacyclopropanes, or by reacting hydrazine with alkyl halides [5,11]. At present, 1,2-dimethylhydrazine is not used commercially, but it has been evaluated experimentally as a rocket fuel and is used in cancer research to induce tumors. The number of workers potentially exposed to 1,2-dimethylhydrazine is not known, but it is probably small.

(e) Phenylhydrazine

Phenylhydrazine, a pale-yellow crystal or an oily liquid, becomes reddish brown when exposed to air and light. It is produced by reducing diazotized aniline and then reacting the product with sodium hydroxide [10]. No production figures are available at this time. Phenylhydrazine is used in analytical chemistry as a reagent for detecting aldehydes and sugars, as an intermediate in organic synthesis, and in the synthesis of dyestuffs and pharmaceuticals. NIOSH estimates that about 5,000 workers in the United States are potentially exposed to phenylhydrazine.

Historical Reports

Although organic derivatives had been prepared for a number of years, the still theoretical compound, hydrazine, was not named until 1875 when Fisher succeeded in isolating the phenyl derivative [11]. Hydrazine sulfate was first prepared by Curtius in 1881, but anhydrous hydrazine was not investigated until 1894 when it was prepared by DeBruyn [11]. Raschig, in 1907, developed a synthetic method, since named after him, whereby

ammonia or urea was oxidized by hypochlorite to produce hydrazine [27]. Later, this method was developed on a commercial scale, and it is widely used for the synthesis of hydrazine. In World War II, the Germans used hydrazine as a torpedo propellant and later as a jet fuel [2]. Following the war, the hydrazines were first used as rocket fuels in the United States. At present, hydrazine alone, or as a 1:1 mixture with 1,1-dimethylhydrazine, is used as a fuel for Titan II missiles; the mixture is the more commonly used rocket fuel [2]. Methylhydrazine has been used in the Apollo service module [2] and in missiles [28] as a fuel.

The toxic properties of hydrazine have long been recognized. Clark [29] stated that a report by Curtius published in 1887 described the effect or "attack" of hydrazine vapor on the membranes of the nose and throat. Another report, prepared by Loew in 1890 and cited by Clark [29], indicated that small quantities of hydrazine could kill plants, fungi, lower animals, and mammals.

In 1908, Underhill and Kleiner [30] reviewed studies of others showing that hydrazine sulfate injected subcutaneously (sc) at 100 mg/kg into starved dogs caused vomiting, restlessness, cardiac and breathing difficulties, coma, and death within a few days of administration. Protein, bile pigments, and allantoin crystals were found in the dogs' urine, and the liver appeared to have fatty degeneration. In their own experiments on well-fed dogs, Underhill and Kleiner found that the allantoin crystals were related to starvation, not to hydrazine sulfate administration. Microscopic examination of the organs of these dogs showed fatty degeneration of the cytoplasm of the liver cells, even though most

functions of the liver were still normal [31]. Changes in other organs were not found.

In 1911, Underhill [32] examined blood samples of dogs given an sc injection of hydrazine sulfate. At 50 mg/kg, hydrazine sulfate reduced the blood glucose content and at 100 mg/kg it was lethal. Similar administration of hydrazine sulfate at 50 mg/kg to rabbits produced inconclusive evidence of hypoglycemia [32]. Underhill and Hogan [33] found that, though the blood glucose content in rabbits was reduced by hydrazine sulfate at doses of 65-85 mg/kg, the time necessary to induce the maximum effect and the resultant blood sugar content were inconsistent with the dose. The hypoglycemic effect caused by hydrazine derivatives was not as pronounced as that caused by hydrazine [34]. A rabbit injected sc with methylhydrazine at 50 mg/kg died within 24 hours; death was preceded by convulsions, tremors, and paralysis. However, at 25 mg/kg, methylhydrazine was nontoxic to another rabbit. Methylhydrazine at a dose of 35 mg/kg injected sc into a dog decreased the blood glucose content to 0.11% in 48 hours. At 50 mg/kg, phenylhydrazine caused no toxic signs in another dog. However, a large amount of methemoglobin was found in the urine, and the blood glucose content was elevated.

