NIOSH

CRITERIA FOR A RECOMMENDED STANDARD....

OCCUPATIONAL EXPOSURE TO

- **n-ALKANE MONO THIOLS**
- **CYCLOHEXANETHIOL**
- **BENZENETHIOL**

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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National Institute for Occupational Safety and Health
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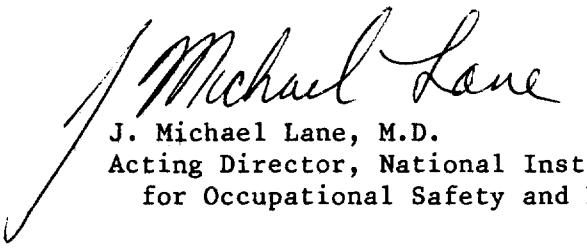
PREFACE

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 thiols 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 (NIOSH), had primary responsibility for development of the criteria and recommended standard for thiols. David J. Brancato of this Division served as the criteria manager. Equitable Environmental Health, Inc. (EEH) developed the basic information for consideration by NIOSH staff and consultants under contract CDC 210-77-0148.

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I. RECOMMENDATIONS FOR A THIOL STANDARD

NIOSH recommends that employee exposure to thiols in the workplace be controlled by adherence to the following sections. The recommended standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, in a 40-hour workweek, during a working lifetime. Compliance with all sections of the recommended standard should prevent adverse effects of exposure to thiols on the health of employees and provide for their safety. Techniques recommended in the standard are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. Although NIOSH considers the recommended workplace environmental limits to be safe levels based on current information, employers should regard them as the upper boundaries of exposure and make every effort to maintain exposures as low as is technically feasible. The criteria and recommended standard will be reviewed and revised as necessary.

These criteria and the recommended standard apply to exposure of employees to selected monofunctional organic sulfhydryl compounds, specifically, the 14 n-alkane thiols having the general molecular formula $C_nH_{2n+1}SH$ (where n = 1, 2...12, 16, and 18), the aliphatic cyclic thiol, cyclohexanethiol, and the aromatic thiol, benzenethiol; hereinafter they may be referred to as "thiols." Synonyms for thiols include mercaptans, thioalcohols, and sulfhydrates.

Because of systemic effects, absorption through the skin on contact, and possible dermal irritation, "occupational exposure to thiols" is defined as work in any area where thiols are produced, processed, stored, or otherwise used. If thiols are handled or stored in intact, sealed containers, eg, during shipment, NIOSH recommends that only Sections 3, 5(a), and 6(g) of this proposed standard apply. If exposure to other chemicals also occurs, provisions of any standard applicable to the other chemicals shall be followed.

Section 1 - Environmental (Workplace Air)

(a) Concentration

(1) Occupational exposure shall be controlled so that no employee is exposed to benzenethiol at concentrations in excess of 0.5 milligrams per cubic meter (mg/cu m) of air (0.1 ppm in air by volume) determined as a ceiling concentration for any 15-minute period.

(2) Occupational exposure to aliphatic thiols shall be controlled so that employees are not exposed at concentrations greater than the limits, in milligrams per cubic meter of air, shown in Table I-1 as a ceiling concentration for any 15-minute period.

(3) Occupational exposure to mixtures of thiols shall be controlled so that no employee is exposed at an equivalent concentration for the mixture greater than that calculated by the formula given in 29 CFR 1910.1000 (d)(2)(i).

(b) Sampling and Analysis

Procedures for the collection and analysis of workroom air samples shall comply with those given in Appendix I or with any method shown to be at least equivalent in precision, sensitivity, and accuracy.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to all workers occupationally exposed to thiols.

(a) Preplacement examinations shall include at least:

(1) Comprehensive medical and work histories with special emphasis directed to symptoms and signs of disorders of the central and autonomic nervous systems, the cardiovascular system, and the skin.

(2) Physical examination giving particular attention to the nervous and cardiovascular systems. For workers subject to occupational exposure to benzenethiol, eye examinations shall be included in addition to the above-mentioned systems.

(3) An evaluation of the worker's ability to use positive pressure respirators. Criteria should include the presence of significant obstructive or restrictive pulmonary disease or cardiopulmonary impairment.

(4) White blood cell counts (WBC's) (total and differential), hematocrit, hemoglobin concentration in whole blood, total bilirubin, and urinalysis. The value of estimations of fecal urobilinogen in distinguishing jaundice due to hemolytic anemia from that due to other common causes should be kept in mind.

