interpreted as evidence that acquired behavior was less stable in the experimental than in the control rats.

The authors [153] concluded that phenylhydrazine injected during pregnancy may adversely affect the performance of the offspring in certain areas of learning by inducing severe neonatal jaundice and anemia. The possibility that phenylhydrazine might act directly on the developing CNS, or that the learning deficit might be a result of the combination of the direct and secondary effects are questions not discussed by the author. It seems that anemia accompanied by jaundice more likely represents fetal toxicity and not teratogenicity; however, to induce terata experimentally, injection should occur at an earlier stage of pregnancy.

Correlation of Exposure and Effect

Little information is available on humans exposed to the hydrazines, so that the toxic effects that would be expected to occur in humans must be established from animal studies. There are both striking similarities and dissimilarites in the effects produced by these structurally related compounds. Judging from animal studies, one finds that the major sites affected appear to be the skin and eyes, the CNS, the liver, the blood, and the kidneys. These effects, along with odor thresholds, metabolism, and changes in biochemical function, are compared for each compound in the following sections, and relevant human information is presented where available.

(a) Skin and Eyes

Dermatitis has been observed in humans who had contact with hydrazine hydrate [38,39], its monohydrochloride [40], sulfate [37], and hydrobromide

[41] salts, and phenylhydrazine [54] and its hydrochloride salt [36]. The degree of skin response to hydrazine and its salts ranged from irritation [40] through mild maculopapular erythema [41]. Contact with phenylhydrazine hydrochloride caused itching, swelling of the fingers, vesicle formation, and desquamation of the hands [36]. In the above-mentioned reports, repeated contact with the hydrazines appeared to sensitize individuals to varying degrees. No reports of dermatitis were found for methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, or any of their salts.

The absorption of certain hydrazines through the skin was examined in animals. Hydrazine [59], methylhydrazine [98], or 1,1-dimethylhydrazine [115] applied to the shaved skin of dogs was rapidly absorbed, and the dogs developed toxic signs. Absorption through the skin and subsequent systemic toxicity are probably dependent on two factors: the amount of the hydrazine compound that can penetrate the outer layers of the skin and the rate of evaporation from the skin. In the absence of any other information, it seems reasonable to conclude that 1,2-dimethylhydrazine and phenylhydrazine would also be absorbed through the skin. While the free bases may be more or less irritating to the skin than the salts, because of pH, there is no good reason to doubt that salts will also penetrate the skin.

The LD50 doses reported for skin absorption in animals seem to some extent to be related to the vapor pressures of the hydrazines. Two drops of anhydrous hydrazine applied to the skin of rats was fatal [57]. In guinea pigs, the LD50 dose was 190 mg/kg; in rabbits, it was 93 mg/kg [58]. For methylhydrazine, the LD50 for topical application was about 180 mg/kg

in rats [97], 47 mg/kg in guinea pigs, and 93 mg/kg in rabbits [58]. For 1,2-dimethylhydrazine, the LD50 was 131 mg/kg in guinea pigs and 466 mg/kg in rabbits [58], compared to 1.2-1.7 g/kg in dogs [115], 1.05 g/kg in rabbits, and 1.31 g/kg in guinea pigs [58] for 1,1-dimethylhydrazine.

Adverse effects have also been reported in animals when certain hydrazines were placed in the eyes. Hydrazine concentrations of 25% or greater were reported to cause severe, irreversible eye damage [57]. However, methylhydrazine [58], 1,1-dimethylhydrazine [114], and 1,2-dimethylhydrazine [58] caused only a mild conjunctivitis and slight reddening of the eye. These effects, to a large extent, may be related to the alkalinity of the compounds; for example, hydrazine has a pKa of 8.07 compared to 7.21 for 1,1-dimethylhydrazine [11]. Thus, the relative degree of expected eye damage for phenylhydrazine and the salts of hydrazines may be related to their respective acidity or basicity.

(b) Odor Detection

The odor threshold ranges have been reported to be 3-4 ppm for hydrazine, 1-3 ppm for methylhydrazine, and 6-14 ppm for 1,1-dimethylhydrazine [20]; in another study, the odor threshold for 1,1-dimethylhydrazine was reported to be less than 0.3 ppm [48]. There are probably insufficient warning properties to afford adequate protection against long-term exposure by reliance on odor, and variations in odor thresholds from such factors as odor fatigue argue against reliance on odor for warning of toxic exposure. However, the odor of these three compounds should alert the worker to the need to leave a contaminated area. Phenylhydrazine was reported to have a faint aromatic odor [10] as compared to the ammoniacal, fishy odor of the others [5]. Thus, it is improbable

that the odor of phenylhydrazine is sufficiently detectable to be of any protective value.

(c) Central Nervous System

There is only one report [42] on the acutely toxic effects of hydrazines on humans. A man who accidentally swallowed an unknown quantity of hydrazine developed pupil dilatation, vomiting, and loss of consciousness, followed by "sporadic violence" and paresthesia.

In animals, the acute toxicity of the hydrazines includes effects in the CNS. Acutely toxic signs observed following the inhalation of hydrazine, methylhydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine include restlessness, breathing difficulties, and convulsions [20]. Other signs included vomiting, salivation, panting, and incoordination in animals exposed to methylhydrazine [20,92] and vomiting and lethargy preceding restlessness in animals exposed to 1,1-dimethylhydrazine [110,111]. Noise increased or hastened toxic signs [111]. No information on acutely toxic effects following the inhalation of phenylhydrazine was found. Rodents injected sc with phenylhydrazine developed progressive cyanosis, breathing difficulties, and convulsions [146], but this may not reflect CNS toxicity.

(d) Liver

Certain hydrazines are hepatotoxic. The long-term inhalation of hydrazine at exposures as low as 30 ppm-hours/week resulted in severe fatty degeneration of the liver in mice [56]. Monkeys may have been affected likewise, but controls showed similar results at necropsy. Liver damage in dogs occurred at higher exposures, about 150 ppm-hours/week; rats' livers

were not affected. Similar effects were observed in these species after ip injections [60].

