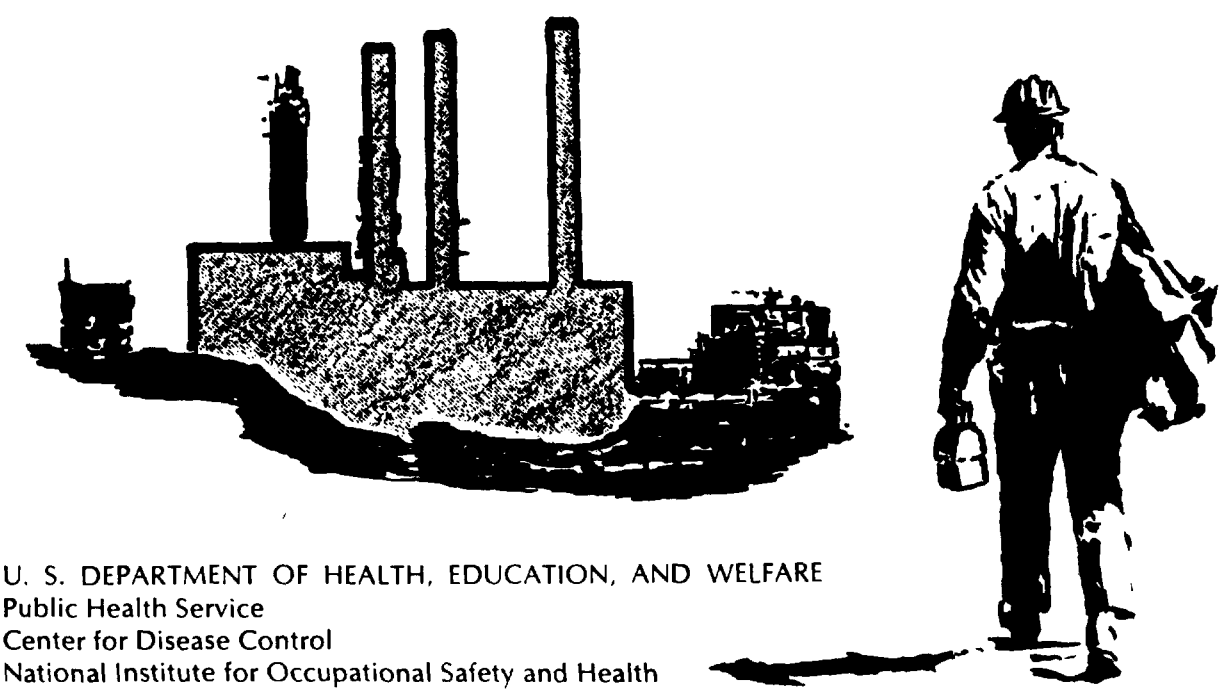
NIOSH

CRITERIA FOR A RECOMMENDED STANDARD....

OCCUPATIONAL EXPOSURE TO

HYDRAZINES



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

criteria for a recommended standard....

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

The contributions to this document on hydrazines by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the Society of Toxicology and the American Industrial Hygiene Association, and Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views and conclusions expressed in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, were considered carefully and were sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages v and vi.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for hydrazines. Imogene F. Sevin, Ph.D., of this Division served as criteria manager. SRI International developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31.

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I. RECOMMENDATIONS FOR A HYDRAZINES STANDARD

NIOSH recommends that employee exposure in the workplace to hydrazine, methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and phenylhydrazine, and their salts formed by addition with acids, such as sulfates, hydrochlorides, or hydrobromides, be controlled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should, as a minimum, substantially reduce the risk of cancer induced by these hydrazines and prevent other adverse effects, both acute and chronic, which could result from exposure in the workplace. Sufficient technology exists to permit compliance with the recommended standard. The employer should regard the recommended environmental limits as the upper boundaries of exposure and make every effort to maintain the exposure as low as is technically feasible. The standard will be subject to review and revision as necessary.

The recommended standard is based on the conclusion that valid evidence of skin absorption, blood and liver effects, and tumor induction in experimental animals by these hydrazines is relevant to human exposure. No demonstrably safe level of exposure is evident, and in view of the severity of the toxic effects, especially carcinogenicity, the limits of exposure recommended represent the lowest detectable concentrations. The environmental limits are likely to offer greater protection from nonneoplastic effects from some hydrazine compounds than from others. They

assure protection to individual compounds only when skin absorption is prevented and they cannot be directly extrapolated to mixtures.

The criteria and recommended standard apply to exposure of workers to hydrazine and its derivatives, methylhydrazine, 1,1-dimethylhydrazine, 1,2-dimethylhydrazine, and phenylhydrazine, and their salts. The term "hydrazines" will be used throughout the document to mean all five compounds and their salts unless a compound is referred to specifically. Common synonyms used for methylhydrazine are monomethylhydrazine and MMH; for 1,1-dimethylhydrazine, unsymmetrical or asymmetrical dimethylhydrazine and UDMH; and for 1,2-dimethylhydrazine, symmetrical dimethylhydrazine and SDMH. "Occupational exposure to hydrazines" is defined as work in any area where one or more of the hydrazines is stored, produced, processed, transported, handled, or otherwise used and present in such a manner that vapors or aerosols may be released in workroom air or that the materials may spill or splash onto the skin or into the eyes.

Section 1 - Environmental (Workplace Air)

(a) Concentrations

Occupational exposure to hydrazines shall be controlled so that employees are not exposed at concentrations greater than those specified below, expressed as milligrams of the free base per cubic meter of air (mg/cu m), determined as ceiling concentrations in any 2-hour period:

hydrazine	- 0.04 mg/cu m (0.03 ppm)*
methylhydrazine	- 0.08 mg/cu m (0.04 ppm)
1,1-dimethylhydrazine	- 0.15 mg/cu m (0.06 ppm)
phenylhydrazine	- 0.6 mg/cu m (0.14 ppm)

*Approximate equivalents in parts of free base per million parts of air (ppm).

These recommended limits are the lowest concentrations measured by the recommended method of analysis with an analytical precision of at least 15%. No limit is recommended for 1,2-dimethylhydrazine, since an acceptable method of sampling and analysis is presently unavailable.

(b) Sampling and Analysis

Samples in the work environment shall be collected and analyzed according to the procedures described in Appendix I or by any methods at least equivalent in precision, accuracy, and sensitivity.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to all persons subject to occupational exposure to hydrazines.

(a) Preplacement medical examinations shall include at least:

(1) Comprehensive medical and work histories.

(2) Comprehensive physical examination.

(3) Specific clinical tests including complete and differential blood count; liver function tests including serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT); urinalysis including specific gravity, glucose, protein, and microscopic examination; and a 14- x 17-inch posteroanterior chest roentgenogram.

(4) A judgment of the worker's ability to use positive pressure respirators.

(5) Urobilinogen and serum bilirubin tests shall be considered by the responsible physician.

(b) Periodic examinations shall be made available at least annually to those working with hydrazines. These examinations shall include at least:

(1) Interim medical and work histories.

(2) Physical examination as outlined in paragraphs (a)(2), (a)(3), and (a)(5) of this section. In addition, for workers over the age of 40, proctosigmoidoscopy shall be made available to those exposed to 1,2-dimethylhydrazine, and it should be considered for those exposed to other hydrazines.

(c) In view of the numerous body systems in which toxic effects of hydrazines have been demonstrated, medical and work histories and physical examinations should be thorough and should give particular attention to combinations of signs or symptoms, including evidence of dermal contact, that may indicate toxicity.

(d) In the event of an illness caused by exposure to hydrazines, appropriate medical services shall be made available.

(e) In an emergency involving massive exposure to the hydrazines, either by inhalation or dermal contact, immediate medical attention and appropriate followup medical care shall be provided.

(f) Pertinent medical records shall be maintained for all employees exposed to hydrazines in the workplace. Such records shall be kept for at least 30 years after the last occupational exposure to hydrazines. Records of environmental exposures applicable to an employee shall be included in the employee's medical records. These records shall be made available to the designated medical representatives of the

Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

All labels and warning signs shall be printed both in English and in the predominant language of non-English reading workers. Workers who cannot read the language used on labels or posted signs shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

All shipping and storage containers for hydrazines shall be labeled, and all areas where any hydrazines are stored, produced, used, or processed shall be posted in accordance with the following paragraphs.

(a) Containers of hydrazines shall bear the following label in addition to, or in combination with, labels required by other statutes, regulations, or ordinances.

(Name of Compound)
(Tradename, Chemical Name, Common Name)

DANGER!
EXTREME HEALTH HAZARD
MAY CAUSE CANCER
MAY BE ABSORBED THROUGH SKIN

Keep container closed.
Avoid contact with skin and eyes.
Avoid breathing air contaminated with this substance.

First Aid: In case of contact, immediately flush with copious amounts of water. Obtain prompt medical attention.

Containers of hydrazines that are considered flammable or combustible shall also bear the following label:

FLAMMABLE (or COMBUSTIBLE)

Keep away from heat, spark, open flame, and oxidants.

Containers of material contaminated with hydrazines, including those holding clothing or animal carcasses, shall bear the following precautionary label:

CAUTION

MATERIAL CONTAMINATED WITH
CANCER-SUSPECT AGENT
(Name of Compound)

(b) The following warning sign shall be posted in readily visible locations where hydrazines are stored, produced, or used, particularly at the entrance to the areas.

WARNING
CANCER-SUSPECT AGENT

(Chemical Name) USED IN THIS AREA
AUTHORIZED PERSONNEL ONLY

Avoid breathing air contaminated with this substance.
In case of contact, flush with copious amounts of water. Wash clothing before reuse. Obtain prompt medical attention.

If respiratory protection is required in accordance with Section 4, the following statement in large letters shall be added to the required sign:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

Where the presence of hydrazines could result in a fire hazard, the sign shall also contain the following information:

FIRE AND EXPLOSION HAZARD

Section 4 - Personal Protective Clothing and Equipment

All systems or equipment containing the hydrazines shall be designed to minimize the possibility of vapor or aerosol inhalation, skin or eye contact, and spills or leaks. When necessary, these controls shall be supplemented by the use of personal protective clothing and equipment.

(a) Protective Clothing

(1) The employer shall provide full-face shields (8-inch minimum) and goggles which shall be worn during any operation in which there is a reasonable possibility that hydrazines may enter the eyes or splash onto the face.

(2) The employer shall provide full-body protective clothing, including gloves and boots, and shall ensure that employees wear this clothing when spills or splashes of hydrazines may occur, such as during repair or during transfer operations.

(3) Gross contamination shall be removed from protective clothing before the clothing is taken off the wearer.

(b) Escape Equipment

Emergency equipment shall be located at well-marked and clearly identified stations and shall be adequate to permit all personnel to escape from the area.

(c) Respiratory Protection

Respirators may be used only when engineering controls are being installed or tested, during nonroutine maintenance or repair, in emergencies that may involve brief exposure in excess of the recommended limits, or for entry into confined spaces. In the situations listed above, employees exposed to 1,2-dimethylhydrazine shall wear a respirator. When use of a respirator is permitted, it shall be selected and used in accordance with the following requirements:

(1) The employer shall provide respirators in accordance with Table I-1 and shall ensure that, when required, they are properly used. The respiratory protective devices provided in conformance with Table I-1 shall be those approved by NIOSH or the Mining Safety and Health Administration (MSHA). The standard for approval is specified under the provisions of 30 CFR 11.

(2) The employer shall ensure that employees are properly instructed in the use of respirators assigned to them and on how to test for leakage, proper operation, and proper fit as judged by quantitative fit tests.

(3) The employer shall provide for the cleaning, sanitizing, inspecting, maintaining, repairing, and storing of respirators and shall ensure that employees are provided with clean respirators that are in good operating conditon.

(5) Protective equipment suitable for emergency entry or reentry shall be located at clearly identified stations outside the work areas.

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR HYDRAZINES

Concentration of Hydrazines	Respirator Type Approved under Provisions of 30 CFR 11
Greater than the environmental limits specified in Section 1*	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode (2) Combination Type C supplied-air respirator with full facepiece and auxiliary self-contained air supply operated in pressure-demand mode
Emergency entry or entry into a confined space	Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode

*or exposure to 1,2-dimethylhydrazine as specified in this section

Section 5 - Informing Employees of Hazards from Hydrazines

(a) At the beginning of employment and at least annually thereafter, the employer shall provide training, supplemented by written information, on the hazards of hydrazines to employees exposed to them.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience or training, to ensure that all employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator use. The instructional program shall include a description of the general nature of the environmental and medical surveillance procedures and of the advantages to the employees of participating in them. As a minimum, instruction shall include the information in Appendix II, which shall be kept on file and be readily accessible to employees assigned to work areas where there is occupational exposure to hydrazines.

(c) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix II or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Control of Airborne Hydrazines

Engineering controls, such as process enclosure or local exhaust ventilation, shall be used when needed to keep concentrations of airborne hydrazines within acceptable levels. Ventilation systems shall be designed to prevent accumulation or recirculation of airborne hydrazines in the workplace environment and to remove hydrazines from the breathing zone of workers. When needed, moving parts shall be sparkproof. Such systems should also be designed to operate under negative pressure to prevent leaks into the work environment. Enclosures, exhaust hoods, duct work, and fans shall be checked periodically, and preventive maintenance and cleaning

shall be performed when necessary to ensure their integrity and proper operation. Airflow at each hood shall be measured at least every 3 months to ensure that design airflow is maintained. A log shall be kept showing design airflow and the results of quarterly inspections. Continuous airflow indicators, such as water or oil manometers, mounted at appropriate points and marked to indicate acceptable airflow are recommended. All adjustments to the ventilation system should be made by authorized maintenance personnel. Before maintenance work on control equipment begins, sources of contamination from hydrazines shall be eliminated to the extent feasible. Exhaust ventilation systems discharging to outside air shall conform with applicable local, state, and Federal air pollution regulations and shall not constitute a hazard to employees or to the general population.

(b) Regulated Areas

Regulated areas shall be established and maintained where the hydrazines are stored, produced, or otherwise used, and access to these areas shall be limited to authorized persons. A log shall be kept of those entering such areas.

(c) Laboratory Activities

When hydrazines are used in laboratory activities, the following provisions, in addition to other sections, shall be followed.

(1) Mechanical pipetting aids shall be used for all pipetting procedures.

(2) Experiments, procedures, and equipment that could produce aerosols or vapors of hydrazines shall be confined to laboratory-type hoods, glove boxes, or other similar control apparatus. Exposure

chambers and associated generation apparatus shall be separately ventilated.

(3) Surfaces on which the hydrazines are handled shall be impervious to absorption or penetration by these hydrazines.

(4) Laboratory vacuum systems shall not be connected to nonregulated areas. These vacuum systems, hoods, and exposure chambers shall be exhaust ventilated in a manner consistent with Federal and local air pollution regulations.

(5) Airflow in the laboratory shall be established in such a pattern as to flow from the least to the most contaminated area. Contaminated exhaust air shall not be recirculated or discharged to other work areas, regulated or nonregulated.

(d) Work Clothing

(1) Employees, including animal handlers, working in regulated areas shall wear coveralls, head, foot, and shoe coverings, and gloves.

(2) Laboratory employees working in regulated areas shall wear appropriate laboratory clothing, such as a solid-front gown, surgical scrub suit, or fully buttoned laboratory coat, and head, foot, and shoe coverings and gloves.

(3) Employees shall remove work clothing when leaving regulated areas. After the last use in a workshift, work clothing shall be placed in a properly labeled, airtight container for decontamination or disposal.

(4) Work clothes shall be changed daily or when accidentally contaminated by the hydrazines.

(5) The employer shall provide for laundering of this clothing and shall ensure that soiled work clothing is not taken home by the employee. Precautions shall be taken to protect personnel who handle and launder soiled clothing. These workers shall be advised of the hazards of exposure to hydrazines and the means of preventing such exposure.

(e) Hygiene

Good personal hygiene practices shall be required. Employees leaving regulated areas shall wash their hands, forearms, face, and neck, particularly before eating and smoking or using toilet facilities. When work for the shift is completed, the employee shall shower and leave the regulated area.

(f) Disposal of Waste

Waste material shall be disposed of in a manner that is not hazardous to employees or to the general population. Contaminated wastes and animal carcasses shall be collected and stored in impervious containers. The containers shall be closed and the outer surface decontaminated before removal from the work area. In selecting the method of waste disposal, applicable local, state, and Federal regulations should be consulted. If the waste is incinerated, release of hydrazines shall be prevented.

(g) Storage and Handling

All hydrazines should be stored at temperatures well below their boiling points. Hydrazines that are ignitable shall be stored in electrically grounded containers and isolated from ignition sources and oxidants. All containers of hydrazines shall be kept tightly closed when not in use and stored in a cool ventilated room or sheltered outside space. In the containers, a blanket of nitrogen or other inert gas should be

placed over the hydrazines. Containers shall be emptied so that the possibility of spills and the escape of airborne hydrazines are minimized.

(h) Entry into Confined Spaces

Entry into confined spaces, such as tanks, pits, tank cars, and process vessels, that have contained hydrazines shall be controlled by a permit system. Permits shall be signed by an authorized employer representative, certifying that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that the prescribed procedure will be followed.

(1) All lines shall be disconnected or blocked while the vessel is being cleaned. All valves or pumps leading to and from the vessel shall be locked out or tagged out.

(2) The vessel shall be either washed with water and purged with air, or purged with nitrogen and then with air.

(3) The vessel shall then be checked by trained personnel for fire or explosion hazard, airborne hydrazines, possible oxygen deficiency, and concentrations of other likely contaminants, to assure that no danger exists.

(4) If a respirator is necessary, a self-contained breathing apparatus as specified in Table I-1 shall be provided to the employee.

(5) Each employee entering the vessel shall be equipped with appropriate respiratory protection, a harness, and a lifeline. At least one other person equipped with appropriate respiratory protection, harnesses, and lifelines shall watch at all times from the outside. At least two more persons should be available to assist in an emergency.

Mechanical ventilation shall be provided continuously when workers are inside the vessel.

(i) Emergency Procedures

For all work areas where there is a potential for emergencies involving hydrazines, employers shall take all necessary steps to ensure that employees are instructed in and follow the procedures specified below and any others appropriate for the specific operation or process.

(1) Instructions shall include designation of medical receiving facilities and prearranged plans for immediate evacuation of employees exposed to or in contact with hydrazines, for any necessary calls for assistance, and for reentry for repairs or cleanup of areas where leaks or spills of hydrazines have occurred.

(2) Telephone numbers for emergency assistance shall be prominently posted.

(3) Employees not essential to emergency operations shall be evacuated from hazardous areas during emergencies.

(4) Personnel inadequately protected against the attendant hazards shall not shut off sources of hydrazines, clean up spills, or control and repair leaks. Spilled hydrazines shall be stabilized with a dilute acid such as acetic or hydrochloric acid, flushed into a holding tank, and inactivated with dilute hypochlorite or another oxidant.

(5) Eye, skin, and approved respiratory protective devices, specified in Section 4, shall be used by personnel essential to emergency operations.

(6) Fire shall be extinguished by coarse sprays of water, when appropriate. Advanced or large fires shall be fought from a safe distance or from a protected area.

(7) Hydrazines in contact with skin or eyes shall be immediately flushed away with copious quantities of water, and medical attention shall be obtained promptly.

Section 7 - Sanitation

(a) The preparation, storage, dispensing (including vending machines), or consumption of food shall be prohibited in regulated areas.

(b) Smoking shall be prohibited in regulated areas.

(c) Employers shall provide emergency showers and eyewash fountains, with adequate pressure of water, that are quickly accessible in areas where hydrazines may contact the skin or eyes. This equipment shall be kept in good working condition and shall be inspected frequently.

(d) Conveniently located washing facilities shall be provided for all employees who work in regulated areas. Locker room facilities, including showers, shall be located in nonexposure areas. Employees shall be required to change from street clothes before entering regulated areas. The locker room facilities shall provide for storing street clothing and clean work clothing away from soiled work clothing. Airtight containers shall be provided for storage and segregation of contaminated work clothing. The clothing shall be held in these containers until it is removed for decontamination or disposal.

Section 8 - Monitoring and Recordkeeping

(a) Industrial Hygiene Surveys

Each employer who has a place of employment in which any of the hydrazines are stored, produced, processed, or otherwise used shall determine by an industrial hygiene survey the areas in which occupational exposure occurs. Records of these surveys shall be retained until the next survey has been completed. If an employer concludes that there is no occupational exposure to hydrazines, the records shall show the basis for this conclusion. Surveys shall be repeated at least annually and within 14 days after any process change likely to result in occupational exposure to hydrazines.

(b) Personal Monitoring

If it has been determined that occupational exposure to hydrazines (other than 1,2-dimethylhydrazine) occurs, the employer shall institute environmental monitoring.

(1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of each employee. Source and area monitoring may be used to supplement personal monitoring.

(2) In all personal monitoring, samples representative of the exposure in the breathing zone of the employee shall be collected.

(3) For each determination of the concentration of hydrazines, a sufficient number of samples shall be taken to characterize the employee's exposure. Variations in the employee's work and production schedules, location, or duties, and changes in production schedules shall be considered in deciding when samples are to be collected.

(4) Each operation in each regulated area shall be sampled at least once every 6 months while hydrazines are being used. For intermittent operations, ie, lasting for less than 6 months, at least one monitoring regimen shall be conducted during each operation period. If an employee is found to be exposed to the hydrazines at concentrations exceeding the recommended ceiling limits, the exposure of that employee shall be measured at least once every week, control measures shall be initiated, and the employee shall be notified of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, at least 1 week apart, indicate that the employee's exposure no longer exceeds the recommended occupational exposure limit; routine semiannual monitoring may then be resumed.

(c) Recordkeeping

Records of environmental monitoring and pertinent medical records shall be kept for at least 30 years after the employee's last occupational exposure to hydrazines. Records of environmental monitoring shall include an identification of the employee being monitored, duties and job locations within the worksite, time and dates of sampling and analysis, sampling and analytical methods used and available evidence of their precision and accuracy, the number, duration, and results of samples taken, environmental concentrations determined from these samples, and the type of personal protective equipment used by the employee. Rosters of authorized persons who enter regulated areas shall also be retained for 30 years. Environmental monitoring records and entry rosters shall be made available to designated representatives of the Secretary of Labor and of the Secretary of Health, Education, and Welfare. Employees shall have access

to data on their environmental exposures. Copies of records of environmental exposures applicable to an employee shall be included in the employee's medical records. These medical records shall be made available to the designated medical representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing impairment of health from exposure to the hydrazines. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20 (a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

NIOSH, after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health and to provide for the safety of employees exposed to hazardous chemical and physical agents. The criteria and recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments and simply complying with the recommended standard should not be the final goal.

These criteria for a standard for hydrazines are part of a continuing series of criteria developed by NIOSH. The proposed standard applies to the processing, manufacture, handling, storage, and use of the hydrazines. The standard was not designed for the population-at-large, and any extrapolation beyond occupational exposures is not warranted. It is intended to (1) protect against injury from hydrazines, (2) be measurable

by techniques that are valid, reproducible, and available to industry and government agencies, and (3) be attainable with existing technology.

The recommended exposure limits for hydrazines are based on the conclusion that these substances are likely to be carcinogenic to humans. This evidence is especially strong in the case of hydrazine and 1,2-dimethylhydrazine but is persuasive in regard to all the compounds.

Although full information is not available on each of the hydrazines, compounds of this group clearly produce toxic effects on the liver, the kidneys, and blood, the severity and type of response being dependent on the individual compound. In some cases, these effects are so severe as to warrant a low environmental limit even without consideration of carcinogenicity. In addition, these compounds are acutely toxic, producing effects on the central nervous system (CNS) that are manifested by convulsions and other less severe signs. Finally, hydrazines are local irritants to the skin and eyes, and systemic toxicity can result from such exposures. NIOSH considered these other effects, as well as carcinogenicity, in deriving a recommended standard for the hydrazines. Particular attention was also given to limit dermal contact with the hydrazines, a potential source of exposure.

At this time, no environmental limit is being recommended for 1,2-dimethylhydrazine, since an acceptable analytical method has not been found. 1,2-Dimethylhydrazine is a potent carcinogen in animals, and its use is apparently limited to the study of colon cancer.

Inhalation studies are needed to determine the potential carcinogenicity of the hydrazines by a route more appropriate to workplace exposure. Such studies are currently in progress for three of the

compounds, and the applicable recommendations will be considered for review and revision, as necessary, when this information becomes available. Little information exists for phenylhydrazine, in particular, on either its carcinogenicity or other effects. Much of this information is primarily of historical interest and needs to be reconfirmed by more modern studies. The impurities resulting from manufacture and decomposition of hydrazines, their role in toxicity, and their carcinogenicity also need to be investigated.

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.

Animal Toxicity

Although toxic effects such as respiratory tract irritation, hemolytic anemia, kidney and liver damage, CNS effects, and tumorigenic effects have been observed in experimental animals given hydrazines, the type and severity of the response induced by each hydrazine may be different, despite the similarity in molecular structures; therefore, each compound will be discussed separately. Relevant literature for each compound will be grouped into three areas: systemic effects, metabolism, and carcinogenicity and effects related to reproduction.

(a) Hydrazine

(1) Systemic Effects

In 1954, Comstock et al [55] described the effects of hydrazine vapor on rats, mice, dogs, and guinea pigs. Several experimental designs were used, from a 6-hour/day, 5-day/week, 6-month exposure to a single exposure of 0.5-4 hours. When rats were exposed at several hundred mg/cu m for 2-4 hours in 20-liter glass jars, 50% or more died and they had pulmonary edema and localized damage of the bronchial mucosa. However, the concentrations of hydrazine at which these rats were exposed were in question; in similar experiments, nominal concentrations of 16,000-27,000 mg/cu m were calculated from mass balance, but titration analysis indicated only 106-831 mg/cu m. The authors found that 74% of the hydrazine in the air was lost in an empty jar, but 96-99% was lost when six rats were placed in the jar. This loss seemed to be largely or entirely caused by surface sorption.

To minimize the adsorption of hydrazine by the walls, the authors then used a 440-liter chamber, and only analytical concentrations were

reported [55]. Of 20 rats and 10 mice exposed at 295 mg/cu m, 6 hours/day, 5 days/week, 16 rats and 8 mice died (80% mortality) in the 1st week of exposure. Fatty degeneration of the liver was found, in addition to pulmonary changes similar to those mentioned above. Of the 16 rats and 10 mice exposed at 70 mg/cu m, 70-87% mortality was reached after 3 weeks of exposure (13 exposures). Of the animals exposed at 26 mg/cu m for 6 weeks, 7 of 10 mice died by the 14th exposure and the rest survived, and 11 of 13 rats died by the end of exposure. For the 6-month study, a 1,000-liter chamber was used. Four dogs, 30 rats, 20 mice, and 10 guinea pigs were exposed at 18 mg/cu m. By the end of the experiment, 2 dogs, 23 rats, 15 mice, and 8 guinea pigs had died. Necropsies on surviving dogs revealed lipid deposition in the spleen and Kupffer cells of the lobular zone of the liver. Two of the dogs also had evidence of anemia. Necropsies on surviving mice showed no abnormalities. No necropsies were performed on the other animals. In addition, 2 dogs and 20 rats were exposed at 6 mg/cu m for 6 months. While two rats died, the dogs survived but had toxic signs such as loss of appetite, loss of body weight, vomiting, irregular breathing, fatigue, and tremors. From these tests, the authors [55] suggested that the maximum allowable concentration for hydrazine should be lower than 6 mg/cu m.

The acutely toxic effects of hydrazine and some derivatives were studied by Jacobson et al [20] in 1955. Rodents exposed to hydrazine were restless, and they had breathing difficulties, convulsions, and exophthalmos. Most of the convulsions were clonic, but some were tonic-clonic. The LC50 values for rats and mice were 570 ppm (750 mg/cu m) and 252 ppm (330 mg/cu m), respectively.

Haun and Kinkead [56], in 1973, reported a 6-month inhalation study of hydrazine. Four experimental groups and a control group were used, each containing 8 male beagle dogs, 4 female Rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR mice. The experimental groups were exposed to anhydrous hydrazine for 6 months at a concentration of 1 or 0.2 ppm continuously, or at 5 or 1 ppm intermittently. Continuous exposure was for 24 hours/day, 7 days/week, and intermittent exposure was for 6 hours/day, 5 days/week. Therefore, the corresponding products of the exposure concentration and the duration of exposure are 168 or 33.6 ppm-hours/week and 150 or 30 ppm-hours/week.

The authors [56] observed that mortality and weight changes were dose-related, regardless of whether exposure was continuous or intermittent. Exposure at 150 or 168 ppm-hours/week caused 35-40% mortality in mice within 2 months, while exposure at 30 or 33.6 ppm-hours/week caused only 2.5-7.5% mortality. No monkeys died and the one rat death was not attributed to hydrazine. Two of the eight dogs exposed at 168 ppm-hours/week died after 16 weeks; there were no other deaths in dogs.

Rats showed a dose-related growth rate depression [56]. At the end of exposure, the largest weight difference, 35 g, was found between the 150 ppm-hours/week group and the controls. Weight loss in dogs occurred only in the groups exposed at 150 and 168 ppm-hours/week, and the four dogs retained after exposure recovered their lost weight in 2 weeks.

Results of clinical chemistry tests and blood cell counts in monkeys and rats were reported to be normal [56]. After 8 weeks of exposure, reductions in the hematocrit value, hemoglobin concentration, and erythrocyte count of 11, 16-22, and 10-12% respectively, were observed in

the dogs exposed at 150 and 168 ppm-hours/week. Although, there was a tendency toward recovery, no value reached normal by the end of exposure. All these hematologic values had returned to normal 2 weeks after exposure ended. Reticulocytosis occurred in the dogs exposed at 168 ppm-hours/week 20 weeks after exposure had begun. These dogs also had increased erythropoietic activity, which was evident in the decreased myeloid-erythroid ratios in marrow samples. Blood counts from dogs exposed to hydrazine at 30 or 33.6 ppm-hours/week were within normal limits. Clinical chemistry, Heinz body counts, and methemoglobin concentrations of all exposed dogs were within normal limits. Dogs exposed at 150 or 168 ppm-hours/week began to show increased resistance to osmotic hemolysis in the erythrocytes at 8 weeks. Similar effects were observed in dogs exposed at 30 or 33.6 ppm-hours/week beginning at week 12; these effects continued for all groups throughout the rest of the exposure period.

Gross and microscopic examination of the tissues of the mice from all exposure levels showed moderate to severe fatty liver changes, which the authors considered to have been the cause of death in those mice dying during exposure [56]. Exposed monkeys had slight to moderate fat accumulation in the liver, but the controls also had some degree of fatty changes. In dogs, only those exposed at 150 or 168 ppm-hours/week had fatty degeneration of the liver. There were no significant changes in rats. Organ weights of the exposed rats, monkeys, and dogs did not differ significantly from those of the controls.

Haun and Kinkead [56] concluded that, if humans are not less sensitive than the mice, a Threshold Limit Value (TLV) of 1 ppm would not be safe.

As part of a series of experiments with hydrazine, Thienes and coworkers [57], in 1948, described the effects of contact application to the skin and eyes of animals. Anhydrous hydrazine applied in a petrolatum well to the shaved bellies of a rat (2 drops) and a guinea pig (3 drops) caused death in 2 hours. Three rabbits had 3 ml of hydrazine applied through a cloth onto a shaved area of the belly for 1 minute. In two rabbits, one of which was anesthetized, the bellies were washed with water after the cloth had been removed; in the third, no effort was made to remove the hydrazine. Two rabbits died at 60 and 90 minutes after application. The anesthetized rabbit survived and within 2 hours, the affected skin first reddened, then turned blue, eventually turning brown with a dry, burned appearance. The site of application in this rabbit became dry, scaly, crusted, and inflamed before healing. Other rabbits had gauze containing 3 cc of 5-25% hydrazine applied to their bellies. When the gauze was left in place for 1 hour, only the 25% solution caused slight skin irritation; this 25% solution applied for 4 hours was lethal to two of three rabbits. When 0.2 cc of anhydrous hydrazine was applied in a cloth band over the shaved belly of two rats, they died even though the band was removed after 1 minute and the area washed.

One drop of anhydrous hydrazine permanently damaged the eyes of rats and rabbits when no effort was made to remove it [57]. When 1 drop of diluted hydrazine was placed on the eyes of rabbits six times at 10-minute intervals, permanent damage resulted with solutions of 25% or greater. At 1% or lower, there was no visible reaction.

Rothberg and Cope [58] measured the acute toxicity of several hydrazines by the intravenous (iv) and percutaneous routes. Rabbits were

injected iv and observed for 24 hours. Each hydrazine compound was applied to a 100-sq cm clipped area on the backs of guinea pigs and rabbits. The animals were protected from inhalation of the compound, but the site of application was not covered. Hydrazine (3 μl) was also placed in the left eyes of two rabbits, and the eyes were examined for damage for 10 days. The LD50 by the iv route was 26 μl/kg (26 mg/kg). By percutaneous absorption, it was 93 mg/kg in rabbits and 190 mg/kg in guinea pigs. Following application of hydrazine, the skin at the site turned bluish-black. After 24 hours, the discoloration penetrated deeply into the dermis, and there was acute local inflammation and moderate edema. By 72 hours, this area had eroded into the subcutaneous tissue and the surrounding area was mildly erythematous and moderately edematous. Hydrazine in the eyes caused corneal damage. Conjunctivitis and erythema of the eyelids occurred at 48 hours and were followed by a slight corneal opacity that persisted throughout the 7-day observation period.

In 1972, Smith and Clark [59] described the effect of hydrazine absorbed through canine skin. Hydrazine at concentrations of 3-15 millimoles/kg (96-480 mg/kg) was applied to a 15- x 20-cm shaved area on the chest of 25 anesthetized mongrel dogs. The appearance of the skin and signs of toxicity were noted for 6 hours. Hydrazine and glucose concentrations in the blood and urine and reduced glutathione and glutathione peroxidase activity in the erythrocytes were measured at specific intervals. Preexposure measurements were made, and the animals served as their own controls.

When hydrazine was applied to the skin, a chemical burn developed [59]. Ten of the 25 dogs died; the time of death, but not the percentage

dying, was dose-related. Hydrazine was detectable in the blood within 30 seconds after application; the concentration increased to a plateau at 20-60 minutes. The concentration of hydrazine in the urine was variable and did not correlate with blood levels. Blood glucose concentrations were elevated initially, but they then declined to subnormal values. There was no effect on reduced glutathione or glutathione peroxidase activity.

The authors [59] noted the rapidity with which hydrazine was absorbed through the skin. They also commented that about one out of three dogs was a "hyperresponder," exhibiting plasma hydrazine concentrations 2-4 times those of the others.

In 1965, Patrick and Back [60] reported the toxic effects of repeated injections of hydrazine on Sprague-Dawley rats and Rhesus monkeys. Groups of 25 male rats, weighing 308-386 g each, received 10 or 20 mg/kg of practical grade hydrazine (64% hydrazine) intraperitoneally (ip) daily, 5 days/week, for 5 weeks. Five control rats received no injections, and 10 others received distilled water ip. Up to five animals from each dose regimen were killed each week to evaluate progressive tissue changes. Ten rats that received 20 mg/kg daily died between the 8th and 21st injections; all others survived. When blood samples were examined, the major finding was an elevated SGOT activity in both groups of experimental rats. In the 25 rats given 20-mg/kg, gross examination showed severe pulmonary congestion and edema in four rats. Microscopically, slight hepatic cell vacuolization was observed in seven animals. The 10-mg/kg group was normal.

Six Rhesus monkeys received hydrazine ip at 5 mg/kg/day for 5 days/week for 4 weeks; two of these monkeys subsequently received 10

mg/kg/day for 8 additional days and then 20 mg/kg for 4-5 more days [60]. Six other monkeys received 20 mg/kg/day of hydrazine ip for 4-5 days. There were no clinical signs of toxicity in the four monkeys that received hydrazine at 5 mg/kg/day for 20 doses. All monkeys, however, lost between 0.4 and 0.9 kg, and they did not regain their initial weights by the end of the experiment. Seven of eight monkeys that received hydrazine doses of 10 mg/kg or more vomited and showed signs of lethargy and weakness; one animal developed tremors. At the 5-mg/kg dosage level, only slight decreases in hematocrit value and hemoglobin concentration were observed. In the monkeys that received 20 mg/kg of hydrazine for 4 or 5 days, the terminal SGOT activity increased 3- to 200-fold, but plasma glucose levels were insignificantly increased. Grossly, the liver was uniformly pale and slightly enlarged in all animals receiving hydrazine at 20 mg/kg/day. Microscopically, the kidneys, heart, skeletal muscles, and liver showed pronounced fatty changes. One animal that received twenty 5-mg/kg doses showed moderate amounts of lipid deposition in the liver and kidneys, and three had lipid deposition in the myocardium. Monkeys that received doses of hydrazine from 5 to 20 mg/kg had normal kidneys and hearts and showed less accumulation of lipids in the liver than did animals that received four to five doses at 20 mg/kg/day. The authors concluded that the major toxic effect of injected hydrazine was lipid accumulation in the liver. It was noted that monkeys were more susceptible to liver and kidney damage than were rats, as reflected by more lipid accumulation and higher SGOT activities in the former.

In 1966, Wong [61] described changes in renal function in anesthetized mongrels for up to 4 hours after the iv injection of

hydrazine. Eight fasted females weighing 12.5-21.0 kg and six control dogs were given creatinine and glucose by sustained infusion and urine was collected by catheterization. In controls, creatinine clearance was measured every 20 minutes for 5 hours. In the experimental group, three baseline values were obtained, then 20 mg/kg of hydrazine was given iv and 20-minute urine samples were collected for the next 4 hours.

The average creatinine clearance and glucose resorption rates in the controls remained relatively constant throughout the test period, ranging from 52 to 57 ml/minute and from 150-170 mg/minute, respectively [61]. In the experimental group, both creatinine clearance and glucose resorption rates were lower than controls and declined throughout the test period. For example, creatinine clearance rates were 48 ml/minute at 20 minutes, 38 at 120 minutes, and 30 at 240 minutes. Glucose resorption rates were 150 mg/minute at 20 minutes, 120 at 120 minutes, and 90 at 240 minutes. These results, indicative of impaired proximal tubular function, suggested a nephrotoxic effect to the author.

Effects of hydrazine and several derivatives on renal function were also observed by Van Stee [62]. Anesthetized dogs were injected iv with 0.50 millimole/kg (16 mg/kg) of hydrazine, and inulin and para-aminohippuric acid (PAH) clearance rates and renal plasma flowrate were measured. All these indicators of renal function were significantly decreased during the first 4 hours after injection. Hydropic degeneration of the tubular epithelium of the kidneys was also seen. The author concluded that the decreased glomerular filtration rate was caused by the decreased renal plasma flow and attributed the decreased PAH clearance rate to the decreased glomerular filtration rate and interference with active

transport by the proximal renal tubular epithelium.