(b) Periodic examinations shall be made available at least annually to any workers who have been occupationally exposed to thiols and shall include:

(1) Interim medical and work histories.

TABLE I-1

RECOMMENDED EXPOSURE LIMITS FOR ALIPHATIC THIOLS

Thiol	Ceiling Concentration Limits	
	mg/cu m	Approximate ppm Equivalents
1-Methanethiol	1.0	0.5
1-Ethanethiol	1.3	0.5
1-Propanethiol	1.6	0.5
1-Butanethiol	1.8	0.5
1-Pentanethiol	2.1	0.5
1-Hexanethiol	2.4	0.5
1-Heptanethiol	2.7	0.5
1-Octanethiol	3.0	0.5
1-Nonanethiol	3.3	0.5
1-Decanethiol	3.6	0.5
1-Undecanethiol	3.9	0.5
1-Dodecanethiol	4.1	0.5
1-Hexadecanethiol	5.3	0.5
1-Octadecanethiol	5.9	0.5
Cyclohexanethiol	2.4	0.5

(2) Physical examination as described in (a)(2) above.

(3) Laboratory examinations as described in (a)(4) above.

(4) Referral for a more detailed diagnostic workup if signs or symptoms of neurologic abnormalities are discovered in workers occupationally exposed to these substances.

(c) Employees and prospective employees having medical conditions, such as fainting spells, neuromuscular weakness, and cardiopulmonary impairment, that could be directly or indirectly aggravated by exposure to thiols shall be counseled on the increased risk to their health from exposure to the substances.

(d) Medical personnel should be aware of the possibility of delayed systemic effects such as fainting spells, neuromuscular weakness, and/or cardiopulmonary impairment. Persons requiring medical attention as a result of exposure to thiols may require observation for up to 72 hours. Medical examinations as described in (a) 2 shall be then made available if warranted.

(e) Pertinent medical records shall be maintained by the employer for all employees occupationally exposed to thiols. Such records shall be retained for at least 30 years after employment ends. These 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.

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 unable to read the labels and signs provided shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

(a) Labeling

All bulk containers that hold thiols shall carry, in a readily visible location, a label that bears the trade name or other common name of the product and information on the effects of exposure to the compound on human health. The information shall be arranged as in the example below for all the thiols except benzenethiol.

SPECIFIC THIOL
(Trade or Common Name)
DANGER
COMBUSTIBLE

MAY BE HARMFUL IF ABSORBED THROUGH SKIN,
INHALED, OR INGESTED
MAY CAUSE IRRITATION OF SKIN
KEEP CONTAINERS CLOSED WHEN NOT IN USE

For methanethiol, ethanethiol, propanethiol, butanethiol, pentanethiol, and cyclohexanethiol, the word FLAMMABLE shall be used instead of COMBUSTIBLE in the above example and the following caution shall be added to the label: Exposure to vapor from large spills may produce unconsciousness.

For benzenethiol, the information shall be arranged as in the example below:

BENZENETHIOL
(Trade or Common Name)
DANGER
COMBUSTIBLE

MAY BE FATAL IF ABSORBED THROUGH SKIN,
INHALED, OR INGESTED
MAY CAUSE IRRITATION OF EYES AND SKIN
KEEP CONTAINERS CLOSED WHEN NOT IN USE

On all labels, the following information shall be included as in the example below:

Do not get on skin, in eyes or mouth, or on clothing.
Avoid breathing vapor.
Use only with adequate ventilation.
Keep containers closed when not in use.
Wash hands and face thoroughly before eating, drinking, smoking, or using toilet.

First Aid: Remove victims to fresh air immediately. Give artificial respiration if needed. Give oxygen if breathing is impaired. Call a physician.

In case of skin contact, immediately flush with copious quantities of water, then wash with soap and water. In case of eye contact with benzenethiol or with mixtures that contain benzenethiol, the affected

eye shall be treated with not more than two drops of 0.5% silver nitrate ($AgNO_3$), applied from a bougie or other previously sealed container, and then flushed with copious quantities of water. Eyes contacted by thiols other than benzenethiol shall be flushed with copious amounts of water. A physician should be consulted promptly about any eye contact with solid or liquid thiols.