Bodansky [35], in 1924, studied the effect of hydrazine and its derivatives on the liver of dogs. Hydrazine injected sc at 28.2 mg/kg caused impaired fructose tolerance in 2 days, and an additional injection of the same amount on the 3rd day produced death. Hydrazine sulfate was similarly tested. After a total dose of 104 mg/kg, equivalent to about 26 mg/kg of hydrazine, had been given in six sc injections, lowered fructose, glucose, and galactose tolerance were observed. Fatty changes of the liver

were observed grossly, and extensive fatty degeneration with small areas of necrosis of the liver cells was found microscopically in these dogs. Necrotic changes were also found in the kidney cortex. Bodansky also gave phenylhydrazine hydrochloride to a dog at a total dose of 61 mg/kg in four sc injections in 4 days and found impaired fructose, dextrose, and galactose tolerances. A single sc injection of phenylhydrazine hydrochloride at 25.4 mg/kg also caused impaired fructose tolerance and an 82% reduction of erythrocytes in 12 days in another dog. In these dogs, the spleen was enlarged, the liver showed fatty changes, and the bone marrow was hyperplastic. Microscopically, there were hyperplasia of the spleen, pigmentation and extensive degenerative and necrotic changes of the liver, and slight fatty changes of the kidney cortex.

A few cases of accidental human exposures to the hydrazines are of historical interest. The toxic effect of hydrazine on the eyes was experienced by workers in Germany making hydrazine hydrate during World War II [29]. The eye injury caused by the hydrazine vapor appeared about 10 hours after exposure and was described as inflammation, swelling, and purulent discharge followed by temporary blindness.

A case of phenylhydrazine-related skin hypersensitivity reported in 1899 was cited in 1930 by Wright and Joyner [36]. The patient, a research chemist, used phenylhydrazine and developed mild eczema. The rash first appeared on his fingers and cleared after he rested from work, but it returned with increasing severity after he again had contact with phenylhydrazine. The cause of the rash remained unknown for a year until he spilled phenylhydrazine on his hands, and hives developed over most of his body.

Effects on Humans

There are few controlled studies available on the toxicity of the hydrazines in humans. The majority of reports of human exposure involve the most widely used compound, hydrazine. No report on human exposure to 1,2-dimethylhydrazine was found and no epidemiologic studies were available for any of the hydrazines. There have been many investigations of the toxicity of hydrazines in experimental animals; these are reviewed in the Animal Toxicity section.

(a) Hydrazine

The odor threshold of humans to hydrazine was determined by Jacobson et al [20] in 1955. An osmoscope was used to expose 15 subjects to hydrazine at various concentrations that were prepared in a chamber. The lowest concentration detected by any subject was recorded, and the median detectable concentration was reported to be 3-4 ppm. The osmoscope is a device that enables volunteers to inhale a measured amount of desired atmospheres. The device allows serial dilutions of an atmosphere from a chamber, the dilutions normally differing by a factor of 2. Human subjects sniff various concentrations, usually at increasing concentrations to avoid encountering odor fatigue, until they just detect an odor. Because of the amount of osmoscope surface involved in the passage of test atmospheres, surface sorption of airborne substances can occur and the concentrations delivered may be lower than calculated, especially when dealing with chemically active substances like the hydrazines. Thus, it may be that the reported thresholds for odor detection based on osmoscope tests are higher than the true values.

Gardenghi [37], in 1952, described a case of eczema in a 21-year-old woman who worked in a department where p-acetylaminobenzaldehyde thiosemicarbazone was prepared. Before coming to this department she had no skin disorders, but about 20 days after being transferred, she developed a diffuse pruritus, and a few days later, acute suppurative eczema of the exposed skin. She was treated and 1 month later, apparently cured, she returned to work, but a few days later she again developed severe eczema. Skin tests revealed that the patient was allergic to hydrazine sulfate, an intermediate used in the synthesis. Since the patient was not allergic to the product or any of the other intermediates, the author considered hydrazine to be the causative agent.

In 1959, Evans [38] described the development of dermatitis on the hands of two workers after they had handled hydrazine hydrate intermittently for about 5 months. The rash on the first worker developed on the back of both hands and between his fingers and consisted of many small vesicles, some of which had ruptured and formed small crusts. Fissures were noted on the fingers. The worker stated that this was the fourth time that he had developed dermatitis after handling hydrazine. He was treated and had no further contact with hydrazine for 10 days. After returning to work, the worker inadvertently came into contact with hydrazine hydrate again. Within 7 hours, irritation developed in his fingers and the rash recurred by the following morning.