In 1966, Fortney [63] reported the effect of hydrazine on liver glycogen, arterial glucose, lactate, pyruvate, and acid-base balance. Blood and liver biopsies were taken from anesthetized male mongrels that had been fasted 12-48 hours and then given hydrazine iv at doses of 25-100 mg/kg. Control dogs received saline or ammonium hydroxide. Serial blood sampling and liver biopsy continued for 6 hours, and then all surviving animals were killed.

There was an immediate rise in blood lactate and pyruvate concentrations at all doses [63]. The pH rose initially and then stabilized in 30 minutes; this transient alkalosis was followed by a slowly developing acidosis beginning 3 hours after injection. In the first 1.5-2 hours, the rise in pyruvate paralleled that of lactate, but by 3 hours the ratio was altered and lactic acidosis developed. After 15 minutes, the rise in lactate and pyruvate was dose-dependent from 25 to 75 mg/kg, but this effect leveled off above 75 mg/kg. All animals with an initial liver glycogen of less than 590 mg/100 g developed hypoglycemia; those with higher glycogen levels developed hyperglycemia, with hypoglycemia following in 3-5 hours as liver glycogen was depleted. Convulsions appeared 4-5 hours after hydrazine injection at 25 mg/kg. At 50-100 mg/kg, convulsions appeared within 1.5-2 hours. None of these effects was observed in any control animal.

Fortney [63] believed that the hyperglycemia, glycogen depletion and hypoglycemia indicated a profound change in normal carbohydrate metabolism. Similar effects on blood glucose and liver glycogen were also observed by Taylor [64].

Aleyassine and Lee [65], in 1971, described the effects of hydrazine on insulin release. Four groups of six rats each were fasted overnight and then given two 1-millimole/kg ip injections of sodium sulfate or hydrazine sulfate 45 minutes apart, with or without simultaneous dextrose injection. Blood samples were collected 15 minutes after the last injection. Serum insulin decreased by 65-74%, both with or without simultaneous injections of dextrose, but serum glucose decreased by 35% only in animals not given dextrose. Thus, hypoinsulinemia occurred even when glucose levels in the blood were artificially elevated.

The authors [65] also conducted in vitro experiments and found that the stimulatory effect of glucose on insulin release in the rat pancreas was inhibited by hydrazine and that this inhibitory effect was reversible. They concluded that hydrazine directly affected the ability of the pancreas to secrete insulin. However, the mechanism of the hydrazine-induced hypoinsulinemia was obscure.

(2) Metabolism

In 1955, McKennis et al [66] studied the excretion of hydrazine and its metabolites. Six male mongrels, weighing 9.5-20 kg, were anesthetized with pentobarbital and then given hydrazine sulfate iv at a dose of 50 mg/kg. Hourly urine samples were collected for up to 8 hours or until the dog died to determine the amount of hydrazino nitrogen present. Urine samples collected prior to injection were used to determine baseline values. Within the first 4 hours, 5-11% of the injected hydrazine was recovered in the urine of five surviving dogs. Four survived 6-8 hours, and 12-20% of the nitrogen in the injected hydrazine was found in their urine. Excretion of hydrazine in the urine of unanesthetized dogs was also

studied. Two dogs were given hydrazine sulfate iv and two others received hydrazine sulfate sc at a dose of 15 mg/kg. At 5 days, 38.6 and 58.4% of the hydrazino nitrogen was recovered in the urine of the dogs given iv injections. The other two dogs died after 1.5-2 days, at which time 21.3 and 29.8% of the hydrazine had been recovered. By reacting the urine with benzaldehyde, the authors were able to determine that 82% (range 66-93%) of the hydrazino nitrogen was from hydrazine or a simple derivative.

In a followup to the study [66] just discussed, McKennis et al [67] also studied the metabolism of hydrazine in rabbits. Unanesthetized rabbits were given hydrazine ip at 24 mg/kg. A total of 12.5% of the hydrazino nitrogen was recovered in the urine; 18.4% of this hydrazino nitrogen (2.3% of the total dose) was identified as 1,2-diacetylhydrazine and the rest was hydrazine. Since 1,2-diacetylhydrazine was found to be nontoxic at up to 87 mg/kg by ip injection, it was viewed as a detoxication product produced by the rabbits. The dogs did not produce this metabolite.

Dambrauskas and Cornish [68], in 1964, reported on the distribution, metabolism, and excretion of hydrazine in rats and mice. Male albino Swiss ICR mice, 22-30 g, were given hydrazine iv or sc at 40-100 mg/kg. Male Sprague-Dawley rats, 330-450 g, were given sc doses of 60 mg/kg. Cumulative urine samples from each animal were collected, and after 0.5, 1, 2, 20, and 48 hours at least three mice were killed. Their carcasses were homogenized in a para-dimethylaminobenzaldehyde solution. The amount of hydrazine in the solution was then determined spectrophotometrically. In rats, blood was collected when the animals were killed and the kidneys, spleen, lungs, heart, liver, skin, stomach, intestinal tract, muscle, brain, and fat were then removed. Each organ was homogenized separately in

para-dimethylaminobenzaldehyde for spectrophotometric analysis.

In those mice given hydrazine at 40 or 60 mg/kg, 31-37% was excreted in the urine within 20 hours and 47-48% within 48 hours [68]. Only 0.3 and 1.4% of the 40 and 60 mg/kg doses, respectively, were found in the carcasses after 48 hours; no hydrazine was found in the carcasses after 72 hours. In rats killed 2 hours after injection, 8.4% of the injected hydrazine was excreted in the urine [68]. Of the organs analyzed, the kidneys had the highest hydrazine concentration, 56 μg/g. The other tissues had hydrazine concentrations ranging from 5.5 to 18.6 μg/g, except the fat, which contained 0.8 μg/g. Twenty hours after injection, 27.4% of the injected hydrazine had been excreted in the urine. The distribution of hydrazine in various organs was qualitatively the same, but it was much lower than that seen 2 hours after injection.

The authors [68] compared their findings with those of McKennis et al [66] in dogs and found that the chemical form and the amounts of hydrazine excreted in the urine agreed; no diacetylhydrazine was identified.

Although the distribution of the injected hydrazine was studied in detail, more than half of the injected dose was still unaccounted for. It appears that metabolites not detectable by para-dimethylaminobenzaldehyde were present and that the release of metabolized hydrazine through exhaled air should also be investigated.

(3) Carcinogenicity and Effects Related to Reproduction

Hydrazine was administered to animals in a 6-month inhalation study and the systemic effects as reported by Haun and Kinkead [56] were described previously. At the end of the exposure period, 10 mice from each group were retained for further study, and these results were reported by

MacEwen [69]. One year after the last exposure, 60-90% of the mice in each group were still alive at which time they were killed and examined. There were five alveologenic carcinomas, two lymphosarcomas, and one hepatoma in six of nine mice (67%) exposed continuously at 1 ppm. Of the group exposed at 5 ppm, 6 hours/day, 5 days/week, five of six (83%) had alveologenic carcinomas. In the groups exposed at 0.2 ppm continuously and at 1 ppm intermittently, three of eight (38%) and two of six (33%), respectively, developed alveologenic carcinomas; the incidence was one of eight (13%) in the control group. MacEwen commented on the importance of these findings in considering an etiologic factor because the incidence of alveologenic carcinoma was dose-related and the other tumors observed in experimental animals did not occur in controls.

In a series of experiments designed to examine carcinogenicity, one investigative group has reported extensively on the effects of hydrazine sulfate when given by intubation to several animal species, including the BALB/c and CBA strains of mice. In one study on BALB/c mice [70], hydrazine sulfate was administered 150 times in daily doses of 1.13, 0.56, 0.28, and 0.14 mg. Another group of BALB/c mice also received 1.13 mg daily but for a total dose of 32 mg given over 4 weeks. There were 39-51 mice, apparently equally divided by sex, in each group, including controls. The mice were 8 weeks old at the beginning of the experiment. Of the males given 1.13, 0.56, 0.28, and 0.14 mg for 150 doses, 90, 65, 62, and 54%, respectively, developed lung tumors. Eighty-five percent of the males receiving a total of 32 mg of hydrazine sulfate also had lung tumors. The tumor-bearing males in the two groups given 1.13 mg/day died at an average age of 67-74 weeks, while the other experimental males died at 80-82 weeks.

The control males lived to 92 weeks and had a lung tumor incidence of 24%. In females given 150 of the aforementioned doses, 90, 76, 89, and 32%, respectively, developed lung tumors. Females receiving 32 mg had a lung tumor incidence of 75%. The average age at death of the females receiving 1.13 mg/day was 74-76 weeks, while the others died at an average age of 84-86 weeks. Only 4% of the female controls developed lung tumors and they reportedly died around 100 weeks of age. Liver tumors were seen in 8% of all mice given hydrazine sulfate at 0.56 mg/kg daily and in 8% of the males given 0.28 mg/kg doses. Mice with liver tumors died at an average age of 88 weeks. Microscopically, the lung tumors were classified as either adenomas or carcinomas, while the liver tumors were vascularized hepatocarcinomas.

The authors [70] suggested that, although lung tumors were the major tumor found, liver tumors would have developed also if the mice had survived longer.

Several other studies [71-73] have reported carcinogenic effects in BALB/c mice when daily doses of 1.13 mg of hydrazine sulfate were given by intubation. When hydrazine sulfate was administered over a 4-week period, the tumorigenic effects were nearly identical to those in the group described above and all lung tumors were classified as adenomas; however, the normal incidence in female controls was 21% [71]. When hydrazine sulfate was given daily until the animals were killed, the first tumor did not appear until the 150th day. By the 200th day, the incidence of lung tumors increased to nearly 100% and the number of tumors/tumor-bearing mouse increased to a maximum of seven when 350 mg of hydrazine sulfate had been given [72]. In females given 150 doses, 90% of the intact virgins and

60% of the gonadectomized mice developed lung tumors, 96% of which were adenomas [73]. However, all breeders developed lung tumors and 47.2% of the tumors were malignant, suggesting to the author that a hormonal factor influenced both the induction and malignancy of these tumors.

In 1966, Milia [74] described the tumorigenic action of hydrazine sulfate on newborn BALB/c mice. One group of 50 mice, starting at 12 hours of age, was given hydrazine by intubation 2-3 times/day in doses increasing in proportion to body weight. In 60 days, each mouse had received about 16.7 mg of hydrazine sulfate, equivalent to 4.15 mg of hydrazine. A second group received sodium bicarbonate according to the same schedule, and a third group was unexposed. These last two groups of 50 mice each served as controls.

Fifty-nine days after the last dose, two mice given hydrazine sulfate were near death [74]. They were found to have adenomas of the lungs, and an additional 13 mice given hydrazine sulfate and 15 mice from each control group were killed for examination of all organs with lesions. While there was no evidence of tumor induction in any control animal, the 15 mice given hydrazine sulfate had a total of 45 lung tumors. Sixty-two percent of the tumors were classified as adenomas, 36% were described as adenomas becoming malignant, and 2% were carcinomas.

The induction time for lung tumors in these newborn mice, less than 17 weeks, was significantly less than that found during other experiments in that laboratory [72], although the doses used in the other study were much higher. Milia believed that an incidence of three tumors/mouse was very high, since mice of such an age usually show no spontaneous lung tumor development.

Biancifiori [75] reported in 1970 on the effect of dose on the incidence of hepatomas in CBA mice induced by hydrazine sulfate. Eight-week-old mice of both sexes were divided into 5 groups, each containing 40-59 animals. In the four experimental groups, each mouse received 1.13, 0.56, 0.28, or 0.14 mg of buffered hydrazine sulfate by gastric intubation daily for 150 days. Since the mice weighed about 25 g, the daily doses were approximately 45, 22, 11, and 5.6 mg/kg. All mice were examined after natural death or when killed while moribund. The lungs, liver, and various endocrine glands were removed for microscopic examinations.

The percentages of male mice dying with hepatomas were 60, 48, 28, and 3.8 in the groups given 1.13, 0.56, 0.28, and 0.14 mg of hydrazine sulfate/day, respectively, while corresponding percentages for females were 62.5, 66.6, 8.0, and 0.0 [75]. Control mice had hepatoma incidences of 10.0 for males and 3.4% for females. For mice with hepatomas, the average age at death was 60-71 weeks at the three highest doses, 80 weeks at the lowest dose, and 87-90 weeks in the controls. All other mice died at 57-83 weeks of age. Most of the tumors seen were characterized as highly vascularized hepatocarcinomas. In the 1.13-mg/day group, there were four instances of lung metastases. The author reported that multiple tumors were present in the lungs of many of the exposed mice, but he did not elaborate on this finding.

Biancifiori [75] found that daily administration of hydrazine sulfate at doses of 1.13 and 0.56 mg was carcinogenic to the liver of CBA mice of both sexes, while 0.28 mg/day had less carcinogenic activity and 0.14 mg/day did not cause cancer.

Other reports by Biancifiori et al [71,76] provide additional information on the effects of hydrazine sulfate administered in CBA mice, particularly on lung tumor incidence. Twenty-one males and 21 females were each given hydrazine sulfate by intubation at a daily dose of 1.13 mg for 36 weeks starting at 8 weeks of age. Sixteen experimental males (76%) developed an average of 3 lung tumors/mouse, and 19 experimental females (90%) had an average of 6 lung tumors/mouse. Of the 176 lung tumors, 138 were adenomas. Five of the adenomas in males and 20 in females were described as adenomas becoming malignant. Seven tumors in males and six in females were classified as carcinomas. In three females, metastasis to the lymph nodes was observed. The controls had a 3% incidence of lung adenomas in 37 males and 9% in 47 females. In addition, hepatomas were found in 62% of the males (13) and in 71% of the females (15). The spontaneous incidence of hepatomas in the controls was 11% in males and 4% in females.

As he had reported for the BALB/c strain of mice [73], Biancifiori [77] thought that incidence of lung tumors in CBA mice could be hormonally influenced, since with hydrazine sulfate given 150 times at doses of 0.14-1.13 mg/kg, the lung tumor incidence in females, but not in males, for virgins was always higher than that for gonadectomized mice.

Another group of investigators, Roe et al [78], reported the incidence of lung tumors in Swiss mice given hydrazine compounds. A group of 25 virgin females was given 0.25 mg of hydrazine by gavage 5 days/week, for 40 weeks. Eighty-five mice served as controls. At 40-50 weeks, there were 3 tumors in 2 of the 9 mice examined, while 4 mice examined at 50-60 weeks had a total of 20 tumors. In controls, there were 1 tumor each in 2 of 37 mice examined at 40-50 weeks and 9 tumors in 6 of 42 mice examined at

50-60 weeks. The tumors were alveologenic or bronchiologenic adenomas or adenocarcinomas. Mice given hydrazine showed a significantly greater incidence ($P<0.001$) of lung tumors than did the controls. The authors believed that the appearance of multiple tumors in mice supported the view that hydrazine was carcinogenic. They did not describe what happened to the 12 unexamined mice.

In 1969, Toth [79] described a study of lung tumor induction and breast adenocarcinoma inhibition by hydrazine sulfate. Three strains of mice, Swiss, AKR, and C3H, were given hydrazine sulfate in drinking water at a concentration of 0.012% for life starting at 6 weeks of age. For the Swiss strain, 50 random-bred mice of each sex had an average daily intake of hydrazine sulfate of 0.65 mg for females and 0.74 mg for males. A total of 110 males and 110 females were used as controls. For AKR mice, 40 males and 40 females were given hydrazine sulfate at an average daily intake of 0.63 mg. The AKR control consisted of 30 females and 30 males. For C3H mice, the average daily intake of hydrazine sulfate was 0.84 mg for 40 females and 0.98 mg for 41 males. Thirty males and 30 females were kept as controls. Complete necropsies were performed on all animals.

In Swiss mice given hydrazine sulfate, 50% of the males and 48% of the females developed lung tumors at average ages of 73 and 77 weeks [79]. Of these tumor-bearing mice, about 72.5% had adenomas, 16% had adenomas and adenocarcinomas, and the rest had either adenocarcinomas or squamous cell carcinomas. The lung tumor incidences in the controls were 10% in the males and 12.7% in the females. In the experimental group, 6% of the males and 8% of the females had malignant lymphomas, compared with 1.8 and 14.5% of the controls, respectively. In addition, the breast cancer incidence in

females was 4% in the experimental group and 8.1% in the control group. A number of other tumors, generally only one of each type, were found in both groups.

Of the AKR mice given hydrazine sulfate, 33 females (82%) and 30 males (75%) developed malignant lymphomas [79]. However, 96% (29) of the control females and 76% (23) of the control males also developed this type of tumor. A few other tumors unrelated to exposure were found. Of the C3H mice, 15 females (37.5%) given hydrazine sulfate developed breast adenocarcinomas compared with 23 control females (76.6%). In addition, four experimental females and two males had lung adenomas.

In 1972, Toth [80] described the effects of long-term ingestion of hydrazine on randomly bred Swiss mice. The mice, 6 weeks of age at the start of experiment, were given hydrazine in their drinking water at a concentration of 0.001% for life. The average daily consumption of hydrazine was 0.056 mg for the females and 0.069 mg for the males. Data for the control group, consisting of 110 mice of each sex from a similar colony, were obtained previously [79]. Of the 50 females that received hydrazine, 27 (54%) developed a total of 47 lung tumors at an average age of 91 weeks (range 26-119) [80]. The female controls had a lung tumor incidence of 12.7%. Nine females developed malignant lymphomas (18% incidence) at an average age of 92 weeks, compared with 16 in the controls (14.5% incidence). Of the 50 males that received hydrazine, 24 (48%) developed 39 lung tumors at an average age of 97 weeks (range 56-119). The incidence of lung tumors in the male controls was 10%. Seven males (14%) developed malignant lymphomas at an average age of 77 weeks, compared with two tumors in male controls (1.8%). The reported data did not indicate

whether or not the same animals with lung tumors had lymphomas. Miscellaneous tumors were also found in 4.2% of the mice receiving hydrazine and in 7% of the controls. Thus, hydrazine administered to mice in drinking water at a concentration of 0.001% throughout life increased the incidence of lung tumors, but apparently did not increase the incidence of malignant lymphomas, at least not in the female mice.

Kelly et al [81], in 1969, compared the carcinogenic activity of hydrazine sulfate and that of several other hydrazine compounds. Thirty male and 30 female offspring of BALB/c x DBA/2 mice (CDF1), 7-8 weeks old, were given weekly doses of hydrazine sulfate for 8 weeks. Males were given 2.6 mg ip injections (about 87 mg/kg) and females were given 5.2 mg oral doses (about 200 mg/kg). Control groups of 10 male and 10 female mice were given saline. All survivors were killed 33 weeks after the initial injection. Necropsy revealed 6 alveologenic carcinomas of the lungs in 6 males (20%) and 25 similar tumors in 13 surviving females (46%) given hydrazine sulfate. In the control groups, 1 of 9 males and 1 of 10 females examined had undescribed lung tumors.

There have been several other studies on the carcinogenic effect of hydrazine or its sulfate salt on mice after ip injection. Hydrazine sulfate was reported to induce lung tumors in SWR, and to a lesser degree, in C57BL/B mice [82]. However, reticular cell sarcomas in the mediastinum and myeloid leukemias were found in another study on hydrazine [83]. Of newborn BALB/C mice injected with a total dose of 19 mg of hydrazine sulfate, all 20 developed an average of 5 lung tumors/mouse compared with only 1 tumor each in 3 of 20 controls [84]. These results agree with those found in other newborn mice given hydrazine sulfate orally [74].

Severi and Biancifiori [76], in 1968, reported the results of a study of the carcinogenicity of hydrazine sulfate in Cb/Se rats. Hydrazine sulfate was given daily via stomach tube to 14 males at a dose of 18 mg and to 18 females at 12 mg over 68 weeks starting when the rats were 8 weeks old. Of these animals, three males (21%) and five females (28%) developed lung tumors, classified as adenomas or adenocarcinomas, with induction periods averaging 75 and 78 weeks, respectively [76]. No lung tumors were found in a control group of 28 males and 22 females. The authors stated that, although they originally intended to study the induction of lung tumors, they observed that the liver had also been affected. Therefore, they examined the livers of 13 experimental rats of each sex. Of these, four males (31%) had hepatic cell carcinomas or sarcomas with an induction time of 85 weeks, but no liver tumors were found in females. Because no spontaneous liver or lung tumors were found, Severi and Biancifiori concluded that hydrazine sulfate was carcinogenic in Cb/Se rats.

In a study of the possible carcinogenic effect of hydrazine sulfate [75], 23 golden hamsters, beginning at 8 weeks of age, were each given 60 doses of 3.0 mg of hydrazine sulfate by intubation for 15 weeks, and 35 were given 2.8 mg 100 times in 20 weeks. There were 56 controls.

Hepatic lesions were present in 60.8% of the those receiving hydrazine sulfate at 3.0 mg/day, in 82.8% of those receiving 2.8 mg/day, and in none of the control hamsters [75]. The liver in almost all animals with hepatic lesions was small, grayish-yellow, and hard. Cirrhosis was confirmed microscopically. The diffuse hepatic lesions were found to be associated with an increase in the fibrous connective tissues. Reticuloendothelial cell proliferation was found in 85.7-96.5% of the

hamsters receiving hydrazine sulfate. Thirty-one percent of the animals that received hydrazine sulfate had bile duct proliferation, and 21% had degeneration of the fibrous cells in hyalinized tissues. The incidence of liver lesions was similar for both sexes, but there was no evidence of tumor induction in either the lungs or the liver.

Toth [85] reported a study in 1972 on the tumorigenic effects of hydrazine sulfate on hamsters. Syrian golden hamsters, 50 males and 50 females, were given drinking water containing 0.012% hydrazine sulfate. The experiment started when the hamsters were 9 weeks old and lasted for their lifespan. The average daily intake of hydrazine sulfate by each hamster was 2.3 mg. All the animals were weighed and checked weekly for gross abnormal changes [85]. A concurrent control group was not maintained, but data [86] previously obtained from a similar colony were used for comparison. Complete necropsies were performed on all animals including those that were killed when in poor condition. All organs were examined, and microscopic studies were performed on any organ that showed gross abnormalities. The author found no detectable tumorigenic effects of hydrazine sulfate in hamsters. Although the 8% incidence of polypoid adenomas of the cecum was somewhat higher than that of the control group, the difference was not statistically significant. Toth pointed out that these findings in hamsters agreed with those reported by Biancifiori [75].

There have been several studies investigating the mutagenicity and possible teratogenicity of hydrazine. In 1972, Rohrborn et al [87] studied the mutagenic potential of hydrazine in a host-mediated assay system. Five to six male NMRI mice, 10-14 weeks old, were each injected ip with a broth containing Salmonella typhimurium G46 and sc with hydrazine sulfate at

doses of 3.5, 3.25, or 3.1 mg/kg. The hydrazine sulfate injections were repeated after 1 and 2 hours. Seven control animals received only the bacteria. One hour after the last hydrazine injection, the animals were killed. The mutated and total bacteria within the peritoneal cavity were counted, and mutation frequency ratios of the hydrazine-administered versus the control animals were calculated. Injection of hydrazine sulfate at doses of 3.5, 3.25, and 3.1 mg/kg resulted in mutation frequency ratios of 362.84, 87.61, and 32.71, respectively. The authors concluded that hydrazine had a dose-dependent mutagenic potential in a host-mediated assay system.

Herbold and Buselmaier [88], in 1976, investigated the mutagenic effects of various substances, including hydrazine. Cultures of Salmonella typhimurium (strains TA 1535, TA 1536, TA 1537, TA 1538, and G46) were incubated in the presence of phenobarbital-activated mouse liver microsomes and 0, 0.12, 1.2, and 12 mg/ml of hydrazine. Forty-eight hours later, revertants were counted and mutation frequencies were determined. Hydrazine caused dose-dependent increases in mutation frequency in both the TA 1535 and G46 strains. The ratios were 1, 1.42, 2.35, and 9.1, respectively, for TA 1535 and 1, 3.6, 3.25, and 312 for G46. The authors concluded that hydrazine was a mutagen based on the finding in these two strains. However, they stated that it was inappropriate to correlate these results to the evaluation of mutagenic risks in humans.

A study of the effect of hydrazine on pregnant rats was described by Lee and Aleyassine [89] in 1970. Seventy-eight Wistar rats at the 11th day of pregnancy were divided into three groups for the experiment. One group received hydrazine sc at 8 mg/kg/day for 10 days, the second group received

hydrazine sc and 200 mg/kg/day of pyridoxine intramuscularly (im) for 10 days, and a control group received sc injections of normal saline at 2 ml/kg/day for 10 days. On the 21st day of pregnancy, 11-12 rats in each group were killed and examined for surviving and dead fetuses and implantation sites. Surviving fetuses were weighed and examined, and selected organs of some fetuses were examined microscopically. The remaining pregnant animals were observed until they delivered, and the live newborn rats were counted 24 hours after delivery.

Repeated injections of hydrazine alone resulted in 2 deaths among 26 pregnant rats, and 1 death occurred in the 26 that received both hydrazine and pyridoxine [89]. No deaths occurred in the controls. Eighty percent of the control rats bore litters of 9-18, and all the newborn subsequently survived. Of the dams that received hydrazine alone, no offspring survived the first 24 hours. Of the dams injected with both hydrazine and pyridoxine, 7 of 13 delivered live newborn, but the litter size was usually smaller (1-14 animals) than that seen in the controls. These newborn rats were very pale and less active than the offspring of the controls. They all showed a moderate degree of dehydration. Twenty-nine of these 33 pups developed and grew normally through weaning. Of the rats killed on the 21st day of pregnancy, two or three in each group had no live fetuses. The fetal survival rates (total fetal survivors/total implantation sites) were 37% for rats given hydrazine, 70% for those given hydrazine and pyridoxine, and 79% for those given saline. The mean body weights of the surviving fetuses were 2.89, 3.44, and 4.70 g for these groups, respectively. Besides being smaller, the fetuses from the rats that received hydrazine were pale and edematous, with occasional petechial hemorrhages. No gross

malformations were observed. Pyridoxine did not improve the appearance of the fetuses. Dams given hydrazine during gestation had weight losses averaging 40-50 g.

In 1976, Greenhouse [90] reported a study on the effect of hydrazine sulfate on the development of South African clawed toad (Xenopus laevis) embryos. The toad embryos were cultured in aquatic media containing various concentrations of hydrazine sulfate. The medium was changed twice every week because of hydrazine degradation, but only initial concentrations were reported. Hydrazine sulfate was not toxic or teratogenic in Xenopus larvae exposed continuously at initial concentrations up to 400 mg/liter, but it was found to be teratogenic at a concentration of 40 mg/liter or higher if exposure started prior to neurulation completion. Malformations seen included foreshortening of the axial skeleton, tail kinks, and edema. If malformed embryos were left in hydrazine sulfate solution, they all died, but they survived if transferred to freshwater. No data were available on whether or not these larvae metamorphosed.

In an additional study [91] on the teratogenicity of hydrazine, clawed toad embryos at the cleavage stage were exposed to hydrazine continuously until hatching. At 10 mg/liter, 35% of the embryos were malformed; at 25, 50, and 100 mg/liter, all exposed embryos were affected. In embryos exposed to hydrazine at 25 mg/liter at different stages of development, only those exposed during neurulation and returned to tap water by the time they had reached the tail bud stage showed teratogenic effects.

(b) Methylhydrazine

(1) Systemic Effects

In a study of the acute toxicity of hydrazines, Jacobson and coworkers [20] found that the toxic signs in rats exposed to methylhydrazine were the same as those reported for hydrazine, and the LC50 values were calculated to be 74 ppm (139 mg/cu m) for rats and 56 ppm (105 mg/cu m) for mice for single, 4-hour exposures. The LC50 for hamsters was reported to be 143 ppm (270 mg/cu m) of methylhydrazine.

Groups of three male dogs were also exposed to methylhydrazine for 4 hours at 15, 21, or 29 ppm and observed for up to 14 days after exposure [20]. Necropsies were performed on the dogs, including those killed when near death, and blood was obtained before and after exposure.

The dogs exposed to methylhydrazine salivated, vomited, panted, choked, and showed incoordinated locomotion and convulsions [20]. At 29 ppm, two of three dogs died during exposure, and at 21 ppm, two of three dogs died the day after exposure. All other dogs survived the 14 days of observation, except for one in the 29-ppm group, which was killed on day 2 for examination. Methylhydrazine exposure caused hemolysis, indicated by a 24% mean decrease in hematocrit value, a 43% decrease in erythrocyte count, and a 41% decrease in hemoglobin content 4 days after exposure. The percentage of reticulocytes in the blood increased from a mean of about 4% before exposure to about 75% 8 days after exposure. A mild bilirubinemia was caused by elevation of the direct-reacting fraction of heme pigments. The sulfobromophthalein (BSP) retention in dogs was unaltered by methylhydrazine exposure, and the ECG's of the dogs were normal. Moderate to marked polymorphonuclear leukocytosis also developed. The hemolytic

effect was most pronounced 4-8 days after exposure, and blood values returned to normal 17-24 days after exposure ended.

In 1969, Haun et al [92] investigated the acute effects of inhalation of methylhydrazine in animals. Groups of 10 male Sprague-Dawley rats, weighing 125-175 g, and 20 male Swiss mice, weighing 17-23 g, were exposed to methylhydrazine for single 30-, 60-, 120-, and 240-minute periods. Twenty-two beagle dogs were exposed at 92 or 104 ppm for 60 minutes, 180-200 ppm for 30 minutes, or 380-400 ppm for 15 minutes. Twenty-five squirrel monkeys were exposed at 75-90 ppm for 60 minutes; 130-170 ppm for 30 minutes, or 300-376 ppm for 15 minutes. Five Rhesus monkeys were exposed to methylhydrazine at 160 or 170 ppm for 60 minutes.

The LC50's, calculated for each exposure interval and species of animal, are listed in Table III-1 [92]. The number and severity of toxic signs in the rats and mice exposed to methylhydrazine were dose-dependent and included nose and eye irritation, diarrhea, frequent urination, rapid and labored breathing, intermittent periods of hyperactivity, tonic-clonic convulsions, and tremors. The rodents appeared to have died during convulsions. Toxic signs observed in the dogs and monkeys were similar to those seen in rodents, but the dogs were also incoordinated and cyanotic.

Of the various tests performed on dogs and Rhesus monkeys (blood counts, liver and kidney function tests), only the hematologic examination showed changes from baseline values [92]. Moderate to severe anemia occurred in all surviving dogs, while mild to moderate anemia was observed in all surviving monkeys. Decreased hematocrit values and hemoglobin concentrations, apparent in both species, were lowest about 7-14 days after exposure. Reticulocyte counts increased in both species and peaked 10 days

after exposure. The authors indicated that the blood taken from the dogs was rusty-brown, which, with observed cyanosis, suggested to them the possibility of methemoglobin formation. About 35 days after exposure, the monkeys had normal blood values, but preexposure levels had not been attained 9 weeks after exposure for dogs.

Microscopic examination of tissues from dogs, rats, and squirrel monkeys after lethal exposure showed pulmonary congestion with hemorrhage, hepatic congestion, and swelling of the renal tubular epithelium [92]. The brains of the dogs and monkeys frequently showed subarachnoid hemorrhages. Renal damage, ranging from mild swelling of the tubular epithelium to vacuolization and coagulative necrosis of tubular epithelial cells, was the most common finding in animals killed 60 days after near-fatal doses of methylhydrazine. Haun et al observed that the amount of visceral congestion and hemorrhage was not sufficient to produce death and that, of the species studied, squirrel monkeys were the most sensitive and rats the least sensitive to the lethal effects of methylhydrazine.

The LC50's determined in this study [92] correlate well with those determined in the other study [20]. Mild to severe anemia appeared to be the major toxic effect on dogs and was observed in both studies.

In 1971, MacEwen and Haun [93] conducted a series of 6-month exposures of animals to methylhydrazine at 0.2, 1, 2, and 5 ppm for 6 hours/day, 5 days/week. Another group was exposed continuously at 0.2 ppm. Each group consisted of 8 beagle dogs, 4 Rhesus monkeys, 50 Wistar rats, and 40 ICR mice. All animals except the rats were female. A series of 15 clinical chemistry and 8 hematologic tests and body weight measurements were conducted every 2 weeks during the study. Surviving animals, except

one-half of the dogs, were killed for examination at the end of exposure, and bone marrow studies were then conducted on the dogs. The remaining dogs were held for 30 days after the end of exposure and were examined for possible reversibility of toxic effects and recovery time.

Death attributed to exposure occurred only in mice at the two highest concentrations, with mortalities of 27% at 5 ppm and 15% at 2 ppm [93]. Growth rate depression in rats was observed, but only in the 2- and 5-ppm groups was that effect sustained. Long-term effects in dogs and monkeys were primarily related to the reaction of methylhydrazine with red blood cells. The hemolytic responses were about the same for the 0.2-ppm continuous exposure group and the 1-ppm intermittent exposure group, as would be expected, since the weekly exposure concentration times, 33.6 and 30 ppm-hours, were essentially the same. Reductions in erythrocyte counts, hemoglobin concentrations, and hematocrit values of 43, 43, and 30%, respectively, were observed in the dogs exposed to methylhydrazine at 150 ppm-hours/week compared with 9, 3, and 2% at 6 ppm-hours/week. A twofold to threefold increase in methemoglobin occurred in the dogs exposed at 5 ppm (150 ppm-hours/week). In monkeys exposed at 150 ppm-hours/week, decreases in hematocrit values, hemoglobin concentration, and erythrocyte counts of 28, 32, and 30%, respectively, were observed. Increased red cell fragility was observed in canine blood. The degree of hemolysis, measured in 0.6% salt solution, was 2.5% at the 6 ppm-hours/week exposure, 15% at 150 ppm-hours/week, and 1% in controls. Samples of canine and primate blood taken at 3-7 months were found to contain 1-5 Heinz bodies/100 red blood cells, and no dose- or species-related effects were found. After the exposure ended, the blood cell counts returned to normal in 2-4 weeks.

Mean bilirubin and alkaline phosphatase values for all groups of exposed dogs were statistically higher than control values at all sampling periods after 3 weeks of exposure, and dose-dependent effects were evident [93]. The increase in total inorganic serum phosphorus was less pronounced, but the authors believed that it indicated, along with the other two tests, intrahepatic cholestasis from liver damage caused by long-term exposure to methylhydrazine. Data on monkeys were not reported. Bone marrow samples from exposed dogs showed a dose-related decrease in the myeloid/erythroid ratio with increasing erythropoietic activity.

The authors [93] concluded that methylhydrazine exposure produced dose-related hemolytic anemia and Heinz body formation without an apparent threshold level and that the anemia was reversible when animals were removed from further exposure, at least up to 5 ppm in intermittent exposure. As a result of their study, they recommended that the TLV of 0.2 ppm be reexamined.

Kroe [94] examined selected tissues from the animals used by MacEwen and Haun [93]. Tissues from the lungs, heart, liver, spleen, and kidneys of all the monkeys and dogs and from 10 rats and 10 mice of each group were examined [94]. There were no lesions in the monkeys and rats. Periportal hepatic hemosiderosis and cholestasis and proximal tubular hemosiderosis were found in the dogs exposed to methylhydrazine at 150 ppm-hours/week. Similar hepatic and renal tubular changes were also seen in the dogs exposed at 60 ppm-hours/week. Hepatic cholestasis was found in dogs exposed at 33.6, 30, and 6 ppm-hours/week. Moderate lymphoid hyperplasia was also noted.

Lung and heart tissues of all exposed mice were normal [94]. The livers of mice exposed at 150 ppm-hours/week had centrilobular cholestasis, bile duct proliferation, and centrilobular hemosiderosis. The kidneys and spleens of the same mice also had hemosiderosis. The liver changes in the mice exposed at 60 ppm-hours/week were similar to those of the 150 ppm-hours/week group, only less pronounced. Splenic and renal tubular hemosiderosis was also less pronounced. In the three lowest exposure groups, hepatic, splenic, and renal tubular hemosiderosis was greatest at the 0.2-ppm continuous level, less at 1 ppm, and still less in the 0.2-ppm intermittent group. There was no cholestasis or bile duct proliferation in the livers of these mice.

The interspecies differences observed in the development of hemosiderosis and cholestasis were attributed to species susceptibility to methylhydrazine-induced hemolysis and to the ability of some species to clear the hemolytic products.

In 1973, Darmer and MacEwen [95] reported the effects of long-term exposure of animals to methylhydrazine vapor. Groups of 8 female beagles, 4 female Rhesus monkeys, and 80 male Sprague-Dawley rats were exposed continuously to methylhydrazine at 0, 0.04, or 0.1 ppm for 90 days. After the animals were exposed for 45 and 90 days, blood samples from 30 rats of each group were examined, while the remaining 20 rats were killed for tissue examination. Blood counts were measured on the dogs and monkeys before the experiment and every 2 weeks thereafter. In addition, total serum inorganic phosphorus, serum alkaline phosphatase, and erythrocyte fragility (dogs only) were determined. The presence of Heinz bodies was noted, and body weight was monitored.

Exposure of rats to methylhydrazine at 0.1 ppm for 90 days (16.8 ppm-hours/week) caused a significant decrease in body weight (about 20 g), but organ-to-body weight ratios were unaffected [95]. Rats exposed at 0.04 ppm (6.7 ppm-hours/week) showed no growth impairment. After 45 days of exposure, rats in both groups had a significant decrease in mean hematocrit value (6%), hemoglobin concentration (4%), and erythrocyte count (8%). After 90 days, rats exposed at 0.04 ppm showed only an increase in serum phosphorus (8%), while those exposed at 0.1 ppm had depressed erythrocyte counts (13%) and increased serum phosphorus levels (13%). In dogs exposed to methylhydrazine at 0.1 ppm, hematocrit value, hemoglobin concentration, and erythrocyte count were found to be decreased by 10, 17, and 24%, respectively, while serum phosphorus was increased by 23% and alkaline phosphatase activity by 465%. Red blood cells from dogs exposed at 0.1 ppm had increased osmotic fragility; changes were insignificant at 0.04 ppm. Reticulocytes increased at both exposure levels. No toxic effects were found in the blood of the monkeys. In all three species, the only gross tissue abnormality was a nutmeg appearance of the livers of dogs exposed at 0.1 ppm considered to be consistent with passive congestion. No microscopic data were reported.

O'Brien et al [96] investigated the acutely toxic effects of several hydrazines, including methylhydrazine, on rats. Thirty-five female rats weighing 180-240 g were given methylhydrazine ip at 10-100 mg/kg. Toxic signs were observed, and the LD50 was determined to be 28 mg/kg. Death generally was preceded by convulsions. Blood glucose, measured before convulsions began in two rats given an LD50 dose, was elevated 2-3 fold in 35 minutes. The authors, however, considered that glucose interference was

not related to the lethal action of methylhydrazine.