Dogs that inhaled methylhydrazine at 6-30 ppm-hours/week developed cholestasis in the liver; effects at higher doses were similar but more severe [94]. At 16.8 ppm-hours/week, livers of dogs were passively congested [95].

In one study of animals that inhaled 1,1-dimethylhydrazine at 150-4,200 ppm-hours/week, no fatty vacuolization of the liver was found [110], but in another study SGPT activity and BSP retention time were significantly increased in dogs exposed at 150 ppm-hours/week [112]. Similar but less severe results were observed at 15 ppm-hours/week; livers were normal at 1.5 ppm-hours/week [112]. However, these hepatotoxic effects may have been caused by the trace amount of nitrosodimethylamine present in the compound used [113]. Fatty infiltration in the livers of some rats [117], and in one of seven monkeys [60], was noted after ip injection of 1,1-dimethylhydrazine.

1,2-Dimethylhydrazine, given ip, orally, or sc, was hepatotoxic in mice [125], miniature swine [126], dogs [126], and, to a lesser degree, in guinea pigs [126] and rats [125]. Dogs and miniature swine became jaundiced [126], possibly because of liver damage but more likely because their bile ducts were affected. The possibility of liver damage caused by phenylhydrazine has not been investigated to a sufficient extent to draw conclusions relevant to occupational exposure. However, several investigators have mentioned without supportive data that hepatic effects were seen in dogs [34,35] and rabbits [149] given phenylhydrazine.

In summary, exposure to hydrazine and methylhydrazine caused liver damage in some species at low concentrations. The toxic effects differed, fatty infiltration being a primary effect, while cholestasis may have been a secondary manifestation of damage to other systems. Data on 1,2-dimethylhydrazine and phenylhydrazine are less conclusive because they are incomplete. However, the severe liver damage observed in some species after oral or sc administration of 1,2-dimethylhydrazine suggests that this compound probably would have some degree of hepatotoxicity in occupationally exposed humans. 1,1-Dimethylhydrazine appears to be hepatotoxic, but it is considerably less potent than hydrazine [60,116,117]. Contradictory experimental results in animals may have been caused by differing levels of nitrosodimethylamine, an impurity produced from decomposition or introduced in production [12,13]. Studies of workers exposed to 1,1-dimethylhydrazine [49,50] support the contention that liver damage is possible, although the reports, themselves, are inconclusive.

(e) Blood

In animals, inhalation of hydrazine [56], methylhydrazine [20,92,93,95], and 1,1-dimethylhydrazine [110] caused a dose-dependent hemolytic anemia. Dogs developed depressed erythrocyte counts, hematocrit values, and hemoglobin concentrations during the course of a 6-month inhalation exposure to hydrazine at 150 or 168 ppm-hours/week; the effect was reversible and was not observed at 30 ppm-hours/week [56].

Dogs exposed to methylhydrazine at 16.8 ppm-hours/week for 3 months or at 6-33.6 ppm-hours/week for 6 months developed anemia [93,95] and Heinz body formation [93]. At 150 ppm-hours/week [93], anemia was more severe, and methemoglobinemia and increased red cell fragility were observed.

Monkeys had similar, although less severe, anemic effects. At 6.7 ppm-hours/week, statistically significant changes in blood cell counts were observed in rats after 45 days of exposure, but not at 90 days [95]. In short-term experiments at near-lethal exposures, anemia [20,92], reticulocytosis [20], and possibly methemoglobinemia [92] were observed in dogs; again, monkeys were less severely affected than dogs [92]. Dogs exposed at 1 ppm for 24 hours, the lowest concentration tested, were normal [95].

Dogs exposed at near-lethal concentrations of 1,1-dimethylhydrazine for 4 hours did not develop anemia [20]. The results of long-term studies differ. In one experiment, dogs exposed to 1,1-dimethylhydrazine at 150 ppm-hours/week developed hemolytic anemia and hemosiderosis of the spleen [110], but in another experiment with an exposure range of 1.5-150 ppm-hours/week, anemia was not observed [112]. Dogs exposed twice weekly for short intervals at about 100 ppm-hours/week for 6 weeks, then at 200 ppm-hours/week for 2 weeks did not develop anemia [111]. Although these reports appear contradictory, in the first experiment [110] it was possible to confirm that a mild anemia did exist because similar, but more severe, changes in erythrocyte counts, hemoglobin concentrations, and hematocrit values were also seen in dogs exposed at 750 ppm-hours/week. Thus, the total concentration time at which the dogs in the other two experiments [111,112] were exposed was probably insufficient to observe anemia. The lowest concentration of 1,1-dimethylhydrazine at which anemia was observed in dogs was, thus, about 5 ppm.

In dogs, methylhydrazine was a stronger hemolytic agent than hydrazine, and 1,1-dimethylhydrazine was the least potent in this regard.

For hydrazine, the lowest level at which hemolytic effects were observed in dogs is equivalent to exposure at about 0.7 ppm for 40 hours/week; for methylhydrazine, it is about 0.15 ppm. In humans, exposure to methylhydrazine at 90 ppm for 10 minutes resulted in the formation of a few Heinz bodies in the red cells [44].

The hemolytic properties of phenylhydrazine have been known since the early 1900's [35], and phenylhydrazine hydrochloride had been used therapeutically for polycythemia vera [51]. In animals, hemolytic anemia [145,148] and Heinz bodies [147] were found after administration of phenylhydrazine by various routes. In dogs, 95-100% of the red cells contained Heinz bodies 24 hours after sc injection of phenylhydrazine at 20-30 mg/kg [147]. Similar results were obtained when methylhydrazine at a concentration of 46 mg/liter was incubated with human blood [45]. If it is assumed that, in the experiment with phenylhydrazine [147], 10% of the dose was retained in the blood (as was reported for rabbits [150]), and that the total dose available was roughly 200 mg/liter of blood, then phenylhydrazine and methylhydrazine at approximately equal concentrations caused the formation of an equivalent number of Heinz bodies. However, canine blood is more susceptible to methemoglobin formation than human blood [47], suggesting that Heinz body formation in the blood of these two species may not be directly comparable. In vitro studies of methemoglobin formation [46] found phenylhydrazine to have about one-half the effect of methylhydrazine. In the absence of any contradictory information, it seems reasonable to conclude that phenylhydrazine, by inhalation, would exert a toxic effect on the blood similar to that of methylhydrazine.