The second worker also developed a rash after handling hydrazine hydrate [38]. When seen 2-3 weeks later, he had several blisters on his fingers. He had previously experienced a similar condition after using hydrazine hydrate. The author mentioned that neither worker showed any

signs of systemic toxicity. Evans conducted a test to detect the presence of hydrazine on the fingers of these two workers. The fingers of the first worker still had traces of hydrazine 1 day after contact, in spite of what was described as normal washing.

Schultheiss [39], in 1959, described a case of allergic eczema in a 61-year-old laboratory aide. Examination of the patient showed erythematous, papular eczema with the beginning of exfoliation on the fingers and backs of the hands and at the bend in the wrist. The patient had contact with hydrochloric acid, hydrazine hydrate solution (15%), trisodium phosphate, and protective rubber gloves.

An allergy test was performed on the patient's skin to determine the causative agent [39]. Schultheiss found that the patient was hypersensitive to hydrazine hydrate (0.015%), moistened rubber gloves, isonicotinic acid hydrazide, potassium dichromate (0.5%), chromium (III) chloride (0.5%), and nickel sulfate. The author assumed that the patient was allergic to the tetramethylthiuram disulfide used as a vulcanization accelerator in producing rubber gloves. The positive skin test for isonicotinic hydrazide indicated a possible cross sensitivity to other hydrazines and related compounds.

In 1959, Frost and Hjorth [40] described the increased occurrence of eczema (dermatitis) on the hands and forearms of women employed in a factory after a new soldering flux containing hydrazine monohydrochloride had been introduced. Three workers sought treatment for eczema, and when patch-tested with dilute soldering flux, two had positive reactions. The plant stopped using the flux after a month, and 4 months later, 12 of 34 exposed women recalled that they also had skin irritation when the new flux

was used. Patch tests using 1% hydrazine sulfate were subsequently performed on these 12. After 48 hours, six showed a positive reaction and five had negative reactions; a twelfth woman had an inconclusive test.

In 1965, Wheeler et al [41] reported a case study of contact dermatitis in workers exposed to hydrazine hydrobromide solder flux. During 6 years, 35 solderers (approximately half of the total workforce) developed contact dermatitis. Results of patch tests with solder flux on five employees using the solder flux were positive, while those of three unexposed controls were negative. Dermatitis first appeared from 3 weeks to several months after initial exposure. The fingers and hands were most commonly affected, but dermatitis was also seen on the wrists, forearms, eyelids, and face. Skin reactions varied from mild, patchy, dry, scaling dermatitis through mild, maculopapular erythema to severe vesiculation and edema. Some workers experienced only mild dermatitis restricted to sites of greatest contact, while others suffered from severe dermatitis following minimal flux contact. Once sensitized, the workers could no longer handle items contaminated with the flux. One woman was so sensitive that dermatitis developed on her face and arms when she walked through the soldering area.

One of the five workers examined returned to work and used protective gloves while handling parts contaminated with the solder flux; she reportedly had no further problems [41]. The other four workers were transferred to jobs with no hydrazine contact.

Reid [42], in 1965, described the case of a sailor who had accidentally swallowed "between a mouthful and a cupful" of hydrazine. He immediately vomited and lost consciousness. When admitted to the hospital,

the patient was described as flushed, afebrile, unconscious, and vomiting. His pupils were dilated but were central and light-reactive. There were no chemical burns of the mouth, and he was able to swallow. Twelve hours after admission, he ceased vomiting, his pupils became smaller and diverged to the right, and he was sporadically violent. Forty-eight hours later, he was treated with pyridoxine. Later, his memory and voluntary movements were normal, but he was ataxic and unable to write, although he could draw. There was a lateral nystagmus to the right, and his ability to sense vibration was lost. Paresthesia was present in his arms and legs. He was unable to reproduce with one hand movements imposed on the other. Though his condition improved and he was discharged from the hospital 2 weeks after the incident, his final condition was not reported.