In 1971, Gregory et al [97] reported on the effect of varying the route of administration on the LD50's for methylhydrazine in hamsters and Sprague-Dawley rats. A 4.2% solution of methylhydrazine was given orally, ip, and iv, and a 50% solution was applied topically. The LD50's observed in rats and hamsters, respectively, were 70.7 and 22.1 mg/kg for oral doses, 183.4 and 239.4 mg/kg for topical applications, and 20.5 and 21.2 mg/kg for ip injections. The LD50 for iv injections in rats was 17.3 mg/kg. The cause of death was respiratory failure. Those rats alive 3 weeks after exposure had mild to severe muscular incoordination and cerebellar demyelinization. The LD50's for methylhydrazine nitrate were similarly calculated. Except for oral administration in hamsters, the nitrate form was slightly more toxic than the free base.

Rothberg and Cope [58] reported LD50's for methylhydrazine of 14.2 µl/kg (12 mg/kg) for iv injection in rabbits and 93 mg/kg and 47 mg/kg for rabbits and guinea pigs, respectively, following skin absorption. A mild edema appeared on the skin at the site of application, disappearing in 24 hours and leaving a blanched appearance to the skin. Application of 3 µl of methylhydrazine to the eye of each of two rabbits resulted in only mild conjunctivitis and slight erythema of the eyelid.

In 1969, Smith and Clark [98] reported on the absorption of methylhydrazine through canine skin. Methylhydrazine at doses of 0.32-5.75 millimoles/kg (14.7-264.5 mg/kg) was applied to a 300-sq cm area on the chest of 16 anesthetized male mongrels. The skin at the site of application quickly reddened, the discoloration deepened, the skin became edematous, and eventually the site appeared slightly gray. Swelling

subsided in 6 hours. Only one animal, receiving 175 mg/kg, died during the 6-hour period, but many convulsed despite the anesthesia. Methylhydrazine was detected in the blood within 30 seconds of application. The concentration in blood continued to rise for 30-60 minutes, eventually reaching a plateau; the amount of both methylhydrazine and methemoglobin in the blood was apparently dose-related. After 100-140 minutes, there was a gradual decline in methemoglobin throughout the 6-hour observation period. The authors noted that a dermal dose 5-7 times that of iv injection was necessary to produce an equivalent amount of methemoglobin.

Fortney and Clark [46] investigated the effect of methylhydrazine on methemoglobin production both in vitro and in vivo. For the in vivo experiment, anesthetized dogs were injected with methylhydrazine iv at 0.54 millimole/kg (25 mg/kg). Arterial blood samples were taken 5, 15, and 30 minutes and 1, 1.5, 2.5, and 4 hours after injection to determine methemoglobin concentration. Blood glucose and lactate concentrations were analyzed at 30-minute intervals from 1 hour before to 2 hours after injection, then at hourly intervals for 2 more hours. The amount of hemoglobin present as methemoglobin peaked at a level greater than 30% an hour after injection and declined gradually to 19% in the next 3 hours. The blood lactate rose markedly 1-2 hours after injection and was still elevated at 4 hours. Blood glucose rose slightly the 1st hour and then fell sharply.

In vitro, methemoglobin was formed when methylhydrazine was incubated with either canine blood or purified oxyhemoglobin, although the rate of reaction was faster in whole blood than in oxyhemoglobin [46].

In 1970, Leahy [47] reported the results of a study of the in vitro effect of methylhydrazine on blood. Canine blood was incubated with methylhydrazine under either unlimited aerobic or anaerobic conditions and reaction rates were determined by sequential spectral analyses.

Under anaerobic conditions, hemoglobin was reduced and only 2-3 g/100 ml of methemoglobin was found [47]. Under aerobic conditions, the hemoglobin-methylhydrazine mixture gradually turned from bright red to purple-brown. The rate of methemoglobin formation and the total amount formed were proportional to the original concentration of methylhydrazine, although the conversion was limited to 75-80% of the original hemoglobin. When the molar ratio of methylhydrazine to heme was 1, a methemoglobin concentration of 12 g/100 ml was detected in 60 minutes. When this ratio was higher than 2, rapid denaturation of globulin and precipitation were observed. The blood of humans, rats, and monkeys was also tested under aerobic conditions. The equilibrium levels of methemoglobin reached in the blood samples differed in each species and were 8.5, 4.0, 3.0, and 2.5 g/100 ml for dogs, humans, rats, and monkeys, respectively, when the methylhydrazine-heme ratio was 0.5. Gas-chromatographic analysis of the gas produced during aerobic incubation showed the presence of nitrogen and methane representing about 80% of the nitrogen and 20% of the carbon of the methylhydrazine.

When one considers the equilibrium amount of methemoglobin that can be accumulated in the blood, the argument that human blood is more sensitive to the effects of methylhydrazine than the blood of rats and monkeys but is less sensitive than canine blood is supported.

Van Stee [62] investigated the effects of methylhydrazine on the renal function of dogs in an experiment identical to the one discussed above for hydrazine. Nine anesthetized dogs were given iv injections of methylhydrazine at 0.63 millimoles/kg (29 mg/kg) and tubocurarine chloride to supress convulsions. Inulin and PAH clearance rates were significantly decreased, although renal plasma flow was not affected. Methemoglobinemia appeared within minutes following injection of methylhydrazine, and methemoglobinuria appeared within a few hours. The author postulated that the mechanism producing impairment in renal function was similar to that for hydrazine, ie, decreased PAH clearance was caused by decreased glomerular filtration and interference with active transport by the proximal renal tubular epithelium.

In 1969, Sopher et al [99] studied the effects of methylhydrazine on dogs. Forty-two beagles were each given a single ip injection of 5-30 mg/kg of methylhydrazine, some with 100-200 mg/kg of pyridoxine to protect against the convulsive effects of methylhydrazine. One hour to 8 days later, the animals were killed and the major organs removed for gross and microscopic examination.

Methylhydrazine at 5 mg/kg caused vomiting and convulsions but no deaths; at 10 mg/kg or more, death occurred within 2 hours [99]. The toxic signs were relieved by pyridoxine, and those animals that received both preparations recovered. In dogs killed 1-2 days after injection with methylhydrazine and not receiving pyridoxine, the most prominent gross findings were in the urinary tract. The kidneys were swollen, and the delineation between the cortex and medulla was obliterated. The bladder contained dark-brown urine and occasional blood clots. All other organs

examined were also congested. In dogs that were killed more than 2 days after injection of both methylhydrazine and pyridoxine, kidney swelling and hyperemia of other organs were diminished or absent. Of the dogs that received a high dose of methylhydrazine, those that convulsed and died had severe congestion and cyanosis in most organs and scattered hemorrhagic areas in the lungs.

The microscopic appearance of the kidney tissues varied with the methylhydrazine dose given and the time between injection and necropsy [99]. The higher the dose, the more pronounced the changes, which included swelling and eosinophilia in the epithelium of the proximal tubules and loops of Henle. Tissues from dogs given methylhydrazine at 5 mg/kg were normal, while the damage in the kidneys of the dogs receiving 7.5-15 mg/kg involved several changes, including overt hemoglobinuria and hyaline droplet degeneration. At 20 or 30 mg/kg, methylhydrazine also caused severe renal epithelial damage characterized by syncytial masses that engulfed the hemoglobin casts. The animals that survived for several days developed hemosiderosis, and the hyaline droplets were either reduced in size and number or no longer present. The authors concluded that methylhydrazine in dogs caused severe erythrocyte damage, leading to severe anemia and formation of methemoglobin and other hemoglobin destruction products, that resulted in hemoglobinuric nephropathy.

The toxic effects of repeated injections of methylhydrazine on monkeys were studied by Back and Pinkerton [100]. In 10 Macaca mulatta monkeys given methylhydrazine ip at 2.5 or 5 mg/kg for 31 days for total doses of 65 or 95 mg/kg, the only clinical or microscopic evidence of toxicity was a decrease in body weight in the 1st week. Back and Pinkerton

therefore administered higher ip doses of methylhydrazine, to induce clinical signs and tissue damage, to three male monkeys weighing from 2.40 to 5.91 kg. Two controls received saline injections. Doses of 7 and 10 mg/kg were alternated daily until the animal died.

No toxic signs were noted in any of the animals on the 1st day, but one animal died on each of the next 3 days; the causes of death were not apparent [100]. Serum enzyme activities, SGOT and alkaline phosphatase, were normal, except that the last blood sample of one monkey had a high SGOT activity. Significant amounts of fatty infiltration and vacuolization of cells were noted in the liver. The kidneys, heart, and bone marrow were normal. One animal had tiny perivascular cerebellar hemorrhages, which the authors attributed to severe convulsions. The authors also noted that there was an extremely narrow range between a no-effect and a lethal concentration of methylhydrazine for monkeys.

Ten male and 10 female Macaca mulatta monkeys, weighing 3-6 kg, were used by George and associates [101] in a study of the nephrotoxicity of methylhydrazine. Eight weeks after translocation of the left kidney to a subcutaneous pocket, baseline values of kidney function and a kidney biopsy were performed.

After another 6 weeks, the monkeys were divided into five groups, apparently of four each [101]. Group I, the control group, was given saline ip daily for 14 days. The other groups received methylhydrazine. Animals in group II received a single injection of 7.5 mg/kg; group III, 2.5 mg/kg/day for 14 days; group IV, 5 mg/kg/day every other day for 14 days; and group V, 5 mg/kg/day for 5-10 days. Forty-eight hours after the

final injection, biopsy specimens were taken for electron microscopic examination.

Although monkeys in groups IV and V developed toxic signs, no methylhydrazine was detected in the blood or urine of any animal 24 hours after the final injection [101]. In group II, there were cellular vacuolization and mitochondrial swelling in both the proximal and distal tubular cells after injections. These changes were neither uniformly distributed nor uniformly severe but were present in all biopsy samples. In the most severe cases, the tubular cells were completely filled with vacuoles and mitochondria were barely recognizable. The monkeys in groups III, IV, and V had similar but less severe changes in renal tubular cells.

George et al [101] noted that the changes observed in renal tubular cell morphology did not cause significant changes in renal function. They hypothesized that there were enough intact, unaffected nephrons to maintain normal function. Comparing their findings in monkeys to those in dogs [62,99], the authors concluded that the nephrotoxic effects on dogs were more severe.

This study [101] appears to complement an earlier study by Back and Pinkerton [100] in which only slight fatty infiltration of the liver was observed using a light microscope. Using an electron microscope, George et al [101] observed changes in renal tubular cells. Both studies agreed that there were no significant changes in renal function of monkeys given ip injections of methylhydrazine at 2.5-7.5 mg/kg.

Reynolds and Back [102] tested the effect of ip injections of methylhydrazine on the learned behavior of macaque monkeys. Four monkeys received methylhydrazine at 2.5 mg/kg and five received 5 mg/kg. Each

monkey was given hourly shock-avoidance tests, eight times/day, for 3 days; injections were given on the 1st and the 3rd days.

Performance did not vary with dose [102]. In over half the tests, a performance decrement preceded or occurred without clinical signs, but clinical signs never preceded a performance decrement. Performance deteriorated 1-2 hours after methylhydrazine injection and returned to normal in 3-30 hours. Clinical signs generally occurred 2-3 hours after injection and disappeared in 3-6 hours. The authors believed that performance tests were a more sensitive index of toxicity than were clinical signs and that operant behavior in monkeys was significantly impaired after ip injection of methylhydrazine at 2.5 or 5 mg/kg.

(2) Metabolism

Male Sprague-Dawley rats, weighing 250 g, in groups of two each, were given ip injections of 14C-labeled methylhydrazine in a study of methylhydrazine metabolism by Dost et al [103]. The rats were then kept in chambers, and radioactivity in their expired air and their urine was monitored. The total respiratory radioactivity measured 27 hours after injection of methylhydrazine at doses of 5.5, 11, and 22 mg/kg was 37, 31, and 24%, respectively, of the injected amount. Of the radioactivity detected, 20-25% was 14C carbon dioxide; the remainder was identified as methane. The output of these two gases peaked at about the same time, but the ratio of yields of methane to carbon dioxide decreased from 10 initially to 3 or 4 after 10 hours, suggesting to the authors that different metabolic pathways might be involved.

Twenty-seven hours after administration of methylhydrazine, the rats given 5.5, 11, or 22 mg/kg had excreted 41, 39, and 22%, respectively, of

the total doses in the urine [103]. The difference between the amount of radioactivity injected and that found in the urine and exhaled air at 27 hours was considered to have been retained by the tissues. These amounts were calculated to be 1.2, 3.2, and 12 mg/kg, respectively. The authors believed that the increased percentage of tissue-retained radioactivity at the highest dose was caused by an impairment of the excretion mechanisms.

Pinkerton et al [104] studied the distribution and excretion of methylhydrazine in four species. Twenty Sprague-Dawley rats, 20 Swiss mice, 17 mongrel dogs, and 16 Macaca mulatta monkeys received 14C-labeled methylhydrazine ip at 15, 22, 10, and 10 mg/kg, respectively. The animals, fasted overnight, were killed 2, 4, 8, or 24 hours after injection, and urine and blood samples were collected for analysis of methylhydrazine. Whole organs were removed and weighed, and radioactivity in each organ was measured individually, except for mice, where organs were pooled in groups of five to obtain sufficient material.

In the more than 20 samples of tissues and serum analyzed, the serum, liver, kidneys, and bladder in all 4 species had the highest concentration of radioactive material [104]. These concentrations in samples from dogs and mice peaked at 4 hours but peaked at 2 hours in those from the monkeys. The radioactivity in samples from rats did not have any apparent pattern. Urinary excretion of methylhydrazine was most rapid in mice, followed by that in rats, monkeys, and dogs. Two hours after injection, dogs excreted only one-half as much of the injected dose as the monkeys, rats, or mice did. Twenty-four hours after injection, 25.6, 31.3, and 39.9% of the injected methylhydrazine had been excreted in the urine of the dogs, monkeys, and rats, respectively.

In a later study of several metabolic effects of methylhydrazine in male Sprague-Dawley rats, Dost [105] examined glucose catabolism during acute and subacute methylhydrazine intoxication. The 14C-labeled glucose was infused intraintestinally at 150 mg/hour, a concentration adequate to prevent glycogen depletion. In acute studies, a single ip injection of 0.45 millimole/kg (21 mg/kg) of methylhydrazine was given 7 hours later. In subacute studies, 0.036 millimoles/kg/hour (1.66 mg/kg/hour) of methylhydrazine was given by iv infusion, starting 4 hours before glucose administration. In both cases, respired 14C carbon dioxide was measured as an index of glucose catabolism. In a third experiment, glucose infusion was started, 7 hours later methylhydrazine infusion began, and blood glucose concentrations were monitored.

Following both acute and subacute methylhydrazine intoxication, there was a substantial depression of glucose catabolism, as measured by the concentration of 14C carbon dioxide in the respired air. In the subacute studies, it was possible to distinguish that for glucose labeled in the first position, oxidation was much less depressed compared with that observed when the label was in the second, third, fourth, or sixth position. Pyridoxine was effective in reversing this depression. In the third experiment, blood glucose concentrations increased following administration of methylhydrazine and they continued to increase for about an hour after the onset of convulsions even though methylhydrazine administration was stopped. Both pyridoxine and insulin were effective in counteracting the hyperglycemia induced by methylhydrazine.

(3) Carcinogenicity and Effects Related to Reproduction

In 1972, Toth [80] reported a study of the tumorigenicity of methylhydrazine in Swiss mice. Fifty males and 50 females, 6 weeks of age, were given 0.01% methylhydrazine in drinking water for life. The average daily intake of methylhydrazine was 0.66 mg/male and 0.71 mg/female. Data from a control group of 110 female and 110 male mice were obtained previously from a similar colony [79].

Methylhydrazine shortened survival, ie, all experimental mice died before they were 80 weeks old while the last of the control animals was still alive at 120 weeks [80]. Of the 50 females given methylhydrazine, 12 (24%) developed 17 lung tumors classified as adenomas at an average age of 51 weeks (range 36-67). The female controls had a lung tumor incidence of 12.7%. Of the 50 males given methylhydrazine, 11 (22%) developed 12 lung adenomas at an average age of 51 weeks (range 34-70), compared with 10% in the male controls. Two malignant lymphocytic lymphomas were observed in females. Fifteen liver cell tumors, both benign and malignant, eight cholangiomas and two cholangiocarcinomas were diagnosed in animals given methylhydrazine.

As part of the same study, 0.001% methylhydrazine sulfate was administered to another group of mice of the same age in an identical manner [80]. The average daily intake of methylhydrazine sulfate for the males was 0.102 mg and 0.078 mg for the females, an equivalent of 0.033 and 0.025 mg of methylhydrazine, respectively. Of the 50 female mice, 23 (46%) developed 46 lung tumors at an average age of 95 weeks (range 71-119). Of these 23 mice, 11 had a total of 17 adenomas, 4 had 5 adenocarcinomas, and 8 had 15 adenomas and 9 adenocarcinomas. Ten females (20%) each had a

malignant lymphoma. Two of these lymphomas were lymphocytic, seven were histocytic, and one could not be classified. Of the males receiving methylhydrazine sulfate, 23 (46%) developed 43 lung tumors at an average age of 87 weeks (range 56-117). Of these 23 mice, 18 had a total of 24 adenomas, 2 had 1 adenocarcinoma each, and 3 had a total of 10 adenomas and 7 adenocarcinomas. Eight males (16%) developed malignant lymphomas. Seven of the lymphomas were histocytic, and one could not be classified. Fifteen controls developed tumors; five were hemangiomas, but none was a lymphoma.

The incidence of lung tumors caused by methylhydrazine sulfate was higher than that caused by methylhydrazine, although the latter was given at a dose 10 times higher than the former [80]. On the average, the mice given methylhydrazine survived 51 weeks while those given the sulfate salt survived 91 weeks. Furthermore, methylhydrazine is less stable than its sulfate salt, and it is possible that methylhydrazine given in the feed water may have degraded.

The previously described study by Roe et al [78] on the carcinogenicity of hydrazine and several of its derivatives included methylhydrazine sulfate. Twenty-five female virgin Swiss mice were each given 0.5 mg of methylhydrazine sulfate by gavage for 5 days/week for 40 weeks. There were 85 controls. The mice were examined 40-50 or 50-60 weeks after exposure began. By 60 weeks, 1 (5%) of the 19 experimental mice examined had evidence of tumor formation, and that mouse had 6 lung tumors, while 8 surviving control mice (10%) had 11 tumors. The authors concluded that methylhydrazine sulfate was not carcinogenic in mice, but they noted that they were unable to administer higher doses because of the toxicity of the compound.

Kelly et al [81] examined the incidence of lung tumors in mice given methylhydrazine. Thirty male and 30 female CDF1 mice, 7-8 weeks old, were given 8 weekly doses of methylhydrazine. Males received 0.23 mg/dose (7 mg/kg) ip and females received 0.46 mg/dose (17 mg/kg) orally. Ten males and 10 females given saline served as controls.

Three experimental males (10%) had developed lung tumors when killed at 33 weeks, but there were no tumors in the nine females examined [81]. The control group had a tumor incidence of 11% in males and 10% in females. Since the difference was not significant, the authors concluded that methylhydrazine was not carcinogenic in mice.

Several weaknesses are apparent in these two studies [78,81]. Considering the number of animals, total dose used, and the latent period observed by Toth [80], the validity of the conclusion by Kelly et al [81] and Roe et al [78] that methylhydrazine is not carcinogenic in mice is questionable. Furthermore, the authors did not mention if tumors had occurred in tissues other than the lungs. In both cases, a significant number of animals apparently were not examined.

In 1973, Toth and Shimizu [106] studied the tumorigenicity of methylhydrazine in Syrian golden hamsters. Groups of 50 male and 50 female hamsters were given 0.01% methylhydrazine, prepared three times a week, in their drinking water for life starting at 6 weeks of age. On the average, the males received 1.1 mg/day of methylhydrazine and the females received 1.3 mg/day. There were 100 males and 100 females in the control group.

Sixteen female hamsters (32%) developed malignant histiocytomas of the liver (Kupffer cell sarcoma) at an average age of 70 weeks (range 46-92) [106]. In males, 27 (54%) developed malignant histiocytomas of the

liver at an average age of 78 weeks with a range of 47-103 weeks. In addition, these animals had six tumors in the lungs, two in the lymph nodes, and two in the spleen. Nine females (18%) developed tumors of the cecum at an average age of 64 weeks (range 50-76). Seven of these animals had nine polypoid adenomas, one had a polypoid adenoma and an adenocarcinoma, and one had two adenocarcinomas. In males, seven (14%) developed nine tumors of the cecum: five had a total of six polypoid adenomas, one had a polypoid adenoma and an adenocarcinoma, and another had an adenocarcinoma. In the controls, one female and one male each developed one polypoid adenoma.

In 1975, a study [107] on the effects of methylhydrazine in Syrian golden hamsters was reported. Methylhydrazine, prepared daily, was administered in the drinking water to 5-month-old hamsters for life. Preliminary experiments indicated that methylhydrazine was not stable in tapwater unless the pH was adjusted. Therefore, 30 hamsters received 0.01% methylhydrazine in tapwater, 30 received it in tapwater adjusted to pH 3.5, and 17 had their drinking water adjusted to pH 3.5.

Four tumors, all adrenocortical, were found in three controls (23% of 13 survivors) [107]. Four tumors in 4 animals given the unbuffered solution (16% of 25 survivors) consisted of an adrenocortical carcinoma, a hemangioendothelioma, and 2 carcinomas of the liver. Six tumors in 5 animals given the buffered solution (20% of 25 survivors) were classified as adrenocortical carcinomas, a melanoma and a cutaneous histocytoma. By comparing the overall tumor incidences, the authors concluded that methylhydrazine was noncarcinogenic under these experimental conditions.

This conclusion [107] is in disagreement with that reached by Toth and Shimizu [106]. There were differences in the preparation of the chemicals and the ages of hamsters at the beginning of the experiments, which could have contributed to the conflicting results.

In a study of the teratogenic effects of some hydrazine derivatives, Chaube and Murphy [108] gave single ip injections of methylhydrazine sulfate at various doses to 23 pregnant rats on the 12th day of gestation and killed them on the 21st day. The authors estimated an LD50 in dams to be 80 mg/kg. In the pups, there were no abnormalities in the palate, appendages, paws, tail, or jaws. The authors concluded that methylhydrazine was not teratogenic. No additional details of the experiment were reported, so there is insufficient information to draw any conclusions beyond those of the authors.

In a 1976 study by Greenhouse [91], previously discussed for hydrazine, the teratogenic effects of methylhydrazine on South African clawed toad embryos were investigated. Embryos were cultured in an aqueous solution of methylhydrazine at various concentrations up to 15 mg/liter. At 3, 5, 10, and 15 mg/liter, 1, 52, 93, and 100%, respectively, of the exposed embryos were malformed. The malformations observed were similar to those caused by hydrazine, and their appearance was independent of concentration. Greenhouse concluded that methylhydrazine was teratogenic in toad embryos.

Brusick and Matheson [109], in 1976, described the results of four tests of the mutagenicity of methylhydrazine: (1) in vitro microbial assays (Ames tests) with five mutant strains of Salmonella typhimurium, an Escherichia coli strain, and a strain of Saccharomyces cerevisiae; (2) an

in vitro mutation assay with cultured mouse cells; (3) an assay for unscheduled DNA synthesis in cultured human diploid cells; and (4) a dominant-lethal assay in mice. In all but the dominant-lethal assay, the tests were run both with and without mouse liver microsomes, a procedure to evaluate the possible effect of metabolic activation of methylhydrazine to a more powerful mutagen. Both positive and negative controls were run in all assays.

In the Ames test, concentrations of methylhydrazine ranging from 0.0001 to 5.0 μl/plate produced negative results with the mutant S. typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100, and with the E. coli and S. cerevisiae strains in standard plate tests [109]. These negative results were obtained both with and without microsomal activation. However, when TA-1535 cells were incubated with liver microsomes and 1 or 5 μl/ml of methylhydrazine in suspension tests and assayed for revertant cells, mutagenic activity was demonstrated. When L5178Y mouse lymphoma cells were incubated with methylhydrazine in nonactivation and activation tests, no mutations were found.

Unscheduled DNA synthesis was evaluated in normal human diploid WI-38 cells in tissue culture, and 3H thymidine was incorporated into DNA to follow the synthesis [109]. Methylhydrazine had no mutagenic activity in either nonactivation or activation assays at concentrations of 0.1, 0.5, and 1.0 μl/ml.

In the dominant-lethal test, 10 male ICR mice each were given methylhydrazine ip at 0.26, 0.86, and 2.60 mg/kg for 5 days and 10 male rats (strain unstated) were similarly given methylhydrazine at 0.215, 0.72, and 2.5 mg/kg. Two days after the last dose, each mouse was caged with two

virgin females for 5 days. The mating schedule was repeated with two new females each week for 7 weeks. Fourteen days after the middle of the mating period, each female was killed and examined for number of living and dead fetuses. There were no significant trends showing that methylhydrazine produced mutation by this test.

The authors [109] concluded that methylhydrazine showed no mutagenic activity in any of the tests used, except in an activation-suspension assay with Salmonella typhimurium T-1535.

(c) 1,1-Dimethylhydrazine

(1) Systemic Effects

Jacobson et al [20], in 1955, investigated the acute inhalation toxicity of some methylated hydrazine derivatives. Rats, mice, and hamsters were exposed to 1,1-dimethylhydrazine for a single 4-hour exposure in an experiment identical to that reported earlier for hydrazine. Toxic signs were the same as those produced by exposure to hydrazine, and LC50 values were calculated to be 252 ppm (618 mg/cu m) for rats, 172 ppm (423 mg/cu m) for mice, and 392 ppm (962 mg/cu m) for hamsters.

Groups of three male beagles were also exposed to 1,1-dimethylhydrazine at 24-111 ppm (59-272 mg/cu m) [20]. Two dogs exposed to 1,1-dimethylhydrazine at 111 ppm had convulsions and died within 192 minutes, and the third dog, near death, was killed for examination. All three dogs vomited and convulsed, two panted, and one had diarrhea. One dog exposed to 1,1-dimethylhydrazine at 52 ppm for 4 hours was killed when near death 1 day after exposure. The other two animals survived; one showed panting, nausea, and incoordination, while the other showed no toxic signs. All dogs exposed at 24 ppm for 4 hours survived, but one vomited

and convulsed. All five surviving dogs were killed on day 14 and necropsies were performed. Results of blood counts, sulfobromophthalein retention, and prothrombin time were normal. Gross examinations of tissue from dogs, rats, and mice showed pulmonary edema and some instances of patchy pulmonary hemorrhage. No other significant change was found.

In 1960, Rinehart et al [110] reported the effects of long-term inhalation of 1,1-dimethylhydrazine on male Wistar rats, female CF-1 mice, and male beagle dogs. All exposures were for 6 hours/day, 5 days/week. Twenty rats and 30 mice were exposed to 1,1-dimethylhydrazine at 140 ppm (342 mg/cu m) for 6 weeks (4,200 ppm-hours/week), and 30 rats and 30 mice were exposed at 75 ppm (183 mg/cu m) for 7 weeks (2,250 ppm-hours/week). Two groups of three dogs, each animal weighing about 11.4 kg, were exposed at 25 ppm (61 mg/cu m) for 13 weeks (750 ppm-hours/week) or 5 ppm (12.2 mg/cu m) for 26 weeks (150 ppm-hours/week).

Rats and mice had occasional tremors during exposure, and those that died had tonic-clonic convulsions [110]. At 342 mg/cu m, 29 of 30 mice and 1 of 20 rats died, and the others gained weight at a slower rate than did controls during the first 2 weeks. At 183 mg/cu m, 8 of 20 mice died within 5 weeks, while the only toxic signs observed in rats were breathing difficulty and lethargy.

During the 3rd day of exposure to 1,1-dimethylhydrazine at 61 mg/cu m, the dogs showed signs of toxicity, including depression, increased salivation, vomiting, diarrhea, incoordination of the hindlegs, tonic-clonic convulsions, hyperemic oral and conjunctival membranes, bradycardia, and fever [110]. One dog died, one had all the toxic signs, and the third

showed only depression and increased salivation. During 13 weeks of exposure, the two survivors lost 2.5 kg of weight, compared with 0.2 kg in three control dogs. No severe toxic signs were observed in the dogs exposed to 1,1-dimethylhydrazine at 12.2 mg/cu m, but an average weight loss of 0.8 kg compared with the controls was noted.

After 4 weeks of exposure to 1,1-dimethylhydrazine at 61 mg/cu m, dogs appeared to have hemolytic anemia, since erythrocyte counts were decreased by 58%, hematocrit values by 28%, and hemoglobin concentrations by 34% [110]. Hematocrit and hemoglobin values later approached preexposure values, but erythrocyte counts remained depressed. Since the blood was first examined at the 4th week of exposure, the time of onset of the blood abnormalities was uncertain. Bilirubin, blood nonprotein nitrogen, blood glucose level, and sulfobromophthalein retention time were all normal throughout the experiment. Dogs exposed at 12.2 mg/cu m had similar evidence of hemolytic anemia after 24 weeks, a 26% decrease in hemoglobin concentration, an 18% decrease in hematocrit value, and a 17% decrease in erythrocyte count. The mean bilirubin level was elevated.

Microscopic examination of the rodent tissues showed no morphologic alteration that could be attributed to 1,1-dimethylhydrazine [110]. Dogs that survived the exposure at 61 mg/cu m showed hemosiderosis of the reticuloendothelial system, including the spleen, lymph nodes, bone marrow, and Kupffer cells of the liver. The bone marrow had significantly increased erythrocytic activity. The lung tissue of the dog that died during exposure at 61 mg/cu m showed alveolar hemorrhaging, emphysema, and collapse but no hemosiderosis. Dogs exposed at 12.2 mg/cu m showed hemosiderosis only in the spleen; no other tissue abnormalities were noted.

The authors [110] concluded that 1,1-dimethylhydrazine at concentrations of 5 ppm (12.2 mg/cu m) or greater was toxic, that the most prominent sign of toxicity in dogs was hemolytic anemia, and that, for humans, 1,1-dimethylhydrazine concentrations should be kept well below 5 ppm. They suggested 0.5 ppm (1.22 mg/cu m) as a guideline for industrial practice.

The toxicity from single, brief exposures to 1,1-dimethylhydrazine vapor for rats and dogs was examined by Weeks et al [111]. Male rats and mongrel dogs were exposed for 5, 15, or 60 minutes and rats alone were exposed for 30 minutes. Selected rats from each group were killed for examination immediately after exposure or 1, 3, or 7 days later. Similarly, dogs were killed immediately or after 7, 14, or 21 days. No microscopic changes were found in tissue samples from either the dogs or the rats. The LC50's for all the groups are given in Table III-1. Ten additional rats were exposed to 1,1-dimethylhydrazine at 1,000 ppm for 60 minutes, and their blood counts were normal following exposure.

The authors [111] noticed that sharp noises made the dogs exposed to 1,1-dimethylhydrazine shiver and cower. Consequently, dogs were exposed for single 5-, 15-, and 60-minute periods at various fractions of the LC50 values of 1,1-dimethylhydrazine. Auditory, visual, and electrical stimuli were added at 15 minutes, 1 hour, and 2 hours thereafter to evaluate the role of external stimulation. The external stimuli added stress to the exposed animals and seemed to magnify or perhaps hasten the development of toxic signs.

Weeks et al [111] also estimated the retention of 1,1-dimethylhydrazine in six pentobarbital-anesthetized dogs. Each animal was exposed through an endotracheal tube or a face mask to 1,1-dimethylhydrazine at 2,900-19,600 mg/cu m for 60 minutes. It was reported that 71-93% of the 1,1-dimethylhydrazine inhaled was retained in the respiratory tract by the dogs.

Weeks et al [111] further investigated the effects of multiple exposure to 1,1-dimethylhydrazine on conditioned avoidance tests. Groups of four dogs each were exposed twice a week for 6 weeks to 1,1-dimethylhydrazine at 50, 200, or 600 ppm for 60, 15, and 5 minutes, respectively. All animals were observed for toxic signs and reflex reactions. No changes from normal were noted in the conditioned avoidance test, and there were no alterations in the patellar, extensor thrust, and hopping reflexes. Doubling the exposure concentrations of the three groups of dogs for 2 additional weeks had no effect on the conditioned avoidance responses, and no changes were noted in neurologic and physical examinations, even though signs of intoxication appeared after the first exposure.

Back et al [112], in 1977, reported the results of 6-month inhalation exposures of C57 black mice, Fischer 344 rats, Syrian golden hamsters, and beagle dogs to 1,1-dimethylhydrazine at 5, 0.5, or 0.05 ppm. At each concentration, 400 female mice, 200 male rats, 200 male hamsters, and 4 dogs of each sex were exposed for 6 hours/day, 5 days/week. An equal number of animals of each species was maintained as controls. Necropsies were performed on all animals that died, and a series of blood measurements and clinical tests were conducted on dogs.

No toxic sign was observed in any animal exposed to 1,1-dimethylhydrazine [112]. The results of clinical chemistry tests were all normal except for SGPT activity and BSP retention. The SGPT values were significantly elevated ($P<0.01$) in dogs exposed at 5 ppm, but they returned to normal 6 months after exposure ended. At 0.5 ppm, fairly frequent increases ($P<0.05$) in SGPT were observed, although the degree of elevation was less than that seen in the 5-ppm group. BSP retention was measured at the end of exposure, and only those exposed at 5 ppm had significantly elevated values ($P<0.05$). These values returned to normal 9 months after exposure ended. The authors [112] stated that the significant effects of 1,1-dimethylhydrazine were limited to slight to moderate hepatotoxicity in dogs exposed at 5 ppm (150 ppm-hours/week) after 6 months of exposure.

Haun [113] reported that in the previous study [112], 1,1-dimethylhydrazine was contaminated with 0.12% nitrosodimethylamine. The author examined the effects of this contaminant by preparing pure 1,1-dimethylhydrazine. Four beagles were exposed to this purified compound at 5 ppm, 6 hours/day, 5 days/week for 8.5 weeks. Four dogs were used as controls. Liver biopsies were taken and the dogs rested 5 days. Then the dogs were exposed to the purified 1,1-dimethylhydrazine at 5 ppm continuously for 13 days. Immediately following the second exposure, two controls were exposed to 1,1-dimethylhydrazine to which 0.12% nitrosodimethylamine had been added. Two dogs, previously exposed to pure 1,1-dimethylhydrazine, were used as controls. Various clinical tests, including measurement of SGPT activity, were performed both before and during exposure. BSP retention times were determined at the beginning and end of the study.

There was no elevation of SGPT activity from either intermittent or continuous exposure to 1,1-dimethylhydrazine, except when the contaminant, nitrosodimethylamine, was also present [113]. In all cases, BSP retention times were unaffected. The author concluded that nitrosodimethylamine was the active agent producing increased SGPT levels, even though the level tested was insufficient to cause discernible hepatocellular changes or alterations in liver function.

A study by Rothberg and Cope [58] on the acute toxicity of hydrazines included the effects of 1,1-dimethylhydrazine. The LD50's for 1,1-dimethylhydrazine in rabbits were found to be 89.2 μl/kg (69.8 mg/kg) by the iv route and 1.05 g/kg by percutaneous absorption. In guinea pigs, the LD50 for skin absorption was 1.31 g/kg. There was no evidence of skin damage. When 3 μl of 1,1-dimethylhydrazine was applied to the eyes of two rabbits, only mild conjunctivitis and slight erythema of the eyelid developed.

Hodge [114], in 1954, reported the results of acute toxicity tests of 1,1-dimethylhydrazine. The oral LD50 in female rats was found to be 0.46 ml/kg (360 mg/kg). 1,1-Dimethylhydrazine was applied to the clipped bellies of rabbits and prevented from evaporating by a watch glass. It was lethal at 156 mg/kg but was tolerated at 23 mg/kg. When six rats inhaled 1,1-dimethylhydrazine at a concentration of 18.4% (v/v), all died within 35 minutes. The effects of 1,1-dimethylhydrazine on eyes were investigated by instilling 2 drops (about 0.05 ml) of the compound into the right eye of a rabbit; only slight vascularization of eyelids, without any evidence of corneal injury, was observed. When 0.01 ml (7.8 mg) of 1,1-dimethyl-

hydrazine was given intracutaneously to a rabbit, no skin irritation was found.

Smith and Clark [115] investigated the dermal absorption of 1,1-dimethylhydrazine in dogs. 1,1-Dimethylhydrazine at doses of 5-30 millimoles/kg (300-1,800 mg/kg) was applied to a 15- x 20-cm shaved area on the chest of 13 anesthetized mongrels. Glucose and 1,1-dimethylhydrazine concentrations in the blood and urine were measured hourly for 6 hours after 1,1-dimethylhydrazine application. The reduced glutathione content and glutathione peroxidase activity of erythrocytes were also estimated at hourly intervals. Two control animals were used to determine normal blood and urinary glucose concentrations.

1,1-Dimethylhydrazine spread rapidly and evenly over the surface [115]. A slight reddening developed within 10-15 minutes of application and quickly disappeared, leaving no sign of skin damage. Six of the dogs died about 6 hours after application. The dermal LD50 for 1,1-dimethylhydrazine was estimated to be 1,200-1,680 mg/kg. Mild clonic convulsions were seen in three dogs, and these convulsions were not always followed by death.

Skin application of 1,1-dimethylhydrazine at all doses tested produced detectable concentrations of the compound in the blood within 30 seconds; however, neither blood nor urine concentrations of 1,1-dimethylhydrazine were dose-dependent [115]. All tested doses of 1,1-dimethylhydrazine caused mild hyperglycemia for 5-6 hours with a corresponding increase in urinary glucose. No effect was seen on reduced glutathione content in erythrocytes. Glutathione peroxidase activity decreased after the two lowest doses were given, remained stable at the

midlevel dose, and increased at the highest dose and during the hour preceding death, regardless of the dose. The authors concluded that 1,1-dimethylhydrazine was toxic if applied dermally but that its mode of action was in biochemical systems other than those tested in their experiment.

O'Brien et al [96] determined the LD50 of 1,1-dimethylhydrazine in rats and studied its effects on carbohydrate metabolism. Ninety-four female rats, weighing 180-240 g, were given 1,1-dimethylhydrazine ip at doses of 50-408 mg/kg. The LD50 was estimated to be 102 mg/kg; this dose also induced the maximum number of convulsions. Higher doses led to a decrease in the time to onset of convulsions, the time between convulsions, and the time to death. Hyperglycemia was also found in two rats given an LD50 dose of 1,1-dimethylhydrazine, the blood glucose increasing from 80 to 160 mg/100 ml in 80 minutes.