(b) Posting

In areas where exposure to thiols can occur, signs containing appropriate health hazard warning statements shall be posted in readily visible locations. Such information for the n-alkane monothiols and cyclohexanethiol shall be arranged as in the example below:

DANGER! COMBUSTIBLE

THIOL PRESENT IN AREA
(THIOL NAME OR NAMES)

MAY BE HARMFUL IF ABSORBED THROUGH SKIN,
INHALED, OR INGESTED

MAY BE IRRITATING TO SKIN

Do not get on skin, in eyes or mouth, or on clothing.
Do not breathe vapor.
Keep containers closed when not in use.

For methanethiol, ethanethiol, propanethiol, butanethiol, pentanethiol, and cyclohexanethiol, the word FLAMMABLE shall be used in place of COMBUSTIBLE in the above example.

For benzenethiol, the information shall be arranged as in the example below:

DANGER! COMBUSTIBLE

BENZENETHIOL PRESENT IN AREA
MAY BE FATAL IF ABSORBED THROUGH SKIN,
INHALED, OR INGESTED

MAY BE IRRITATING TO EYES AND SKIN

Do not get on skin, in eyes or mouth, or on clothing.
Do not breathe vapor.
Keep containers closed when not in use.

In an emergency involving thiols, all affected personnel shall be provided with immediate first aid, followed by prompt medical evaluation and care. In the event of skin or eye contact with liquid thiols, skin and eyes shall be flushed with copious amounts of water. In case of eye contact with benzenethiol or with a mixture including benzenethiol, the affected eye shall be treated with no more than two drops of a 0.5% solution of silver nitrate ($AgNO_3$), applied from a bougie or other previously sealed container, and then flushed with copious quantities of water. For further discussion, see Appendix II.

(c) When respirators are permitted under Section 4(c), the following statement shall be added in large letters to the signs required in Section 3(b):

RESPIRATORY PROTECTION REQUIRED
IN THIS AREA

(d) In any area where emergency situations may arise, signs required by Section 3(b) shall be supplemented with signs giving emergency and first-aid instructions and procedures, the location of first-aid supplies and emergency equipment, and the location of emergency showers and eyewash fountains.

Section 4 - Personal Protective Equipment and Clothing

Engineering controls shall be used when needed to keep concentrations of airborne thiols at or below the recommended environmental limit and to minimize skin and eye contact. In addition, employers shall provide protective equipment and clothing to employees when necessary.

(a) Eye Protection

Safety glasses with side shields shall be worn whenever there is occupational exposure to thiols. Chemical safety goggles and face shields (8-inch minimum) meeting the requirements of 29 CFR 1910.133 and ANSI Z87.1-1968 shall be provided and worn in any operation in which there is a reasonable possibility that thiols may be splashed into the eyes.

(b) Skin Protection

Depending on the operations involved and the probable or likely extent of dermal exposure, protective clothing and equipment, including gloves, aprons, suits, boots, and face shields (8-inch minimum) with goggles, shall be worn to prevent skin contact with particulate or splashed liquid thiols.

(c) Respiratory Protection

(1) Use of respiratory protective equipment shall be permitted only in the following circumstances to protect employees from exposure to airborne thiols at concentrations that may exceed the recommended environmental limit:

(A) During the time necessary to install and test the controls required in Section 6(b).

(B) For nonroutine operations, such as maintenance or repair activities.

(C) In emergencies.

(2) When use of respirators is permitted, the respirator shall be selected and used pursuant to the following requirements:

(A) Employers shall establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134.

(B) Employers shall provide respirators in accordance with Tables I-2 and I-3 and shall ensure that employees use the respirators when necessary. The respiratory protective devices provided in conformance with Tables I-2 and I-3 shall comply with the standards jointly approved by NIOSH and the Mine Safety and Health Administration (formerly by the Mine Enforcement and Safety Administration and the Bureau of Mines) as specified under the provisions of 30 CFR 11.

(C) Employers shall ensure that respirators are properly cleaned and maintained and that employees are trained and drilled at least annually in the use of respirators assigned to them and in ways to test for leaks.

(D) Respirators shall be easily accessible, and employees shall be informed of their location.

Section 5 - Informing Employees of Hazards from Thiols

(a) Employees occupationally exposed to thiols shall be verbally informed of the hazards of such exposure, the symptoms associated with such exposure, appropriate emergency procedures, and proper procedures for the safe handling and use of thiols.