In 1971, Sotaniemi et al [43] cited a fatality they attributed to hydrazine hydrate exposure. The victim was a 59-year-old Finnish worker who had handled hydrazine once a week for an unreported number of hours for 6 months. The man had previously experienced lethargy, conjunctivitis, and tremors after he had handled hydrazine. On the day following his last exposure, he developed fever, vomiting, and diarrhea. Four days later, he also developed abdominal pains and black feces and became incoherent. By then, his abdomen was enlarged, and the liver was palpable and tender. A chest roentgenogram showed fluid in the chest cavity and lung shadowing. Blood counts were normal, but other blood chemistry tests indicated elevated bilirubin and creatinine levels. His urine volume was very low (200 ml/day) and the urine contained protein and erythrocytes. Treatment was given to correct the patient's fluid balance and the condition of the

patient improved; but, 12 days later, his condition worsened and he died 3 days later, 20 days after his last exposure.

An autopsy showed severe tracheitis and bronchitis and the lungs filled with exudate [43]. The kidneys were enlarged, and petechiae were visible on the outer surfaces. Microscopic examination revealed severe tubular necrosis, interstitial hemorrhages, and inflammation indicative of toxic nephrosis. The liver appeared to be normal macroscopically, but microscopically there were small focal areas of necrosis and granular cytoplasmic degeneration. Patches of lymphocytes were seen in the portal areas. The heart was enlarged and the myocardium was discolored. Microscopic examination showed nonspecific muscle fiber degeneration and hyperemia.

Based on other investigators' findings in animals, Sotaniemi and coworkers [43] considered the damage to the lungs, liver, and kidneys to be the result of hydrazine poisoning. The patient's work environment was simulated, and the hydrazine concentration in the air was found to be 0.071 mg/cu m, but no other details were given. Although the death of this worker does appear to be related to hydrazine exposure, the actual exposure condition or the presence of other compounds was not reported by the authors. Dermal exposure may also have been a significant factor contributing to the toxic effects of hydrazine. If so, the death can hardly be correlated with the simulated hydrazine concentration in air of 0.071 mg/cu m.

Hydrazine and its salts will produce skin irritation and allergic reactions in humans. It also appears that the hydrate [38,39] and the monohydrochloride [40], sulfate [37], and hydrobromide [41] salts are irri-

tating to the skin. Other effects on humans have not been adequately studied.

(b) Methylhydrazine

The odor threshold of human volunteers to methylhydrazine was determined by Jacobson et al [20] using the method described for hydrazine. The median detectable concentration by odor for 22 persons tested was 1-3 ppm.

In 1970, MacEwen et al [44] evaluated the adequacy of the methylhydrazine Emergency Exposure Limit (EEL) of 90 ppm (162 mg/cu m) for 10 minutes for rocket fuel manufacturing and handling personnel. The primary effects looked for were tearing and bronchospasms. The group of seven male volunteers, aged 23-44 years, contained blacks and whites; nonsmokers, former smokers, and heavy smokers; and professional and technical workers. They were given pretest physical examinations, including a neurologic evaluation, pulmonary function tests, hematologic studies, and 16 blood chemistry tests. Each subject was exposed for 10 minutes by inserting his head through a rubber diaphragm into a chamber containing 90 ppm of methylhydrazine and was monitored for 60 days thereafter.

None of the subjects developed excessive tearing or bronchospasms during exposure, but most had increased moisture in the eyes without overflow tearing, and some had slight redness in the eyes [44]. Most subjects felt a slight tickling sensation of the nose. All clinical chemistry test results were normal. The only hematologic abnormality was the presence of Heinz bodies in 3-5% of the erythrocytes by the 7th day. No signs of anemia or reticulocytosis were observed, and the number of

Heinz bodies decreased in the next week and disappeared in 60 days. There were no significant changes in ventilatory capacity in six subjects; one subject had a respiratory infection, and his lung volume began to increase to the baseline value a week later. MacEwen et al concluded on the basis of these results that an EEL of 90 ppm for 10 minutes was adequate. It should be noted that in recommending EEL's, some reversible irritation or intoxication is accepted, and these limits should not be considered to be effect-free.