In 1964, Cornish and Barth [116] studied the effects of practical grade 1,1-dimethylhydrazine on urinary amino acid and creatinine excretion in male Sprague-Dawley rats. In groups of four rats each receiving 1,1-dimethylhydrazine ip at 40, 60, or 80 mg/kg, creatinine nitrogen values were relatively constant for any given rat and were not affected by 1,1-dimethylhydrazine. Amino acid nitrogen excretion, however, was increased on the 1st day after injection. When the amino acid nitrogen-to-creatinine ratios were calculated, the initial enhanced excretion of amino acid was followed by a period of decreased excretion; by day 5, the ratios were only 74-77% of those of controls. Paper chromatography showed that there were no abnormalities in the relative amounts of individual amino acids excreted. The authors speculated that the observed increase in amino acid excretion could have been caused by interference with amino acid

metabolism, protein synthesis, or gluconeogenesis. Toxic effects on the kidneys could not be ruled out, but examined tissue samples and SGOT activity were normal, so the authors did not believe that the effect was produced by tissue damage.

Patrick and Back [60] described the toxicologic effects of repeated injections of practical grade 1,1-dimethylhydrazine in 1965. Seven Rhesus monkeys, weighing 3.2-3.5 kg, each received 10 mg/kg of 1,1-dimethylhydrazine ip daily, 5 days/week, for 4 weeks. The only observed toxic effect was an initial weight loss of 0.2-0.8 kg, and the only abnormal finding in the blood was a 90% increase in the plasma glucose level. There was slight lipid deposition near the central vein in the liver of one monkey and in the tubular membranes of the kidneys of a second animal. Significant amounts of lipids were found in the heart muscle of two monkeys; there were trace amounts in two others.

In 1969, Cornish and Hartung [117] reported the effects of repeated administration of 1,1-dimethylhydrazine to rats. Groups of 10 female Sprague-Dawley rats with an average weight of 225 g were given daily ip injections of 0, 10, 30, 50, or 70 mg/kg of 1,1-dimethylhydrazine for 3 weeks. Body weights and urine from seven animals in each group were taken daily; at necropsy, organs were weighed and tissue samples from two rats in each group were examined.

All the rats receiving 18 daily injections of 1,1-dimethylhydrazine at 10 mg/kg survived. The numbers of animals surviving 21 injections of 30, 50, and 70 mg/kg were 5, 4, and 1, respectively [117]. All deaths occurred during the first 3 days. There was an initial dosage-related weight loss of 10-20 g in the animals that received 10, 30, or 50

mg/kg/day, but the organ-to-body weight ratio remained normal. Daily injections of 30 mg/kg or more of 1,1-dimethylhydrazine resulted in substantial and sustained diuresis throughout the experiment; the total urine output in these rats was more than twice that of the controls. A low white cell count occurred only in the one survivor of the 70-mg/kg group. Animals receiving 10 or 30 mg/kg/day had mean blood urea nitrogen (BUN) values similar to those of controls (about 15 mg/100 ml), but in the animals given 50 mg/kg/day, the BUN value increased about 70%. 1,1-Dimethylhydrazine administration caused a dose-dependent increase in SGOT activity. The average SGOT activities for the animals receiving 0, 10, 30, 50, and 70 mg/kg/day were 47.2, 63.7, 79.8, 80.5, and 124 units, respectively. Cloudy swelling and lipid infiltration were found in the renal tubules of the only surviving animal that received 70 mg/kg/day; less pronounced changes were observed at 50 mg/kg/day. Early degenerative fatty infiltration was found in the liver of the 70-mg/kg/day survivor; some control animals also showed similar changes.

In 1966, Wong [61] examined the effects of 1,1-dimethylhydrazine on the renal function of female mongrels. Creatinine and glucose were administered as described earlier for hydrazine to both the control and experimental groups, each containing six dogs [61]. 1,1-Dimethylhydrazine was given iv to the experimental animals at 45 mg/kg. From 20-120 minutes after administration, the control and experimental creatinine clearance values were roughly the same, approximately 56 ml/minute. From 120-240 minutes, the experimental group showed about a 10% elevation in creatinine clearance. No significant effect on urinary glucose resorption rates (approximately 170 mg/minute) was seen. The author found that 45 mg/kg of

unbuffered 1,1-dimethylhydrazine produced no harmful effects in the kidneys that could be seen by the two tests used.

Another study by Van Stee [62], in which inulin and para-aminohippurate clearance rates were measured, also indicated that 1,1-dimethylhydrazine caused no significant changes in the renal function of dogs. However, three of eight dogs died with severe pulmonary edema and subsequent circulatory failure within 2 hours after being given 1,1-dimethylhydrazine.

In 1962, Reynolds et al [118] performed three experiments on Java monkeys to assess the effects of 1,1-dimethylhydrazine on shock avoidance. Before the experiments, the monkeys were trained in a shock avoidance test and matched according to performance. In the first experiment, two monkeys received 1,1-dimethylhydrazine ip at 30 mg/kg, the threshold dose for vomiting. Two control animals received saline injections. Eight 15-minute test sessions, given hourly, began 20 minutes after injection. In the second experiment, 3 weeks later, the same test procedure was repeated with the control and experimental groups reversed. In another experiment, performed 60 days after the second experiment, three of the above monkeys and one new one served as the experimental group, and the other monkey and two new ones were controls. In all experiments, the number of lever-presses/minute was used to measure shock avoidance. McNemar's comparison of change statistic was used to evaluate the results.

No controls in any experiment showed significant performance changes after saline injection [118]. The first experimental group had significantly more lever-presses/minute ($P<0.001$) than did either the controls or the experimental group themselves before injection. In the

second and third experiments, no significant differences between the control and experimental groups were observed. One monkey in the third experiment had a significantly poorer performance ($P<0.05$); all others were normal.

In a second experiment, Reynolds and coworkers [119] administered 1,1-dimethylhydrazine ip at 30 mg/kg to four adult male Java monkeys trained to perform different and more difficult tasks from those in the previous study [118]. Two 2-day tests were conducted, with an intervening 1-day rest period [119]. The monkeys were given a saline injection on the 1st day and 1,1-dimethylhydrazine on the 2nd day. On each test day, 3-minute work and 2-minute rest periods were alternated and repeated for six to nine sessions. Performances on lever press, discrete avoidance, auditory monitoring, and visual monitoring were tested.

Although all monkeys developed toxic signs such as gagging, coughing, and vomiting, there were wide differences in individual responses on the performance tests [119]. Of the 32 possible performance combinations of 4 monkeys, 2 injections, and 4 performance tasks, only 8 cases of significant performance decrement ($P<0.05$) were observed. Six of eight cases occurred 3-3.5 hours after the second test replication, when the monkeys were ill. In all other cases, the monkeys performed normally, although some showed toxic signs. Both clinical illness and performance impairment disappeared between 6 and 9 hours after injection.

Thus, it appears that the impaired performance from 1,1-dimethylhydrazine intoxication was probably associated with the illness because it occurred earlier than did the performance decrement. It may be that repeated exposure to 1,1-dimethylhydrazine would more greatly affect

primate behavior, since almost all impaired performances were observed after the second injection.

(2) Metabolism

In 1962, Mitz et al [120] studied the metabolism of 1,1-dimethylhydrazine. Six female Sprague-Dawley rats were given 14C-labeled 1,1-dimethylhydrazine ip at 40 mg/kg. Three animals were killed 30 minutes after injection and the remaining three after 4 hours. The brain, kidneys, liver, heart tissue, and carcass, as well as blood and urine samples, were analyzed for radioactivity. Approximately 19% of the injected dose was found in the urine after 4 hours. The liver and blood after 4 hours contained 3.7 and 2.7% of the injected 1,1-dimethylhydrazine, respectively; the other organs tested each had less than 1%. Since the remaining carcass contained only 51.2% of the radioactivity, a total recovery of 77.7% was reported. The distribution of 1,1-dimethylhydrazine 30 minutes after injection was similar but there was less radioactivity in the urine (5.7%), and it was higher in the carcass (75.8%). The authors did not give specific data for dogs but stated that dogs showed the same pattern observed in the rats. The authors also found that only about 2% of the injected radioactivity was lost by respiration. Analysis of the radioactive compounds in the urine confirmed the presence of three major metabolites. However, only two metabolites were identified. One was 1,1-dimethylhydrazine constituting 50-60% of the total radioactivity, and another 3-10% was glucose dimethylhydrazone.

Reed and associates [121] studied the metabolism and distribution of 1,1-dimethylhydrazine and the effects of this agent on glucose catabolism in Sprague-Dawley rats. For the metabolic studies, rats were injected ip

with 14C-labeled 1,1-dimethylhydrazine at 20, 40, and 60 mg/kg and at 11 mg/kg for the distribution studies. For glucose catabolism studies, rats were administered 1.5 grams of glucose twice, 9 hours apart, by stomach tube. For the second administration, glucose was labeled with 14C at the first, second, third, fourth, or sixth position. The rats were simultaneously injected ip with 1,1-dimethylhydrazine at 40-60 mg/kg.

Seven hours after labeled 1,1-dimethylhydrazine administration, 23% of the original dose of 20 mg/kg was recovered as 14C carbon dioxide in the respired air, while 19 and 12% were recovered from the 40 and 60 mg/kg injection, respectively [121]. When rats were injected with labeled 1,1-dimethylhydrazine at 11 mg/kg, 12% was converted to respired carbon dioxide in 4 hours. About 25% of this dose was distributed in the body, while 43% was excreted in the urine in 4 hours. There was little, if any, preferential tissue uptake of 1,1-dimethylhydrazine.

In the glucose catabolism studies, 14C carbon dioxide formation from different carbon atoms of glucose was altered by the administration of 1,1-dimethylhydrazine [121]. 1,1-Dimethylhydrazine preferentially inhibited glucose catabolism to carbon dioxide via glycolysis and the pentose phosphate pathway. A decarboxylation process of the sixth carbon, the glucuronate pathway, appeared to be unaffected by 1,1-dimethylhydrazine.

There appears to be some conflicting data reported by Mitz et al [120] and by Reed et al [121]. Although rats were similarly given an ip injection of 1,1-dimethylhydrazine at 40 mg/kg, Mitz et al found that only 2% was excreted in respired air, while Reed et al found that 19% was expired as carbon dioxide in 7 hours. Reed et al used a more elaborate system to measure labeled carbon dioxide and used more rats in the

experiment, so their data would seem to be more reliable.

Back et al [122] studied the absorption, distribution, and excretion of 1,1-dimethylhydrazine in a number of species. Twelve albino rabbits weighing 1.7-4.4 kg each were given 14C-labeled 1,1-dimethylhydrazine iv at 50 mg/kg. Two rabbits each were killed at intervals from 2 to 24 hours after injection to determine the amount of radioactivity in major organs. There was no preferential concentration of 1,1-dimethylhydrazine in any of these organs, and retention remained high even at 24 hours. At 2 hours, 28.3% of the dose could be accounted for, while 14.7% was accounted for at 24 hours. Urine and tissue representing the bulk of the body weight were not analyzed, and this factor probably accounted for the low recovery.

To study the concentration of 1,1-dimethylhydrazine in the blood and urine, the authors gave 14C-labeled 1,1-dimethylhydrazine ip at 50 mg/kg to two dogs and two cats [122]. Fifteen to 60 minutes after injection, the amount of radioactivity in the blood reached a maximum that was about 13-14% of the original dose for dogs and 7-9% of that for cats. About half of this radioactive material was unchanged 1,1-dimethylhydrazine. As much as 30-50% of the radioactive compound, believed to be unchanged 1,1-dimethylhydrazine, was excreted in the urine during the first 5 hours after injection. The percentage of the dose recovered in urine was similar for cats and dogs given 50 mg/kg of unlabeled 1,1-dimethylhydrazine iv, but in cats given 10 mg/kg only 11-28% was recovered in the urine in 6 hours.

As part of the same study [122], a number of rats, cats, dogs, and monkeys were injected ip with unlabeled 1,1-dimethylhydrazine at 1-100 mg/kg, and the plasma concentrations of 1,1-dimethylhydrazine were determined colorimetrically. 1,1-Dimethylhydrazine at doses of less than

10 mg/kg could not be detected in the plasma of monkeys. There was considerable individual variation, so that plasma concentrations were not a good indicator of dose. For example, 1 hour after injection, plasma concentrations of 1,1-dimethylhydrazine were 0.5-11.5 μg/ml and 6.5-16.0 μg/ml in rats given 10 and 30 mg/kg, respectively. There was, however, a good correlation of the average concentration for a group with time. For example, in 15 monkeys given 100 mg/kg of 1,1-dimethylhydrazine, the average plasma concentrations at 1, 2, and 4 hours after injection were 70.4, 52.9, and 33.9 μg/ml, respectively.

These experiments showed that 1,1-dimethylhydrazine was not preferentially concentrated in specific organs. Exposure was not accurately determinable from the 1,1-dimethylhydrazine concentration in blood; urinary concentration was a more sensitive indicator of exposure to 1,1-dimethylhydrazine.

(3) Carcinogenicity and Effects Related to Reproduction

In 1973, Toth [123] reported on tumor formation in random-bred Swiss mice after oral administration of 1,1-dimethylhydrazine for life. A 0.01% solution of 1,1-dimethylhydrazine in drinking water was given ad libitum to 50 male and 50 female mice starting at 5 weeks of age. The average daily intake of 1,1-dimethylhydrazine was 0.7 mg. The controls were 110 male and 110 female mice from a similar colony as reported in an earlier study [79].

The ingestion of 1,1-dimethylhydrazine in the drinking water significantly shortened the survival time of the experimental group [123]. At 60 weeks, only 13 male (26%) and 23 female (46%) mice given 1,1-dimethylhydrazine were still alive, compared with 55 male (50%) and 89

female (81%) control mice. Of the females given 1,1-dimethylhydrazine, 37 (74%) developed blood vessel tumors at an average age of 59 weeks (range 41-76). Forty-two of the experimental males (84%) developed blood vessel tumors at an average age of 42 weeks (range 35-66). There were 78 blood vessel tumors, characterized as angiosarcomas, found in the liver, 18 in the muscles, 11 in the heart, 7 in the lungs, 4 in the fat, 3 in the subcutis, and 1 each in the glandular stomach, the pancreas, and pararenal tissue.

Thirty-two (64%) of the female mice given 1,1-dimethylhydrazine developed 103 lung tumors, 96 of which were adenomas; 6 of these animals had, in addition, 7 adenocarcinomas [123]. The average age for tumor development was 62 weeks (range 44-76). In the exposed males, 39 (78%) developed 119 lung tumors; they had a total of 115 adenomas and 4 of them also had an adenocarcinoma. The average age at which lung tumors were observed was 53 weeks (range 40-66).

Only one female mouse given 1,1-dimethylhydrazine developed a kidney tumor, which appeared at 60 weeks of age [123]. Of the experimental males, 9 developed 11 kidney tumors at an average age of 59 weeks (range 42-66). Microscopically, some of these tumors were classified as cystic-papillary adenomas; others had developed into the solid form. Six males given 1,1-dimethylhydrazine developed benign hepatomas at an average age of 58 weeks (range 46-66).

In exposed females, seven malignant lymphomas were observed, an incidence of 14% [123]. These tumors occurred when the mice were 26-74 weeks of age, with an average of 55 weeks. Microscopically, six lymphomas were classified as one lymphocytic type, one mixed lymphocytic and

histocytic type, and four histocytic types; one could not be classified. One such tumor, first seen in exposed males aged 61 weeks, was classified microscopically as lymphocytic.

In summary, the tumor incidences in the blood vessels, lungs, kidneys, and liver were 79, 71, 10, and 6%, respectively [123]. Corresponding incidences in nonconcurrent controls were 2, 11, 0, and 0%.

Roe et al [78] also examined the carcinogenicity of 1,1-dimethylhydrazine. Virgin female Swiss mice were given 1,1-dimethylhydrazine by gavage at 0.5 mg/day, 5 days/week, for 40-60 weeks. There were 28 experimental mice and 85 controls. Necropsies were performed on some mice at 40-50 weeks, and there were two lung tumors in one of eight animals examined. There were 24 tumors in 4 of 9 animals examined at 50-60 weeks. The control group had 2 tumors in 2 of 37 animals at 40-50 weeks and 9 tumors in 6 of 42 animals at 50-60 weeks. The tumors were classified as alveologenic or bronchiologenic adenomas or adenocarcinomas. The incidence of tumors in mice given 1,1-dimethylhydrazine was not statistically greater at the 95% confidence level than that observed in the controls. However, some mice developed multiple tumors, and the authors concluded that this finding supported the view that 1,1-dimethylhydrazine was tumorigenic. No mention was made of any studies on the fate of the remaining nine mice, so their cause of death is unknown, and possible tumors in other organs were not identified.

Kelly et al [81], in 1969, reported the results of a study on the carcinogenicity of hydrazine compounds, including 1,1-dimethylhydrazine. Thirty CDF1 male mice, aged 7-8 weeks, were given 1,1-dimethylhydrazine in 8 weekly ip injections totaling 3.6 mg (120 mg/kg), and 30 females of the

same age were given 8 oral doses totaling 7.2 mg (277 mg/kg). A group of 10 males and 10 females given saline served as controls. After 28-32 weeks, 1 of the 25 females (4%) examined and 1 of the 30 males (3%) developed lung tumors, while the controls had a tumor incidence of about 10% in both sexes. The authors, therefore, concluded that 1,1-dimethylhydrazine was not carcinogenic in mice. While these results would appear to conflict with those of Toth [123] and Roe et al [78], the first lung tumor did not occur in Toth's study [123] until 35 weeks after administration, with the average latent period being 48 weeks, an experimental period longer than that used by Kelly et al [81]. The total dose used by Toth [123] was also much higher than that used by Kelly et al [81].

In 1976, Greenhouse [90] investigated the effects of several hydrazines, including 1,1-dimethylhydrazine, on the development of embryos of the South African clawed toad (Xenopus laevis). The animals were raised in aquatic media containing various concentrations of the test compounds. 1,1-Dimethylhydrazine at concentrations up to 1 mg/liter was neither toxic nor teratogenic to the exposed embryos, but at 10 mg/liter, 1,1-dimethylhydrazine was teratogenic to all embryonic stages (cleavage, gastrulation, neurulation, and tailbud). At 100 mg/liter, 1,1-dimethylhydrazine was lethal. The most common malformations observed were foreshortening of the body and tail, tail kinks, and edema. A number of embryos also had abnormally small heads and brains. In a continuation of this study, Greenhouse [91] found that the embryos were susceptible to 1,1-dimethylhydrazine-induced teratogenicity only at the neurulation stage.

Brusick and Matheson [109] investigated the mutagenicity of 1,1-dimethylhydrazine using the same assay techniques employed for methylhydrazine. In the Ames test, 1,1-dimethylhydrazine at concentrations of 0.01, 0.1, 1, 0, and 5.0 μl/plate produced negative results with the mutant Salmonella typhimurium strains TA-1535, TA-1537, TA 1538, TA-98, and TA-100, and with Escherichia coli and Saccharomyces cerevisiae strains. These negative results were obtained without activation by liver microsomes. Except for marginally positive responses with TA-98 and possibly with TA-1538, negative responses occurred under activation conditions as well.

L5178Y mouse lymphoma cells were incubated with 0.01, 0.05, 0.1, and 0.25 μl/ml of 1,1-dimethylhydrazine in the nonactivation tests and 0.005, 0.01, 0.05, and 0.1 μl/ml of 1,1-dimethylhydrazine in the activation tests [109]. A moderate dose-related response occurred in the nonactivation trials. In the activation tests, a 15-fold increase in mutation frequency occurred at the highest concentration of 1,1-dimethylhydrazine compared with negative controls.

Unscheduled DNA synthesis was evaluated in normal human diploid WI-38 cells in tissue culture, and tritiated thymidine was incorporated into DNA to follow the synthesis [109]. There was no response without the addition of liver microsomes at 1,1-dimethylhydrazine concentrations of 0.1, 0.5, and 1.0 μl/ml, but there was a positive effect in the microsomal activation tests. In the activation tests, the positive control, 2-acetylaminofluorene, produced a 430% response while 1,1-dimethylhydrazine produced responses of 186-237%, the lowest response resulting from the

highest concentrations. The authors attributed this inverted relationship to cellular toxicity.

In the dominant-lethal test, 3 groups of 10 male ICR mice, 7-8 weeks of age, were given 1,1-dimethylhydrazine ip at 1.25, 4.2, or 12.5 mg/kg daily for 5 days [109]. Two days after the last dose, each mouse was caged with two virgin females for 5 days. The mating schedule was repeated with two new females each week for 8 weeks. Fourteen days after the middle of the mating period, each female was killed and examined for numbers of living and dead fetuses. There were no significant trends showing that 1,1-dimethylhydrazine produced dominant-lethal mutation.

(d) 1,2-Dimethylhydrazine

(1) Systemic Effects

In 1955, Jacobson et al [20] reported on the acute toxicity of 1,2-dimethylhydrazine. The LC50 was estimated to lie between 280 and 400 ppm (686 and 980 mg/cu m). The toxic signs observed were similar to those previously described for hydrazine. The authors reported that short-term exposure caused primarily respiratory irritation and convulsions.

Rothberg and Cope [58] investigated the toxicity of 1,2-dimethylhydrazine in a manner identical to that already described for hydrazine. The LD50's in rabbits were 53.0 μl/kg (43.8 mg/kg) from iv injection and 466 mg/kg by the percutaneous route. For guinea pigs, the LD50 for skin absorption was 131 mg/kg. There was no skin damage. When 3 μl of 1,2-dimethylhydrazine was placed in the eyes of two rabbits, only a mild conjunctivitis and slight erythema of the eyelid developed.

Weir et al [124], in 1964, reported on the acute toxicity of 1,2-dimethylhydrazine. Male Swiss-Webster mice were given 1,2-

dimethylhydrazine dihydrochloride ip at pH 7 to determine mortality at 24 and 168 hours. The LD50's were 940 mg/kg (425 mg/kg free base) at 24 hours and 47 mg/kg (21 mg/kg free base) at 168 hours. Some animals were hyperactive at low doses, but convulsions were observed only at doses above 750 mg/kg. Convulsions alone and violent aggression usually started 90-170 minutes after injection but death was delayed until about 48 hours except at very high doses. Mice that suffered delayed death showed decreased responsiveness and less spontaneous movement before dying. Because of the immediate and delayed signs of toxicity, the authors suggested that there might be two different toxic mechanisms involved.

Weir et al [125] later expanded their study to include the effect of the solution's pH on the toxicity of 1,2-dimethylhydrazine in mice, the LD50's for other species, and a study of hepatotoxicity. There was little difference between the LD50's in mice at 24 hours for hydrochloric acid as a control, 89 mg/kg, and unbuffered 1,2-dimethylhydrazine dihydrochloride, 83 mg/kg as the free base dose. Both solutions had a pH of less than 1.0. However, with the pH of 1,2-dimethylhydrazine dihydrochloride adjusted to 3, 7, and 11, the 24-hour LD50's were increased to 621, 462, and 245 mg/kg, respectively. This marked difference in toxicity led the authors to believe that the 24-hour toxicity of unbuffered 1,2-dimethylhydrazine dihydrochloride was largely caused by the hydrochloric acid. The 168-hour LD50's of hydrochloric acid and 1,2-dimethylhydrazine dihydrochloride, buffered or unbuffered, were similar, ranging from 32 to 54 mg/kg as the free base dose. A different mechanism from that of the 24-hour toxicity was suspected.

Weir and coworkers [125] then compared the toxicity of 1,2-dimethylhydrazine in rats and dogs to that found in mice. When male Long-Evans rats, 150-225 g, and male mongrels, 5-8 kg, were given 1,2-dimethylhydrazine dihydrochloride ip at pH 7, the immediate and delayed toxicity in mice, previously observed, was not seen. The LD50's at 24 and 168 hours, as free base doses, were 297 and 275 mg/kg for rats and 63 and 53 mg/kg for dogs.

To examine hepatotoxicity, 10 male Long-Evans rats were given 1,2-dimethylhydrazine dihydrochloride, adjusted to pH 7, ip at 495 mg/kg [125]. In addition, 2 groups of 10 male Swiss Webster mice were given 1,2-dimethylhydrazine dihydrochloride ip at 54 mg/kg unadjusted for pH or at 77 mg/kg adjusted to pH 7. Control groups were injected with distilled water. At 24, 48, 72, and 96 hours after injection, two animals from each group were killed, and liver sections were removed and studied.

The livers of experimental rats showed moderate focal necrosis of an indefinite pattern and leukocyte infiltration [125]; the degree of change was not time-dependent. The livers of mice killed 24 hours after injection of buffered 1,2-dimethylhydrazine dihydrochloride showed marked vacuolization and granularity of the cytoplasm. At 48 hours, in addition to these effects, widespread areas of focal necrosis were noted. Liver tissues of mice killed 72 and 96 hours after injection showed areas of regeneration and vacuolization but no necrosis. Unbuffered 1,2-dimethylhydrazine dihydrochloride caused more intense and persistent liver damage in mice than did the buffered form. Controls showed no liver lesions at any time.

The hepatotoxicity of 1,2-dimethylhydrazine dihydrochloride in several species was examined in 1976 by Wilson [126]. 1,2-Dimethylhydrazine dihydrochloride, at pH 7.0, was given sc and, at an unadjusted pH, it was given by gastric intubation. Four groups of 6 to 8 male miniature swine were given 8-10 weekly doses of 30 or 60 mg/kg with and without pH adjustment. Four swine served as controls. Twenty-eight male dogs received oral or sc doses of 5-60 mg/kg for 2-10 weeks for a total dose of either 50, 105, or 120 mg/kg. Two dogs served as controls. Groups of 6 male Hartley strain guinea pigs each received 60 mg/kg for 7 weekly doses or 30 mg/kg for 10 weekly doses by either route. Six guinea pigs were used as controls. Two groups of 10 male Sprague-Dawley rats were given oral doses of 30 mg/kg for 8 or 4 weekly doses. Six rats were used as controls.

In swine given 1,2-dimethylhydrazine dihydrochloride at 60 mg/kg, only three animals survived past 10 weeks [126]. All those that died earlier had hemorrhagic, hepatic degeneration and necrosis. Jaundice, bile duct proliferation, and megalocytosis were common. Most of the swine given 30 mg/kg survived, and when they were killed at 18 months, focal megalocytosis and postnecrotic fibrosis were observed in their livers. All dogs receiving 30-60 mg/kg died in the 2nd week, and all had jaundice, weight loss, hepatic degeneration, and hemorrhagic necrosis. Karyolysis in the hepatocytes was common. At 5 mg/kg, all dogs survived, but they had a transitory loss of appetite and jaundice. At 18 months, necropsies revealed postnecrotic hepatic fibrosis, hemosiderosis, and mild ascites. In guinea pigs, only one in each group receiving 60 mg/kg survived 8 months, and each had developed bile duct carcinomas. Those dying early had

extreme bile duct hyperplasia and hepatic necrosis. In the groups given 30 mg/kg, all survived at least 11 months. They were killed when near death during the next 7 months, and all had hepatic fibrosis and ascites. Nine of these animals had bile duct carcinomas, and two had hepatomas. In all groups, the experimental rats survived, but 16 of 20 developed 56 tumors of the colon. Three had carcinomas of the ear canal. The development of colon tumors was inversely related to hepatotoxicity, although the tumors might have developed in other species had they survived longer.

(2) Carcinogenicity and Effects Related to Reproduction

Kelly et al [81], in 1969, studied the effects of the hydrazines, including 1,2-dimethylhydrazine dihydrochloride, on lung tumor formation. Thirty male CDF1 mice, 7-8 weeks old, were given 1,2-dimethylhydrazine dihydrochloride in 8 weekly ip injections totaling 5.3 mg (189 mg/kg), and 30 females of the same age were given a total of 10.6 mg (424 mg/kg) by gavage over 8 weeks. A group of 10 males and 10 females given saline served as controls. Ninety percent of the females died, and at 33 weeks, one (33%) of the remaining three had lung tumors. One male died and 3 (10%) of the remaining 29 developed lung tumors. About 10% of the control males and females developed similar tumors. The authors concluded that 1,2-dimethylhydrazine was not carcinogenic in mice. However, the number of females surviving the toxicity of the compound was insufficient to draw any conclusion on long-term tumorigenic effects, and only lung tumors were examined.

In 1971, Toth and Wilson [127] reported on blood vessel tumors induced in mice by 1,2-dimethylhydrazine dihydrochloride. A 0.001% solution of the compound in drinking water was given to 50 male and 50

female randomly bred Swiss albino mice for life, starting at 7 weeks of age. The average daily intake of 1,2-dimethylhydrazine dihydrochloride was 0.058 mg for females and 0.087 mg for males. Controls consisted of 110 males and 110 females. All organs were examined macroscopically, and microscopic studies were performed on any gross, abnormal changes.

The lifespan of mice given 1,2-dimethylhydrazine dihydrochloride was considerably shortened when compared with that of the previously studied controls; 81% of the female and 50% of the male controls were alive at 60 weeks of age, while all of the exposed mice had died [127]. Subcutaneous generalized edema, hemoperitoneum, and anemia were noted in experimental mice. Forty-nine of the 50 exposed females (98%) developed blood vessel tumors at an average age of 45 weeks (range 28-58 weeks). Forty-six of the 50 males (92%) developed blood vessel tumors at an average of 42 weeks (range 29-58 weeks). The control group had a blood vessel tumor incidence of 3.6% in females and 1.8% in males at average ages of 68 and 76 weeks, respectively. The major locations of blood vessel tumors in females, in order of decreasing frequency, were 40 in the muscle, 37 in the liver, 36 in pararenal tissue, 32 in the fat, and 15 in parametrial tissues, while in the males the corresponding numbers were 39 in pararenal tissue, 37 in the muscle, 36 in fat, 28 in paraepididymal tissues, 26 in the liver, 15 in the subcutis, and 12 in the lymph nodes. The blood vessel tumors were classified as angiosarcomas.

Of the 50 females given 1,2-dimethylhydrazine dihydrochloride, 22 (44%) developed 35 lung tumors, all adenomas, at an average age of 49 weeks (range 31-58) [127]. Twelve of the 50 males (24%) developed 17 lung tumors, all adenomas except for 1 adenocarcinoma, at an age of 44 weeks

(range 29-58). Controls had lung tumor incidences of 13% in the females and 10% in males, at an average age of 90 and 74 weeks, respectively. The average latent period for lung tumor formation, about 40 weeks, in this experiment [127] was longer than the 33-week observation period of Kelly and coworkers [81], so that the results of the two papers are not necessarily inconsistent.

In another study of identical experimental design, conducted by the same investigative group [85], blood vessel tumors (85% incidence), classified as angiosarcomas, were induced in Syrian golden hamsters given 1,2-dimethylhydrazine dihydrochloride at about 0.16 mg/day. An increased incidence of cecal tumors (23%), mostly adenomas, and liver tumors (17%), both benign and malignant, was also found; however, lung tumors were not present.

In 1976, Toth and coworkers [128] reported on the induction of tumors in mice following sc injection of 1,2-dimethylhydrazine dihydrochloride. One group of 50 male and 50 female Swiss mice, 5 weeks old, were injected sc at a single dose of 20 mg/kg; a similar group received 10 injections. One hundred male and 100 female mice reported on earlier [129] were used as controls.

Repeated injection of 1,2-dimethylhydrazine dihydrochloride drastically reduced the survival rate, but single injection reduced it only slightly [128]. Of the mice given a single injection, one female (2%) and one male (2%) each developed a tumor of the cecum. Of the animals given repeated injections, 41 of 50 females (82%) developed 130 tumors of the large intestine at an age of 29-90 weeks, while of the males, 45 (90%) developed 156 tumors of the large intestine at 32-77 weeks of age. In both

males and females, polypoid adenomas and adenocarcinomas of the cecum, colon, and rectum were found, with the tumors occurring most frequently in the cecum adjacent to the ileum, in the lower part of the colon, and in the rectum. There were no tumors of the large intestine in the control group.

Blood vessel tumors, classified as angiomas or angiosarcomas, were found in 10 females (20%) and 12 males (24%) of the single injection group [128]. Most of the tumors were in the liver. Of the mice given 10 injections, 23 females (46%) and 25 males (50%) developed blood vessel tumors. Eight females had angiomas and 15 had angiosarcomas. The tumors were found, in decreasing order of frequency, in the following organs: liver, lungs, muscle, fat, lymph nodes, uterus, ovaries, and kidneys. In the males, 22 had angiosarcomas, and 3 had angiomas. In decreasing order of frequency, the liver, paraepididymial tissues and muscle, fat, pararenal tissues, subcutaneous tissues, lymph nodes, kidneys, brain, lungs, and spleen were affected. In the control group, 5% of the females and 6% of the males developed blood vessel tumors.

Fourteen of the females (28%) given a single injection of 1,2-dimethylhydrazine dihydrochloride developed 16 lung tumors, and 15 of the males (30%) developed 24 lung tumors [128]. All tumors were adenomas except for four cases in which the mice had a total of six adenocarcinomas. Of the animals receiving repeated injections, 24 females (48%) developed 62 lungs tumors, 3 of which were adenocarcinomas. In addition, 19 males (38%) developed 26 adenomas of the lungs. In the control groups, 21% of the females and 23% of males developed lung tumors.

Of the animals given 10 weekly injections of 1,2-dimethylhydrazine dihydrochloride, 3 (6%) females and 24 (48%) males developed kidney tumors,

mostly adenomas [128]. Tumors of the anus were also found in 12% of the females and in 16% of the males.

Toth and Wilson [127] had reported in another study that 1,2-dimethylhydrazine dihydrochloride in drinking water given to mice caused mainly blood vessel tumors. In this study [128], however, injected 1,2-dimethylhydrazine dihydrochloride induced tumors of the large intestine and lungs as well. The authors suggested that this was caused by differences in routes of administration, resulting in different metabolism.

In a study designed to detect the effects of vitamin A on colon cancer, Rogers et al [130] induced tumors by gastric intubation of 1,2-dimethylhydrazine in male Sprague-Dawley rats. Three groups of rats were given 1,2-dimethylhydrazine at total doses of 420, 275, or 197 mg/kg over 18 weeks. An equal number of controls were given 0.9% saline. In addition, animals of each group were fed normal diets, diets deficient in vitamin A, or diets supplemented with vitamin A. At 420 mg/kg, 10 of 14 rats developed carcinomas of the gastrointestinal tract and the colon. At 275 mg/kg, 48 of 62 rats had the same types of tumors. At the lowest dose, 8 of 10 rats had carcinomas of the gastrointestinal tract and 6 had carcinomas of the colon. In all 86 rats, there were, in addition, 3 hemangiosarcomas, 19 carcinomas of the ear canal, 2 hepatocarcinomas, and 1 embryonal nephroma. The results were reported only on rats retained 18-30 weeks after administration of the first dose, and there was no effect on tumor incidence attributable to vitamin A.

Druckrey [131], in 1970, reported a study of the production of carcinomas by 1,2-dimethylhydrazine dihydrochloride. The compound was given to 2 groups of 13 BD rats sc at a weekly dose of 15.6 or 47 mg/kg for

36 weeks. An additional group of 14 BD rats was given 47 mg/kg by intubation weekly for 11 weeks, and another was given 6.7 mg/kg in drinking water daily for 5 days/week, for 11 weeks.

After 3-4 months, the rats given 1,2-dimethylhydrazine dihydrochloride sc at 47 mg/kg developed diarrhea, weight loss, and jaundice; some rats developed a prolapse of the tumorous rectum [131]. All 13 rats died with what was described as multiple malignant intestinal cancer; 5 had multiple tumors of both the colon and rectum, 5 had colon tumors, and 3 had rectal tumors. The median latent period was 26 weeks, at which time a total dose of 517 mg/kg had been given. Additional tumors were found in the duodenum of seven rats, in the small intestine of four, and in the liver of two. Twelve rats that received 15.6 mg/kg developed tumors of the colon, 6 had rectal tumors, and 2 had duodenal tumors. The median latent period for these tumors was 48 weeks. All tumors were classified as adenocarcinomas, often associated with polyps in all stages of progressing malignancy. They reportedly bore striking resemblance to human colonic and rectal carcinomas.

One of 14 rats given 1,2-dimethylhydrazine by stomach tube died of pneumonia; the remaining 13 died with multiple colonic carcinomas [131]. In addition, four had rectal carcinomas, three had duodenal tumors, one had a nephroblastoma, and six had pronounced cystic degeneration of the liver. In the rats given 1,2-dimethylhydrazine in drinking water, only hemangioendotheliomas of the liver with multiple metastases to the lungs were found. The difference in organ response caused by sc and oral administration of 1,2-dimethylhydrazine was attributed to metabolic activation in the liver. Druckrey suggested that, in animals, 1,2-

dimethylhydrazine was first enzymatically oxidized to methylazoxymethanol and then converted to methylating carcinogens, including methyldiazohydroxide and methyldiazonium hydroxide. Azoxymethane, a derivative of 1,2-dimethylhydrazine, was also studied and was found to induce tumors similar to those caused by 1,2-dimethylhydrazine.

Many other investigators [132-143] have used sc injections of 1,2-dimethylhydrazine to study the induction of colon cancers. Colonic tumors have been induced in CF1 [132,133], NMRI [134,135], and Swiss [136] strains of mice and in BD rats [137], but one group of investigators [136] was unable to induce tumors in C57/B mice. A strain specificity in germ-free rats was also reported [138], Sprague-Dawley rats being more susceptible to colon tumor induction than Buffalo rats; the Wistar strain was the least susceptible. Differences in tumor induction between rats and mice have been noted [139]. Germ-free rats have been used to determine the effects of bacterial flora in the intestine, and Reddy et al [140] reported a 20% incidence of colonic tumors in germ-free rats as compared with a 93% incidence in conventionally raised animals. Tumors of the ear canal, kidneys, and small intestine were also found in the conventional rats. The effects of diet have also been considered. Rats fed a high-fat diet had a higher incidence of colonic tumors than those on normal or low-fat diets [138,141]. Rats fed cholestyramine developed more colonic tumors with a greater concentration in the distal end of the colon than did regularly fed rats [142]. Mice fed disulfiram concurrently with 1,2-dimethylhydrazine injection failed to develop colonic tumors, whereas 100% of the other animals did [143].

The previously mentioned study by Greenhouse [90] on the effect of hydrazines on the embryonic development of the South African clawed toad included 1,2-dimethylhydrazine. Continuous exposure of the embryos and larvae to 1,2-dimethylhydrazine at concentrations up to 10 mg/liter had no toxic effects. Continuous exposure at 100 mg/liter beginning at the blastula stage was toxic to all exposed embryos; by 2 weeks, 50% of the embryos were dead and the rest had tail malformations. Cleavage stage embryos were then exposed to aqueous media containing 1,2-dimethylhydrazine at various concentrations and malformations were counted at the hatching stage [91]. At concentrations of 10, 20, 40, 50, and 80 mg/liter, 4, 4, 5, 100, and 100%, respectively, of the exposed embryos were malformed.

(3) Metabolism

Fiala et al [144] identified metabolites of 1,2-dimethylhydrazine exhaled by rats. Male F344 rats, kept in metabolism cages, were given 14C-labeled 1,2-dimethylhydrazine sc at 21 or 200 mg/kg, and expired air was analyzed for azomethane and carbon dioxide.