(b) A continuing education program, conducted at least annually by qualified health and safety personnel, shall be instituted to ensure that employees whose jobs may involve exposure to thiols, including those engaged in maintenance and repair, have

TABLE I-2

RESPIRATOR SELECTION GUIDE FOR BENZENETHIOL

Concentration Range	Respirator Type Approved under Provisions of 30 CFR 11
Less than or equal to 5 mg/cu m	(1) Chemical cartridge respirator with half-mask facepiece and organic vapor cartridge (2) Supplied-air respirator operated in demand (positive pressure) mode with full facepiece
Less than or equal to 25 mg/cu m	(1) Gas mask with chin-style or front- or back-mounted organic vapor canister with full facepiece (2) Supplied-air respirator in demand (positive pressure) mode with full facepiece (3) Self-contained breathing apparatus operated in demand (positive pressure) mode with full facepiece
Greater than 25 mg/cu m	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand mode (2) Combination supplied-air respirator with full facepiece and auxiliary self-contained air supply operated in the pressure-demand mode
Emergency (entry into area of unknown concentration for purposes such as firefighting)	(1) Self-contained breathing apparatus with full facepiece, operated in pressure-demand mode (2) Combination supplied-air respirator with full facepiece and auxiliary self-contained air supply, operated in the pressure-demand mode

TABLE I-3

RESPIRATOR SELECTION GUIDE FOR n-ALKANE THIOLS (C_1-C_{12}, C_{16}, C_{18}) AND CYCLOHEXANETHIOL

Concentration Range	Respirator Type Approved under Provisions of 30 CFR 11
Less than or equal to 5 ppm	(1) Chemical cartridge respirator with half-mask facepiece and organic vapor cartridge (2) Supplied-air respirator operated in demand (positive pressure) mode with half-mask facepiece
Less than or equal to 25 ppm	(1) Gas mask with chin-style or front- or back-mounted organic vapor canister with full facepiece (2) Supplied-air respirator in demand (positive pressure) mode with full facepiece (3) Self-contained breathing apparatus operated in demand (positive pressure) mode with full facepiece
Greater than 25 ppm	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand mode (2) Combination supplied-air respirator with full facepiece and auxiliary self-contained air supply operated in the pressure-demand mode
Emergency (entry into area of unknown concentration for purposes such as firefighting)	(1) Self-contained breathing apparatus with full facepiece, operated in pressure-demand mode (2) Combination supplied-air respirator with full facepiece and auxiliary self-contained air supply, operated in the pressure-demand mode

current knowledge of job hazards, proper maintenance procedures, and cleanup methods.

Employees shall be informed of the general nature of the medical surveillance program and of the advantage of participation in the program. Each employee shall be told about the availability of the required information that shall include, as a minimum, that prescribed in paragraph 5(c).

(c) Required information shall be recorded on the US Department of Labor form OSHA-20, Material Safety Data Sheet, shown in Appendix III, or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

(d) Each employee shall be informed of the location of the information described in paragraph 5(c). This information shall be kept on file at each establishment or department and shall be readily accessible to all employees occupationally exposed to thiols.

(e) In an emergency involving thiols, all affected personnel shall be provided with immediate first aid, followed by prompt medical evaluation and care. In the event of skin or eye contact with liquid thiols, skin and eyes shall be flushed with copious amounts of water. In case of eye contact with benzenethiol or with a mixture including benzenethiol, the affected eye shall be treated with no more than two drops of a 0.5% solution of silver nitrate ($AgNO_3$), applied from a bougie or other previously sealed container, and then flushed with copious quantities of water. For further discussion, see Appendix II.

Section 6 - Work Practices

(a) Protective clothing and equipment, as set forth in Section 4, shall be worn by all employees who work where there is the possibility of skin or eye contact with particulate thiols.

(b) Emergency Procedures

For all work areas, emergency procedures as specified below, as well as any other procedures appropriate for a specific operation or process, shall be formulated in advance and employees shall be instructed in their implementation.

(1) The plan shall include pertinent information for obtaining emergency medical care and transportation to the hospital of injured workers.

(2) Firefighting procedures shall be established and implemented. These shall include procedures for emergencies involving the release of thiol vapor. In case of fire, thiol sources shall be shut off, flared (methanethiol), removed, or controlled by special instructions. Containers shall be removed or cooled with water spray. Chemical foam, carbon dioxide, or dry chemicals shall be used for fighting thiol fires, and proper respiratory protection and protective clothing shall be worn.

(3) Approved eye, skin, and respiratory protection as specified in Section 4 shall be used by personnel essential to emergency operations.

(4) Nonessential employees shall be evacuated from exposure areas during emergencies. Perimeters of hazardous exposure areas shall be delineated, posted, and secured.