Hemolytic anemia, as such, has not been studied with respect to 1,2-dimethylhydrazine exposure. In a study on tumorigenicity [127], it was mentioned that the animals were anemic. In vitro, methemoglobin was found in blood incubated with 1,2-dimethylhydrazine [46]. Thus, it is probable that 1,2-dimethylhydrazine does have a toxic effect on red cells.

Because of the toxic effect on red cells resulting from exposure to the various hydrazines, secondary effects on the reticuloendothelial system, such as marrow hyperplasia and hemosiderosis, would be expected. Reticulocytosis [20], a decreased myeloid/erythroid ratio in the marrow [92,93], and hemosiderosis of the spleen [94,99] have been observed in animals after exposure to methylhydrazine. After injection of phenylhydrazine, enlargement of the spleen [147,148], congestion of the liver and kidneys [147], and transformation of yellow marrow to red marrow [149] have been reported. Although the reports did not explicitly state such a conclusion, the effects described for phenylhydrazine can probably be attributed to hemosiderosis and stimulation of erythropoiesis. For hydrazine, a decreased myeloid/erythroid ratio has been observed [56], and for 1,1-dimethylhydrazine hemosideroses of the lymph nodes, marrow, Kupffer cells, and the spleen, along with increased erythrocytic activity in the marrow, have been noted [110].

(f) Kidneys

Exposure to methylhydrazine has caused kidney damage in animals [92,94,99,101], although some of the effects observed may be secondary to red cell destruction. After short-term exposures, effects on the renal tubules ranged from swelling to coagulative necrosis of the epithelium

[92]. In long-term studies, hemosiderosis of the proximal tubules was observed at exposures as low as 6 ppm-hours/week for 6 months [94].

In dogs, ip injections of methylhydrazine at 7-30 mg/kg caused dose-related, time-related, partly reversible renal lesions [99]. The survival of some animals at the high doses was achieved only with the concomitant injection of pyridoxine. In one ip study, the kidneys of monkeys were unaffected when examined by a light microscope even at fatal doses [100], but in a later study in which the monkeys' kidneys were transplanted to a subcutaneous site, damage was observed in the proximal and distal tubular cells through an electron microscope; kidney function was not impaired [101].

Lipid deposition in the kidneys of monkeys injected ip with hydrazine was observed [60]; probably this effect was related to similar damage seen in the liver. In dogs given iv injections of hydrazine [61,62] and methylhydrazine [62], glomerular filtration and proximal renal tubular function were affected. 1,1-Dimethylhydrazine, given ip to rats in near-fatal doses, caused diuresis, elevated BUN, and lipid infiltration in the renal tubules [117], but in monkeys, only one of seven had lipid deposits in the tubular membranes [60]. In another experiment in which 1,1-dimethylhydrazine was given ip, no kidney damage was observed microscopically, although amino acid excretion was enhanced [116]. No adverse effects on the kidney were observed after long-term inhalation exposure to 1,1-dimethylhydrazine in animals [110] or after iv injection [61,62].

After phenylhydrazine administration in dogs, the epithelial lining of the convoluted tubules was hypertrophied and filled with blood [147].

This was probably a secondary effect of red cell destruction. No study on kidney damage from 1,2-dimethylhydrazine was found.

The kidney effects observed from methylhydrazine and phenylhydrazine appear to some extent to be secondary effects caused by hemolysis. Even though these two compounds caused the most severe kidney damage observed with any of the hydrazines, a standard that would protect against hematologic effects should be adequate to prevent kidney damage, since hematologic effects were observed at concentrations lower than those causing kidney damage. Hydrazine appears to exert an effect on the kidneys similar to but less severe than that on the liver. 1,1-Dimethylhydrazine was the least nephrotoxic of the five hydrazines excluding 1,2-dimethylhydrazine, for which no relevant information is available.

(g) Biochemical Function

Since the hydrazines are reactive molecules that can become widely distributed throughout the body, numerous disturbances of normal biochemical function might be expected. The literature contains many such references; however, they are often difficult to equate to an observed impairment in health. Most of these reports were, therefore, not discussed in the criteria document. However, there were several studies in which metabolic disturbances resulting from exposure to hydrazines could have serious consequences, as the result of an accidental massive exposure, a secondary illness, or an enzyme deficiency, and these reports were cited.

Hydrazine and, to a greater extent, methylhydrazine caused lactic acidosis and disturbances of glucose metabolism in dogs [46,63]. After hydrazine administration, hyperglycemia developed when liver glycogen levels were high. When liver glycogen was depleted, hypoglycemia was

induced [63]. Similar effects on blood glucose were also seen in rats given an ip injection of methylhydrazine [96,105]. Hypoinsulinemia was induced in rats injected ip with hydrazine sulfate even in the presence of excess glucose; the ability of the pancreas to secrete insulin appeared to be impaired [65].

1,1-Dimethylhydrazine was reported to have little effect on carbohydrate metabolism [46], but it induced hyperglycemia in rats [96]. In a study on monkeys, plasma glucose levels were also increased [60]. Recent studies of the effects of phenylhydrazine on biochemical function were not found. However, in a report [35] in 1924 on dogs given phenylhydrazine, reduced sugar tolerance was described.

(h) Metabolism

Various aspects of the metabolism of the hydrazines, including routes of excretion, tissue retention, and major metabolites, have been studied [66-68,103-105,120,121,144,150,122], but some uncertainty exists in determining the relevance of these studies to occupational exposure. The routes of administration were not typical of those encountered in the workplace, and studies in humans were not found. Regardless of the route of administration (iv, ip, or oral), 2-5 days were required for animals to excrete one-half the dose of hydrazine, methylhydrazine, or phenylhydrazine in the urine [66,68,103,150].