In 1973, George [45] examined the effects of methylhydrazine, in vitro, on human erythrocytes. Being a reducing agent, methylhydrazine caused characteristic oxidative damage to the erythrocytes, such as formation of Heinz bodies, production of methemoglobin, and a decrease of reduced glutathione. All these effects were related to the methylhydrazine concentration in the incubation medium and the length of exposure. For instance, Heinz bodies were found in about 20% of the erythrocytes incubated in a medium with a methylhydrazine concentration of 4.6 mg/liter in 24 hours, while 95-100% of the cells exposed to methylhydrazine at 460 mg/liter had one to nine Heinz bodies in 1 hour. The maximum concentration of methemoglobin increased from 15% (at 46 mg/liter after 90-120 minutes) to 36% (at 460 mg/liter after 30-60 minutes). The reduced glutathione level in erythrocytes incubated with methylhydrazine at 461 mg/liter decreased with time and was almost completely depleted in 4 hours; when glucose was added to the medium, however, the glutathione level decreased only in the first 2 hours and returned to the baseline value in 4 hours. Morphologic changes were noted in the erythrocytes exposed to

methylhydrazine. The changes included altered configuration and a loss of the central concavities of the cells.

Fortney and Clark [46] also examined the effect of methylhydrazine on the in vitro formation of methemoglobin. Human erythrocytes were incubated in media containing methylhydrazine at concentrations of 1.25, 2.5, and 5.0 millimoles/liter. Methemoglobin concentrations were found to be 10.2, 19.4, and 23.7%, respectively, 1 hour after incubation. The effects of other hydrazines were compared at a concentration of 5 millimoles/liter, and the methemoglobin concentrations were 0.5, 0.3, 8.2, and 12.2% for hydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and phenylhydrazine, respectively.

Leahy [47] compared the in vitro methemoglobin formation caused by methylhydrazine in blood samples of different species and reported that the equilibrium concentration of methemoglobin in human blood was higher than that in the blood of rats and monkeys. However, the amount of methemoglobin formed in human blood was lower than that in canine blood. Details of this study are presented in the Animal Toxicity section.

(c) 1,1-Dimethylhydrazine

Jacobson et al [20], in 1955, reported that the median concentration at which 1,1-dimethylhydrazine was detectable by odor by 16 volunteers was 6-14 ppm.

In 1970, Rumsey and Cesta [48] reported the results of a study of the odor threshold for 1,1-dimethylhydrazine. Several years of field monitoring data of 1,1-dimethylhydrazine concentrations collected during fuel transfer operations, in support of various missile programs, were used to correlate measured concentrations with the perception of odor as

reported by those performing the monitoring. A total of 11 personnel performed monitoring activities between September 1963 and November 1966. In 19 cases odor perception was reported when the vapor detector showed no reading at all or a reading of less than 1 ppm. In no case was there an absence of odor recorded when there were positive vapor detector readings.

To supplement the field data, a test atmosphere containing either dried air or 0.5 ppm of 1,1-dimethylhydrazine was delivered at low velocity to the subject's face through a polyethylene tunnel 15 inches long and 7.5 inches in diameter [48]. Nine office personnel were tested, and all reported perceiving an odor when 1,1-dimethylhydrazine was present. None detected an odor when dried air was tested alone. In a subsequent test, an adequate amount of 1,1-dimethylhydrazine was evaporated in an office with a volume of 32,000 cu ft. The office personnel were not given prior notice and their spontaneous responses were solicited immediately after entry. All 11 persons who entered the room containing 1,1-dimethylhydrazine detected an odor. The concentration range was 0.2-0.3 ppm. None of the 10 persons who entered the room lacking 1,1-dimethylhydrazine detected an odor.

Rumsey and Cesta [48] concluded that the odor threshold for 1,1-dimethylhydrazine was less than 0.3 ppm. This is probably a more accurate representation of the threshold than the 6-14 ppm determined with the osmoscope.

In 1957, Shook and Cowart [49] reported that, in five laboratory workers (chemists, engineers, and technicians) and six storers and handlers, all of whom were exposed to 1,1-dimethylhydrazine, there were

several instances in which positive cephalin flocculation tests were observed in a 6-month period. One worker also had a positive thymol turbidity test and one exhibited abnormal erythrocyte and leukocyte counts and had casts in his urine.