(5) Personnel adequately protected against the attendant hazards shall shut off sources of thiols, clean up spills, and immediately repair leaks. Personnel shall flare methanethiol rather than shut off its source.

(c) Control of Airborne Thiols

Engineering controls shall be used to keep the concentration of thiols at or below the recommended limits. The use of a closed system is an effective method for controlling the escape of vaporized thiols into the air of the workplace. Local exhaust ventilation, used alone or in combination with the closed system, may also be effective. Ventilation systems shall be designed to prevent accumulation or recirculation of thiols in the workroom, to keep concentrations within the limits of the recommended standard, and to remove thiols from the breathing zones of workers. Where a fan is located in ductwork and the concentration of thiols is greater than 25% of the lower explosive limit of the material being handled, the fan rotating element shall be constructed of nonsparking material and the casing shall consist of or be lined with nonsparking material. There shall be sufficient clearance between the fan rotating element and the fan casing to prevent contact between these two structures. Ventilation systems shall be inspected for corrosion and shall receive preventive maintenance at least every 3 months. Airflow measurements (face velocities, static pressures, etc) should be included as part of the preventive maintenance program. The cleaning and repairing of the ventilation system shall be immediately initiated if sufficient deterioration to indicate imminent development of leaks is found during the physical inspection and preventive maintenance program. This inspection may be required more frequently than every 3 months according to the judgment of an industrial hygienist. Tempered makeup air shall be provided as required to workrooms in which exhaust ventilation is operating.

(d) Storage

Storage of bulk amounts of thiols shall meet the requirements for flammable or combustible liquid storage as specified in 29 CFR 1910.106. The C_1 through C_5 alkane thiols have the class IB designation. Hexanethiol and octanethiol have the class IC designation. Heptanethiol, nonanethiol, and higher molecular weight alkane thiols have the class III designation.

(e) Entry into Confined or Enclosed Spaces

(1) Entry into confined spaces, such as tanks, pits, tank cars, barges, and process vessels, shall be controlled by a permit system. Permits shall be signed by an authorized representative of the employer and shall certify that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that precautions have been taken to ensure that prescribed procedures will be followed.

(2) Before they are entered for repair, modification, or cleaning, confined spaces shall be inspected and tested for oxygen deficiency and for the presence of thiols and other known or suspected contaminants.

(3) No employee shall enter any confined space that does not have an entry large enough to admit a person wearing safety harness, lifeline, and appropriate respiratory equipment as specified in Section 4(c).

(4) Confined spaces shall be ventilated while work is in progress to keep the concentration of airborne thiols at or below the ceiling limit, to keep the concentration of other contaminants below dangerous levels, and to prevent oxygen deficiency.

(5) Anyone entering a confined space shall be observed from the outside by another properly trained and protected worker. The person entering the confined space shall maintain continuous communication with the standby worker.

(6) Cleaning, maintenance, and repair of tanks, process equipment, and lines shall be performed only by properly trained, adequately protected employees under supervisory control.

(f) Maintenance

Periodic maintenance shall be performed on all equipment and machinery in areas of potential exposure to thiols. Firefighting equipment and other emergency equipment shall be maintained in good working order, as prescribed by local, state, or Federal regulations.

(g) Spills, Leaks, and Waste Disposal

(1) If thiols are leaked or spilled, the following steps shall be taken:

(A) Evacuate all nonessential personnel from the area.

(B) Adequately dike the area of the spill or leak to prevent further contamination.

(C) Collect spilled material for reclamation or absorb in vermiculite, dry sand, earth, activated charcoal, household bleach solution, or other decontaminating material.

(2) Personnel entering the spill or leak area shall be furnished with appropriate personal protective equipment. All other personnel shall be excluded from the area.

(3) Water used to flush thiols shall be treated with hypochlorite to convert thiols to disulfides, eg, by addition of household bleach. The disposal method shall conform to applicable local, state, and Federal regulations and shall not constitute a hazard to the surrounding population or environment.

Section 7 - Sanitation Practices

(a) Plant sanitation shall meet the requirements of 29 CFR 1910.141.

(b) Clean and well-ventilated change rooms equipped with separate storage facilities for street clothes and work clothing shall be provided. Showers and washing facilities shall be provided in accordance with applicable regulations. Employers shall encourage personnel who work with thiols to shower before leaving the workplace at the end of a workshift.