At 21 mg/kg, 11% of the administered dose was metabolized to carbon dioxide and 14% to azomethane in 24 hours [144]. The corresponding figures at 200-mg/kg were 4 and 23%, respectively. Azomethane, detected almost immediately after injection, reached about 90% of its 24-hour value in 4-5 hours. In the same time, carbon dioxide recovery was only 60% of its 24-hour level. This lag in carbon dioxide production was interpreted as being caused by the time required for complete metabolism of 1,2-dimethylhydrazine.

That azomethane was found to be a major metabolite of 1,2-dimethylhydrazine, and that it was present in the exhaled air gives support

to Druckrey's hypothesis [131] that 1,2-dimethylhydrazine is metabolically activated. Fiala et al [144] also noted that, if azomethane itself is a carcinogen, investigators handling large numbers of animals given 1,2-dimethylhydrazine should take special precautions to avoid exposure.

(e) Phenylhydrazine

(1) Systemic Effects

In 1935, Bolton [145] described changes in the blood cells of a dog weighing 16.2 kg and given phenylhydrazine hydrochloride at 18.5 mg/kg by stomach tube daily for 4 days. Blood counts were determined before phenylhydrazine administration and intermittently for the next 16 days. On the day of the last phenylhydrazine administration, the erythrocyte count had decreased 25% from the baseline value. Four days later it was reduced by 79%, and the hemoglobin concentration was less than 18% of the initial value. On the next day, the leukocyte count had increased from the preexposure level of 12,000/cu mm to 45,000/cu mm. Two weeks after the last dose was given, the leukocyte count was normal and the erythrocyte count was 90% of the baseline value.

In 1936, Von Oettingen and Deichmann-Gruebler [146] reported their study on the pharmacologic action of phenylhydrazine and its derivatives in mice and rats. Groups of mice were injected sc with phenylhydrazine at 170, 180, and 200 mg/kg. At 170 mg/kg, 45% of the mice died within 70 minutes. Phenylhydrazine at 180 and 200 mg/kg killed all the exposed mice in 50 and 40 minutes, respectively. The authors stated that the minimum lethal dose for rats, determined essentially the same way, was the same although they did not present supporting data. Phenylhydrazine in toxic doses produced progressive cyanosis, irregular and spasmodic respiration,

progressive depression, and asphyxial convulsions in mice and rats. In another part of this study, an ointment containing 1% phenylhydrazine was applied to a shaved area on the backs of five rats every other day. The rats lost an average of 15 g of body weight in 7 days, but microscopically the internal organs appeared normal. In a third phase of this study, one-tenth the minimum lethal dose injected sc into rats once a day for 3 days produced a 63% reduction in the number of erythrocytes by day 5.

In 1965, Ekshtat [16] determined the oral LD50 of phenylhydrazine in six guinea pigs, six rabbits, and an unstated number of mice and rats. The LD50's reported were 175 and 188 mg/kg for mice and rats, respectively, and 80 mg/kg for both rabbits and guinea pigs. Toxic signs reported were motor excitation and tonic-clonic convulsions.

Witchett [147], in 1975, reported the effects of phenylhydrazine on erythrocytes. Three male beagles were given phenylhydrazine sc at 20, 30, or 40 mg/kg for 2 consecutive days. Two dogs were used as controls. Blood was drawn daily from 4 days before exposure until death. On the 5th day, all survivors were killed.

Hemoglobin concentration, hematocrit value, and erythrocyte count were significantly reduced at the two lower doses [147]. The dog given the highest dose died shortly after the second injection. Methemoglobin was present in the blood of all three dogs, but leukocyte count and blood glucose concentration were normal. Reduced glutathione levels were decreased 2 hours after the first injection and 30-40% of the erythrocytes contained Heinz bodies; by 24 hours, they were present in 95-100% of the erythrocytes. Reticulocytes could not be counted because of the presence of Heinz bodies. The day after the second injection, the urine of the two

surviving dogs contained blood, and nearly 100% of their erythrocytes contained Heinz bodies. At necropsy, the internal organs were dark brown and the spleen, liver, and kidneys were severely congested. Large amounts of blood pigments were found in these organs, and the spleen was three to five times the normal size. The Kupffer cells in the liver and the epithelium of the convoluted tubules of the kidneys were hypertrophied and filled with blood pigment, apparently hemoglobin. There was also a striking reduction of spermatogenesis.

Chen and Weiss [148] investigated the effects of phenylhydrazine administration on the spleen of rats. Male Sprague-Dawley rats were given phenylhydrazine hydrochloride ip at 100 mg/kg and saline injected rats served as controls. Groups of five rats were killed 4 and 12 hours and 1, 3, 5, and 7 days after injection. Blood samples were collected when the animals were killed, and the spleen was examined by electron microscopy.

All experimental rats developed acute anemia [148]. By day 3, the hematocrit value had decreased from 45 to 25%, but it subsequently increased to near normal by the 7th day. Spleen weights in experimental rats were three times those in controls by day 5 and remained higher than usual throughout the experiment. Cells containing Heinz bodies were found to impede the passage of normal erythrocytes through the walls of the splenic sinuses. When the passageways were occupied because of delayed clearance of damaged erythrocytes, circulation through the spleen was impaired. Damaged cells accumulated in the cords, and coincidentally the number of macrophages also increased. The authors concluded that these factors contributed to the development of splenomegaly.

Saterborg [149] investigated bone marrow response to phenylhydrazine-induced anemia. Colloidal 198Au was used to determine the transformation of fatty, inactive marrow to active marrow capable of hematopoiesis. Eighteen rabbits, given phenylhydrazine hydrochloride at a daily iv dose of 2.5 mg, were killed at various intervals up to 45 days. Before they were killed, the animals were injected with colloidal 198Au and blood samples were taken. In 4-6 days, the reticulocyte count was raised, and it eventually increased to 50%. By day 10, the uptake of colloidal gold in the tibia was three times that of the controls. Hyperemia and capillary proliferation were found in an additional group of rabbits that received phenylhydrazine for 6-14 days. In those rabbits given phenylhydrazine for 14 days, a small area of fatty marrow, dilatated vessels and bleeding were seen. Immature hematopoietic cells were frequently found in dilatated blood vessels. The author concluded that phenylhydrazine was effective in causing the blood destruction that stimulated the transformation of yellow marrow to red active marrow. Toxic effects, not otherwise defined, were also observed in the liver, but hemolysis, not the secondary hepatic injury, was considered the cause of the bone marrow stimulation.

(2) Metabolism

In 1958, McIsaac et al [150] reported a study of the metabolism of phenylhydrazine. Groups of Chinchilla doe rabbits were given 14C-labeled phenylhydrazine hydrochloride at 50 mg/kg orally, and their urine was collected. Urinary excretion was measured in seven rabbits for up to 10 days and two were killed after 4 days to determine the distribution of phenylhydrazine in tissues. The metabolites in the urine were purified by extraction and descending chromatography, located by

autoradiography, and identified by spray reagents. The amount of each metabolite in 2-day urine samples from four rabbits was then determined by isotope dilution. All radioactivity was measured on infinitely thick samples using an end window counter.

The urine of rabbits given phenylhydrazine hydrochloride at 50 mg/kg was dark brown, had a pH of 9, and reduced Benedict's solution [150]. Thirty-four percent of the dose was excreted in the urine in 1 day. By the 4th day, 50% was recovered, and excretion continued more slowly for at least 10 days. Only small amounts were found in any tissue. On the 4th day of a separate experiment, 10% of the phenylhydrazine was found in the erythrocytes, compared to 59% in the urine.

The authors determined from autoradiography that pyruvic acid phenylhydrazone and oxoglutaric acid phenylhydrazone were present in the urine [150]. They confirmed this finding by adding a known amount of each compound, labeled with 14C, to the urine of animals which received unlabeled phenylhydrazine hydrochloride. After considering the total weight and percentage of radioactivity recovered after purification, the authors determined that these two hydrazones were in the urine. A third compound was identified as p-hydroxyphenylhydrazine glucuronide. Isolation of a derivative prepared from a urine sample supported this finding. A fourth component found by autoradiography was not identified. Isotope dilution studies were conducted and showed that 17.2% of the given dose was excreted within 2 days in the urine as p-hydroxyphenylhydrazine, 8.5% as pyruvic acid phenylhydrazone, and 5.2% as oxoglutaric acid phenylhydrazone; these compounds accounted for 79% of the total radioactivity in the urine.

The authors [150] concluded that the main metabolic reactions of phenylhydrazine in rabbits were hydroxylation of the ring and subsequent conjugation and reaction with keto acids. They also noted that there was no evidence of acetylation or decomposition to aniline or benzene.

(3) Carcinogenicity and Effects Related to Reproduction

In 1966, Clayson et al [151] reported the results of a study on the induction of lung tumors in BALB/c mice by phenylhydrazine. Phenylhydrazine hydrochloride was administered to 30 mice of both sexes at a daily dose of 1 mg via stomach tube 7 times a week for 42 weeks; the total dose reported was 200 mg instead of the expected 294 mg because administration was suspended if the mice showed signs of toxicity. Thirty mice were used as controls; a control mouse of similar age was killed whenever an exposed mouse died and both were examined.

Sixteen (53%) of the mice given phenylhydrazine hydrochloride developed lung tumors, compared with 4 (13%) of the control group [151]. The average number of lung tumors in each tumor-bearing mouse was 1 in the control group and 1.5 in the exposed group. Of the 24 tumors found in the exposed group, 17% (4) were carcinomas, 42% (10) were adenomas, and 42% (10) were described as adenomas becoming malignant. Clayson et al concluded that phenylhydrazine hydrochloride was a weak carcinogen, although they pointed out that a relatively high percentage of the tumors induced were malignant.

In 1967, Roe and coworkers [78] reported a study on the carcinogenicity of several hydrazines, including phenylhydrazine, on groups of 25 virgin female Swiss mice. Phenylhydrazine in doses of 0.5-0.25 mg/kg was given by gavage 5 days/week for 40 weeks. At weeks 40-50 or 50-60, 17

surviving mice were killed, and no lung tumors were found. The authors concluded that phenylhydrazine was not carcinogenic. However, six mice were apparently not examined and only lung tumors were considered.

Kelly et al [81] conducted similar experiments on the carcinogenicity of phenylhydrazine. Thirty male CDF1 mice, 7-8 weeks old, were given 8 weekly ip injections totaling 11.6 mg (387 mg/kg) of phenylhydrazine hydrochloride. Thirty females of the same age were given phenylhydrazine hydrochloride in 8 weekly oral doses totaling 23.2 mg (892 mg/kg). Ten male and 10 female mice given saline served as controls. Of the surviving experimental females, 14% developed lung tumors by 28 weeks, while 13% of the surviving males had lung tumors at 26 weeks. The corresponding incidences in the controls were 10 and 11%, respectively. Since the difference in the incidence of lung tumors was not significant, Kelly et al concluded that phenylhydrazine was not carcinogenic in mice. This conclusion is weakened by the fact that all animals were killed by 33 weeks and only the possibility of lung tumors was examined.

Shimizu and Toth [152], in 1976, reported the tumorigenic effects of phenylhydrazine hydrochloride in Swiss mice given a 0.01% solution in drinking water for life starting at an age of 5 weeks. The average daily consumption of phenylhydrazine hydrochloride was 0.63 mg for 50 females and 0.81 mg for 50 males. Data obtained previously from 100 controls of each sex were used for comparison [129].

Of the experimental mice, 11 females (22%) developed blood vessel tumors at an average age of 71 weeks, and 10 males (20%) developed such tumors at an average age of 87 weeks [152]. In the controls, five females (5%) and six males (6%) developed blood vessel tumors. The increased tumor

incidence in the experimental group was statistically significant, with $P<0.008$ for females and $P<0.02$ for males. These blood vessel tumors, classified as angiosarcomas and angiomas, were found in the liver, spleen, and ovaries. Lung tumors, malignant lymphomas, hepatomas, and a few other tumor types were also found, but their incidences were not significantly different than those of the controls.

Tamaki et al [153] investigated the functional disturbances of offspring of rats given phenylhydrazine hydrochloride during pregnancy. Some pregnant Wistar rats received phenylhydrazine hydrochloride ip at 10 mg/kg on days 17-19 of pregnancy, while others received 20 mg/kg ip on days 18 and 19. Twelve male offspring with severe jaundice and anemia at birth were chosen for subsequent experiments. Nine normal males served as controls. Testing began when the pups were 9-22 weeks of age. The general reflexes of 7 control and 8 experimental rats were examined, the spontaneous activity of 8 control and 12 experimental animals was monitored over 24 hours, and 4 control and 4 experimental rats were used to test the acquisition and extinction of conditioned avoidance-escape behavior.

No performance differences were observed between the offspring of the two groups of experimental dams, and there were no significant differences between control and experimental groups in tests of general reflexes or of spontaneous activity. In the conditioned avoidance tests, the experimental group was significantly retarded ($P<0.05$) in response acquisition and speed of acquisition, and, during the extinction phase of the test, it lost the response significantly faster ($P<0.05$). This extinction factor was

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

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(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

IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

Hydrazines are generally handled and used in enclosed systems; thus, the concentrations of hydrazines present in workroom air should be very low. Higher concentrations may be expected during the transfer of the hydrazines from one container to another, when the containers are open, or during an accidental spill, since vapors or aerosols of these hydrazines may escape into the air. However, insufficient information has been found on the concentrations of hydrazines in workroom air to reach any conclusions on typical worker exposures. Many analytical methods have been developed, but most were not designed for air monitoring. Some methods were developed for this purpose, but few reports were found concerning their application to actual monitoring. The available methods will be reviewed, and appropriate sampling and analytical methods will be recommended. Engineering control techniques will also be discussed.

Air Sampling

Air sampling techniques used for collecting gases or vapors can be used to collect hydrazine bases in air. These techniques include absorption in a liquid medium and adsorption on a solid sorbent. Generally, the latter is favored because a solid is easier to handle than a liquid. However, other factors, such as collection efficiency, stability, and subsequent analysis, should also be considered in the selection of a sampling method. A reactive medium should be used so that only a 10- to 20-ml volume of a liquid medium or a few hundred milligrams of a solid

sorbent can collect the hydrazines at concentrations several times the recommended exposure limits. The collection efficiency for either medium should also be independent of the concentrations of the hydrazines. For solid sorbents, a solvent capable of desorbing the collected hydrazines with a constant efficiency should be available.

Because of their alkalinity, the hydrazine bases have been collected in midget bubblers containing an acid medium such as dilute sulfuric or hydrochloric acid [154,155]. At a flowrate of 1 liter/minute, the collection efficiency was nearly 100% in 10-15 ml of hydrochloric acid for known concentrations of up to 3.44, 0.78, 2.22, and 44.8 mg/cu m of hydrazine, methylhydrazine, 1,1-dimethylhydrazine, and phenylhydrazine, respectively [155]. In these studies, the collected samples were also found to be stable for at least 5 days. No report has been found on the collection efficiency of hydrazines in sulfuric acid. Pinkerton et al [156] used 20 ml of a buffered solution containing citric acid and disodium acid phosphate to collect 1,1-dimethylhydrazine at 1 liter/minute and found a collection efficiency of 91.6% for amounts up to 0.24 mg.

Hydrazines have been collected on a sulfuric acid-coated silica gel sorbent for subsequent gas-chromatographic analysis [157-160]. At a flowrate of 1 liter/minute, 400 mg of sulfuric acid-coated silica gel equally divided in two sections in a glass tube was found to collect 32 mg of 1,1-dimethylhydrazine, which was considered to be less reactive than hydrazine, methylhydrazine, or phenylhydrazine [157]. Sorption efficiency was independent of vapor concentration and humidity.

Only a few reports were found on the application of the above-mentioned methods in actual air sampling; therefore, the results of

laboratory studies are used as the basis for a recommended method for sampling. Since the concentrations of hydrazines to be expected in workroom air are much lower than the concentrations tested for hydrochloric acid or silica gel media, either one can be used to collect airborne hydrazines. Other collection media are not recommended because of their lower efficiency or the lack of information on their performance. At a flowrate of 0.2-1.0 liter/minute with 200 mg of sulfuric acid-coated silica gel packed in a 6-mm internal diameter, 8-cm long glass tube, virtually 100% of the hydrazines that pass through the sorbent will be collected. At 0.2 liter/minute, the pressure drop across sampling tubes is 6 mmHg; at 1 liter/minute, it is 33 mmHg [159]. Thus, at 0.2 liter/minute, sampling can be continued for a full workshift, but at 1 liter/minute, sampling should last no more than 2 hours. Sorbent tubes are convenient to use, but the sorbent and the tube used for sampling may need to be prepared by the person responsible for measurement pending commercial availability. Details of the recommended method of sampling and preparation of silica gel tubes are given in Appendix I [161]. Salts of hydrazines would be present in air as aerosols. A particulate collecting filter, such as a glass-fiber filter, should be used for their collection. How efficient the sampling method in Appendix I is when both vapor and particulate forms of the hydrazines are present is not known. A modification involving a filter and a silica gel adsorber should be efficient for the collection of both, but the ability of the pump to cope with the greater resistance to flow needs checking. Also, combining of two samples for analysis or the separate analyses of two samples probably involves more error than collection of a single sample for analysis.

Chemical Analysis

In considering an analytical method, the sensitivity of the method is an important factor. Since there are instances when hydrazine, methylhydrazine, and 1,1-dimethylhydrazine are used simultaneously, the analytical method also should be either specific for individual hydrazines or capable of measuring all with equal sensitivity. Titration with acids and oxidants and reaction with color-forming reagents have been used to analyze hydrazines. Generally, these methods do not distinguish different hydrazines, although some methods are very sensitive. More specific techniques, such as gas-chromatographic or other separation methods, have to be used to analyze mixtures of hydrazines. Many analytical methods have been developed and tested under controlled conditions, but only a few reports are available on the actual analysis of workroom air samples for the hydrazines. Again, laboratory studies provide the basis for recommendations.

Kolthoff [162], in a 1924 report, found that the rate of reaction of iodine with hydrazine sulfate in a buffered solution decreased with increasing hydrogen ion concentration, which made the titration end point difficult to determine. When sodium bicarbonate was used as a buffer, 100% accuracy was reported for a sample containing 162.5 mg of hydrazine sulfate. Titration of hydrazine sulfate with iodate, bromate, or permanganate was also examined by Kolthoff, who found that accurate results were obtained when 81-163 mg of hydrazine sulfate were tested using a sufficient amount of hydrochloric acid. The permanganate titration had to be carried out with a boiling sample solution.

Feinsilver et al [154], in 1959, reported on the iodate and bromate methods to determine the concentration of salts of hydrazine, methylhydrazine, 1,1-dimethylhydrazine, or 1,2-dimethylhydrazine in aqueous solution. The acidified solution of hydrazines was titrated with potassium iodate to a visual end point or with potassium bromate to a potentiometric end point. The iodate method was tested to analyze samples containing 14 mg or more of each of the four hydrazines, and recoveries of at least 96% were found. Potassium iodate titration has been used to determine exposure chamber concentrations of 0.1-5 ppm for methylhydrazine [93,95] and 5-140 ppm for 1,1-dimethylhydrazine [110]. The potassium bromate method was tested to detect 3 mg of each of the four compounds, and recoveries were at least 92.5% for all except 1,1-dimethylhydrazine, for which the results were not reproducible. No detection limits for these titration methods were reported.

Manometric methods, which measure the amount of nitrogen evolved from the oxidation of hydrazine, have also been used to determine the concentrations of several hydrazine compounds in aqueous solution [163]. Nitrogen was released almost instantaneously when hydrazine and methylhydrazine were reacted with iodate. The reaction of iodate with 1,2-dimethylhydrazine required 15 minutes, but the reaction with phenylhydrazine required almost 5 hours. Of the 1.28 and 1.84 mg of hydrazine and methylhydrazine tested in samples, respectively, almost 100% was recovered. However, only 88% of 5.1 mg of phenylhydrazine in a sample could be detected after 5 hours of reaction. A recovery of 93% of 2.4 mg of 1,2-dimethylhydrazine in a sample was determined. This procedure was rather cumbersome, and the sensitivity was not optimal.

Several colorimetric methods have also been developed and widely used. In one method [154], phosphomolybdic acid added to the sample was reduced by the hydrazines, including 1,2-dimethylhydrazine, to form a molybdenum blue complex, whose color intensity could then be measured. NIOSH has validated this method for methylhydrazine over a range of 0.169-0.78 mg/cu m for a 15-minute sample at a flowrate of 1.5 liters/minute, 1,1-dimethylhydrazine at 0.566-2.22 mg/cu m for a 100-liter air sample, and phenylhydrazine at 10.37-44.8 mg/cu m also for a 100-liter air sample, the last two collected at 1 liter/minute [155]. Because the absorbance of these three compounds was measured at the same wavelength, this method was not specific. For methylhydrazine and 1,1-dimethylhydrazine, there may be positive interference from agents such as stannous ion, ferrous ion, zinc, sulfur dioxide, and hydrogen sulfide. Oxidizing agents such as halogens and oxygen will cause negative interferences. Because phenylhydrazones may form in an acid medium, aldehydes and ketones in air may interfere with the analysis of phenylhydrazine.

Another colorimetric method has been used to determine the concentration of hydrazine or methylhydrazine in aqueous solutions [164-168] and to determine hydrazine concentrations in test air samples [155,169]. This method was based on the formation of a yellow-orange complex in acid solution following the reaction of hydrazine or methylhydrazine with para-dimethylaminobenzaldehyde. Peak absorbance was measured at 460-480 nm for methylhydrazine [164,165] and 460 nm [166] or 480-490 nm for hydrazine [164,167]. Since the absorbance bands for hydrazine and methylhydrazine overlap, this method cannot be used to distinguish the two compounds. McKennis and Witkin [169] tested this

method with a prepared air sample containing hydrazine at a concentration of 4-5 mg/cu m. In other studies, 0.5-0.75 μg of hydrazine [164,168] or 1.5 μg of methylhydrazine [164] in a sample was detected. NIOSH has validated this method over a range of 0.589-3.44 mg/cu m for a 100-liter air sample [155].

In addition to the molybdenum blue and the potassium iodate methods, 1,1-dimethylhydrazine concentrations in air, water, or biologic samples were also measured colorimetrically with trisodium pentacyanoamino ferrate as a reagent. The reaction produced a red complex that could be measured with a spectrophotometer at 480 nm [170] or 500 nm [156]. Pinkerton et al [156] tested this method at a concentration of 6 mg/cu m. Nitrogen dioxide was found to inhibit the colored-complex formation, while hydrazine had no effect on it.

Continuous monitoring methods have been developed to evaluate the exposure of rocket fuel workers and to determine the concentrations in animal exposure chambers. Buck and Eldridge [171] developed a continuous coulometric titration method for determining 1,1-dimethylhydrazine concentrations in the air in the vicinity of rocket launching areas. Air samples were drawn though the inner chamber of a four-electrode potentiostat titration cell. The electrolyte used was potassium bromide buffered to pH 8. Bromine was evolved in the outer chamber of the titration cell when 1,1-dimethylhydrazine was introduced. Production continued until the reaction was complete and a null point was again attained. At a flowrate of 835 ml/minute, a current of 42 microamperes for 0.2 mg/cu m was reported, as compared to a background noise level of ±3

microamperes. No interference from nitrogen dioxide, unsaturated hydrocarbons, or acid gases was found.

Geiger and Vernot [172] used the reaction of iodine with methylhydrazine to continuously determine methylhydrazine concentrations in an exposure chamber. Air was drawn through a reaction cell, where iodine reacted with methylhydrazine stoichiometrically in a buffered potassium iodate solution, and the absorbance of iodine was monitored by a colorimeter. At a flowrate of 200 ml/minute, the collection efficiency was virtually 100% at a concentration of 300 ppm (560 mg/cu m). However, the response time was 10 minutes.

In 1976, Saunders and Larkins [18] described a direct-reading instrumental method that used paper tapes impregnated with phosphomolybdic acid to detect hydrazine. The stain developed on exposure to hydrazine gave a photomultiplier reading proportional to the hydrazine concentration. An instrument based on this principle and marketed in the United States reportedly has a lower limit of detection for hydrazine of 50 ppb with a response time of 2-3 minutes. The detection limit for methylhydrazine or other hydrazines was not described. Although the method appears to be rather sensitive, the specificity is poor, since phosphomolybdic acid will respond to all the hydrazines and some other nitrogen compounds.

Saunders and Larkins [18] also reported on two sensitive methods for continuous monitoring of hydrazine and methylhydrazine concentrations in air. The hydrazine compound was catalytically converted to nitric oxide and measured at very low concentrations by a chemiluminescent method. The method was able to detect 10 ppb of nitric oxide, the equivalent of 5 ppb of hydrazine. However, nitric oxide and nitrogen dioxide, frequently found

in the air at concentrations of 50-100 ppb, were interferences. Therefore, this method is not suitable in an industrial hygiene survey for measuring hydrazines in the ppb range. The second method also involved conversion of hydrazine compounds to nitric oxide, but the detection of nitric oxide was based on electrochemical oxidation-reduction. An instrument was available to measure 10 ppb of nitric oxide, which was equal to 5 ppb of hydrazine or methylhydrazine. Since nitric oxide and nitrogen dioxide concentrations in the air could be determined separately from the hydrazines with this instrument, the interferences were eliminated. This method cannot differentiate between hydrazine compounds, and the instrument used is not commercially available.

Direct-reading detector tubes have also been used to detect hydrazines in air. Glass tubes, packed with an acid-base indicating solid, changed color when a measured and controlled flow of air containing hydrazine was passed through the packing. The length of the color zone was proportional to the concentration for a given sample volume, and a detection range of 0.25-3 ppm for hydrazine, 1,1-dimethylhydrazine, and methylhydrazine tubes was reported [173,174]. Since the tubes react to bases, any other substance with the same property, such as hydrazine derivatives, ammonia, or amines, would cause interferences. Although detector tubes are widely used for on-the-spot checking [28], they lack specificity and have low sensitivity, so they are not recommended for measuring the concentrations of hydrazines in air for the purpose of compliance.

Since some rocket fuels contain more than one of the hydrazines, methods are needed to analyze the composition of a mixture.

Salicylaldehyde has been used as a reagent to determine the concentration of hydrazine and 1,1-dimethylhydrazine in a mixture [175-177], because it reacts with hydrazine to form a neutral crystalline azine and with 1,1-dimethylhydrazine to form a basic hydrazone. Malone [175] used perchloric acid titration to determine the total amount of the two hydrazines in the mixture; hydrazine was then precipitated from solution as salicylaldazine, and the 1,1-dimethylhydrazine in solution was determined. The maximum absolute error for either component of the mixture was 0.36%. The titration end point of this method was rather ill defined, and Burns and Lawler [176] used potentiometric or spectrophotometric titration to reduce human error. The potentiometric method was preferred because it was relatively simple and gave more reproducible results, although there was no decrease in average error. Bailey and Medwick [177] used ultraviolet spectral absorbance to determine the amount of the compounds produced from the reaction of salicylaldehyde and the hydrazine/1,1-dimethylhydrazine mixture. Although absorption spectra overlapped, simultaneous equations could be used to calculate individual absorbance. Tests with a single compound had shown that the method was sensitive to hydrazine at a concentration of 0.3 μg/ml and to 1,1-dimethylhydrazine at 0.25 μg/ml. A test mixture containing 0.2109-0.5454 g of hydrazine and 0.7292-0.2421 g of 1,1-dimethylhydrazine was separated and showed a standard deviation of 0.8% in the recovery of hydrazine and 1.6% for 1,1-dimethylhydrazine. The applicable limits of detection for other separation methods were not reported.

Previous studies [175,176] have shown that the reaction of salicylaldehyde and methylhydrazine did not produce a stable hydrazone that

could be titrated with perchloric acid. Serencha et al [178] found that, with excess perchloric acid, the hydrazone formed from methylhydrazine was hydrolyzed back to salicylaldehyde and methylhydrazine. With hydrazine precipitated out as salicylaldazine, the hydrolyzed methylhydrazone could be titrated; thus, a mixture of the hydrazine and methylhydrazine was separated. Clark and Smith [179] used Chloramine-T solution and sodium hypochlorite to separate hydrazine and methylhydrazine in mixtures based on different rates of oxidation of methylhydrazine.

1,1-Dimethylhydrazine can be analyzed in the presence of methylhydrazine by using the differential acetylation of the two compounds [180]. In an acetic acid medium, methylhydrazine and acetic anhydride reacted immediately to form a neutral compound, while the reaction between 1,1-dimethylhydrazine and acetic anhydride was slow, forming a basic compound. 1,1-Dimethylhydrazine was determined by perchloric acid titration after neutralization of methylhydrazine. Hydrazine has the same acetylation property as methylhydrazine; therefore, a mixture of hydrazine and 1,1-dimethylhydrazine could be similarly analyzed.

These separation methods can only be used in a binary mixture; in mixtures containing three or more hydrazines, gas-chromatographic methods can be used. A chromatographic column containing Celite C22 as the support phase and Carbowax 400 as the stationary phase has been used to separate a mixture of hydrazine, methylhydrazine, and 1,1-dimethylhydrazine [181,182]. The peak in the chromatogram of each component was well defined, separated by at least a 5-minute retention time difference. With a thermal conductivity cell, detection limits of 8, 12, and 2 μg of hydrazine, methylhydrazine, and 1,1-dimethylhydrazine, respectively, in a sample were

reported. Dee [183] used the quantitative formation of each hydrazine to its corresponding substituted pyrazole by reaction with 2,4-pentanedione to enhance the sensitivity of separation of hydrazine and methylhydrazine by gas chromatography. With a dual flame ionization detector, a range of 0.5-250 ng of either hydrazine or methylhydrazine in a sample was tested. No interference from 1,1-dimethylhydrazine, urea, aluminum, iron, copper, or alanine was found. The sensitivity of this method was very high, but the method was designed to analyze aqueous solutions.

Liu et al [184] described a chromatographic method for determining hydrazine concentrations in cigarette smoke. Hydrazine was trapped with pentafluorobenzaldehyde. The resulting stable derivative was detected chromatographically with an electron capture detector. A limit of 0.1 ng of hydrazine in a sample was reported.

Wood and Anderson [157-159] studied the sampling and analysis of hydrazine compounds in air to monitor work environments. Test air samples were collected in a sulfuric acid-coated silica gel sorbent. The hydrazinium hydrogen sulfates were desorbed from the silica gel with water. The resulting solution was neutralized with sodium acetate and reacted with 2-furaldehyde to form 2-furaldazine or the methylhydrazone, dimethylhydrazone, or phenylhydrazone from hydrazine, methylhydrazine, 1,1-dimethylhydrazine, or phenylhydrazine, respectively. These derivatives were extracted into ethyl acetate and determined by gas chromatography, using flame ionization detection. Single peaks of hydrazine, methylhydrazine, and 1,1-dimethylhydrazine and double peaks of phenylhydrazine were obtained in the chromatogram. This method was very sensitive, detecting as little as 2 ng/injection for hydrazine and 35

ng/injection for methylhydrazine. In a 15-minute, 15-liter air sample, the limits of sensitivity correspond to concentrations of 0.0065 mg/cu m (0.005 ppm) of hydrazine, 0.14 mg/cu m (0.08 ppm) of methylhydrazine, 0.06 mg/cu m (0.03 ppm) of 1,1-dimethylhydrazine, and 0.022 mg/cu m (0.005 ppm) of phenylhydrazine. However, the reaction time of methylhydrazine with 2-furaldehyde needs to be carefully controlled to prevent the formation of a secondary product that cannot be eluted from the gas-chromatographic column. The desorption efficiency for methylhydrazine was 75%, while it was close to 100% for the other hydrazines. However, it has been found (V Carter, written communication, November 1977) that 100% recovery for hydrazine and 1,1-dimethylhydrazine at low concentrations was difficult to achieve. This same investigator has also found that hydrazine adsorbed on an acidified silica gel sorbent was stable for only 24 hours. 1,1-Dimethylhydrazine was stable for 5 days [157].

Of the analytical methods reviewed, the gas-chromatographic method described by Wood and Anderson [157-159] has the best sensitivity and specificity for hydrazine, methylhydrazine, 1,1-dimethylhydrazine, and phenylhydrazine. Therefore, this method is recommended for analyzing concentrations of these four hydrazines in workroom air. The lowest amounts of hydrazines in a sample that can be detected with an analytical precision of about 15% relative standard deviation were 4 μg for hydrazine, 9 μg for methylhydrazine, 15 μg for 1,1-dimethylhydrazine, and 66 μg for phenylhydrazine [159]. Since short-term sampling is preferable for carcinogens, a flowrate of 1 liter/minute is recommended. For a 2-hour sample collected at this flowrate, a concentration of 0.04 mg/cu m (0.03 ppm) for hydrazine, 0.08 mg/cu m (0.04 ppm) for methylhydrazine, 0.15 mg/cu m (0.06

ppm) for 1,1-dimethylhydrazine, and 0.6 mg/cu m (0.14 ppm) for phenylhydrazine can be accurately determined. Details of the recommended method for sampling and analysis are given in Appendix I [161].

The colorimetric para-dimethylaminobenzaldehyde method for hydrazine and the molybdenum blue method for methylhydrazine, 1,1-dimethylhydrazine, and phenylhydrazine are at least as sensitive as the recommended gas-chromatographic method, although they are not specific. When no interfering substances are present, these colorimetric methods can be considered as a reasonable alternative. The method described by Dee [183] might also be an acceptable alternative, especially for methylhydrazine. However, air sampling was not performed, and the applicability of this method [183] for samples collected from air needs to be established before it can be recommended.

There is insufficient information to recommend a sampling and analytical method for 1,2-dimethylhydrazine for compliance purposes. The method recommended in Appendix I is not applicable, since the complex with 2-furaldehyde would not form. The titration method of Feinsilver et al [154] lacks adequate sensitivity to measure a concentration that could afford protection to workers. The colorimetric method of NIOSH using phosphomolybdic acid [155] should be applicable to 1,2-dimethylhydrazine, since it is essentially the same as that tested by Feinsilver et al [154]. However, no limit of sensitivity is available for 1,2-dimethylhydrazine. para-Dimethylaminobenzaldehyde is probably not a suitable reagent for colorimetric determination of 1,2-dimethylhydrazine, since it was not adequate as a spray reagent for thin-layer chromatography [185].

Gas chromatography using a technique different from that recommended for other hydrazines has been tested for 1,2-dimethylhydrazine (E Sowinski, written communication, November 1977). In this method, a 19-foot x 1/8-inch stainless steel column containing 10% Carbowax 20 M and 2% Igepal CO-880 and a nitrogen detector were used. A peak was observed at the 0.1-μg level in 13.5 minutes when the temperature was programmed from 70-170 C at 4 C/minute with a helium flow of 20 ml/minute. Acetone, methanol, and tetrahydrofuran were suitable solvents. The applicability of this method to the analysis of air samples and the range of detection would have to be established before it can be recommended as an appropriate analytical method. Therefore, no sampling and analytical methods for 1,2-dimethylhydrazine are recommended at this time.

Environmental Levels

From July 1972 to June 1977, the Occupational Safety and Health Administration [186] conducted three investigations of workplaces in which air samples were collected to determine concentrations of hydrazines. Measurements of phenylhydrazine were taken in a paint shop and a produce warehouse, and samples for hydrazine were taken in a chemical company. No place inspected was found to be in violation of the Federal standards, which were 1.3 mg/cu m for hydrazine and 22 mg/cu m for phenylhydrazine.

The US Army Environmental Hygiene Agency [187] conducted two surveys to evaluate worker exposure to hydrazine and 1,1-dimethylhydrazine at the Rocky Mountain Arsenal hydrazine facility in October 1976 and January 1977. The gas-chromatographic method as described by Wood and Anderson [157-159] was used to determine concentrations of hydrazine and 1,1-dimethylhydrazine

during various phases of drum filling and tank car loading operations. Depending on the location of sampling sites, phase of operation, and wind direction, the concentration determined from area monitoring varied over a wide range. During the first survey, 32 samples were analyzed for hydrazine and 12 samples had no detectable concentration. The lowest detected concentration reported was 0.002 ppm, and the highest, 0.64 ppm, was found in a metering house for tank car loading during the cleaning of filters on feedlines. Of the 52 samples analyzed for 1,1-dimethylhydrazine, 13 had no detectable concentration. The lowest reported concentration was 0.0004 ppm, and the highest concentration, 1.66 ppm, occurred 3 feet away from the loading station during drum filling operations. There were some leaks in the transfer pumps during this survey; when the leaks were repaired and air samples retaken in January 1977, the concentrations at the same locations were generally lower than those determined before. The highest concentrations found were 0.39 ppm for hydrazine 7 feet from the loading station during the drum filling operation, and 0.35 ppm for 1,1-dimethylhydrazine 60 feet from a blend metering house during an equipment maintenance operation. All personnel performing the drumming and loading operations were required to wear respirators, and personal air samples were collected both outside and inside the masks during various operations. Although rather high concentrations were found outside the mask, 0.22-1.98 ppm for hydrazine and 0.14-4.61 ppm for 1,1-dimethylhydrazine in both surveys, the concentrations of these two compounds inside the mask were usually not detectable or less than 0.001 ppm. On one occasion, 0.03 ppm of 1,1-dimethylhydrazine was detected inside a mask during a drumming operation. This reading was

considered to be caused by a leak in the face seal of the mask. It was concluded that both hydrazine and 1,1-dimethylhydrazine were present around the hydrazine facility, but adequate protection to the workers was afforded by the use of respirators. The report [187] also indicated that nitrosodimethylamine was present in the ambient air near 1,1-dimethylhydrazine storage and tank car unloading areas, although the concentrations were not determined because of the lack of a suitable method.

Engineering Controls

Engineering design for controlling exposure to the hydrazines and their salts should accomplish the purpose of maintaining concentrations in workroom air at or below the recommended environmental limits and of minimizing skin and eye contact.

In manufacturing and formulating plants, laboratories, and other places where it is suitable and practicable, closed systems, properly operated and maintained, should be used to reduce the possibility of vapors or aerosols escaping into the workroom air and to minimize the likelihood of skin and eye contact. Where closed systems are not feasible, well-designed local exhaust ventilation should be provided. Such systems should be designed, if possible, to operate under negative pressure to prevent leaks into the workroom atmosphere. Guidance for design can be found in Industrial Ventilation--A Manual of Recommended Practice [188], in Fundamentals Governing the Design and Operation of Local Exhaust Systems Z9.2-1971 [189], and in NIOSH's Recommended Industrial Ventilation Guidelines [190]. Specifically, when a fire hazard exists, particular

attention must be given to the need for sparkproof fans and explosion proof motors in ventilation systems. An average face velocity of 150 feet/minute should be maintained when handling hydrazines or other suspected carcinogens in a hood [191]. Where a fire hazard could exist, all electrical fixtures used in the ventilation system or in the work area should be sparkproof, and all wiring should be enclosed in rigid metal conduits [192]. Exhaust air containing hydrazines should not be recirculated, and applicable Federal, state, and local regulations should be adhered to when exhaust air is released to the outside. Where exhaust ventilation is required, adequate makeup air, conditioned as needed for comfort, must be provided. Connections between exhaust air vents from a regulated area and those from other areas are prohibited, but a common makeup air inlet may be used. Exhaust ventilators must be located away from intake manifolds to prevent short circuiting. Respiratory protective equipment is not an acceptable substitute for proper engineering controls, but it should be available for emergencies, for nonroutine maintenance and repair situations, and for entry into confined spaces.