The laboratory workers were exposed intermittently to 1,1-dimethylhydrazine in small quantities for 10 hours/day, 6 days/week, for the first 3 months and 6-8 times for no more than 4 hours/week for the next 3 months [49]. The other workers were exposed 3-4 days every few weeks while loading and transferring the substance outside. An accidental spill occurred after about 3 months, but no workers showed signs of acute toxicity. However, the extent of exposure to 1,1-dimethylhydrazine or to other toxic chemicals was not discussed for either group.

Members of the Danish Air Force who worked with liquid rocket propellants received physical examinations and several laboratory tests, including SGPT activity, 3-4 times a year [50]. The concentrations of 1,1-dimethylhydrazine to which these men were exposed were unknown. From March 1961 to January 1964, SGPT activity was elevated at least once in 47 (4%) of 1,193 persons examined. Liver biopsies were performed on 26 volunteers. Of these 26 persons, 6 had slight-to-pronounced fat in the liver and 5 had uncertain tissue changes, including 4 with fatty degeneration in a few cells and 1 with slight lymphocytic infiltration. At the time of biopsy, SGPT's were elevated in all six persons with fat depositions in the liver. SGPT's were normal in 14 of the other 15; the abnormality in the 15th was attributed to alcohol consumption. Thus, a weak correlation between the microscopic findings and SGPT activity at the time of biopsy was found. There was no followup of these workers, and it was not possible to confirm

that the hepatic effects resulted from exposure to 1,1-dimethylhydrazine. However, other conditions known to cause liver damage were ruled out.

These two studies [49,50] suggest that liver damage in humans is a possible effect of 1,1-dimethylhydrazine exposure, but the findings reported were not unexpected in otherwise healthy individuals. Thus, it cannot be concluded definitely that 1,1-dimethylhdyrazine causes liver damage in humans.

(d) Phenylhydrazine

Phenylhydrazine hydrochloride was used in 1908 to induce experimental anemia in animals and was first used clinically to induce hemolysis in the treatment of polycythemia vera (a disease of abnormally high erythrocyte counts) in 1918 [51]. Generally, phenylhydrazine hydrochloride was given orally until a total dose of 3-4 g had been administered, or less was given if hemolysis was already evident [52]. In a few early cases, thrombosis occurred during excessive hemolysis, but it apparently was not caused by phenylhydrazine hydrochloride alone [51]. Later, thrombosis was controlled by excluding patients with vascular abnormalities, the very old, and those confined to bed and by carefully adjusting the dose. Treatment with phenylhydrazine was later replaced by the use of more effective drugs or therapy [53].

In addition to the case described in Historical Reports, Wright and Joyner [36] reported a case they had observed of skin hypersensitivity to phenylhydrazine hydrochloride. The patient was in contact with a mixture of phenylhydrazine hydrochloride and sodium acetate. Initially, pruritus developed on his thumbs and on the left index finger. This later progressed to severe swelling of the fingers, vesicle formation, and

desquamation on the hands. Skin tests revealed that the patient was sensitive to both phenylhydrazine hydrochloride and the mixture, though not to the phenylhydrazine base.

In 1937, Downing [54] reported a case of dermatitis in a rubber mill worker who came into contact with a new mixture containing zinc chloride and phenylhydrazine. Initial contact with the new substance, which lasted 1 hour, produced no apparent ill effects, but subsequent exposure produced swelling of the left eyelid, a bloodshot eye, and a rash on both hands and arms. When he used this mixture again, he was forced to stop work because of swelling of his eyes, face, hands, and forearms. Later, lesions appeared on his face and hands. Physical examination revealed impetiginous lesions on the left side of his nose and on the back of both hands, which were erythematous, edematous, and desquamating. The worker was given a patch test with both the dry and moistened powder of the phenylhydrazine-zinc chloride mixture. After 24 hours, there were erythematous and edematous areas at both application sites. Small blisters also appeared on the dry application site. The author concluded that this dermatitis was caused by phenylhydrazine. However, zinc chloride has been reported to be a skin irritant [10] and may have contributed to the development of dermatitis.

The presented data suggest that both phenylhydrazine [54] and its hydrochloride salt [36] are possible dermal sensitizers. Of more significance, though, in terms of human exposure, is the hemolytic effect of phenylhydrazine.