(c) Employers shall instruct employees who handle thiols to wash their hands thoroughly with soap and water before eating, smoking, or using toilet facilities.

(d) The storage, dispensing, preparation, and consumption of food, beverages, or tobacco shall be prohibited in work areas containing thiols.

Section 8 - Monitoring and Recordkeeping Requirements

Employers shall determine by an industrial hygiene survey whether exposure to airborne thiols is in excess of the

environmental limit. Records of these surveys shall be kept, and if an employer concludes that air levels are at or below the environmental limit, the records shall confirm this. Surveys shall be repeated at least annually and within 30 days of any process change. When the industrial hygiene survey demonstrates that the environmental concentration of thiols exceeds the environmental limit, the following requirements shall apply:

(a) Personal Monitoring

(1) A program of monitoring shall be instituted to identify occupationally exposed employees and to measure or permit calculation of their exposures to thiols. 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. Procedures for sampling and analysis of thiols shall be in accordance with Appendix I.

(3) For each ceiling limit determination, a sufficient number of samples shall be collected to characterize employee exposures during each workshift. Variations in work and production schedules, as well as employee locations and job functions, shall be considered in decisions on sampling locations, times, and frequencies.

(4) Each operation shall be sampled at least once every 3 months or as otherwise indicated by a professional industrial hygienist. If an employee is found to be exposed at a level in excess of the environmental limit, the exposure of that employee shall be measured at least weekly, 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, 1 week apart, indicate that exposures no longer exceed the environmental limit. Quarterly monitoring shall then be resumed.

(b) Recordkeeping

Records of environmental monitoring shall be retained for at least 30 years after employment ends. These records shall include the dates and times of measurements; duties and location of the employees within the worksite; sampling and analytical methods used; number, duration, and results of the samples taken; ceiling concentrations estimated from these samples; type of personal protective equipment used, if any; and employees' names. Records of environmental exposures applicable to an employee shall be included in the employee's medical records. Records of environmental monitoring shall be available to the designated 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 that were prepared to meet the need for preventing occupational disease or injury arising from exposure to thiols. 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."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria on 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 standards should enable management and labor to develop better engineering controls and work practices resulting in more healthful work environments; mere compliance with the recommended standards should not be regarded as a final goal.

These criteria and recommended standard for occupational exposure to thiols are part of a continuing series of documents published by NIOSH. The proposed standard applies to the manufacture, formulation, processing, storage, and use of thiols. The recommended standard was not designed for the population-at-large, and its application to any situation other than the occupational environment is not warranted. The recommended standard is intended to protect against the development of both systemic toxic effects and local effects on the skin and eyes of employees.

Occupational exposure to thiols in the United States occurs primarily to employees involved in the formulation of thiols and their use as odorants. Inhalation of the vapor is the most common route of occupational exposure. Mucosal irritation, respiratory changes leading to respiratory failure, muscular weakness culminating in paralysis, mild to severe cyanosis, coma, and death are major reasons for concern about employee exposure to thiols.

Several areas in which further research is needed have been identified. For example, studies, including epidemiologic ones, of the long-term health effects of exposure to thiols at concentrations around the recommended environmental limit would aid in assessing the hazards of low-level exposure. Followup examinations of employees who have had skin contact with thiols would help to quantitate the risks of systemic effects from dermal exposure. Investigations of the carcinogenic, mutagenic, and teratogenic potentials of thiols are needed also.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

The thiols constitute a group of aliphatic and aromatic organic compounds characterized by the presence of sulfhydryl (-SH) groups. The word "mercaptans" is derived from the Latin "corpus mercurium captans" [1], meaning entity seizing mercury, mercaptans being so named because the hydrogen of the -SH group is easily replaced by mercury or other heavy metals to form compounds called mercaptides [2]. The terms thiol, mercapto, and sulfhydryl are used interchangeably, with thiol being the preferred term to refer to the sulfur-containing analog of the hydroxyl group that characterizes alcohols [3].

The thiols considered in this document are those monofunctional primary thiols containing one free -SH group and no other functional group; specifically, the 14 n-alkane thiols ($C_nH_{2n+1}SH$ where n = 1,2,...12, 16, 18), one aliphatic cyclic thiol (cyclohexanethiol), and one aromatic thiol (benzenethiol). The selection of these compounds was based on a preliminary survey of the industrial importance of thiols, the number of persons occupationally exposed to thiols, and the biologic effects of thiols. The physical and chemical properties of these thiols are presented in Tables XII-1 and XII-2. Synonyms for the 16 thiols are listed in Table XII-3.