The results of several studies [66,68,104] show that dogs apparently excrete hydrazine and methylhydrazine in the urine about half as fast as do rodents. Although there was a considerable degree of variability in the results, 1,1-dimethylhydrazine was excreted more rapidly in the urine than were the other hydrazines. In dogs, cats, and rats given ip or iv doses of

1,1-dimethylhydrazine, 11-46% was excreted in 4-6 hours [121,122]. Since the metabolism of inhaled hydrazines was not studied, it is not possible to determine if their retention in the lungs is likely. Respiration was shown to be a major route of elimination of methylhydrazine metabolites; in rats, as much as 37% of an ip dose was exhaled as carbon dioxide or methane in 27 hours [103]. In rats given 1,2-dimethylhydrazine, 11% of the dose was respired as carbon dioxide and 14% as azomethane in 24 hours [144]. Twelve to 23% of the injected 1,1-dimethylhydrazine was excreted as carbon dioxide by rats in 7 hours [121]. Similar data were not available for hydrazine or phenylhydrazine.

In dogs, hydrazine was excreted unchanged in the urine [66], but, in rabbits, some of the hydrazine was metabolized to diacetylhydrazine, an apparent product of detoxification [67]. Metabolites of 1,1-dimethylhydrazine identified in the urine were the parent compound (possibly conjugated), glucose dimethylhydrazone, and a neutral hydrazone or hydrazide [120]. For phenylhydrazine, the major metabolic processes were the hydroxylation of the ring and probable conjugation to form hydroxyphenylhydrazone glucuronide and formation of pyruvic acid and oxoglutaric acid phenylhydrazones [150]. Thus, the results from phenylhydrazine suggest that the ability of the hydrazines to react with aldehydes and ketones may be an important mechanism of detoxification. The metabolic products of 1,2-dimethylhydrazine have been suggested to be responsible for the development of colon cancer [131]. Metabolites of other hydrazines need to be studied to determine their possible toxic action or their role as detoxification products.

Hydrazine [68], methylhydrazine [104], and 1,1-dimethylhydrazine [150] were not preferentially concentrated to a greater extent in any one organ. In rabbits, however, 10% of the administered dose of phenylhydrazine was retained in erythrocytes [150]. In rats given hydrazine sc, the highest concentration of hydrazine was found in the kidneys after 2 hours [68]. In animals given methylhydrazine ip, the highest concentrations of the compound were in the serum and liver, followed by the kidneys and bladder [104]. The highest concentrations of 1,1-dimethylhydrazine in animals were found in the colon [122], liver, and blood [120,122].

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No studies have been found in which cancer of humans can be related to exposure to hydrazines. Tumors, often malignant, have been found in at least one animal species after the administration of each of the five hydrazines. These results are summarized in Table III-7.

(a) Carcinogenicity of Hydrazine

Hydrazine and its sulfate salt have been reported to be tumorigenic in mice after administration by several routes [69-75,77-84]. When hydrazine sulfate was given to BALB/c mice by intubation, an increased incidence of lung tumors, mostly adenomas but also carcinomas, was found [70-72]. Tumor incidence was dose dependent [70], and the mice appeared to be more susceptible if administration began shortly after birth [74]. There was some suggestive evidence of a hormonal effect [73]. A few mice in one study had hepatocarcinomas [70]. In CBA mice, both lung tumors (adenomas and adenocarcinomas) and hepatomas were found [71,75]; the

hepatoma incidence was dose related [75], but no similar study concerning lung tumors was found. Again, a hormonal effect on tumor induction was suggested [77]. Swiss mice developed lung tumors when given hydrazine orally [78] and CDF1 mice given hydrazine sulfate had carcinomas of the lung [81] even though in both cases the animals were killed after relatively short periods of time. Swiss mice given a 0.001% hydrazine solution in drinking water throughout life developed adenomas in the lungs [80]. Malignant lymphomas were also found. Similar results were found in Swiss mice given 0.012% solutions of hydrazine sulfate; however, an increased tumor incidence was not found in AKR or C3H strains [79].

The CDF1 [81], SWR [82], C57BL/B [82], and BALB/c (newborn) [84] strains of mice all developed lung tumors when given ip injections of hydrazine sulfate. However, tumors in the mediastinum, not the lungs, were found in mice injected ip with hydrazine [83].

A dose-related increase in alveologenic carcinomas in mice exposed to hydrazine by inhalation at 30-33.6 or 150-168 ppm-hours/week for 6 months was found at necropsy 1 year after the end of exposure [69].

Regardless of the route of administration, in drinking water, by gavage, ip, or by inhalation, hydrazine and its sulfate salt were tumorigenic in mice and the main target organ was the lungs. There was no indication of a true difference in tumorigenic potential between hydrazine and its sulfate salt, although differences in strain susceptibility were apparent. In some studies there were tumors classified as adenomas becoming malignant. This description appears to apply to tumors in which there was a peripheral infiltration tendency compared with adenomas which had clearly defined margins and with carcinomas that were invasive.

Lung tumors, both benign and malignant, were also induced in rats given hydrazine sulfate orally [76]. However, negative results were obtained in hamsters [75,85], even though the studies were identical in design to others in which mice developed tumors. These results may represent a true difference in susceptibility, or they may suggest that the metabolism of hydrazine is species specific. The results in mice and rats suggest that hydrazine may have a tumorigenic potential in humans.

(b) Carcinogenicity of Methylhydrazine

About 23% of the Swiss mice given 0.7 mg of methylhydrazine in drinking water daily for life developed lung tumors [80]. In the same study [80], male mice given 0.102 mg and females given 0.078 mg of methylhydrazine sulfate in drinking water daily for life had a lung tumor incidence of 46%. From the normal incidence of lung tumors observed in this colony, it cannot be determined with certainty that the incidence of lung tumors after methylhydrazine administration was significantly increased. However, the latent period of about 45 weeks was short compared with the 81 weeks observed for methylhydrazine sulfate. The higher incidence of lung tumors observed for a lower dose of the sulfate salt may have been caused by the toxicity of methylhydrazine at the higher dose, or methylhydrazine may have decomposed in the drinking water.