An enclosed system for the materials, processes, and operations is effective only if the integrity of the system is maintained. Such systems must be inspected regularly by qualified persons, and any leaks or worn parts must be repaired promptly. The conditions of seals, joints, access ports, and other such potential release points should be given special attention. Scheduled preventive maintenance, which offers more protection to the employee than nonroutine maintenance, should be practiced.

V. WORK PRACTICES

The recommended work practices for hydrazines are formulated by considering the nature of their industrial applications and their chemical, physical, and toxicologic properties, from information obtained from various sources [2,192-197], and from plant visit observations [28]. Generally, work practices adopted for hydrazine, 1,1-dimethylhydrazine, and methylhydrazine have been similar [2].

Toxicologic data discussed in Chapter III established that these hydrazines present hazards from both inhalation and skin or eye contact. From the standpoint of acute toxicity, methylhydrazine is the most toxic of the hydrazines [2,20,96,110,111]. Eye damage may depend on the basicity of the hydrazines, and if so, hydrazine would cause the most severe effect if contact occurs. When one considers vapor pressures of the various hydrazines, given in Tables XI-1 to XI-5, it can be seen that 1,1-dimethylhydrazine vapors have the greatest potential to escape into workroom air.

Although specific information on work practices for 1,2-dimethylhydrazine and phenylhydrazine was not found, the information on toxicity and chemical properties indicates that recommendations based on information available for the other three hydrazine bases should be adequate for all five compounds and their salts.

So far as is known, the salts of the hydrazines are not flammable or combustible, but all the free bases are flammable or combustible as liquids and present both fire and explosion hazards as vapors [2,195]. 1,1-Dimethylhydrazine, with a vapor pressure of about 120 mmHg at 70 F, a

flashpoint of 34 F, and flammability limits in air from 2 to 95% (v/v) at normal temperatures, presents the greatest fire hazard. Hydrazines may react explosively with some oxidizing agents, such as fuming nitric acid or nitrogen dioxide, and great care must be exercised when circumstances require handling of such combinations together, such as in rocket operations. Because of these hazards, extreme precautions must be taken in the manufacture, handling, transport, storage, and use of these compounds. Where a potential for fire or explosion exists, adequate procedures for emergency exit and reentry, decontamination of spills or leaks, firefighting, and storage are especially important. Potential sources of sparks and open flames must be prohibited where there is a fire or explosion hazard.

In all situations where hydrazines are present, engineering controls should be designed to maintain concentrations in the worker's breathing zone at or below the recommended limits, and work practices should be implemented to prevent eye and skin contact.

Storage, Handling, and Transport

The recommended procedures for safe storage, handling, and transport of hydrazines are based on an understanding of their toxicity, ease of oxidation, and flammability. Glass bottles, drums, and tank cars constructed of proper material have been used for storing or transporting hydrazines [194]. According to a bulletin prepared by Olin Chemicals [1], each drum should have a 3/4-inch and a 2-inch screw-type closure in the top head, sealed by a polyethylene gasket. The drums may be emptied with a small gear pump, sparkproof as necessary, or by nitrogen pressure. When nitrogen pressure is used to unload hydrazines, nitrogen should be supplied

at a pressure of 3 or 4 psig. When a pump is used, nitrogen should be supplied at 0.4-0.5 psig.

For storing large quantities of hydrazines, the Air Force [193] and FMC Corporation [194] have recommended using horizontal cylindrical tanks kept under slight pressure with nitrogen or other inert gases. Each tank should be electrically grounded and fitted with a fluid-inlet connection, level gauge, pressure gauge, rupture disc, relief valve, and a flame arrestor at its top. Rupture-disc discharge should be directed so that no working areas will be contaminated. A top outlet with sump and dip-leg should be used to eliminate leakage [193]. Large horizontal tanks should be mounted on reinforced-concrete saddles, and vertical tanks should be set on concrete pads. Drums should be stored on concrete pads with low curbs to control drainage [193]. Before drums are emptied, the drums and other equipment used in the operation should be electrically bonded and grounded [194].

Hydrazines should be stored at temperatures well below their respective boiling points, away from ignition sources and oxidants, and preferably outdoors. Containers of hydrazines stored outdoors should be sheltered against direct sunlight, dirt, snow, water, and ice accumulation [194,196]. Within inside storage areas, continuous ventilation should be provided [193,196]. Major storage facilities should be diked with concrete to hold at least 110% of the total storage capacity and have a concrete slab below the storage tank [193], so that the spilled hydrazines will not be soaked up by the ground. The diked area should be kept clean, and the diking system should drain to a burn basin, a collection basin, or reclamation sump [193]. The Air Force [193] has published quantity-

distance tables to be used as guidelines in determining proper tank locations within storage areas. Entrances to the storage area should be properly posted, and all containers should be properly labeled.

Materials of Construction

Materials used in equipment that contains or directly contacts hydrazines have been selected mostly on the basis of their effects on the purity and decomposition of the hydrazines. Cloyd and Murphy [2] recommended certain materials for use with hydrazine and methylhydrazine. The US Advisory Panel on Fuels and Lubricants [192] also prepared lists of materials that are compatible with the three hydrazines used as rocket fuels. These recommendations are shown in Table V-1. Other recommendations made by the Air Force [193] and the FMC corporation [194] are also listed in the table.

Equipment Cleaning

Surfaces that will be in contact with hydrazines should be cleaned to limit the introduction of impurities and potential decomposition. In this regard, the Air Force [193] has established recommended procedures for cleaning all systems and component parts. Cloyd and Murphy [2] recommended that, before any stainless steel part is to be used with the hydrazines, it should be descaled by etching with an aqueous solution of 3-5% hydrofluoric acid and 15-20% nitric acid for approximately 1 hour. The component should be made chemically inert; for stainless steel, this may be done by immersion in 50% nitric acid for 30 minutes. Plastics can be cleaned with a 4% detergent solution for 30 minutes at 120 F [193].

TABLE V-1

MATERIAL COMPATIBILITY WITH HYDRAZINE COMPOUNDS

Compatible with Hydrazine and Methylhydrazine

Aluminum Alloy Nos. 356, B356, 1100, 2014, 2024, 4043, 5052, 6061, 6066, and Tens 50	Inconel and Inconel-X
Chromium plating	Sinclair L743
Dow Corning Number 11	Kel-F and polyethylene
Graphite	Stainless Steel 304,321,347, and 1707 PH
	Teflon

Not Compatible with Hydrazine and Methylhydrazine

Carbon steel	Johns-Manville Packing No. 76
Copper	Nickel
Iron-Base Superalloy A-236*	Stainless steel AM-350* and AM-355*

Not Compatible with Methylhydrazine

Lead	Monel
Hastelloys	Zinc
Iron	

Compatible with 1,1-Dimethylhydrazine

Aluminum and its alloys	Mylar A
Hydropol OT Plastic	Nickel
Kel-F and polyethylene	Silicone rubber AMS 3305
Mild steel	Teflon
Monel	Graphite
Stainless steel types-303,304 321,347	

Not Compatible with 1,1-Dimethylhydrazine

Copper and its alloys	Isocyanate polyester
Phenolic resin	Phenolic-asbestos plastic
Polyvinyl alcohol polymer	Vinylchloride-vinylidene copolymer
Cellulose acetate butyrate	Organic polysulfide
Vinyl chloride-acetate copolymer	

*Contains over 0.5% molybdenum; should not be used with hydrazine or methylhydrazine at temperatures above 160 F

Adapted from references 2,192-194

Special precautions are necessary for entering tanks or vessels that may contain the hydrazines to clean or perform flame- or spark-generating operations such as welding and cutting. Before any employee enters a vessel, all pipelines leading into or out of the vessel must be blanked to prevent the entry of hydrazines. The vessel interior should then be washed with water and purged with air or with nitrogen followed by air. After purging the vessel interior, trained personnel should test the vessel atmosphere with suitable instruments to ensure that no hazards from fire, explosion, oxygen deficiency, or vapor inhalation exist. No one should enter a tank or vessel without first being equipped with an appropriate respirator (if necessary) and a secured lifeline and harness. Mechanical ventilation should be provided continuously when workers are inside the tank. At least one other worker should watch at all times from outside the vessel. This worker should be equipped with similar respiratory protection and secured lifelines and harnesses. An effective communication system should be established between workers in the tank and those outside. Two additional employees should be available to assist in the event of an emergency. Cutting or welding may be performed only when an authorized representative of the employer signs a permit indicating that all necessary safety precautions have been taken.

Spills and Leaks

Spills and leaks may present hazards from inhalation, skin or eye contact, ingestion, and fire and explosion. Cloyd and Murphy [2] recommended the following basic design considerations to decrease the likelihood of these hazards:

(1) Reduce mechanical joints to a minimum.

(2) Consider maximum pressure in system design.

(3) Eliminate low-lying liquid traps wherever possible.

(4) Provide an inert gas purge system.

(5) Install high stack or scrubber for vent.

In the event of spills or leaks, a self-contained breathing apparatus and protective clothing should be worn during the cleanup operation [193]. All areas of operation involving hydrazines should have proper drainage systems so that leaks and spills can be flushed away immediately. For small quantities, spilled hydrazines can be flushed with water and collected in holding tanks [198]. Hydrazine will decompose to water, nitrogen, and ammonia by oxidation or by bacterial action. Hydrazines should not be discharged into the sewers or waterways, unless first decomposed. Dilute solutions of hydrazines, at concentrations less than 2%, can be collected in open containers and oxidized by adding 10% hydrogen peroxide, calcium hypochlorite, or household bleach [198]. Comparatively large quantities may be disposed of by burning under proper supervision. If leaks develop during transit, the spilled material should be washed away with water before the remaining materials are salvaged [193].

Fire and Explosions

The hydrazine bases are flammable or combustible. In aqueous solutions, hydrazine at a concentration higher than 50%, methylhydrazine higher than 50%, and 1,1-dimethylhydrazine higher than 25% are ignitable at normal temperatures [199]. Vapors of hydrazines are explosive in a wide range of mixtures with air, 4.7-100% for hydrazine, 2.5-92% for

methylhydrazine, and 2-95% for 1,1-dimethylhydrazine [9]. The lower limits for all but hydrazine can easily be reached in a confined space because of relatively high vapor pressures. To avoid the formation of such a mixture, and also to retard oxidation, an inert gas such as nitrogen should be used to blanket the hydrazine compounds in containers. Hydrazines can ignite spontaneously in air when in contact with porous materials such as earth, asbestos, wood, or cloth [9,193]. If these materials become soaked with hydrazines, they must be thoroughly wetted with water [1] before disposal. Rags should never be used to wipe up spills because of the danger of spontaneous ignition [29].

Buildings that house equipment for handling or processing hydrazines must be well ventilated to prevent the accumulation of vapors or aerosols. Automatic water sprinkler systems should be installed in these buildings to provide deluge water for fires and with an appropriate triggering device to dilute the concentrations of spilled hydrazines [1]. In an enclosed space, all personnel must be evacuated when the atmospheric concentration reaches 20% of the lower explosive limit [193] because of the imminent danger of fire and explosion. Oxidants such as hydrogen peroxide, nitric acid, and halogens should be kept away from storage areas for hydrazines because of the potential for spontaneous ignition.

When an explosion occurs in a closed vessel with nitrogen present, the pressure will increase 12-14 times. If air is present, even higher pressure will be generated [200]. All equipment used with hydrazines should have a working pressure sufficiently greater than the venting pressure to accommodate any pressure resulting from an explosion [196]. Processing or manufacturing equipment should be located away from open

flame, high temperatures, and congested areas.

Fire involving hydrazines may be supported either by air or by oxidants. Air-supported fires may be extinguished by diluting hydrazines with a quantity of water one to three times the original volume [193,194]. Applying water in a coarse spray is the most efficient method [193]. Water both cools and dilutes, and the diluted solution of hydrazines is nonflammable. For fires supported by oxidants, water may be used if it does not aggravate the situation with the specific oxidant involved. Dry chemicals and carbon dioxide may be used to extinguish both air- and oxidant-supported fires, but flooding with water will also be necessary to prevent reignition [9]. Chemical foam extinguishers are not recommended, because hydrazine compounds may deactivate the foam-forming surfactant and destabilize the foam [193,194]. Protective clothing and a self-contained breathing apparatus must be worn by any person involved in firefighting [9]. Advanced or large fires must be fought from a safe distance or from a protected location because of the explosion hazard.

Regulated Areas

Regulated areas must be established and maintained where hydrazines are manufactured, processed, stored, or otherwise used. To limit the number of employees exposed to hydrazines, only those persons needed for the job should be allowed access to these areas. A daily roster of the employees who enter the regulated areas must also be maintained along with environmental monitoring records for later reference. Signs warning of the hazards of entry into regulated areas must be prominently displayed.

Personal Protective Clothing and Equipment

Because hydrazine compounds are dermal irritants and can penetrate the skin to cause systemic toxicity, dermal exposure must be prevented. All hydrazine-processing equipment or systems should be designed to be as enclosed as possible. The immediate surrounding areas should be provided with ventilation to prevent the buildup of vapors or aerosols. Personal protective equipment for safeguarding the health of workers should not be used as a substitute for adequate engineering controls; however, where adequate engineering controls are impractical, personal protective equipment must be used. Workers in regulated areas must wear work clothing consisting of coveralls or any other combination of clothing that offers the same protection, hat or head covering, and shoes or shoe covering. If there is any possibility of spilling or splashing hydrazines, a plastic full-face shield (8-inch minimum) and goggles, rubber or plastic wrist and arm protectors, gloves, boots, and a rubber-type apron must be worn [193]. Gloves should be made of an impervious material such as natural rubber, reclaimed rubber, or vinyl-coated cotton, and footwear should be "fireman-type" rubber boots [193,194]. Whenever the splashing of hydrazines is likely, such as during loading, unloading, or transfer, impervious clothing must be worn. This clothing may be made of rubber, rubberized, or fiberglass material impregnated with a corrosion-resistant plastic or vinyl-coated cotton [193].

When it is necessary to work in an atmosphere in which the vapor or aerosol concentration exceeds the recommended environmental limits, approved respirators, as specified in Chapter I, must be used. In confined spaces or where concentrations of hydrazines may be high, a self-contained

breathing apparatus should be used [193]. The employer must establish a respiratory protection program in accordance with 29 CFR 1910.134 to ensure that clean and well-maintained respirators are available to employees required to wear them in the course of their work. In addition, workers who are required to wear respirators must be trained in their proper use and be able to know how to test them for leakage and proper fit and operation.

Safety showers and eyewash fountains must be installed in or close to storage and handling areas. Emergency exits must be provided and be accessible at all times. The water supply provided should be adequate for dilution, flushing, washing, decontamination, and firefighting. All emergency eyewash, shower, protective, and firefighting equipment should be checked periodically to ensure its serviceability.

Sanitation

Good sanitation and personal hygiene must be practiced to minimize the risk of exposure to hydrazines, especially by ingestion. Oral intake has been shown to be one of the routes by which hydrazines cause health effects [42,145]. Thus, food and beverage consumption, vending machines, and open smoking or chewing materials must not be allowed in any area where the hydrazines are manufactured, processed, stored, or otherwise used. A separate changing room, adjacent to such areas, with showers, washing facilities, and lockers that permit separation of street and work clothing should be provided for and used by employees working in regulated areas. Separate toilet facilities and designated smoking areas, if needed, must be provided adjacent to or near the changing room. When leaving the work

area, employees must wash their hands and face. After a spill or when exiting from regulated areas for the last time in a workshift, workers should place work clothing in a suitably marked and covered container for disposal or laundering prior to further use. Before the last exit from the regulated area and before changing into street clothes, the employee must shower. Work clothes should not be taken home, and the employer must provide for the laundering of the work clothes. Persons laundering the clothing must be apprised of the hazards from hydrazines.

Emergency and Decontamination

In case of accidental exposure, the exposed worker should be removed from the hazardous environment immediately and all contaminated clothing should be removed. The worker should then shower with water for 15 minutes; if the worker is unconscious, then emergency personnel should wash the worker's skin with water. If hydrazines have contacted the eyes, they must be flushed copiously with water [193]. Signs and symptoms of poisoning by the hydrazines include irritation of eyes, nose, and throat, dizziness, nausea, vomiting, and convulsions [196]. Medical assistance should be obtained if these signs and symptoms are present. Gross contamination must be taken off of protective clothing before removal from the wearer. Contaminated work clothes and protective equipment should be rinsed with water and stored in a container prior to being cleaned and decontaminated for reuse or final disposal. Equipment contaminated by hydrazines should be flushed thoroughly with a large volume of water or with diluted acid and dried before it is returned to service [194].

Laboratory Activities

When the hydrazines are used for research or quality-control purposes, several precautions should be taken. For this purpose, guidelines established by the National Cancer Institute as published in Safety Standards for Research Involving Chemical Carcinogens [201] should be followed.

Experiments that are conducted in an open hood should be in a hood with an average face velocity of 150 feet/minute or higher [191]. Glove boxes kept under a negative pressure of 0.5 inches water gauge or more or laminar flow biologic cabinets with the face velocity required in an open hood can also be used [201]. Discharge of exhaust air from laboratory-type hoods should comply with the appropriate Federal and local regulations. All work surfaces should be covered with material impervious to absorption or penetration by hydrazines. All pipetting should be performed with mechanical devices to prevent accidental ingestion of hydrazines. Contaminated wastes and animal carcasses should be collected in impermeable containers. These containers must be kept closed until being removed for disposal.

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In the United States, the present Federal standards for occupational exposure are 8-hour TWA limits of 1.3 mg/cu m for hydrazine, 1.0 mg/cu m for 1,1-dimethylhydrazine, 22 mg/cu m for phenylhydrazine, and a ceiling concentration of 0.35 mg/cu m for methylhydrazine (29 CFR 1910.1000). These present standards are based on the Threshold Limit Values (TLVs) adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1968. Several foreign countries also have standards for occupational exposure to various hydrazines. These exposure limits are listed in Table VI-1.

(a) Documentation for Hydrazine

A TLV of 1 ppm (1.3 mg/cu m) for workplace exposure to hydrazine was adopted in 1956 by the ACGIH [203]. In addition, the ACGIH suggested that the dermal route, as well as mucous membranes and eyes, might contribute to the overall exposure to hydrazine by either airborne or direct contact with the substance.

The 1962 edition of the Documentation of the Threshold Limit Values for Substances in the Workroom Air [204] indicated a basis derived from the work of Comstock et al [55]. The 1966 edition of the documentation [205] also listed 1.3 mg/cu m as the TLV but added a study by Thomas and Back [206] as a further basis. In the 1971 documentation [207], the review of Smyth [208], and the studies of Reinhardt and Dinman [209], Patrick and Back [60], and Weatherby and Yard [210] were included to support the TLV

TABLE VI-1

OCCUPATIONAL EXPOSURE LIMITS (MG/CU M)
FOR HYDRAZINES IN FOREIGN COUNTRIES

Country	Hydrazine	Methylhydrazine	1,1-Dimethylhydrazine	Phenylhydrazine
Australia	1.3	0.2	1	22
Belgium	1.3	0.2	1	22
Federal Republic of Germany	0.13	-	-	-
Finland	0.13	0.2	1	22
German Democratic Republic	0.11	-	-	-
Netherlands	0.13	0.2	1	22
Rumania*	0.7	0.1	0.7	15
Sweden	0.13	-	-	-
Switzerland	0.13	0.2	1	22
USSR	0.1**	-	-	-
Yugoslavia	1.3	0.2	1	22

*Average concentration limit
**Hydrazine derivatives

Adapted from reference 202

for hydrazine. The 1976 documentation [211] referred to a study by Haun and Kinkead [56] in which animals were exposed to hydrazine at 1 or 5 ppm intermittently and 1 or 0.2 ppm continuously for 6 months. Depressed erythrocyte counts, hemoglobin concentrations, and hematocrit values were observed in dogs exposed at 1 ppm continuously. At the two highest

concentrations, dogs also developed fatty livers. Liver damage occurred in mice at all exposure levels. In the exposed mice that survived for a year, MacEwen [69] found a dose-related increase of lung tumors. The ACGIH concluded from these two additional studies that the TLV for hydrazine should be lowered to 0.1 ppm as a TWA concentration for a 40-hour workweek.

In Czechoslovakia, the committee for documentation of MAC's has recommended a maximum allowable concentration (MAC) of 0.1 mg/cu m for hydrazine with a peak of 0.2 mg/cu m [212]. In 1974, a commission of the German Research Association concluded that 1.0 ppm, the previous standard in the Federal Republic of Germany, could not assure protection in chronic exposure [213]. In addition, consideration was given to the carcinogenicity demonstrated in animal experiments, and the maximum workplace concentration (MAK) for hydrazine was reduced to 0.1 ppm. The conclusions of the commission were based on a review of the literature that included reports on humans [20,37,39,42,214], acute [20,57,58,215] and subchronic [55,216,210] animal experiments, and studies on the carcinogenic potential of hydrazine sulfate in animals [76,78,79,217,218].

(b) Documentation for Methylhydrazine

In 1966, the ACGIH [219] adopted as a TLV a ceiling concentration of 0.2 ppm (0.35 mg/cu m). In addition, the ACGIH pointed out that the dermal route, as well as the mucous membranes and eyes, might contribute to the overall exposure to methylhydrazine. The selection of the ceiling concentration was based on a comparison of the acute toxicity of methylhydrazine with that of 1,1-dimethylhydrazine [20,208]. This was largely based on the observation of Jacobson et al [20] that methylhydrazine resembled 1,1-dimethylhydrazine and hydrazine in its toxic

effects and that the acute toxicity of methylhydrazine was about three times that of 1,1-dimethylhydrazine. Since neither intermittent nor continuous exposure data were available for methylhydrazine, the ACGIH recommended that methylhydrazine exposure be limited to 0.2 ppm as a ceiling, which is about one-third the TLV for 1,1-dimethylhydrazine. The ACGIH ceiling concentration limit for methylhydrazine has not been changed since it was established. The documentation published in 1971 [207] referred to the studies of Haun et al [92] and Back and Pinkerton [100], but the conclusion reached in the 1971 edition did not differ from that in the 1966 edition.

In a 1974 report [213] prepared by a commission of the German Research Association, subacute and subchronic experiments on animals given methylhydrazine were cited [101,220]. On the basis of other animal studies [58,96,99,102,215,221,222], the commission concluded that methylhydrazine was more acutely toxic than hydrazine and 1,1-dimethylhydrazine so that an MAK should be below 0.1 ppm. However, the commission found no practical need for an exposure limit in the Federal Republic of Germany.

(c) Documentation for 1,1-Dimethylhydrazine

A TLV of 0.5 ppm (1.0 mg/cu m) for workplace exposure to 1,1-dimethylhydrazine was adopted in 1960 by the ACGIH [223]. In addition to recommending this environmental limit, the ACGIH stated that the dermal route, as well as mucous membranes and eyes, was a potential contributor to the overall exposure to 1,1-dimethylhydrazine. Although no basis for this TLV was provided in 1960, the 1962 edition of the Documentation of the Threshold Limit Values for Substances in the Workroom Air [204] indicated that the TLV was based primarily on studies of acute toxicity by Jacobson

et al [20] and Hodge [114]; anemia, weight loss, and lethargy observed by Reinhart et al [110] in dogs exposed at 5 ppm; and questionable evidence of liver dysfunction that Shook and Cowart [49] observed in workers exposed to 1,1-dimethylhydrazine. After considering data from these studies, the ACGIH recommended that a concentration of 0.5 ppm, or one-tenth the concentration causing anemia, weight loss, and lethargy in dogs, be adopted as the TLV for 1,1-dimethylhydrazine. The ACGIH TLV has not been modified since it was originally recommended, and the documentation [207] published in 1971 referred to the same information as the 1962 edition.

In 1974, a commission of the German Research Association of the Federal Republic of Germany recommended an MAK of 0.1 ppm (0.25 mg/cu m) for 1,1-dimethylhydrazine [213]. Although supporting results from several other studies [20,49,111,117,215,] were mentioned, the study of Rinehart et al [110] was the main basis for the conclusion of the commission that a maximum tolerated dose had not yet been determined in animal experiments. Because the possibility of the previous MAK of 0.5 ppm causing damage could not be discounted and because 1,1-dimethylhydrazine was considered more toxic than hydrazine in short-term exposure, the commission lowered the MAK for 1,1-dimethylhydrazine to 0.1 ppm. Dermal absorption was also noted as a possible route of entry. Several studies [78,81,224-226] on the carcinogenicity of 1,1-dimethylhydrazine were reviewed, but the carcinogenic potency of this compound was considered to be very weak.

(d) Documentation for 1,2-Dimethylhydrazine

There currently is no Federal standard for occupational exposure to 1,2-dimethylhydrazine. In 1974, a commission of the German Research Assocation of the Federal Republic of Germany cited several estimates

[20,215,227] of LC50's or LD50's in a report on 1,2-dimethylhydrazine [213]. It also mentioned that 1,2-dimethylhydrazine caused carcinomas in the intestines of rats after sc and oral administration [227-229], and in the colon of mice after sc injection [135]. The commission concluded that 1,2-dimethylhydrazine was highly carcinogenic, but it saw no practical need for establishing an MAK.

(e) Documentation for Phenylhydrazine

In 1956, the ACGIH established a TLV for phenylhydrazine of 5 ppm (22 mg/cu m) [203]. The ACGIH noted that the dermal route was a potential contributor to the overall exposure to phenylhydrazine. The 1962 edition of the Documentation of the Threshold Limit Values for Substances in the Workroom Air [204] suggested that the TLV should be the same as that for aniline or phenol, ie, 5 ppm. The current TLV for phenylhydrazine still is 5 ppm. Later editions of the documentation [207] contained the same substance and conclusion as the 1962 edition.

Basis for the Recommended Standard

(a) Permissible Exposure Limits

The potential for worker exposure to the hydrazines is primarily through two routes of exposure, inhalation and contact with skin or eyes. Hydrazine [59], methylhydrazine [98], and 1,1-dimethylhydrazine [115] were all readily absorbed through the shaved skin of dogs. Each compound was detectable in the blood in 30 seconds, and signs of acute toxicity ensued. Two drops of anhydrous hydrazine applied to the shaved skin of rats, as well as 3 ml applied to rabbits, were lethal [57], suggesting that even a small spill on the skin of workers could be toxic. In general, the

compound with the highest vapor pressure, 1,1-dimethylhydrazine, should be the least toxic by skin absorption because of rapid evaporation. Since 1,1-dimethylhydrazine is toxic by this route [115], other hydrazines are likely to have a similar effect. In regard to eye damage, as little as two drops of a 25% solution of hydrazine applied to the eyes of animals caused permanent damage [57]. Methylhydrazine, 1,1-dimethylhydrazine, and 1,2-dimethylhydrazine, however, produced only temporary, mild effects [58]. These effects are probably pH dependent, since alkaline compounds would be expected to cause more damage to eye surfaces; thus, the eye damage expected for phenylhydrazine and the salts of hydrazines may be similarly related to pH. The salts would be at least as water soluble, if not more so than the free bases, and many are acidic, suggesting they would be more readily removed by tear formation or induced flushing.

Results of animal studies [20,92,111] suggest that methylhydrazine may be the most acutely toxic of the hydrazines. In humans, 90 ppm (169 mg/cu m) of methylhydrazine when inhaled for 10 minutes was tolerated [44]. The median concentrations for detectable odor have been reported to be 3-4 ppm (3.92-5.22 mg/cu m) for hydrazine, 1-3 ppm (1.88-5.64 mg/cu m) for methylhydrazine, and 6-14 ppm (14.7-34.3 mg/cu m) for 1,1-dimethylhydrazine [20], but, as was discussed in Effects on Humans, actually may be lower for many people. An additional report [48] indicated a lower value for 1,1-dimethylhydrazine, 0.3 ppm (0.74 mg/cu m). The odor of phenylhydrazine, described as faint [10], may not be strong enough to warn workers of its presence. Since methylhydrazine at 90 ppm did not impair a worker's ability to escape, other less acutely toxic hydrazines at the same concentration would not be expected to interfere with this ability. To

this end, the odor of the three hydrazines studied could provide warning of acutely dangerous concentrations; however, odor should not be relied on routinely because of such problems as individual variations in threshold and odor fatigue.

Hydrazine and its salts are believed to pose a carcinogenic risk to humans since a wide variety of studies have shown that exposed rodents have developed an elevated incidence of lung tumors. Adenomas and some carcinomas have been observed in mice receiving hydrazine or its sulfate salt in drinking water [80,79] and by intubation [70-75,77,78,81], ip injection [78,81,82,84], and inhalation [69]. Lung tumors were also found in rats [76]; however, hydrazine was not carcinogenic in hamsters [75,85]. In a few cases [70,71,75], liver tumors were also reported. Some studies may be deficient in certain areas, such as inadequate controls, insufficient numbers of experimental animals, insufficient time of observation, or failure to examine all animals or all target organs; nevertheless, these deficiencies are not enough to negate the obvious conclusion, namely, that hydrazine is a carcinogen in mice and rats and that the lungs are the primary target organ.

Liver damage is the most serious effect, other than cancer, of hydrazine toxicity. In one study [56], 4 of 80 mice exposed to hydrazine at 30-33.6 ppm-hours/week died of liver damage in the form of lipid accumulation, and some survivors developed lung tumors [69]. This exposure is equivalent to 1 mg/cu m over a 40-hour week. In dogs, both anemia and fatty livers were seen in those exposed at 150 or 168 ppm-hours/week [56].

In considering the environmental limit, it is not possible to derive a level that can be demonstrated to protect workers against the predicted

carcinogenic effect of hydrazine. The control of hydrazine in breathing zone air should be attained better by a ceiling rather than a TWA limit, in large part because of the resultant limitation on excursions. However, certain restrictions are imposed by the limited sensitivity of the recommended analytical method. At a sampling rate of 1 liter/minute, if a 2-hour sample is collected and a relative standard deviation of 15% in the reproducibility of the analysis is accepted, then the lowest concentration of hydrazine in the air that is detectable should be sufficiently low to protect against hepatotoxicity and significantly lower the risk of cancer. A permissible limit for hydrazine of 0.04 mg/cu m (0.03 ppm) measured over 2 hours is, therefore, recommended.

Animal studies also provide evidence of the carcinogenicity of methylhydrazine. Lung tumors were found in mice given either methylhydrazine or its sulfate salt in drinking water [80]. In hamsters, malignant histiocytomas of the liver (54% incidence) and tumors of the cecum (14% incidence) were found in a similar drinking water study [106]. In another study [107], with a different experimental design, no tumors were found in hamsters given methylhydrazine adjusted to pH 3.5; a 12% incidence of liver tumors was found only in hamsters given unbuffered solutions of methylhydrazine. Since the site of tumor formation was species specific, it is not possible to conclude what the primary site affected might be in humans; however, the results in animals suggest that methylhydrazine poses a carcinogenic risk to workers.

As mentioned above, in considering the environmental limit for hydrazine, a short-term ceiling limit provides better control than a TWA limit. As in the case of hydrazine, there are severe limitations placed on

the environmental limit because of the lack of sensitivity of the analytical method. Even without consideration of possible carcinogenicity, there are severe toxic effects that can occur as the result of exposure to methylhydrazine. In dogs, hepatic choleostasis [93,94] and anemia [93] have been observed at exposures of 30-33.6 ppm-hours/week. Anemia was also observed in dogs and rats exposed at 16.8 ppm-hours/week [95] and in dogs exposed at 6 ppm-hours/week [93]. This lowest dose would correspond to a 40-hours/week exposure concentration of about 0.3 mg/cu m (0.15 ppm). In a 2-hour sample, the lowest concentration at which a 15% relative standard deviation in the reproducibility of the analysis is obtained is about 0.08 mg/cu m (0.04 ppm). This concentration is therefore recommended as a 2-hour limit for methylhydrazine. Even though carcinogenicity is the primary concern, the results of animal studies suggest that this environmental limit may not have a great margin of safety for other effects of exposure.

Mice given 1,1-dimethylhydrazine in drinking water for life developed a 79% incidence of blood vessel tumors and a 71% incidence of lung tumors, primarily adenomas but also some adenocarcinomas [127]. A second study suggests that lung tumors in mice were induced after intubation of 1,1-dimethylhydrazine [78]. The other effects of 1,1-dimethylhydrazine in animals appear to be mild compared with those of the other hydrazines. At 5 ppm (12.2 mg/cu m), slight anemia [110] and elevation of SGPT activity [112] have been observed in dogs. However, toxic effects on the liver have been ascribed to nitrosodimethylamine contamination [113] and, indeed, nitrosodimethylamine has been reported to be present in the air over containers of 1,1-dimethylhydrazine [187]. Though 1,1-dimethylhydrazine is toxic by itself, it is perhaps not heptotoxic unless contaminated. While

it can be speculated that contaminants also play a role in the induction of tumors in animals given 1,1-dimethylhydrazine, the evidence for this is not strong enough to suggest that pure material would not cause cancer; thus, 1,1-dimethylhydrazine should be regulated as a carcinogen. From the recommended analytical method, it can be shown that the lowest concentration of 1,1-dimethylhydrazine that can be detected with a 15% relative standard deviation is about 0.15 mg/cu m (0.06 ppm) in a 2-hour sample at 1 liter/minute, so this concentration is recommended as the environmental limit for 1,1-dimethylhydrazine. It does offer a high degree of protection against all except anticipated carcinogenic effects, and, if adhered to, it should substantially reduce, if not prevent, the expected development of 1,1-dimethylhydrazine induced cancer.

Even though there are no data on humans or on inhalation studies of 1,2-dimethylhydrazine, it appears obvious that this compound should be considered as a carcinogen for humans. The exact form of cancer that would be expected in humans, however, is less clear since metabolic activation is likely to play a role in the selection of target organs at which tumors appear. Rats [131] and mice [127] given 1,2-dimethylhydrazine in drinking water developed hemangiosarcomas and lung tumors; hamsters developed primarily hemangiosarcomas [85]. 1,2-Dimethylhydrazine, given by intubation, induced colonic tumors in rats [130,131]. Guinea pigs developed bile duct carcinomas [126]. Colon tumors have been the predominant finding after sc injections in mice [128,132-136,143] and in rats [131,137,138,140,142]. In one injection study [85], blood vessel tumors, lung tumors, and kidney tumors were also reported, but these tumors were not found in other studies [131,132], which indicates that these

tumors are probably not of major significance in animals when compared to colon tumors. No tumors were found in miniature swine and dogs, but these animals had severe liver damage and most died of intoxication [126]. Even though an acceptable analytical method has not been developed for the measurement of 1,2-dimethylhydrazine, the overwhelming evidence of its carcinogenicity in animals argues for the strict regulation of 1,2-dimethylhydrazine in the workplace. Stringent work practices, proper engineering controls, and closed systems must be considered where this compound is encountered in the workplace.

Angiomas and angiosarcomas of the blood vessels were found in mice given phenylhydrazine hydrochloride in the drinking water [152]. In mice given the same compound by intubation, an increased incidence of adenomas and adenocarcinomas of the lungs was observed [151]. The difference in the sites of tumor formation according to the route of administration is not unlike the results seen for 1,2-dimethylhydrazine. The information presented indicates that phenylhydrazine should be regulated as a carcinogen. Phenylhydrazine is also a hemolytic agent [145,147,148], but sufficient information on which to establish a safe environmental limit for protecting against blood effects is not available. The lowest concentration tested in which the reproducibility of the analysis was within 15% relative standard deviation is the equivalent of 0.6 mg/cu m (0.14 ppm) when the sample is collected over 2 hours at a flowrate of 1 liter/minute. Thus, this concentration is proposed as the environmental limit for phenylhydrazine. The protective value of this limit cannot now be determined.

The worker must be protected to minimize the risks of systemic toxicity, eye damage, and sensitization that can result from contact with the hydrazines and their salts and of cancer that is predicted to be a possible result from contact with or inhalation of these hydrazines. For these reasons, occupational exposure to hydrazines is defined as work in any area where one or more of the hydrazines is stored, produced, processed, transported, handled, or otherwise used and present in such a manner that vapors or aerosols may be released in workroom air or that the hydrazines may spill or splash onto the skin or into the eyes. Because even small spills of hydrazines on the skin can result in severe systemic toxicity, all employees assigned to such a work area, even temporarily, for any purpose, including maintenance or repair, should be regarded as occupationally exposed. Workers in areas where hydrazines are used, either in open or closed systems should be considered to be occupationally exposed, since there is no effective way to demonstrate that a closed system remains completely free of leaks. Conversely, workers assigned only to control rooms in which no air from other hydrazine containing areas is present, should not be considered occupationally exposed.

Although information is not available on the effects of exposure to mixtures of hydrazines or to combinations of the free bases and the acid salts, it seems reasonable that their toxicity would be additive. While the analytical method outlined in Appendix I is not capable of the reliable measurement of concentrations below the recommended limits, it will provide at least a semiquantitative indication of potentially hazardous combinations. Should such a situation exist, employee exposure must be

lowered below the recommended limits for individual compounds to ensure adequate protection of employees.

(b) Sampling and Analysis

The recommended method of sampling and analysis should be simple, sensitive, and selective for the individual compounds. In addition, sampling should be representative of the workers' breathing zone air without impeding their normal job performance. As was discussed in more detail in Chapter IV, sampling on silica gel tubes followed by gas chromatographic analysis is recommended. Detailed information on these methods is given in Appendix I. The sampling tubes are easily handled and do not interfere with the worker and the method is specific for each hydrazine compound. Where mixtures are present, all compounds can be determined at the same time on a single sample. However, the method has been developed only recently, so that its limitations are not as well known as are those of the colorimetric methods [155]. A suitable method for collection of the salts of hydrazines has not been attempted, either in the laboratory or in field studies. There is some question as to whether or not the other compounds are as stable as 1,1-dimethylhydrazine when they are stored in the collection tube for several days, a factor of great importance if the samples must be shipped from their collection site to a laboratory in a different location. Even more important, information on the precision, accuracy, and sensitivity of the method is limited and appears to indicate that the method may be less sensitive than would be desired. While slight alterations in the method might improve sensitivity, necessary information is not available at the present time. In addition, since the complex with furaldehyde would not form, the same gas-

chromatographic method is not suitable for measurement of 1,2-dimethylhydrazine.