Naturally occurring thiols exist in all living systems. Most of the thiols in living cells are contributed by the amino acid cysteine and the tripeptide glutathione. Cysteine is an intrinsic structural component of proteins and thus is the precursor of reactive thiols in proteins. The major nonprotein thiol in cells is glutathione, which occurs ubiquitously in living systems [4]. Thiols and disulfides occur together in cells and react both spontaneously and catalytically as oxidation-reduction (redox) reagents in various electron transport systems, as catalytic components of enzymes, as reactive groups of coenzymes, and as reactants in cellular detoxification systems [4,5]. The enzymatic reduction of disulfides that takes place in the living systems occurs through disulfide reductases. A glutathione reductase requiring reduced nicotinamide adenosine dinucleotide phosphate (NADPH) as hydrogen donor is present in plant and animal cells, and there is accumulating evidence that the reduction of disulfide groups is brought about by a transhydrogenation reaction with glutathione [6]. The thiol-disulfide exchange reaction is, in fact, a most important unifying concept that dominates the biochemistry of thiols and disulfides in living systems and forms the subject of an extensive literature [6-8]. Considerable information also is available on the chemistry, biochemistry, and analytical determination of thiols [7,9-11].

The most important biologic effects of the thiols appear to be those of high concentrations on neurons [12-15] and obnoxious odor at ppb to ppm concentrations [16]. Methanethiol is a gas at room temperature, and the other thiols are liquids. The C_1-C_6 n-alkane thiols have relatively high vapor pressures at ambient temperatures. Their boiling points range between 6.2 and 151 C at 760 mmHg. On the other hand, the C_7-C_{12}, C_{16}, and C_{18} n-alkane thiols, cyclohexanethiol, and benzenethiol have relatively lower vapor pressures, with boiling points above 151 C. The C_1-C_6 alkane thiols and benzenethiol give rise to perceptions of obnoxious odors at much lower concentrations than do the other thiols. For the most part, thiols are "insoluble" in water but soluble in bases, alcohol, and ether. They act as weak acids in chemical reactions. Thiols form insoluble mercaptides with a variety of metal cations [17], including those of mercury, lead, silver, copper, and cadmium, and undergo oxidation (in vitro) to yield disulfides.

Methanethiol and ethanethiol occur naturally in the "sour" gas of West Texas, in coal tar, and in petroleum distillates [3]. Methanethiol at ppb levels is detected in foods and vegetables [18] and is a major contributor to normal and abnormal human mouth odor [19-22]. Onions contain 1-propanethiol [23], and 1-butanethiol occurs in the secretions of skunks [3,24].

The most important industrial method for the manufacture of thiols involves the reaction of hydrogen sulfide with olefins or alcohols, at various temperatures and pressures, in combination with a variety of catalysts and promoters (acids, bases, peroxides, and metal sulfates). Primary thiols are produced in the presence of influences, such as UV radiation, that generate free radicals. Other methods for their synthesis include the reaction of alkyl halides or sulfates with metallic hydrosulfides, the hydrolysis of thiol esters with alkali, and the reduction of alkyl and aryl disulfides and alkyl sulfonyl chlorides.

Methanethiol is used extensively in the manufacture of methionine [25]. The lower molecular weight alkane thiols and benzenethiol are intermediates in the synthesis of pharmaceuticals and pesticidal chemicals (herbicides, insecticides, defoliants, fungicides, miticides, and nematocides) [17]. Because of their penetrating, disagreeable odor at concentrations as low as 0.02 ppb [26-28] (see Odor Threshold Studies), ethane-, propane-, and butanethiol are employed as warning agents for gas leaks in mines, underground gas pipes, and refrigeration units. The higher molecular weight alkane thiols are used in the preparation of tin derivatives for use as thermal stabilizers for polyvinyl chloride (PVC) resins, particularly in PVC pipe. They are also used as modifiers and chain-length control agents in emulsion-polymerization systems for the large-scale manufacture of synthetic rubbers of the butadiene and acrylate types [29-32]. The higher alkane thiols are used in froth flotation procedures to increase the yield of copper ore [17]. Thiols are also used as inhibitors of oxidation in

pickling of steel sheets, for improving the quality of molding powders, and as anticorrosion agents, industrial surfactants [33], vulcanization accelerators, rodenticides, repellants for flies [17], and depilatories for removing hair from hides [34]. They are used also in hair-waving preparations [35] and in moisture proofing of Cellophane [17]. Other uses of individual thiols are described in Table III-1.