In two other studies, one in which mice were given methylhydrazine by intubation and ip injection [81] and one in which the sulfate salt was given orally [78], no evidence of carcinogenicity was found. In the methylhydrazine sulfate study [78], all animals were killed about 30-40 weeks before the average latent period observed in another study [80] in which lung tumors were found. In the methylhydrazine study [81], the

animals were killed still earlier and the small number of females examined suggests that the dose may have been acutely toxic.

Hamsters given 1.1-1.3 mg of methylhydrazine each day in drinking water had an increased incidence of malignant histocytomas [106]. In a similar study, two other groups of hamsters given methylhydrazine did not develop histocytomas [107]. When the solution was unbuffered, 12% of the hamsters developed liver tumors. However, the significance of these tumors is questionable, since there were two different cell types and the number of animals used, especially controls, was small. When the solution was buffered, neither histocytomas nor liver tumors were found.

There are two apparent differences in these studies. In one study [107], 60% of the unbuffered methylhydrazine was found to degrade in 24 hours. Thus, the results of both studies [106,107] may have been affected by degradation products. That decomposition products, themselves, may possibly be carcinogenic is a problem that needs to be investigated. However, the more stable salt form resulted in a higher tumor incidence in mice than the free base [80]; therefore, methylhydrazine itself must be considered the causative agent. The hamsters in one study [106] were 6 weeks old at the start of the experiment; in the other [107], they were 5 months old. This difference may have influenced the results.

(c) Carcinogenicity of 1,1-Dimethylhydrazine

In Swiss mice given 0.7 mg of 1,1-dimethylhydrazine daily in drinking water for life, 79% developed angiosarcomas; normal incidence in this colony was about 2% [123]. Many lung tumors, primarily adenomas, were also found. In males, 18% had kidney tumors and 12% had hepatomas; similar tumors were not seen in controls, suggesting that while the incidences

were relatively low, the tumors may have been related to exposure. In another study [78], Swiss mice given 0.5 mg/day of 1,1-dimethylhydrazine for 40-60 weeks showed inconclusive evidence of lung tumor induction. In a third study [81], at much lower doses, there was no evidence of a carcinogenic effect in mice. Because only a 32-week observation was used in this study, the results cannot be considered conclusive.

One additional factor that must be considered in evaluating the tumorigenicity of 1,1-dimethylhydrazine is the role of nitrosodimethylamine contamination. One study [113] has described this trace contaminant as the cause of liver toxicity. It may be that this contaminant was related either directly or indirectly to the induction of some of the tumors.

(d) Carcinogenicity of 1,2-Dimethylhydrazine

Angiosarcomas were found after 1,2-dimethylhydrazine was administered in drinking water to mice [127], hamsters [85], and rats [131]. One study [127] reported adenomas of the lungs in mice, but another [131] reported that the lung tumors in rats were metastatic. In hamsters, lung tumors were not reported, but many animals had tumors of the cecum or liver [85]. When given to rats by intubation, 1,2-dimethylhydrazine produced carcinomas of the colon [130,131], gastrointestinal tract [130], and rectum [131]. Guinea pigs developed bile duct carcinomas and hepatomas [126]. 1,2-Dimethylhydrazine, administered ip and by gavage, was reported to be noncarcinogenic in mice [81]. However, the animals were examined for lung tumors, not for colonic tumors, and the observation period was short.

After repeated sc injections with 1,2-dimethylhydrazine, Swiss mice [128] and CF1 mice [132] developed tumors of the large intestine. In one study [128], tumors of the lungs, blood vessels, and kidneys were also

reported. All rats given multiple sc injections of 1,2-dimethylhydrazine died with malignant tumors of the large intestine [131]. The sc route has also been used by numerous investigators interested primarily in the study of colon cancer. Colon tumors have been induced in CF1 [133], NMRI [134], and Swiss mice [136], but not in C57/B mice [136]. Strain specificity for tumor induction in rats has also been noted [139]. Other factors that influenced colon tumor production in rats included cholestyramine [142], disulfiram [143], and the amount of fat in the diet [138,141]. Germ-free rats were less susceptible than conventional rats [140].

Several points indicate that, at least by the sc route and by intubation, 1,2-dimethylhydrazine is metabolized to an active carcinogen: first, the site of tumor formation itself; second, the decreased susceptibility of germ-free animals; and third, the exhalation of azomethane in rats after sc injection [144].

Two factors may account for the high incidence of tumors at sites other than the colon. There may be different metabolic pathways available when a low dose is given slowly but continuously. It is also possible that some of the compound decomposed in solution on standing. No long-term inhalation studies on 1,2-dimethylhydrazine are available. The results from sc injection may be similar to what would be expected from dermal application. However, it is unclear to what extent administration in the drinking water would be relevant to inhalation. It is possible that not all sites of tumor formation have been identified. However, since at least four species, the mouse, rat, hamster, and guinea pig, have all developed malignant tumors after being given 1,2-dimethylhydrazine, this compound is likely to be carcinogenic to humans.

(e) Carcinogenicity of Phenylhydrazine

When phenylhydrazine hydrochloride was administered by intubation to BALB/c mice, 53% developed lung tumors, some of which were malignant [151]. The incidence in control animals was 13%. In another study [152] in which phenylhydrazine was administered in the drinking water of Swiss mice for life, the only significant increase found was in blood vessel tumors. The differences found in these two studies could have been either the result of strain specificity or metabolic alteration arising from the difference in the route of administration. In two additonal studies [78,81], no evidence of carcinogenicity was found. As described before, these two studies have serious inadequacies in their experimental designs, and consequently little significance is placed on them.

(f) Other Effects

Hydrazine was mutagenic in the host-mediated assay system [87] and weakly mutagenic in two mutant strains of Salmonella typhimurium [88]. Methylhydrazine was mutagenic in tests with Salmonella typhimurium TA-1535. 1,1-Dimethylhydrazine appeared to be metabolically activated to a mutagenic intermediate in liver microsomes, and it was active in a microbial test (TA-90) but not in the dominant-lethal assay [108]. This evidence of mutagenicity could be interpreted as being consistent with a suggestion that the tumors found in animals affected by these compounds were caused by somatic mutations. Whether germinal mutations should be expected from these compounds is not evident from the limited data.