(c) Medical Surveillance

Mandatory medical surveillance for workers exposed to the hydrazines should include comprehensive preplacement and periodic examinations giving particular attention to signs of liver, kidney, or blood cell damage, such as jaundice or anemia, and to evidence of possible dermal exposure. The frequency of periodic examinations should depend on the probable exposure of the workers, but in all cases examinations should be conducted at least annually. For those who work with hydrazines intermittently, examinations should be conducted during or shortly after such work. Because the hemolytic effects ranged from moderate to severe in animals exposed to all the hydrazines, specific clinical tests should include complete blood counts including differential. Similarily, varying degrees of liver damage have been observed, so tests of liver function, including SGOT and SGPT are recommended. Complete urinalysis should be performed and should include microscopic examination, determination of specific gravity, and glucose content. Tests for urobilinogen and serum bilirubin should also be considered. Chest roentgenograms should be performed to aid in the detection of any adverse effects of hydrazines on the lungs. In workers over 40, proctosigmoidoscopy must be performed on those exposed to 1,2-dimethylhydrazine, and it should be considered for workers exposed to the other hydrazines.

Preplacement and interim medical and work histories should supplement the information obtained from medical tests. Because animal studies show that numerous body systems have been adversely affected by exposure to the

hydrazines, regardless of the type of exposure, medical and work histories and physical examinations should be thorough, with particular attention being paid to combinations of signs or symptoms that may point to a toxic action of the hydrazines. The results of animal experiments make it evident that these hydrazines are eye irritants. If hydrazines are accidentally splashed into the eyes, they should be treated by immediate flushing with copious quantities of water. All of the free bases, and probably the salts as well, are readily absorbed through the skin. Responsible medical personnel should ensure that plant personnel are properly instructed on these points, as appropriate to the forms of hydrazines being handled.

Since there is evidence from animal experiments to suggest that these hydrazines are carcinogenic, all pertinent medical records should be kept for 30 years after the last occupational exposure to the hydrazines.

(d) Personal Protective Equipment and Clothing

The hydrazines, especially hydrazine, may damage the eyes, and they are likely to be dermal irritants that penetrate the skin to cause systemic toxicity. Therefore, full-face plastic shields (8-inch minimum) and goggles, gloves, boots, and other impervious protective clothing should be used to prevent direct contact. During emergencies, nonroutine maintenance, or entry into confined spaces, respirators may be used to minimize inhalation exposure. Since these hydrazines are judged to pose a risk of cancer to employees, only self-contained, air-supplied respirators with positive pressure in the facepiece are recommended for working in areas where vapors or aerosols of the hydrazines are present.

All foreseeable events that could result in a need to escape from a hazardous area should be evaluated to establish evacuation procedures and to determine the equipment needed. Escape equipment should be kept in readily accessible locations. A self-contained breathing apparatus with positive pressure in the face piece should be provided for escape except for those situations where the time otherwise needed for escape from the area is less than that required to put on the respirator or those cases in which an immediate life-threatening situation, such as explosion, exists.

(e) Informing Employees of Hazards

A continuing education program is an important part of preventive hygiene. At the beginning of employment and periodically thereafter, employees who are potentially exposed to hydrazines should be instructed by properly trained persons about job hazards, signs and symptoms of overexposure, proper procedures for routine handling and disposal, and proper use and maintenance of protective clothing and equipment. The function of monitoring equipment, such as personal samplers, should be explained so that employers understand their part in workplace monitoring. Medical monitoring procedures and their importance in detecting possible adverse effects should be explained and the importance of employees participating in these procedures emphasized. Periodic drills on emergency situations, evacuation procedures, spill cleanup, and decontamination procedures should be held to ensure that employees can perform their assigned duties in these situations.

(f) Work Practices

Severe health effects, both acute and chronic, can result from exposure to hydrazines and their salts. For this reason, both the number

of persons handling hydrazines and their exposures should be limited to the greatest extent possible. Regulated areas should be established where hydrazines are present and only those employees needed to perform the job and knowledgeable of the hazards associated with the handling of hydrazines should be given access. Records of persons entering regulated areas should be maintained to provide documentation of those employees who may be occupationally exposed to hydrazines. Proper exhaust ventilation, waste disposal, and hygiene practices, including the removal of work clothing and showering when leaving the regulated area, should minimize the spread of contamination to other areas.

Within the regulated area, workrooms should be designed to prevent the buildup of vapor or aerosol concentrations of hydrazines. Engineering controls, such as process enclosure, can be an effective way to minimize airborne contamination. All process equipment should be designed to minimize the possibility of leaks. Sanitation measures, such as prohibiting smoking or eating in work areas where hydrazines are present, are necessary to limit ingestion of hydrazines.

Contact with hydrazines can result in irreversible eye damage, and the five hydrazines, as well as their salts, probably all penetrate the skin readily. When hydrazines are used in open systems, a condition often found in laboratories or following a spill or leak, it is especially important that the employee not come into contact with hydrazines or their concentrated solutions. Proper procedures must be followed to prevent such contact.

Hydrazine can be ignited either in the liquid or vapor phase. At normal temperatures, aqueous solutions of hydrazine, methylhydrazine, and

1,1-dimethylhydrazine at concentrations greater than 40, 50, and 25%, respectively, are also ignitable. Because of relatively high vapor pressures, the lower explosion limits for methylhydrazine and 1,1-dimethylhydrazine can be reached at room temperature. While it is unlikely that the lower explosion limit for hydrazine would be reached at normal temperatures, as pointed out in Chapter V, hydrazine, methylhydrazine, and 1,1-dimethylhydrazine are pyrophoric under some conditions and hypergolic with some oxidizing substances. To avoid the formation of explosive concentrations in air and also to retard air oxidation, an inert gas should blanket these hydrazines. In storing, handling, and transporting flammable or combustible hydrazines, employees should remove all sources of sparks and oxidants and keep other incompatible material away to reduce the possibility of fire or explosion. The explosion hazard, along with the toxicity of hydrazines, makes it necessary to establish stringent procedures in case of emergencies, including fires, or for entry into confined spaces.

(g) Monitoring and Recordkeeping Requirements

The need for medical and environmental monitoring is established by an evaluation of the work situation. Likewise, whether or not protective clothing and equipment are needed to prevent direct skin and eye contact must be determined by conditions present in the workplace. Those areas that must be regulated also have to be established. For these reasons an industrial hygiene survey should be conducted before any new operation is begun to determine the areas where employees may be exposed to hydrazines. A similar survey should be conducted once a year and within 14 days after

any process changes likely to increase the concentration of hydrazines to ensure that employees continue to be adequately protected.

In work areas in which occupational exposure to hydrazines is found, a program of monitoring of the breathing zone of workers should be instituted. Other monitoring, such as area monitoring, may be a useful supplement to personal monitoring, especially for evaluation of the process and of methods of controlling the process. Records of monitoring and logs of those entering regulated areas should be kept, and copies should be maintained together with individual medical records to help answer questions about possible associations, casual or otherwise, between health effects and the work environment. Environmental and medical records should be kept for 30 years after the individual's last occupational exposure to hydrazines because of the long induction time, often 20 or more years, in tumor development. This is also compatible with requirements of the Toxic Substances Control Act.

VII. RESEARCH NEEDS

Few studies have reported the toxic effects of exposure to hydrazines on humans, and when these effects were reported, the extent of exposure was not determined nor were the cases followed up. No epidemiologic studies and little environmental data were found. Epidemiologic studies are needed of worker populations whose length of exposure to hydrazines approaches a normal working lifetime. These studies could determine possible chronic effects, such as blood or liver abnormalities and cancer, and possible interactions such as smoking and alcohol consumption. Environmental and medical data are needed to establish the validity of the present recommendations.

CNS effects, hemolytic changes, renal and hepatic damage, and tumorigenic effects caused by exposure to the hydrazines have been well documented, mostly in animal studies. However, there are species differences for many of these effects, and it is not apparent at this time which effects on animals most closely resemble those on humans. This problem needs clarification. In addition, toxic effects caused by inhaling phenylhydrazine and 1,2-dimethylhydrazine need to be investigated, especially as they relate to long-term exposure. Better information on questions of whether or not the hydrazines cause prenatal or perinatal changes (teratogenicity), inherited changes (germinal mutagenicity), or other effects on reproduction is needed.

The stability of the hydrazines needs to be examined with particular emphasis on the quantity and identity of impurities that occur either from

manufacture or decomposition. Possible effects of these impurities on toxicity of the hydrazines should be investigated.

Available data from animal studies support the conclusion that hydrazine and 1,2-dimethylhydrazine may be carcinogenic in humans; the exposure routes were usually sc, ip, or oral. The role of nitrosodimethylamine in tumorigenicity and the amount present in 1,1-dimethylhydrazine need to be examined. Data on the carcinogenicity of methylhydrazine and phenylhydrazine are less definitive, and more information on these compounds is needed. In many cases, only specific sites of tumor induction were examined; these studies should be extended to include other organs or systems. It is likely that these hydrazines are carcinogens when inhaled, but confirmation is desirable. A mechanism of carcinogenicity for 1,2-dimethylhydrazine has been postulated, but no similar information is available for the other hydrazines. Further studies on the metabolism of these compounds may reveal possible mechanisms and species differences relevant to tumor induction.

A gas-chromatographic method has been recommended for monitoring hydrazines except for 1,2-dimethylhydrazine. A method for 1,2-dimethylhydrazine, although it may have limited use, needs to be developed. The gas-chromatographic method itself is not as sensitive as would be desirable, and it has not been tested for its ability to measure hydrazine salts. The method needs to be tested in the field and modified to improve sensitivity. A sampling method capable of collecting both vapors and aerosols needs to be tested. In addition to the gas-chromatographic method, a specific and continuous monitoring method would be desirable to

document exposure in the workplace and to warn of overexposure. A method capable of measuring total hydrazines would also be useful, especially in situations where employees are exposed to mixtures of hydrazines.

VIII. REFERENCES

1. Hydrazine Solution--85% Technical Monohydrate (N_2H_4 54.4% min). New York, Olin Mathieson Chemical Corp, Chemical Division, 1964, 4 pp

2. Cloyd DR, Murphy WJ: Hydrazine compounds, in Handling Hazardous Materials, report No. NASA SP-5032. Greenbelt, Md, National Aeronautics and Space Administration, 1965, pp 81-93

3. Clark DA, Bairrington JD, Bitter HL, Coe FL, Medina MA, Merritt JH, Scott WN: Pharmocology and toxicology of propellant hydrazines in Aeromedical Reviews, review 11-68. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1968, 126 pp (NTIS AD 688 500)

4. Melvin WW, Johnson WS: Survey of Information Relevant to Occupational Health Standards for Hydrazines. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1976, 75 pp (NTIS AD A022 851)

5. Some Aromatic Amines, Hydrazine and Related Substances, n-Nitroso Compounds and Miscellaneous Alkylating Agents. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Lyon, France, International Agency for Research on Cancer, 1974, vol 4, pp 127-72

6. Guides for Short-Term Exposures of the Public to Air Pollutants--V. Guide for Hydrazine, Monomethylhydrazine, and 1,1-Dimethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1974, 57 pp (NTIS PB 244 337)

7. Cristensen HE, Fairchild EJ, Carroll BS, Lewis RJ Sr: Registry of Toxic Effects of Chemical Substances, 1976 ed, DHEW publication No. (NIOSH) 76-191. Rockville, Md, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1976, pp 594-98

8. Christopher GLM, Brown CT: Hydrazine Impurity Survey. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, 57 pp (NTIS AD 764 365)

9. Sax NI: Dangerous Properties of Industrial Materials, ed 3. New York, Van Nostrand Reinhold Co, 1968, pp 691,819-20,927,974,1013-14

10. Phenylhydrazine, in Stecher PG, (ed.): The Merck Index--An Encyclopedia of Chemicals and Drugs, ed 8. Rahway, NJ, Merck and Co Inc, 1968, pp 377,817-18,862,1128

11. Raphaelian LA: Hydrazine and its derivatives, in Kirk-Othmer Encyclopedia of Chemical Technology, ed 2 rev. New York, Interscience Publishers, 1963, vol 2, pp 762-806

12. Urry WH, Olsen AL, Bens EM: Autoxidation of 1,1-Dimethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1965, 37 pp (NTIS AD 622 785)

13. Miller RL, Conkle JP, Lackey WW, Dixon GA: Comparison of Analytical Methods for Measurement of n-Nitrosodimethylamine in 1,1-Dimethylhydrazine-enriched Atmospheres, paper No. 22. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1967, pp 64-94 (NTIS AD A04 1973)

14. Gormley WT, Ford RE: Deoxygenation of environmental waters by hydrazine-type fuels, in Proceedings of the 4th Annual Conference on Environmental Toxicology. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, pp 387-400 (NTIS AD 781 031)

15. Hoover WL, Bloodworth ME, Clark WJ, Heck WW, Hold L: Environmental Pollution by Missile Propellants, report No. AMRL-TDR-64-5. Wright-Patterson Air Force Base, Ohio, US Air Force, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratories, 1964, 54 pp

16. Ekshtat BY: Maximum permissible concentrations of hydrazine hydrate and phenylhydrazine in water bodies. Hyg Sanit 30:191-97, 1965

17. Vernot EH, MacEwen JD, Geiger DL, Haun CC: The air oxidation of monomethylhydrazine. Am Ind Hyg Assoc J 28:343-47, 1967

18. Saunders RA, Larkins JT: Detection and Monitoring of Hydrazine, Monomethylhydrazine, and Their Decomposition Products--A Final Report, NRL memorandum report No. 3313. US Navy, Naval Research Laboratory, Chemistry Division, Physical Chemistry Branch, 1976, 23 pp

19. Martignoni P, Duncan WA, Murfree JA, Nappier HA, Phillips J, Wharton WW: The Thermal and Catalytic Decomposition of Methylhydrazines. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, 57 pp (NTIS AD 764 365)

20. Jacobson KH, Clem JH, Wheelwright HJ, Rinehart WE, Mayes N: The acute toxicity of the vapors of some methylated hydrazine derivatives. Arch Ind Health 12:609-16, 1955

21. Sutton WL: Hydrazine, in Patty FA (ed.): Industrial Hygiene and Toxicology, ed 2 rev; Toxicology (Fassett DW, Irish DD, eds.). New York, Interscience Publishers, 1963, vol 2, pp 2218-29

22. Hawley GG (ed.): The Condensed Chemical Dictionary, ed 8. New York, Van Nostrand Reinhold Co, 1975, pp 314,451,575-76,681-82

23. Gafafer WM (ed.): Occupational Diseases--A Guide to Their Recognition, PHS publication No. 1097. US Dept of Health, Education, and Welfare, Public Health Service, Division of Occupational Health, 1964, pp 131-32,158-59,200-01

24. Toth B: Synthetic and naturally occurring hydrazines as possible cancer causative agents. Cancer Res 35:3693-97, 1975

25. Lowenheim FA, Moran MK (eds.): Faith, Keyes, and Clark's Industrial Chemicals, ed 4. New York, John Wiley and Sons, 1975, pp 449-53

26. Knight OA: New synthetic fuel--Monomethylhydrazine. Hydrocarbon Processing Pet Refiner 41:179-84, 1962

27. Formation and preparation of hydrazine, in Audrieth LF, Ogg BA: The Chemistry of Hydrazine. New York, John Wiley and Sons Inc, 1951, pp 13-14

28. Plant observation reports and evaluation. Menlo Park, Calif, SRI International, March 31, 1978, 110 pp (submitted to NIOSH under contract No. CDC-99-74-31)

29. Clark CC: Hydrazine. Baltimore, Mathieson Chemical Corp, 1953, pp 1-2,110-13

30. Underhill FP, Kleiner IS: The influence of hydrazine upon intermediary metabolism in the dog. J Biol Chem 4:165-78, 1908

31. Wells HG: The pathological anatomy of hydrazine poisoning. J Exp Med 10:457-65, 1908

32. Underhill FP: Studies in carbohydrate metabolism--I. The influence of hydrazine upon the organism, with special reference to the blood sugar content. J Biol Chem 10:159-68, 1911

33. Underhill FP, Hogan AG: Studies in carbohydrate metabolism--VIII. The influence of hydrazine on the utilization of dextrose. J Biol Chem 20:203-10, 1915

34. Underhill FP: Studies in carbohydrate metabolism--IV. Do hydrazine derivatives show the typical hydrazine effect upon blood sugar content? J Biol Chem 17:295-98, 1914

35. Bodansky M: The action of hydrazine and some of its derivatives in producing liver injury as measured by the effect on levulose tolerance. J Biol Chem 58:799-811, 1924

36. Wright IS, Joyner EN: Skin hypersensitivity to phenylhydrazine hydrochloride. Am J Med Sci 179:683-87, 1930

37. Gardenghi G: [Occupational eczema caused by hydrazine sulfate.] Rass Med Ind 21:270-72, 1952 (Ita)

38. Evans DM: Two cases of hydrazine hydrate dermatitis without systemic intoxication. Br J Ind Med 16:126-27, 1959

39. Schultheiss E: [Hypersensitivity to hydrazine.] Berufs Dermatosen 7:131-36, 1959 (Ger)

40. Frost J, Hjorth N: [Contact dermatitis from hydrazine hydrochloride in soldering flux--Cross sensitization to Apresoline and isoniazid.] Acta Derm Venereol 39:82-86, 1959 (Ger)

41. Wheeler CE, Penn SR, Cawley EP: Dermatitis from hydrazine hydrobromide solder flux. Arch Dermatol 91:235-39, 1965

42. Reid FJ: Hydrazine poisoning. Br Med J 5472:1246, 1965

43. Sotaniemi E, Hirvonen J, Isomaki H, Takkunen J, Kaila J: Hydrazine toxicity in the human--Report of a fatal case. Ann Clin Res 3:30-33, 1971

44. MacEwen JD, Theodore J, Vernot EH: Human Exposure to EEL Concentrations of Monomethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1970, pp 355-63 (NTIS AD 727 527)

45. George ME: Effects of Monomethylhydrazine on Human Red Blood Cells. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, 24 pp (NTIS AD 770 283)

46. Fortney SR, Clark DA: Effect of monomethylhydrazine on methemoglobin production in vitro and in vivo. Aerosp Med 38:239-42, 1967

47. Leahy HF: Monomethylhydrazine effect on blood, in vitro, in Proceedings of the 1st Annual Conference on Environmental Toxicology. Springfield Va, US Dept of Commerce, National Technical Information Service, 1970, pp 365-73 (NTIS AD 727 528)

48. Rumsey DW, Cesta RP: Odor threshold levels for UDMH and NO2. Am Ind Hyg Assoc J 31:339-42, 1970

49. Shook BS, Cowart OH: Health hazards associated with unsymmetrical dimethylhydrazine. Ind Med Surg 26:333-36, 1957

50. Petersen P, Bredahl E, Lauritsen O, Laursen T: Examination of the liver in personnel working with liquid rocket propellant. Br J Ind Med 27:141-46, 1970

51. Giffin HZ, Conner HM: Untoward effects of treatment by phenylhydrazine hydrochloride. J Am Med Assoc 92:1505-07, 1929

52. Giffin HZ, Allen EV: The control and complete remission of polycythemia vera following the prolonged administration of phenylhydrazine hydrochloride. Am J Med Sci 185:1-13, 1933

53. Polycythaemia, erythraemia and erythrocytosis, in Whitby LE, Britton CJ: Disorders of the Blood, ed 7. London, J and A Churchill Ltd, 1957, pp 496-503

54. Downing JG: Dermatitis from phenylhydrazine compounds--Report of a case. N Engl J Med 216:240-41, 1937

55. Comstock CC, Lawson LH, Greene EA, Oberst FW: Inhalation toxicity of hydrazine vapor. AMA Arch Ind Hyg Occup Med 10:476-90, 1954

56. Haun CC, Kinkead ER: Chronic Inhalation Toxicity of Hydrazine, in Proceedings of the 4th Annual Conference on Environmental Toxicology. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, pp 351-63 (NTIS AD 781 031)

57. Thienes CH, Roth HP, Swenson EA, Morgan VC, Lombard CF: Final Report on Acute and Chronic Toxicity of Hydrazine. Los Angeles, University Park, University of Southern California School of Medicine, Dept of Pharmacology and Toxicology, 1948, 51 pp

58. Rothberg S, Cope OB: Toxicity Studies on Hydrazine, Methylhydrazine, Symmetrical Dimethylhydrazine, Unsymmetrical Dimethylhydrazine and Dimethylnitrosamine (U), Chemical Warfare Laboratories report No. 2027. Army Chemical Center, Edgewood, Md, US Army Chemical Corps Research and Development Command, Chemical Warfare Laboratories, Toxicology Division, 1955, 21 pp

59. Smith EB, Clark DA: Absorption of hydrazine through canine skin. Toxicol Appl Pharmacol 21:186-93, 1972

60. Patrick RL, Back KC: Pathology and toxicology of repeated doses of hydrazine and 1,1-dimethylhydrazine in monkeys and rats. Ind Med Surg 34:430-35, 1965

61. Wong ET: Renal functional response to hydrazine and 1,1-dimethylhydrazine. Toxicol Appl Pharmacol 8:51-56, 1966

62. Van Stee EW: Acute effects of exposure to hydrazine and hydrazine derivatives on renal function in the dog. Aerosp Med 36:764-67, 1965

63. Fortney SR: Effect of hydrazine on liver glycogen, arterial glucose, lactate, pyruvate and acid-base balance in the anesthetized dog. J Pharmacol Exp Ther 153:562-68, 1966

64. Taylor GD: Effects of Hydrazine on Blood Glucose and Muscle and Liver Glycogen in the Anesthetized Dog, report No. SAM-TR-66-12. Brooks Air Force Base, Tex, US Air Force, USAF School of Aerospace Medicine, 1966, 10 pp

65. Aleyassine H, Lee SH: Inhibition by hydrazine, phenelzine and pargyline of insulin release from rat pancreas. Endocrinology 89:125-29, 1971

66. McKennis H, Weatherby JH, Witkin LB: Studies on the excretion of hydrazine and metabolites. J Pharmacol Exp Ther 114:385-90, 1955

67. McKennis H, Yard AS, Weatherby JH, Hagy JA: Acetylation of hydrazine and the formation of 1,2-diacetylhydrazine in vivo. J Pharmacol Exp Ther 126:109-16, 1959

68. Dambrauskas T, Cornish HH: The distribution, metabolism, and excretion of hydrazine in rat and mouse. Toxicol Appl Pharmacol 6:653-63, 1964

69. MacEwen JD: The Effects of 6-Month Chronic Low Level Inhalation Exposures to Hydrazine on Animals. Springfield Va, US Dept of Commerce, National Technical Information Service, 1974, 19 pp (NTIS AD A011 865)

70. Biancifiori C: [Lung and liver tumors induced by low doses of hydrazine sulfate in BALB/c/Cb/Se mice.] Lav Ist Anat Istol Patol Univ Studi Perugia 30:89-99, 1970 (Ita)

71. Biancifiori C, Bucciarelli E, Clayson DB, Santilli FE: Induction of hepatomas in CBA/Cb/Se mice by hydrazine sulfate and the lack of effect of croton oil on tumour induction in BALB/c/Cb/Se mice. Br J Cancer 18:543-50, 1964

72. Biancifiori C, Ribacchi R, Bucciarelli E, DiLeo FP, Milia U: [Lung carcinogenesis from hydrazine sulfate in BALB/c female mice.] Lav Ist Anat Istol Patol Univ Studi Perugia 23:115-28 1963 (Ita)

73. Biancifiori C: Ovarian influence on pulmonary carcinogenesis by hydrazine sulfate in BALB/c/Cb/Se mice. J Natl Cancer Inst 45:965-70, 1970

74. Milia U: Early findings in pulmonary carcinogenesis by hydrazine sulfate, in Lung Tumors in Animals, Proceedings of the Third Perugia Quandrennial International Conference on Cancer. Perugia, Italy, University of Perugia, Division of Cancer Research 1966, pp 863-68

75. Biancifiori C: Hepatomas in CBA/Cb/Se mice and liver lesions in golden hamsters induced by hydrazine sulfate. J Natl Cancer Inst 44:943-53, 1970

76. Severi L, Biancifiori C: Hepatic carcinogenesis in CBA/Cb/Se mice and Cb/Se rats by isonicotinic acid hydrazide and hydrazine sulfate. J Natl Cancer Inst 41:331-49, 1968

77. Biancifiori C: [The existance of a hormonal factor in pulmonary carcinogenesis from hydrazine.] Lav Ist Anat Istol Patol Univ Studi Perugia 29:29-41, 1969 (Ita)

78. Roe FJC, Grant GA, Millican DM: Carcinogenicity of hydrazine and 1,1-dimethylhydrazine for mouse lung. Nature 216:375-76, 1967

79. Toth B: Lung tumor induction and inhibition of breast adenocarcinomas by hydrazine sulfate in mice. J Natl Cancer Inst 42:469-75, 1969

80. Toth B: Hydrazine, methylhydrazine and methylhydrazine sulfate carcinogenesis in Swiss mice--Failure of ammonium hydroxide to interfere in the development of tumors. Int J Cancer 9:109-18, 1972

81. Kelly MG, O'Gara RW, Yancy ST, Gadekar K, Botkin C, Oliverio VJ: Comparative carcinogenicity of n-isopropyl-a-(2-methylhydrazino)-p-toluamide HCl (procarbazine hydrochloride), its degradation products, other hydrazines, and isonicotinic acid hydrazide. J Natl Cancer Inst 42:337-44, 1969

82. Mirvish SS, Chen L, Haran-Ghera N, Berenblum I: Comparative study of lung carcinogenesis, promoting action in leukaemogenesis and initiating action in skin tumorigenesis by urethane, hydrazine and related compounds. Int J Cancer 4:318-26, 1969

83. Juhasz J, Balo J, Szende B: Tumour-inducing effect of hydrazine in mice. Nature 210:1377, 1966

84. Milia U, Biancifiori C, Santilli FEG: Late findings in pulmonary carcinogenesis by hydrazine sulfate in newborn BALB/c/Cb/Se substrain mice. Lav Ist Anat Istol Patol Univ Studi Perugia 25:165-71, 1965

85. Toth B: Tumorigenesis studies with 1,2-dimethylhydrazine dihydrochloride, hydrazine sulfate, and isonicotinic acid in golden hamsters. Cancer Res 32:804-07, 1972

86. Toth B: Studies on the incidence, morphology, transplantation, and cell-free filtration of malignant lymphomas in the Syrian Golden hamster. Cancer Res 27:1430-42, 1967

87. Rohrborn G, Propping P, Buselmaier W: Mutagenic activity of isoniazid and hydrazine in mammalian test systems. Mutat Res 16:189-94, 1972

88. Herbold B, Buselmaier W: Induction of point mutations by different chemical mechanisms in the liver microsomal assay. Mutat Res 40:73-83, 1976

89. Lee SH, Aleyassine H: Hydrazine toxicity in pregnant rats. Arch Environ Health 21:615-19, 1970

90. Greenhouse G: Effects of Pollutants on Eggs, Embryos and Larvae of Amphibian Species. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1976, 24 pp (NTIS AD A025 403)

91. Greenhouse G: Evaluation of the teratogenic effects of hydrazine, methylhydrazine, and dimethylhydrazine on embryos of Xenopus laevis, the South African clawed toad. Teratology 13:167-77, 1976

92. Haun CC, MacEwen JD, Vernot EH, Egan GF: The Acute Inhalation Toxicity of Monomethylhydrazine Vapor, report No. AMRL-TR-68-169. Wright-Patterson Air Force Base, Ohio, US Air Force, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratories, Toxic Hazards Division, Toxicology Branch, 1969, 48 pp

93. MacEwen JD, Haun CC: Chronic Exposure Studies with Monomethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1971, 15 pp (NTIS AD 751 440)

94. Kroe DJ: Animal Pathology Resulting from Long-Term Exposure to Low Levels of Monomethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1971, pp 271-78 (NTIS AD 751 441)

95. Darmer KI Jr, MacEwen JD: Monomethylhydrazines--Chronic low level exposures and 24-hour emergency exposure limits, in Proceedings of the 4th Annual Conference on Environmental Toxicology. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, pp 373-85 (NTIS AD 781 031)

96. O'Brien RD, Kirkpatrick M, Miller PS: Poisoning of the rat by hydrazine and alkylhydrazines. Toxicol Appl Pharmacol 6:371-77, 1964

97. Gregory AR, Warrington HP, Bafus DA, Bailey JW, Legg CA, Cornish MH, Evans DQ: Monomethylhydrazine nitrate toxicity. Proc West Pharmacol Soc 14:117-120, 1971

98. Smith EB, Clark DA: The absorption of monomethylhydrazine through canine skin. Proc Soc Exp Biol Med 131:226-32, 1969

99. Sopher RL, Esoparza AR, Robinson FR: Renal pathology of acute methylhydrazine intoxication in dogs. Aerosp Med 40:55-61, 1969

100. Back KC, Pinkerton MK: Toxicology and Pathology of Repeated Doses of Monomethylhydrazine in Monkeys, report No. AMRL-TR-66-199. Wright-Patterson Air Force Base, Ohio, US Air Force, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratories, Biomedical Laboratory, 1966, 15 pp

101. George ME, Mautner W, Back KC: Nephrotoxic Effects of Monomethylhydrazine in Monkeys, report No. AMRL-TR-68-110. Wright-

Patterson Air Force Base, Ohio, US Air Force, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Laboratories, Biomedical Laboratories, 1968, 18 pp

102. Reynolds HH, Back KC: Effect of injected monomethylhydrazine on primate performance. Toxicol Appl Pharmacol 9:376-89, 1966

103. Dost FN, Reed DJ, Wang CH: The metabolic fate of monomethylhydrazine and unsymmetrical dimethylhydrazine. Biochem Pharmacol 15:325-32, 1966

104. Pinkerton MK, Hagan EA, Back KC: Distribution and Excretion of 14C-Monomethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1967, 20 pp (NTIS AD 666 662)

105. Dost FN: Metabolic Effects of Monomethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1973, 36 pp (NTIS AD 767 596)

106. Toth B, Shimizu H: Methylhydrazine tumorigenesis in syrian golden hamsters and the morphology of malignant histiocytomas. Cancer Res 33:2744-53, 1973

107. Toxic Hazards Research Unit Annual Technical Report--1975. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1975, pp 101-11 (NTIS AD A019 546 LLC)

108. Chaube S, Murphy ML: Fetal malformation produced in rats by N-isopropyl-1-(2-methylhydrazino)-p-toluamide hydrochloride (procarbazine). Teratology 2:23-32, 1969

109. Brusick D, Matheson D: Mutagenic Evaluation of 1,1-Dimethylhydrazine, Methylhydrazine and n-Phenyl-a-naphthylamine, paper No. 4 Springfield, Va, US Dept of Commerce, National Technical Information Service, 1976, pp 108-39 (NTIS AD A04 1973)

110. Rinehart WE, Donati E, Green EA: The sub-acute and chronic toxicity of 1,1-dimethylhydrazine vapor. Am Ind Hyg Assoc J 21:207-10, 1960

111. Weeks MH, Maxey GC, Sicks ME, Greene EA: Vapor toxicity of UDMH in rats and dogs from short exposures. Am Ind Hyg Assoc J 24:137-43, 1963

112. Back KC, Carter VL Jr, Thomas AA: Occupational Hazards of Missile Operations with Special Regard to the Hydrazine Propellants, in JANNAF Working Group on Safety and Environmental Protection--Minutes of April 10-77 Meeting--John F. Kennedy Space Center, Florida. Laurel, Md, Johns Hopkins University, Chemical Propulsion Information Agency, Applied Physics Laboratory, 1977, pp 25-47

113. Haun CC: Canine Hepatotoxic Response to the Inhalation of 1,1-Dimethylhydrazine (UDMH) and 1,1-Dimethylhydrazine with

Dimethylnitrosamine (DMNA), paper No. 9. Springfield Va, US Dept of Commerce, National Technical Information Service, 1967, pp 188-92 (NTIS ADA04 1973)

114. Hodge HC: Screening Toxicity Tests of Unsymmetrical Dimethylhydrazine. Rochester, NY, University of Rochester School of Medicine and Dentistry, Division of Pharmacology and Toxicology, 1954, 9 pp

115. Smith EB, Clark DA: Absorption of unsymmetrical dimethylhydrazine (UDMH) through canine skin. Toxicol Appl Pharmacol 18:649-59, 1971

116. Cornish HH, Barth ML: Biochemical response to 1,1-dimethylhydrazine (UDMH). Toxicol Appl Pharmacol 6:568-75, 1964

117. Cornish HH, Hartung R: The subacute toxicity of 1,1-dimethylhydrazine. Toxicol Appl Pharmacol 15:62-68, 1969

118. Reynolds HH, Rohles FH, Fineg J: The Effect of UDMH Injection on Learned Behavior in the Java Monkey. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1962, 20 pp (NTIS AD 283 846)

119. Reynolds HH, Rohles FH, Prine JR, Back, KC: The effect of 1,1-dimethylhydrazine (UDMH) on complex avoidance behavior in the Java monkey. Aerosp Med 35:377-82, 1964

120. Mitz MA, Aldrich FL, Vasta BM: Study of the Intermediary Metabolic Pathways of 1,1-Dimethylhydrazine (UDMH), report No. AMRL-TDR-62-110. Wright-Patterson Air Force Base, Ohio, US Air Force, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratories, Biomedical Laboratory, 1962, 28 pp

121. Reed DJ, Dost FN, McCutcheon RS, Barbour, RD, Wang CH: Biochemical and Pharmacological Studies of 1,1-Dimethylhydrazine. Springfield, Va, US Dept of Commerce National Technical Information Service, 1963, 18 pp (NITS AD 431 216)

122. Back KC, Pinkerton MK, Cooper AB, Thomas AA: Absorption, distribution, and excretion of 1,1-dimethylhydrazine (UDMH). Toxicol Appl Pharmacol 5:401-13, 1963

123. Toth B: 1,1-Dimethylhydrazine (unsymmetrical) carcinogenesis in mice--Light microscopic and ultrastructural studies on neoplastic blood vessels. J Natl Cancer Inst 50:181-94, 1973

124. Weir FW, Nemenzo JH, Bennett S, Meyers FH: A Study of the Mechanism of Acute Toxic Effects of Hydrazine, UDMH, MMH, and SDMH, report No. AMRL-TDR-64-26. Wright-Patterson Air Force Base, Ohio, US Air Force, Air Force Systems Command, Aerospace Medical Division, Aerospace Medical Research Laboratories, Biomedical Laboratory, 1964, 32 pp

125. Weir FW, Meyers FH, Arbuckle RH, Nemenzo JH: Further Study of the Mechanism of Acute Toxic Effects of 1,1-Dimethylhydrazine, Methylhydrazine, and 1,2-Dimethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1965, 22 pp (NTIS AD 617 692)

126. Wilson RB: Species variation in response to dimethylhydrazine. Toxicol Appl Pharmacol 38:647-50, 1976

127. Toth B, Wilson RB: Blood vessel tumorigenesis by 1,2-dimethylhydrazine dihydrochloride (symmetrical)--Gross, light and electron microscopic descriptions--I. Am J Pathol 64:585-93, 1971

128. Toth B, Malick L, Shimizu H: Production of intestinal and other tumors by 1,2-dimethylhydrazine dihydrochloride in mice--I. A light and transmission electron microscopic study of colonic neoplasms. Am J Pathol 84:69-86, 1976

129. Toth B, Shimizu H: 1-Carbamyl-2-phenylhydrazine tumorgenesis in Swiss mice--Morphology of lung adenomas. J Natl Cancer Inst 52:241-251, 1974

130. Rogers AE, Herndon BJ, Newberne PM: Induction by dimethylhydrazine of intestinal carcinoma in normal rats and rats fed high or low levels of vitamin A. Cancer Res 33:1003-09, 1973

131. Druckrey H: Production of colonic carcinomas by 1,2-dialkylhydrazines and azoxyalkanes, in Burdette WJ (ed.): Carcinoma of the Colon and Antecedent Epithelium. Springfield, Ill, Charles C Thomas, 1970, pp 267-79

132. Thurnherr N, Deschner EE, Stonehill EH, Lipkin M: Induction of adenocarcinomas of the colon in mice by weekly injections of 1,2-dimethylhydrazine. Cancer Res 33:940-45, 1973

133. Deschner EE: Experimentally induced cancer of the colon. Cancer Suppl 3 34:824-28, 1974

134. Pegg AE, Hawks A: Increased transfer ribonucleic acid methylase activity in tumors induced in the mouse colon by the administration of 1,2-dimethylhydrazine. Biochem J 122:121-23, 1971

135. Wiebecke B, Lohrs U, Gimmy J, Eder M: [Production of tumors in the intestines of mice by 1,2-dimethylhydrazine.] Z Gesamte Exp Med 149:277-78, 1969 (Ger)

136. Evans JT, Lutman G, Mittleman A: The induction of multiple large bowel neoplasms in mice. J Med 3:212-15, 1972

137. Martin MS, Martin F, Michiels R, Bastien H, Justrabo E, Bordes M, Viry B: An experimental model for cancer of the colon and rectum--Intestinal carcinoma induced in the rat by 1,2-dimethylhydrazine. Digestion 8:22-34, 1973

138. Reddy BS, Narisawa T, Maropot R, Weisburger JH, Wynder EL: Animal models for the study of dietary factors and cancer of the large bowel. Cancer Res 35:3421-26, 1975

139. Wiebecke B, Drey U, Lohrs, U, Eder M: Morphological and autoradiographical investigations on experimental carcinogenesis and polyp development in the intestinal tract of rats and mice. Virchows Arch A 360:179-93, 1973

140. Reddy BS, Narisawa T, Wright P, Vukusich D, Weisburger JH, Wynder EL: Colon carcinogenesis with azoxymethane and dimethylhydrazine in germ-free rats. Cancer Res 35:287-90, 1975

141. Reddy BS, Weisburger JH, Wynder EL: Effects of dietary fat level and dimethylhydrazine on fecal acid and neutral sterol excretion and colon carcinogenesis in rats. J Natl Cancer Inst 52:507-11, 1974

142. Nigro ND, Bhadrachari N, Chomchai C: A rat model for studying colonic cancer--Effect of cholestyramine on induced tumors. Dis Colon Rectum 16:438-43, 1973

143. Wattenburg LW: Inhibition of dimethylhydrazine-induced neoplasia of the large intestine by Disulfiram. J Natl Cancer Inst 54:1005-06, 1975

144. Fiala ES, Kulakis C, Bobotas G, Weisburger JH: Detection and estimation of azomethane in expired air of 1,2-dimethylhydrazine-treated rats. J Natl Cancer Inst 56:1271-73, 1976

145. Bolton VL: A laboratory study of amidopyrine, barbital, phenylhydrazine, and benzene in relation to agranulocytic angina. J Lab Clin Med 20:1199-1203, 1935

146. Von Oettingen WF, Deichmann-Gruebler W: On the relation between the chemical constitution and pharmacological action of phenylhydrazine derivatives. J Ind Hyg Toxicol 18:1-16, 1936