Hydrazine administration to female rats on the 11th day of pregnancy resulted in fetal resorption and pup deaths; pyridoxine hydrochloride afforded some protection [89]. Solutions containing hydrazine sulfate were

teratogenic to South African clawed toad embryos cultured in this medium [90,91]. Methylhydrazine sulfate, administered to rats on the 12th day of pregnancy, was not teratogenic in doses that were apparently fatal in half of the dams [108]. However, methylhydrazine was found to be a potent teratogen to South African clawed toad embryos, 52% of the embryos becoming malformed in a culture medium containing 5 mg/liter of methylhydrazine [91]. 1,1-Dimethylhydrazine and 1,2-dimethylhydrazine at concentrations of 10 and 50 mg/ml, respectively, also caused more than half of the exposed toad embryos to be malformed [91]. Rats born to dams injected with phenylhydrazine hydrochloride on the 17-19th days of pregnancy were jaundiced and anemic at birth and they were slower in conditioned avoidance learning [153], but this is more likely the result of a fetal toxicity than a development deficiency.

There is insufficient information from these teratogenicity studies on which to base conclusions for recommendations for a standard for the hydrazines. Embryos of toads, a species without placenta, bathed in solutions of hydrazines provide poor data on which to base implications about teratogenicity or other effects on reproduction.

Summary Tables of Exposure and Effect

Tables III-1 through III-7 summarize the effects of the hydrazines on animals. The LC50's for rodents [20] suggest that methylhydrazine is the most acutely toxic compound, followed in order by 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and hydrazine. The dog has consistently been a more susceptible species than the rat [20,92,111]. Because of the lack of data,

acute toxicity of phenylhydrazine can only be inferred from other hydrazines. The oral LD50 for rats was 188 mg/kg [16] compared with 71 mg/kg for methylhydrazine [97]. This finding would suggest, when the formula weights of the two compounds are taken into consideration, that the acute toxicity of phenylhydrazine may be about the same as that of methylhydrazine.

TABLE III-1

LC50 OR LD50 DATA FOR HYDRAZINES

Route of Exposure	Species	LC50 or LD50	No. of Doses or Duration of Dosage	References
HYDRAZINE				
inhalation	Rats	570 ppm	4 hr	20
"	Mice	252 ppm	"	20
ip	Rats	64 mg/kg	Once	96
iv	Rabbits	26 mg/kg	"	58
dermal	"	93 mg/kg	"	58
"	Guinea pigs	190 mg/kg	"	58
METHYLHYDRAZINE				
inhalation	Squirrel monkeys	340 ppm	15 min	92
"	"	145 ppm	30 min	92
"	"	82 ppm	1 hr	92
"	Rhesus monkeys	162 ppm	"	92
"	Dogs	390 ppm	15 min	92
"	"	195 ppm	30 min	92
"	"	96 ppm	1 hr	92
"	Rats	427 ppm	30 min	92
"	"	244 ppm	1 hr	92

TABLE III-1 (CONTINUED)

LC50 OR LD50 DATA FOR HYDRAZINES

Route of Exposure	Species	LC50 or LD50	No. of Doses or Duration of Dosage	References
inhalation	Rats	127 ppm	2 hr	92
"	"	74-78 ppm	4 hr	20, 92
"	Mice	272 ppm	30 min	92
"	"	122 ppm	1 hr	92
"	"	92 ppm	2 hr	92
"	"	56-65 ppm	4 hr	20, 92
"	Hamsters	143 ppm	4 hr	20
oral	Rats	71 mg/kg	Once	97
"	Hamsters	22 mg/kg	"	97
dermal	Rats	183 mg/kg	"	97
"	Rabbits	93 mg/kg	"	58
"	Guinea pigs	47 mg/kg	"	58
"	Hamsters	239 mg/kg	Once	97
ip	Rats	20 mg/kg	"	97
"	"	28 mg/kg	"	96
"	Hamsters	21 mg/kg	"	97
iv	Rats	17 mg/kg	"	97
"	Rabbits	12 mg/kg	"	58

TABLE III-1 (CONTINUED)

LC50 OR LD50 DATA FOR HYDRAZINES

Route of Exposure	Species	LC50 or LD50	No. of Doses or Duration of Dosage	References
1,1-DIMETHYLHYDRAZINE				
inhalation	Rats	24,500 ppm	5 min	111
"	"	8,230 ppm	15 min	111
"	"	4,010 ppm	30 min	111
"	"	1,410 ppm	60 min	111
"	"	252 ppm	4 hr	20
"	Mice	172 ppm	"	20
"	Dogs	22,300 ppm	5 min	111
"	"	3,580 ppm	15 min	111
"	"	981 ppm	60 min	111
"	Hamsters	392 ppm	4 hr	20
ip	Rats	102 mg/kg	Once	96
iv	Rabbits	70 mg/kg	"	58
dermal	"	1,049 mg/kg	"	58
"	Guinea pigs	1,314 mg/kg	"	58
oral	Rats	360 mg/kg	"	114

TABLE III-1 (CONTINUED)

LC50 OR LD50 DATA FOR HYDRAZINES

Route of Exposure	Species	LC50 or LD50	No. of Doses or Duration of Dosage	References
1,2-DIMETHYLHYDRAZINE				
inhalation	Rats	280-400 ppm	4 hr	20
ip	"	275 mg/kg*	Once	125
"	Mice	462 mg/kg**	"	125
"	"	46 mg/kg*	"	125
"	Dogs	53 mg/kg*	"	125
PHENYLHYDRAZINE				
oral	Rats	188 mg/kg	Once	16
"	Mice	175 mg/kg	"	16
"	Rabbits	80 mg/kg	"	16
"	Guinea pigs	80 mg/kg	"	16

* Death in 7 d, free base dose
** Death in 1 d, free base dose

TABLE III-2

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO HYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure	No. of Doses or Duration of Dosage	Observed Effects	References
inhalation	Rats	20-225 ppm 5-14 ppm	6 wk* 6 mo*	Death of 83% in 1-6 wk Some deaths	55
"	"	30-168 ppm-hr/wk	6 mo	Weight loss	56
"	Mice	"	"	Moderate to severe fatty liver	56
"	Dogs	150-168 ppm-hr/wk	"	Weight loss, fatty liver, anemia	56
"	"	30-33.6 ppm-hr/wk	"	Some increased resistance to osmotic hemolysis	56
"	"	14 ppm	6 mo*	Fatty liver, anemia, death in 2 of 4	55
"	"	5 ppm	"	Weight loss, vomiting, irregular breathing	55
"	Monkeys	30-168 ppm-hr/wk	"	Slightly fatty liver	56
dermal	Dogs	96-480 mg/kg	Once	Hypoglycemia, some deaths	59
ip	Rhesus monkeys	5-20 mg/kg	25-33 x	Weight loss, slight anemia, fatty liver, kidney, and heart	60
"	"	32 mg/kg	2 x	Inhibit insulin release	65

TABLE III-2 (CONTINUED)

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO HYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure	No. of Doses or Duration of Dosage	Observed Effects	References
iv	Dogs	25-100 mg/kg	Once	Hypoglycemia, convulsions	63
"	"	16-20 mg/kg	"	Impaired kidney function	61, 62

*6 hr/d, 5 d/wk

TABLE III-3

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO METHYLHYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure	No. of Doses or Duration of Dosage	Observed Effects	References
inhalation	Monkeys	6-150 ppm-hr/wk	6 mo	Anemia	93
"	"	6.7-33.6 ppm-hr/wk	3 mo	None	95
"	"	1 ppm	24 hr	"	95
"	Dogs	21-29 ppm	4 hr	Convulsions, many deaths, anemia	20
"	"	15 ppm	"	Vomiting, tremors, incoordination, anemia	20
"	"	60-150 ppm-hr/wk	6 mo	Anemia, cholestasis, hemosiderosis	93 94
"	"	6-33.6 ppm-hr/wk	"	Anemia, cholestasis	93 94
"	"	33.6 ppm-hr/wk	3 mo	Slight anemia, liver congestion	95
"	"	6.7 ppm-hr/wk	"	None	95
"	"	1 ppm	24 hr	"	95
"	Rats	6-150 ppm-hr/wk	6 mo	Weight gain lag above 60 ppm-hr/wk	93
"	"	6.7-33.6 ppm-hr/wk	3 mo	Anemia	95
"	Mice	60-150 ppm-hr/wk	6 mo	Cholestasis, bile duct proliferation, hemosiderosis, some deaths	93 94

TABLE III-3 (CONTINUED)

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO METHYLHYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure	No. of Doses or Duration of Dosage	Observed Effects	References
inhalation	Mice	6-33.6 ppm-hr/wk	6 mo	Hemosiderosis	93 94
ip	Monkeys	7 and 10 mg/kg/d	2-4 doses	Death	100
"	"	2.5-5 mg/kg/d	23 doses	Initial weight loss	100
"	"	2.5-7.5 mg/kg/d	1-14 doses	Renal tubule damage	101
"	Dogs	10 mg/kg	Once	Death, organ congestion	99
"	"	7.5 mg/kg	"	Mild kidney damage	99
"	"	5 mg/kg	"	Vomiting, convulsions	99
iv	"	29 mg/kg	"	Methemoglobinemia, methemoglobinuria, impaired kidney function	62
"	"	25 mg/kd	-	Methemoglobinemia	46
dermal	"	15-265 mg/kg	"	Methemoglobinemia, convulsions	98

TABLE III-4

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO
1,1-DIMETHYLHYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure	No. of Doses or Duration of Dosage	Observed Effects	References
inhalation	Dogs	111 ppm	4 hr	Convulsions, death	20
"	"	24-52 ppm	"	Convulsions	20
"	"	25 ppm	13 wk*	Anemia, hemosiderosis, death in 1 of 3	110
"	"	5 ppm	26 wk*	Mild anemia, hemosiderosis in spleen	110
"	"	0.5-5 ppm	6 mo*	Increased SGPT	112
"	Rats	140 ppm	6 wk*	Convulsions	110
"	"	18.4%	35 min	Death of all	114
"	"	75 ppm	7 wk*	Occasional tremors, breathing difficulties, lethargy	110
"	Mice	140 ppm	6 wk*	Convulsions, death	110
"	"	75 ppm	7 wk*	Death of 40%	110
"	"	100-120 mg/kg	Once	Convulsions, death	116
"	"	40-80 mg/kg	"	Altered amino acid excretion, mild convulsions at 80 mg/kg	116
ip	Rats	50-70 mg/kg	3 wk 21 x	Kidney damage, many deaths	117
"	"	10-30 mg/kg	3 wk 18 x	Increased SGOT	117

TABLE III-4 (CONTINUED)

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO
1,1-DIMETHYLHYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure	No. of Doses or Duration of Dosage	Observed Effects	References
iv	Dogs	38-45 mg/kg	Once	Kidney function unchanged	61, 62
dermal	"	300-1,800 mg/kg	"	Hyperglycemia, death of all at highest dose	115

*6 hr/d, 5 d/wk

TABLE III-5

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO
1,2-DIMETHYLHYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure*	No. of Doses or Duration of Dosage	Observed Effects	References
oral	Rats	13.5 mg/kg	4-8 x	(Colonic tumors)	126
sc and oral	Dogs	2.3-27 mg/kg	2-10 x	Liver damage, death at 14 mg/kg or higher	126
"	Pigs	13.5-27 mg/kg	8-10 x	Liver damage, many deaths	126
"	Guinea pigs	"	7-10 x	Weight loss, liver damage, bile duct hyperplasia (and carcinomas)	126
ip	Rats	223 mg/kg	Once	Liver damage**	125
"	Mice	24-35 mg/kg	"	"	125