147. Witchett CE: Exposure of Dog Erythrocytes In Vivo to Phenylhydrazine and Monomethylhydrazine--A Freeze-Etch Study of Erythrocyte Damage. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1975, 33 pp (NTIS AD A011 555)

148. Chen LT, Weiss L: The role of the sinus wall in the passage of erythrocytes through the spleen. Blood 41:529-37, 1973

149. Saterborg NE: Bone marrow abnormalities after phenylhydrazine induced hemolysis in rabbits. Acta Radiol Ther Phys Biol 13:345-55, 1974

150. McIsaac WM, Parke DV, Williams RT: Studies in detoxification--77. The metabolism of phenylhydrazine and some phenylhydrazones. Biochem J 70:688-97, 1958

151. Clayson DB, Biancifiori C, Milia U, Santilli FEG: The induction of pulmonary tumours in BALB/c/Cb/Se mice by derivatives of hydrazine, in Lung Tumors in Animals, Proceedings of the Third Perguia Quandrennial International Conference on Cancer. Perugia, Italy, University of Perugia, Division of Cancer Research, 1966, pp 869-80

152. Toth B, Shimizu H: Tumorigenic effects of chronic administration of benzylhydrazine dihydrochloride and phenylhydrazine hydrochloride in Swiss mice. Z Krebsforsch 87:267-73, 1976

153. Tamaki Y, Ito M, Semba R, Yamamura H, Kiyono S: Functional disturbances in adult rats suffered from icterus gravis neonatorum due to maternal application of phenylhydrazine hydrochloride. Congenital Anomalies (Senten Ijo) 14:95-103, 1974

154. Feinsilver L, Perregrino JA, Smith CJ: Estimation of hydrazine and three of its methyl derivatives. Am Ind Hyg Assoc J 20:26-31, 1959

155. Part II--Standards completion program of validated methods, in NIOSH Manual of Analytical Methods, ed 2, DHEW (NIOSH) publication No. 77-157-C. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Measurements Research Branch, 1977, vol 3, pp S143-1 to S143-14,S149-1 to S149-16, S160-1 to S160-15,S237-1 to S237-14

156. Pinkerton MK, Lauer JM, Diamond P, Tamas AA: A colorimetric determination for 1,1-dimethylhydrazine (UDMH) in air, blood, and water. Am Ind Hyg Assoc J 24:239-44, 1963

157. Wood GO, Anderson RG: Sampling and Analysis of Hydrazine Compounds in Air. Los Alamos, N Mex, University of California, Los Alamos Scientific Laboratory, Industrial Hygiene Group, 1975, 7 pp

158. Wood GO, Anderson RG: Development of Air-monitoring Techniques Using Solid Sorbents, progress report No. LA-6513-PR. Los Alamos, N Mex, University of California, Los Alamos Scientific Laboratory, Industrial Hygiene Group, 1976, 22 pp

159. Wood GO, Anderson RG: Development of Air-Monitoring Techniques Using Solid Sorbents, progress report No. LA-6738-PR. Los Alamos, N Mex, University of California, Los Alamos Scientific Laboratory, Industrial Hygiene Group, 1977, 26 pp

160. Wood GO, Anderson RG: Development of Air-monitoring Techniques Using Solid Sorbents, progress report No. LA 6216 PR. Los Alamos, N Mex, University of California, Los Alamos Scientific Laboratory, Industrial Hygiene Group, 1975, 13 pp

161. Hydrazine compounds in air, Physical and Chemical Analysis Branch Method No. 248, in NIOSH Manual of Analytical Methods, ed 2, DHEW (NIOSH) publication No. 77-157-A. Cincinnati, US Dept Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Measurements Research Branch, 1977, vol 1, pp 248-1 to 248-6

162. Kolthoff IM: The volumetric analysis of hydrazine by the iodine, bromate, iodate and permanganate methods. J Am Chem Soc 46:2009-16, 1924

163. McKennis H, Weatherby JH, Dellis EP: Gasometric determination of hydrazine and derivatives. Anal Chem 30:499-502, 1958

164. Reynolds BA, Thomas AA: A colorimetric method for the determination of hydrazine and monomethylhydrazine in blood. Am Ind Hyg Assoc J 26:527-31, 1965

165. McKennis H Jr, Yard AS: Determination of methylhydrazine. Anal Chem 26:1960-63, 1954

166. Watt GW, Chrisp JD: A spectrophotometric method for the determination of hydrazine. Anal Chem 24:2006-08, 1952

167. Dambrauskas T, Cornish HH: A modified spectrophotometric method for the determination of hydrazine. Am Ind Hyg Assoc J 23:151-56, 1962

168. Dmitriyev MT: [Photocolorimetric determination of hydrazine in an aqueous solution.] Tr Nauchno Issled Inst Gidrometeorol Priborostr 11:62-66, 1963 (Rus)

169. McKennis H Jr, Witkin LB: Determination of hydrazine and ammonia in air. AMA Arch Ind Health 12:511-14, 1955

170. Diamond P, Thomas AA: Determination of 1,1-Dimethylhydrazine (UDMH) in Urine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1962, 19 pp (NTIS AD 288 876)

171. Buck RP, Eldridge RW: Continuous coulometric titration of unsymmetrical dimethylhydrazine. Anal Chem 37:1242-45, 1965

172. Geiger DL, Vernot EH: The continuous analysis of monomethylhydrazine in toxicological exposure chambers, in Automation in Analytical Chemistry, Technicon Symposia. White Plains, NY, Mediad Inc, 1968, vol 2, pp 427-30

173. Grosskopf K: [New Draeger tubes.] Draeger-Hefte No. 256/257. Lubeck, Federal Republic of Germany, Draeger-Werke AG Lubeck, 1964, pp 6-13 (Ger)

174. Diamond P: Testing of Colorimetric Tubes for Nitrogen Dioxide and Monomethylhydrazine. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1970, 12 pp (NTIS AD 752 527)

175. Malone HE: Determination of mixtures of hydrazine and 1,1-dimethylhydrazine. Anal Chem 33:575-77, 1961

176. Burns, EA, Lawler EA: Determination of mixtures of hydrazine and 1,1-dimethylhydrazine (UDMH). Anal Chem 35:802-06, 1963

177. Bailey LC, Medwick T: Spectrophotometric determination of hydrazine and 1,1-dimethylhydrazine, separately or in admixture. Anal Chim Acta 35:330-36, 1966, 21 pp

178. Serencha NM, Hanna JG, Kuchar EJ: Determination of mixtures of hydrazine and monomethylhydrazine by reaction with salicyaldehyde. Anal Chem 37:1116-18, 1965

179. Clark JD, Smith JR: Titrimetric analysis of mixtures of hydrazine and methyl hydrazine. Anal Chem 33:1186-87, 1961

180. Malone HE, Biggers RA: Acid-base method for determining mixtures of either hydrazine-1,1-dimethylhydrazine or monomethylhydrazine-1,1-dimethylhydrazine. Anal Chem 36:1037-39, 1964

181. Bighi C, Saglietto G: The gas-chromatographic separation of mixtures of hydrazine, methylhydrazine and 1,1-dimethylhydrazine. J Chromatogr 18:297-301, 1965

182. Bighi C, Saglietto G, Betti A: [Comparison of stationary phases in the gas chromatography of hydrazine.] Ann Univ Ferrara Sez 5 2:163-70, 1967 (Ita)

183. Dee LA: Gas chromatographic determination of aqueous trace hydrazine and methylhydrazine as corresponding pyrazoles. Anal Chem 43:1416-19, 1971

184. Liu YY, Schmeltz I, Hoffmann D: Chemical studies on tobacco smoke--Quantitative analysis of hydrazine in tobacco and cigarette smoke. Anal Chem 46:885-89, 1974

185. Fiala ES, Weisburger JH: Thin-layer chromatography of some methylated hydrazines and detection by a sensitive spray reagent. J Chromatogr 105:189-92, 1975

186. Test for Hazardous Substance--Hydrazine. Occupational Safety and Health Administration, July 1972-May 1977, 2 pp (Available through BW Mintz, US Dept of Labor)

187. Evaluation of Atmospheric Concentrations of Hydrazine and Unsymmetrical Dimethylhydrazine in and around the Rocky Mountain

Arsenal Hydrazine Facility, Industrial Hygiene Special Study No. 35-0101-77. Aberdeen Proving Ground, Aberdeen, Md, US Dept of the Army, US Army Environmental Hygiene Agency, 1977, 21 pp

188. American Conference of Governmental Industrial Hygienists, Committee on Industrial Ventilation: Industrial Ventilation--A Manual of Recommended Practice, ed 14. Lansing, Mich, ACGIH, 1976, 351 pp

189. American National Standards Institute Inc: Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971. New York, ANSI, 1971, 63 pp

190. Hagopian JH, Bastress EK: Recommended Industrial Ventilation Guidelines, HEW publication No. (NIOSH) 76-162. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Technical Services, 1975, 63 pp

191. Industrial hygiene practices guide--Laboratory hood ventilation. Am Ind Hyg Assoc J 29:611-17, 1968

192. The Handling and Storage of Liquid Propellants. Office of the Director of Defense Research and Engineering, US Advisory Panel on Fuels and Lubricants, 1963, pp 109-21,175-86,297-315

193. UDMH and MAF-Fuels, in Liquid Propellant Handling, Storage and Transportation, report No. AFM 161 30. US Air Force, 1976, vol 2, pp 10-1 to 10-15,C-1 to C-10

194. Dimazine--Unsymmetrical Dimethylhydrazine--Properties--Applications--Reactions--Storage and Handling. New York, FMC Corp, Organic Chemicals Division, 1972, 37 pp

195. National Fire Codes--A Compilation of NFPA Codes, Standards, Recommended Practices, and Manuals; Combustible Solids, Dusts, and Explosives. Boston, National Fire Protection Association, 1974, vol 3, pp 49-152 to 49-153

196. Hydrazine, report No. C-57, in Chemical Hazards Information Series. New York, Association of Casualty and Surety Companies, Accident Prevention Dept, Special Hazards Committee, 1961, 11 pp

197. Hydrazine, AIHA Hygienic Guide Series. Akron, Ohio, American Industrial Hygiene Association, 1956, pp 445-46

198. Disposal of wastewater containing hydrazine, in Pollution Solution. Port Heuneme, Calif, US Navy, Naval Environmental Protection Support Service, Naval Construction Battalion Center, Navy Environmental Support Office, 1975, 2 pp

199. Prevention and Extinguishment of Fires Involving Hypergolic Propellants, final report No. 4053. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1968, 59pp (NTIS CR 101 226)

200. Frierson WB: Use of pyridoxine HCl in acute hydrazine and UDMH intoxication. Ind Med Surg 34:650-51, 1965

201. National Cancer Institute Safety Standards for Research Involving Chemical Carcinogens, DHEW publication No. (NIH) 76-900. National Cancer Institute, Office of Research Safety, 1975, pp 1-27

202. Occupational Exposure Limits for Airborne Toxic Substances--A Tabular Compilation of Values from Selected Countries, Occupational Safety and Health Series No. 37. Geneva, International Labour Office, 1977, pp 3,11-12,33,102-03,126-27, 148-49,172-73, 285-87

203. Threshold Limit Values for 1956. Adopted at the 18th Annual Meeting of the American Conference of Governmental Industrial Hygienists. AMA Arch Ind Health 14:186-89, 1956

204. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of Threshold Limit Values. Cincinnati, ACGIH, 1962, pp 40-41,55,83

205. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of Threshold Limit Values, rev. Cincinnati, ACGIH, 1966, pp 101-02

206. Thomas AA, Back KC: The environmental toxicity of space cabin atmospheres, in Honma M, Crosby HJ (eds.): A Symposium on Toxicity in the Closed Ecological System. Springfield, Va, US Dept of Commerce, National Technical Information Service, 1964, pp 134-42 (NTIS PB 166 233)

207. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3, 1971. Cincinnati, ACGIH, 2nd printing, 1974, pp 91,127-28,174-75

208. Smyth HF: Hygienic standards for daily inhalation. Am Ind Hyg Assoc Q 17:129-85, 1956

209. Reinhardt CF, Dinman BD: Toxicity of hydrazine and 1,1-dimethylhydrazine (UDMH)--Hepatostructural and enzymatic change. Arch Environ Health 10:859-69, 1965

210. Weatherby JH, Yard AS: Observations on the subacute toxicity of hydrazine. Arch Ind Health 11:413-19, 1955

211. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3, 1971. Cincinnati, ACGIH, 4th printing, 1976, pp 379-80

212. Fuchs A: Hydrazine, in Documentation of MAC in Czechoslovakia. Praha, Czechoslovak Committee of MAC, 1969, pp 85-87

213. [Hydrazine and Methylhydrazines, in Work Substances Harmful to Health--Toxicologic and Occupational-Medical Justifications to MAK Values (Maximum Work Place Concentrations), installment 3.] Wurzburg, Germany, German Research Association, Commission for Studying Work Substances Harmful to Health, Determination of MAK Values Work Group and Limit for Determination of Limit Values for Dusts Work Group, 1974, pp 265-75,491-99 (Ger)

214. Sonneck HJ, Umlauf H: [Occupational skin diseases from hydrazine.] Z Haut Geschtskr 31:179-84, 1961 (Ger)

215. Witkin LB: Acute toxicity of hydrazine and some of its methylated derivatives. AMA Arch Ind Health 13:34-36, 1956

216. Cier A, Rouganne JP, Schmitt M: [Hematologic effects of subacute intoxication produced by hydrazine and asymmetric dimethylhydrazine in mice and in rabbits.] C R Seances Soc Biol 161:854-58, 1967 (Fre)

217. Biancifiori C, Ribacchi R: Pulmonary tumors in mice induced by oral isoniazid and its metabolites. Nature 194:488-89, 1962

218. Juhasz J: [The tumor-inducing effect of hydrazine.] Z Krebsforsch 70:150-56, 1967 (Ger)

219. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1967--Recommended and Intended Values. Cincinnati, ACGIH, 1967, pp 10-11

220. MacEwen JD, Haun CC, Thomas AA: The chronic inhalation toxicity of monomethylhydrazine. Toxicol Appl Pharmacol 22:278, 1972 (Abst)

221. Gregory AR, Legg CA, Cornish MH, Evans DQ: Space propellant residues. Clin Toxicol 4:435-50, 1971

222. Haun CC, MacEwen JD, Vernot EH, Eagan GF: Acute inhalation toxicity of monomethylhydrazine vapor. Am Ind Hyg Assoc J 31:667-77, 1970

223. Threshold Limit Values for 1958. Adopted at the 20th Annual Meeting of the American Conference of Governmental Industrial Hygienists. AMA Arch Ind Health 18:178-82, 1958

224. Druckrey H, Preussmann R, Schmahl D, Muller M: [Chemical constitution and carcinogenic effect with nitrosamines.] Naturwissenschaften 48:134-35, 1961 (Ger)

225. Argus MF, Hoch-Ligeti C: Comparative study of the carcinogenic activity of nitrosamines. J Natl Cancer Inst 27:695-701, 1961

226. Preussmann R, Druckery H, Ivankovic S, Hodenberg AV: Chemical structure and carcinogenicity of aliphatic hydrazo, azo, and azoxy compounds and of triazenes, potential in vivo alkylating agents. Ann NY Acad Sci 163:697-716, 1969

227. Lorhs U, Wiebecke B, Eder M: [Morphological and autoradiographic investigation of the alterations of intestinal mucosa of the mouse after a single injection of 1,2-dimethylhydrazine.] J Gesamte Exp Med 157:297-307, 1969 (Ger)

228. Springer P, Springer J, Oehlert W: [The early stages of carcinoma of the small and large intestine of rats, induced by 1,2-dimethylhydrazine.] Z Krebsforsch 74:236-40, 1970 (Ger)

229. Pataki A, Klotzsche C: [Light microscopic changes in the rat liver after prolonged administration of 1,2-dimethylhydrazine.] Naunyn-Schmiedebergs Arch Pharmakol 266:421-22, 1970 (Ger)

IX. APPENDIX I

SAMPLING AND ANALYTICAL METHOD FOR HYDRAZINES

This sampling and analytical method for hydrazines is adapted from NIOSH Method No. P&CAM 248 [161].

Principle of the Method

A measured volume of air is drawn through a tube containing sulfuric acid-coated silica gel to trap the hydrazine compounds. The sorbent is treated with distilled water to desorb the hydrazines. Reagent containing sodium acetate and 2-furaldehyde is added and the resulting derivatives are extracted into ethyl acetate and analyzed by gas chromatography with flame-ionization detection.

Range and Sensitivity

The ranges of the method in terms of the weight of analyte collected are:

hydrazine	4- 6,000	µg/sample
methylhydrazine	9- 9,000	"
1,1-dimethylhydrazine	15-12,000	"
phenylhydrazine	66-21,000	"

The lower ends of the ranges are the lowest levels at which the analytical method was evaluated. At these levels, the precision was no worse than 14% relative standard deviation, and the desorption efficiency was 75% or

higher. The maximum amount of each hydrazine compound retained prior to breakthrough of the first sorbent section is at least 0.2 millimole. The practical upper limit for the analysis is 0.2 millimoles of total hydrazine compounds in 2 ml of eluent. This is 25 mole% of the acid present and 20 mole% of the 2-furaldehyde reagent added. When hydrazine, methylhydrazine, or phenylhydrazine are present at such high concentrations, derivatives may not be entirely soluble in the reaction mixture. However, they will be dissolved by the ethyl acetate added for extraction.

Interferences

(a) Water vapor is not a sampling interference since it activates, rather than deactivates, the sulfuric acid in the sorbent.

(b) Any compound that has nearly the same retention time on the gas-chromatographic column as one of the derivatives of the hydrazines is an interferent.

(1) Atmospheric contaminants. A bulk sample of liquid or solid sources of vapors should be submitted at the same time as the sample tubes so that chemical identification of possible interferents can be made. The bulk sample must not be transported in the same container as the sample tubes.

(2) Reagent contaminants. Reagent grade chemicals of the highest purity available must be used. 2-Furaldehyde is unstable and must be redistilled prior to use and stored in a freezer (-20 C).

Precision and Accuracy

The volume of air sampled can be measured to within ±2% if a pump with a calibrated volume indicator is used. Volumes calculated from initially set flowrates may be less accurate (±5-10%) unless changes in flowrate are manually or electronically monitored and compensated. The collection efficiency is 100% under most conditions. This is demonstrated by a negligible amount of compound measured in the backup section of the sorbent tube. Desorption may be incomplete, particularly for methylhydrazine, near the lower limit of analytical measurement. In preparing calibration curves, desorption of standards from sorbent sections compensates for such losses, so that accuracy is increased. No losses have been observed for 1,1-dimethylhydrazine stored on sorbent sections in sealed tubes for up to 28 days at ordinary room temperatures.

The precision of the analysis is dependent on the precision and sensitivity of the technique used to quantitate the gas-chromatographic peaks of samples and standards. An electronic digital integrator with baseline correction capability is useful for this purpose. Near the lower limits of analytical measurement manual peak height measurements are more reproducible. A relative standard deviation of 0.04 has been determined for analyses of two sets of six consecutive 20-liter air samples of 1.6 and 3.8 mg/cu m of 1,1-dimethylhydrazine in air. This method gave results for 1,1-dimethylhydrazine at the levels 1-10 mg/cu m.

Advantages and Disadvantages

The method uses a small, portable sampling device involving no liquids. This is an advantage for sampling air in a worker's breathing zone without interfering with normal work activities. It also simplifies

transportation to the analytical laboratory. The sorbent tube has a high capacity. It can be used for at least 8 hours to measure a workday average concentration, or for shorter times to measure excursion concentrations. Desorption and preparation of samples for analysis involve simple procedures and equipment. Several hydrazine compounds can be collected and determined simultaneously. The gas-chromatographic analysis distinguishes which are present and at what individual concentrations they occur. Interferences by amines are less serious than in a colorimetric method.

The major disadvantage of the method is that 2 hours are required for desorption and reaction of samples and standards. Also, when methylhydrazine is present, the reaction time must be carefully controlled.

Apparatus

(a) Air Sampling Equipment

(1) Sorbent. The silica gel substrate should be high quality, such as Silica Gel D-08, chromatographic grade, activated and fines-free, 45/60 mesh, a product of Coast Engineering Laboratories, or an equivalent grade of silica gel. The sulfuric acid coating is prepared as follows: a selected amount, W, of silica gel is weighed in a glass bottle. Reagent grade concentrated sulfuric acid (95-98%) is added directly to the silica gel with a glass dropper until the total weight in the bottle becomes 1.25 W. The bottle is immediately sealed and shaken to uniformly distribute the sulfuric acid on the silica gel. Mixing is repeated intermittently for an hour as the mixture cools. The resulting material is quite hygroscopic and should not be exposed to air any longer than necessary.

(2) Sampling Tubes. Glass tubes 8-cm long and 6-mm internal diameter, tapered and flame-sealed at one end, are packed with two 200-mg sections of sulfuric acid-coated silica gel. Glass-wool plugs are used to separate and enclose the sections. The other end of the tube is flame-sealed to prevent contamination during storage prior to use. Polyethylene caps are used to seal the tubes after sampling is completed. Pressure drops across these tubes average 6 mmHg at 200 cc/minute and 33 mmHg at 1,000 cc/minute flowrates. The primary absorbing section of the tube is that further away from either end; the backup section is butted against a taper.

(3) Personal Sampling Pump. Pumps must be capable of operation at 1 liter/minute for 2 hours with a sampling device in line and should have flow indicators. Each pump is calibrated with a representative sorbent tube in line. A wet or dry test meter or a bubble meter capable of measuring a flowrate of 1 liter/minute to within ±2% is used in the calibration. Figure XI-1 shows a typical calibration setup for sampling pumps with a soapbubble meter.

(b) Gas chromatograph with a flame-ionization detector. Temperature programming capability is desirable.

(c) Gas-chromatographic column, 1-meter x 2-mm internal diameter glass, silanized and packed with 10% (by weight) Silicone OV-7 on 80/100-mesh Supelcoport or equivalent support.

(d) Strip chart recorder compatible with the gas chromatograph. An electronic digital integrator is desirable.

(e) Test tubes, 5-ml, sealed by insertion of a septum.

(f) Syringes, 10-μl.

(g) Pipettes, 0.5-ml and 2-ml.

(h) Volumetric flasks, 10-ml.

(i) File.

(j) Forceps.

Reagents

All chemicals must be ACS Reagent Grade or better.

(a) Hydrazine.

(b) Methylhydrazine.

(c) 1,1-Dimethylhydrazine.

(d) Phenylhydrazine.

(e) Water, double distilled, aldehyde-free.

(f) 2-Furaldehyde (furfural), boiling point 39-40 C at 5 mmHg. If this reagent is not clear, it must be redistilled prior to use to remove oxidation products. Store distillate under refrigeration.

(g) Sodium acetate solution, 0.50 moles/liter (41 g/liter).

(h) Reagent solution. Prepared by diluting 2 ml of 2-furaldehyde to 50 ml with the sodium acetate solution. This should be prepared fresh daily.

(i) Gas-chromatographic gases.

(1) Carrier helium, Bureau of Mines Grade A.

(2) Hydrogen prepurified.

(3) Air, compressed and filtered.

Procedure

(a) Cleaning of Glassware. Wash with detergent solution, rinse with tap water and distilled water, and dry in an oven.

(b) Collection and Shipping of Samples

(1) Immediately before beginning the collection of a sample, break each end of the sorbent tube so as to provide openings of at least 2-mm diameter.

(2) Attach the tubing from the sampling pump to the backup end of the sampling tubes. Sample air must not pass through any hose or tubing before entering the sorbent tube.

(3) With the sorbent tube in a vertical position, sample the air at 1 liter/minute for 2 hours. Record the volume of air sampled on the sampling flow and time.

(4) Immediately after sampling is completed, cap the sorbent tubes with the polyethylene caps. Rubber caps must not be used.

(5) Obtain a blank sample by handling one tube in the same manner as the sample tubes (break, seal, and ship) except pump no air through it.

(6) Pack the tubes tightly to minimize chances of breakage during transit. Tubes should not be subjected to extremes of high temperature or low pressure.

(c) Analysis of Samples

(1) Preparation of Samples. Score each tube with a file 5 mm in front of the first glass-wool plug and break it open. Remove the glass-wool plug that precedes the first sorbent section and transfer it along with this initial section to a 5-ml test tube that can be septum-

sealed. Likewise, transfer the second plug and sorbent section to another test tube. Label each appropriately for separate analysis.

(2) Desorption. Desorb the hydrazine compounds from the sulfuric acid-coated silica gel by adding 2 ml of distilled water to each sorbent section. Seal the tubes. Shake the mixtures occasionally over a period of 1 hour. Tests have shown that desorption reaches a maximum within an hour.

(3) Derivatization. Add 2 ml of reagent solution to each test tube containing sorbent and eluent. When methylhydrazine is expected in the sample or standard, the time of reagent addition must be exactly noted for each mixture. Mix the reagents thoroughly.

(4) Extraction. After 1 hour of reaction, add 0.5 ml of ethyl acetate to each test tube, seal tightly, and shake vigorously for 1 minute. For methylhydrazine, the reaction time must be exactly 1 hour, since a secondary reaction is occurring in the aqueous solution. Allow the ethyl acetate layer to settle out on top of the aqueous layer. Centrifuging accelerates this process. Samples of the ethyl acetate extracts are then analyzed by gas chromatography.

(d) Gas-Chromatographic Conditions. Typical operation conditons for the gas chromatograph are as follows:

(1) Helium carrier gas flowrate, 50 ml/minute.

(2) Hydrogen gas flowrate to detector, 40 ml/minute.

(3) Air flowrate to detector, 540 ml/minute.

(4) Injection port temperature, 150 C.

(5) Detector temperature, 200 C.

(6) Column temperature--programmed, 80 C for 12 minutes, to 185 C at 24 C/minute, and for 8 minutes. When only methylhydrazine and 1,1-dimethylhydrazine are present, isothermal analysis at 80 C is appropriate; when only hydrazine and phenylhydrazine are present, 185 C is appropriate.

(e) Injection of Sample. To eliminate difficulties arising from blowback or distillation within the syringe, use the solvent-flush injection technique. Flush the 10-μl syringe several times with ethyl acetate to clean the barrel and plunger. Draw in 1 μl of ethyl acetate. With the needle removed from contact with liquid, pull the plunger back about 0.4 μl to form a pocket of air. Then immerse the tip of the needle in the ethyl acetate extract layer of a sample and withdraw a 3-μl portion, taking into consideration the volume in the needle. Remove the needle from the sample and pull the plunger back another 0.4 μl to minimize evaporation from the tip of the needle. Inject and analyze duplicate 3-μl aliquots of each sample and standard extract.

(f) Gas-Chromatographic Peak Measurement. Measure the areas or peak heights of the hydrazine derivative peaks obtained from analyses of samples and standards. At lower concentrations peak-height measurements may be more precise.

Calibration and Standards

(a) Preparation of a Standard Solution in Water. Calculate for each compound i the volume Vi (μl):

$$Vi = \frac{Xi \times Vs}{Di \text{ (or } Ci)}$$

Xi = the anticipated average concentration (mg/cu m) of compound i in air.
Vs = volume (liters) of air sampled.
Di = density (g/ml) of a pure compound i.
Ci = concentration (g/ml) of the compound i in a known standard aqueous solution

Add the calculated volumes of each compound or aqueous standard solution to a 10-ml volumetric flask and dilute to the mark. A 10-μl portion of this new standard contains amounts of compounds equal to the amounts collected from Vs of concentration Xi. Aqueous solutions of hydrazine compounds are unstable and should be prepared fresh when used.

(b) Preparation of Standards on Sorbent Sections. Add 200 mg of sulfuric acid-coated silica gel to each of 10 test tubes that can be tightly sealed with a septum. These may be weighed from bulk sorbent or obtained from unused tubes. Add 2.5, 5.0, 10.0, 15.0, and 20.0 μl of the prepared standard to pairs of silica gel sections in the tubes. Use a 10-μl syringe and inject through the septum onto the walls of the tube containing sorbent. Withdraw the syringe and shake the tube to distribute the hydrazines. These standards correspond to 0.25, 0.5, 1, 1.5, and 2 times Xi in Vs, respectively. Other standards may be similarly prepared, if desired.

If samples are to be stored for longer than 1 week before analysis, prepare standards on sulfuric acid-coated silica gel soon after receipt of the samples in the laboratory. Store samples and standards at the same conditions so that storage losses (if any) will be similar.

Calculations

(a) Prepare a calibration curve for each hydrazine compound by plotting peak areas (or heights) obtained from the analyses of standards against nominal amounts on the standard sorbent sections (Ai, μg).

$$Ai = Vi \times Di$$

where Vi and Di are defined in Calibration and Standards.

(b) Read the amount of each compound from the appropriate calibration curve, using average peak heights from each sample. Correct each value for the amount found in the corresponding blank, if any. Add the amounts found in the front and backup sections (if any) of the same sample tube to obtain the total weight of compound in the air volume sampled.

(c) Divide the total weight of each compound on each tube volume of air sampled (Vs) to obtain the concentration of that compound in μg/liter or mg/cu m.

X. APPENDIX II

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially

formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the

American National Standards Institute Inc. Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.
>
> Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and Federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or MSHA approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION		
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO	
ADDRESS		
TRADE NAME		
SYNONYMS		

II. HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA		
BOILING POINT, 760 MM HG		MELTING POINT
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)
APPEARANCE AND ODOR		

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER	
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

XI. TABLES AND FIGURE

TABLE XI-1

PHYSICAL AND CHEMICAL PROPERTIES OF HYDRAZINE

Molecular formula	H2NNH2
CAS Number	000302012
Formula weight	32.05
Appearance	Colorless, oily liquid; fumes in air
Autoignition temperature	24 C on iron-rust surface, 270 C on a glass surface
Boiling point	113.5 C
Explosive limits	4.7-100% by volume in air
Flashpoint (open cup)	38-52 C
Freezing point	1.4-1.5 C
Odor	Ammonia-like or fishy
Specific gravity (25/4 C)	1.004
pKa	8.07
Solubility	Soluble in water, ethanol, and isobuthanol; insoluble in chloroform and ether
Vapor density (air = 1)	1.04
Vapor pressure	14.4 mmHg at 25 C
Saturation concentration at 25 C	18,900 ppm
Conversion factors (at 760 mmHg and 25 C)	1 ppm = 1.31 mg/cu m 1 mg/cu m = 0.76 ppm

Adapted from references 9-11,20-22

TABLE XI-2

PHYSICAL AND CHEMICAL PROPERTIES OF METHYLHYDRAZINE

Molecular formula	CH3NHNH2
CAS Number	000060344
Formula weight	46.07
Appearance	Colorless liquid
Autoignition temperature	Unknown
Boiling point	87.5 C
Explosive limits	2.5-92% by volume in air
Flashpoint (open cup)	63 C (145 F)
Freezing point	-21 to -52 C
Odor	Ammonia-like
Specific gravity (20/4 C)	0.874
pKa	7.87
Solubility	Soluble in water, ethanol, and ether
Vapor density (air = 1)	1.59
Vapor pressure	49.6 mmHg at 25 C
Saturation concentration at 25 C	65,300 ppm
Conversion factors (at 760 mmHg and 25 C)	1 ppm = 1.88 mg/cu m 1 mg/cu m = 0.53 ppm

Adapted from references 9-11,20-22

TABLE XI-3

PHYSICAL AND CHEMICAL PROPERTIES OF 1,1-DIMETHYLHYDRAZINE

Molecular formula	(CH3)2NNH2
CAS Number	000057147
Formula weight	60.10
Appearance	Colorless, mobile liquid
Autoignition temperature	249 C
Boiling point	62.5-63.9 C
Explosive limits	2-95% by volume in air
Flashpoint (open cup)	1 C
Freezing point	-58 C
Odor	Ammonia-like or fishy
Specific gravity (25 C)	0.782
pKa	7.21
Solubility	Soluble in water, ethanol, and ether
Vapor density (air = 1)	2.08
Vapor pressure	157 mmHg at 25 C
Saturation concentration at 25 C	206,600 ppm
Conversion factors (at 760 mmHg and 25 C)	1 ppm = 2.46 mg/cu m 1 mg/cu m = 0.41 ppm

Adapted from references 9-11,20-22

TABLE XI-4

PHYSICAL AND CHEMICAL PROPERTIES OF 1,2-DIMETHYLHYDRAZINE

Molecular formula	CH3NHNHCH3
CAS Number	000540738
Formula weight	60.1
Appearance	Colorless liquid
Autoignition temperature	Unknown
Boiling point	80-81 C
Explosive limits	Unknown
Flashpoint	"
Freezing point	"
Melting point	-9 C
Odor	Ammonia-like or fishy
Specific gravity (20/4 C)	0.827
Solubility	Soluble in water, ethanol, and ether
Vapor density (air = 1)	2.08
Vapor pressure	69.9 mmHg at 25 C
Saturation concentration at 25 C	92,000 ppm
Conversion factors (at 760 mmHg and 25 C)	1 ppm = 2.46 mg/cu m 1 mg/cu m = 0.41 ppm

Adapted from references 5,20

TABLE XI-5

PHYSICAL AND CHEMICAL PROPERTIES OF PHENYLHYDRAZINE

Molecular formula	C6H5NHNH2
CAS Number	000100630
Formula weight	108.14
Appearance	Yellow, monoclinic crystals or oil
Autoignition temperature	174 C
Boiling point	243.5 C with decomposition
Explosive limits	Unknown
Flashpoint (open cup)	378 C
Freezing point	19.4-19.6 C
Odor	Faint aromatic
Specific gravity (25/4 C)	1.0978
pKb	8.79
Solubility	Soluble in alcohol, benzene, chloroform, and ether; sparingly soluble in water, petroleum ether, and dilute acid solutions
Vapor density (air = 1)	3.74
Vapor pressure	0.04 mmHg at 25 C
Saturation concentration at 25 C	50 ppm
Conversion factors (at 760 mmHg and 25 C)	1 ppm = 4.42 mg/cu m 1 mg/cu m = 0.23 ppm

Adapted from references 9-11,20-22

TABLE XI-6

OCCUPATIONS WITH POTENTIAL EXPOSURE TO HYDRAZINES

Agricultural chemical workers	Water treaters
Analytical chemists	Jet fuel handlers
Anticorrosion additive workers	Jet fuel makers
Boiler operators	Nitron makers
Catalyst reclaimers	Organic chemical synthesizers
Chlorine scavenger makers	Oxygen scavenger makers
Drug makers	Photographic developer makers
Dyemakers	Rocket fuel handlers
Explosive makers	Rocket fuel makers
Foamed plastic makers	Rubber workers
Fuel cell makers	Silverplating workers
Herbicide makers	Solder flux makers
Hydraulic fluid workers	Solderers
Hydrazine and hydrazine-derivative makers	Textile dyers, acrylic and vinyl
Insecticide makers	Vat dyemakers

Adapted from references 11,23

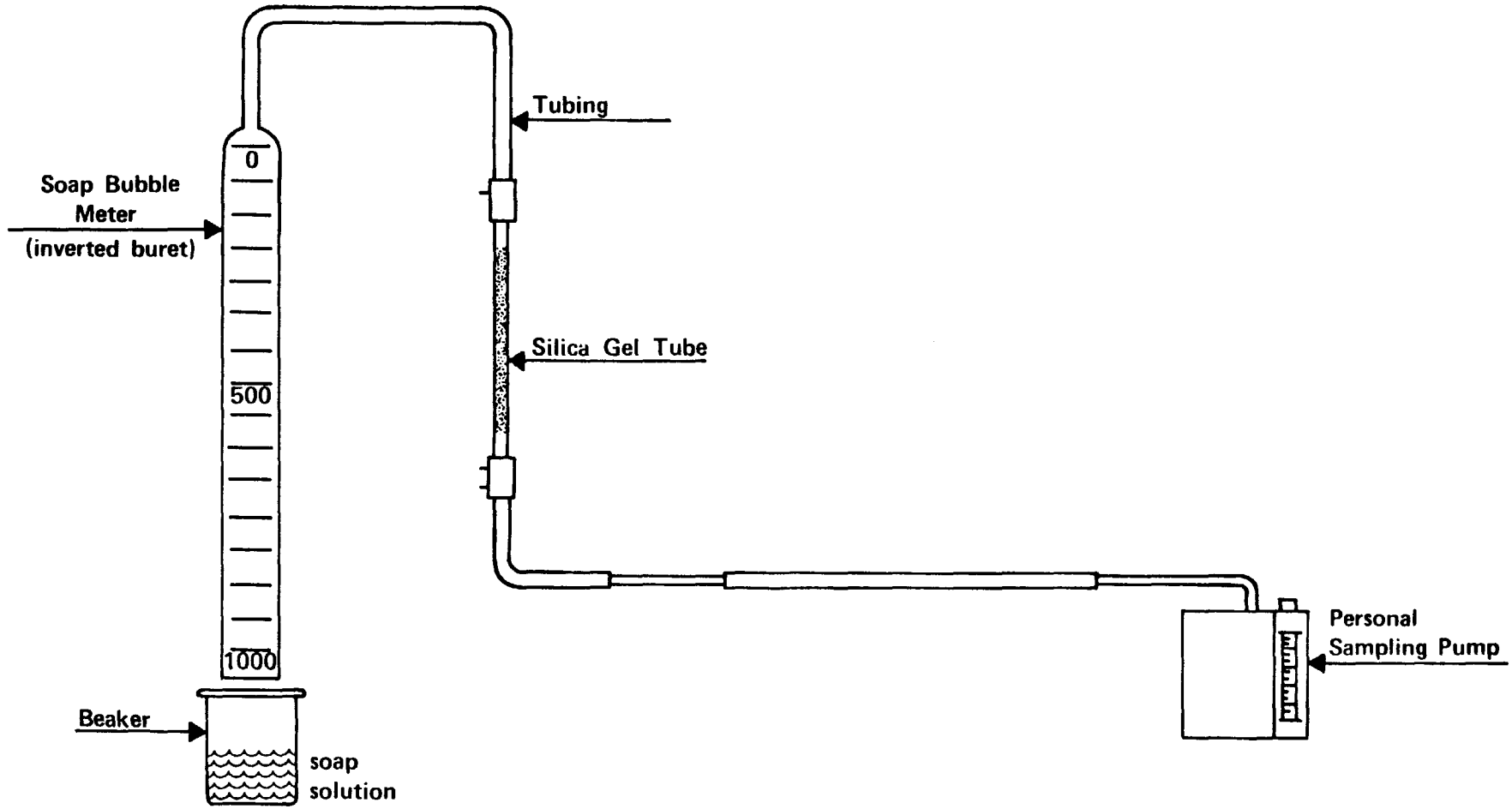

FIGURE XI–1

CALIBRATION SETUP FOR PERSONAL SAMPLING WITH SILICA GEL TUBE

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