*Doses reported as free base doses
**Animals killed before 168 hr

TABLE III-6

EFFECTS (OTHER THAN NEOPLASTIC) OF EXPOSURE TO PHENYLHYDRAZINE ON ANIMALS

Route of Exposure	Species	Exposure*	No. of Doses or Duration of Dosage	Observed Effects	References
sc	Mice	0.18-0.20 g/kg	Once	Cyanosis, convulsions, death	146
"	"	0.17 g/kg	"	Death of 45%	146
"	Dogs	20-40 mg/kg	2 x	Anemia, organ congestion	147
iv	Rabbits	1.9 mg	Several in 45 d	Increased reticulocytes, hyperemia in bone marrow	149
ip	Rats	75 mg/kg	Once	Anemia, splenomegaly	148
oral	Dogs	14 mg/kg	4 x	Anemia	145

*Doses reported as free base doses

TABLE III-7

TUMORIGENIC EFFECTS OF HYDRAZINES ON ANIMALS

Compound	Species	Route of Exposure	Daily Dose (mg)	Number of Doses or Duration of Dosage	Animals with Tumors (%)				References
					LG	BV	I	LV*	
Hydrazine	Mice	oral	0.06	Life	51	3	1	1	80
"	"	"	0.25	40 wk	46	-	-	-	78
"	"	-	0	-	10	-	-	-	
"	"	inhalation	5 ppm	6 mo	83	-	-	-	69
"	"	"	1 ppm	"	33	-	-	-	
"	"	-	0	-	13	-	-	-	
Hydrazine sulfate	Rats	"	15	68 wk	25	-	-	15	76
"	"	"	0	-	0	-	-	0	
"	Hamsters	"	2.3	Life	-	-	8	-	85
"	Mice (CBA)	oral	1.13	150 x	-	-	-	61	75
"	"	"	0.56	"	-	-	-	57	
"	"	"	0.28	"	-	-	-	18	
"	"	"	0.14	"	-	-	-	2	
"	Mice	"	0.7	Life	49	3	-	1	79
		-	0	-	11	3	-	-	
"	Mice (BALB)	oral	1.13	150 x	90	-	-	-	70
"	"	"	0.56	"	70	-	-	8	
"	"	"	0.28	"	76	-	-	4	
"	"	"	0.14	"	43	-	-	-	
"	"	-	0	-	14	-	-	-	
"	Mice (Newborn)	oral	16.7**	60 d	100	-	-	-	74
"	Mice (CBA)	"	1.13	36 wk	83	-	-	66	71
"	"	-	0	-	6	-	-	4	
"	Mice (BALB)	oral	32**	4 wk	87	-	-	2	
"	"	-	0	-	24	-	-	-	
"	Mice	oral	41.6**	8 wk	46	-	-	-	81
"	"	-	0	-	10	-	-	-	
"	"	ip	20.8**	8 wk	20	-	-	-	81

TABLE III-7 (CONTINUED)

TUMORIGENIC EFFECTS OF HYDRAZINES ON ANIMALS

Compound	Species	Route of Exposure	Daily Dose (mg)	Number of Doses or Duration of Dosage	Animals with Tumors (%)				References
					LG	BV	I	LV*	
Methylhydrazine	Mice	oral	0.69	Life	23	9	-	7	80
"	"	"	3.7**	8 wk	0	-	-	-	81
"	"	-	0	-	10	-	-	-	
"	Hamsters	oral	1.2	Life	-	6	20	44	106
"	"	-	0	-	-	-	1	1	
"	"	"	52.5***	Life	-	-	-	12	107
"	"	-	0	-	-	-	-	0	
"	Mice	ip	1.8**	8 wk	10	-	-	-	81
Methylhydrazine sulfate	"	oral	0.5	40 wk	5	-	-	-	78
"	"	-	0	-	10	-	-	-	
"	"	oral	0.09	Life	46	5	-	1	80
1,1-Dimethylhydrazine	Mice	"	0.7	"	71	79	-	7	123
"	"	"	7.2**	8 wk	4	-	-	-	81
"	"	-	0	-	10	-	-	-	
"	"	oral	0.5	40 wk	29	-	-	-	78
"	"	-	0	-	10	-	-	-	
"	"	ip	3.6**	8 wk	3	-	-	-	81
1,2-Dimethylhydrazine dihydrochloride	Hamsters	oral	0.16	Life	-	85	23	17	85
"	Rats	sc	47***	36 wk	-	-	100	-	131
"	"	"	16***	"	-	-	100	-	
"	"	oral	47***	11 wk	-	-	93	-	131
"	Mice	sc	20***	10 x	43	48	86	1	128
"	"	"	20***	1 x	29	22	2	6	
"	"	-	0	-	22	6	-	-	
"	"	sc	20***	24 wk	-	-	90	-	132
"	"	"	20***	6 wk	-	-	37.5	-	
"	"	oral	0.07	Life	34	95	-	2	127

TABLE III-7 (CONTINUED)

TUMORIGENIC EFFECTS OF HYDRAZINES ON ANIMALS

Compound	Species	Route of Exposure	Daily Dose (mg)	Number of Doses or Duration of Dosage	Animals with Tumors (%)				References
					LG	BV	I	LV*	
1,2-Dimethylhydrazine dihydrochloride	Mice	oral	10.6**	8 wk	33	-	-	-	81
"	"	-	0	-	10	-	-	-	
"	"	ip	5.3**	8 wk	10	-	-	-	81
Phenylhydrazine	"	oral	0.25-0.5	40 wk	-	-	-	-	78
"	"	-	0	-	10	-	-	-	
Phenylhydrazine hydrochloride	"	oral	200**	42 wk	53	-	-	-	151
"	"	-	0	-	13	-	-	-	
Phenylhydrazine hydrochloride	Mice	oral	23.2**	8 wk	14	-	-	-	81
	"	-	0	-	10	-	-	-	
"	"	oral	0.72	Life	13	21	1	3	152
"	"	-	0	-	22	6	-	5	
"	"	ip	11.6**	8 wk	13	-	-	-	81

*LG=lungs, BV=blood vessels, I=intestines, LV=liver
**Total dose
***mg/kg/wk