The major routes of exposure to thiols in the workplace are by inhalation of vapor and aerosols and by skin absorption. The likelihood of such exposures is greatest during the handling, transfer, and sampling of thiols. Exposure may also occur during maintenance operations and repair of equipment; on entry into tanks, vessels, or other confined spaces; and during emergencies or when nonroutine procedures are used. Although eye exposure rarely occurs in the occupational environment, this potential exposure route should not be underestimated.

The total production in 1976 of "methane-, ethane-, propane-, butane-, octane-, nonane-, decane-, hexadecane-, and miscellaneous thiols and other hydrocarbon derivatives (from petroleum and natural gas by chemical conversion)" was 264,797,000 pounds according to the US International Trade Commission [36]. Sales of n- and tert-dodecanethiol as polymerization regulators totaled 7,698,000 pounds in 1975 [37]. No other published production data were found.

NIOSH estimates that 178,860 employees are potentially exposed to thiols in the United States. This estimate, based on the National Occupational Hazard Survey, is nearly 50% greater than the number of workers exposed to 6 of the 16 thiols for which estimates of the numbers exposed are given in Table III-1.

Historical Reports

The first member of the monofunctional organic thiol class was synthesized in 1834 by Zeise as reported by Liebig [1]. Zeise heated barium sulfide saturated with hydrogen sulfide in a retort with calcium ethyl sulfate to yield ethanethiol. He suggested the name mercaptan for this class of compounds because ethanethiol had the unusual property of being able to remove mercury from solution as a crystalline salt.

In 1886, Fischer and Penzoldt [38] demonstrated the human olfactory threshold by waving a cloth containing various quantities of ethanethiol about a classroom. The students easily detected odors from an amount as low as "1/460,000,000 mg" (2.17 pg) of ethanethiol.

Pichler [14], in 1918, reported on the accidental exposure to ethanethiol vapor of 28 male and 2 female high school students 16-18 years old. The classroom was connected by a door to a storeroom for chemicals.

TABLE III-1

INDUSTRIAL USE AND OCCUPATIONAL EXPOSURE PROFILES FOR 16 THIOLS

Thiol	Uses	Estimated No. of US Workers
Methanethiol	Chemical intermediate, especially methionine synthesis; catalyst modifier; jet fuel additives; fungicides	19,140
Ethanethiol	Liquid propane gas odorant; adhesive stabilizer; pesticide intermediate; solvent; intermediate and starting materials, plastics and antioxidants; "sulfonal" related	23,130
1-Propanethiol	Pesticides; gas odorant	18,180
1-Butanethiol	Solvent; gas odorant; pesticide intermediates, rubber chemicals, oil additives; polymerization regulator	19,410
1-Pentanethiol	Intermediate in the synthesis of organosulfur compounds	-*
1-Hexanethiol	Chemical intermediates; antioxidant, white oil; synthetic rubber processing	-
1-Heptanethiol	Froth flotation	-
1-Octanethiol	Polymerization conditioner; organic synthesis	18,660
1-Nonanethiol	See 1-octanethiol	-
1-Decanethiol	"	-
1-Undecanethiol	"	-
1-Dodecanethiol	Stabilizer, pyrethrum-DDT aerosols; pharmaceuticals; insecticides; fungicides; nonionic detergents; synthetic rubber processing; froth flotation agents for metal refining, particularly for copper ores	21,150

TABLE III-1 (CONTINUED)

INDUSTRIAL USE AND OCCUPATIONAL EXPOSURE PROFILES FOR 16 THIOLS

Thiol	Uses	Estimated No. of US Workers
1-Hexadecanethiol	See 1-octanethiol; tarnish-preventing agents	-
1-Octadecanethiol	See 1-hexadecanethiol	-
Cyclohexanethiol	Chemical intermediate; pesticides; flavoring agents; synthetic rubber processing	-
Benzenethiol	Chemical intermediate, primarily for pesticides; pharmaceutical intermediate; amber dyes	-

*Figures not available

Adapted from National Occupational Hazard Survey (NOHS), 1972-74

The students were disturbed during morning classes by a stench emanating from the adjacent room, and instruction was discontinued after 1 hour. Ten students, including the 2 girls, experienced dull headache, general discomfort, and abdominal pain; three students vomited and had diarrhea. By afternoon, they apparently felt well and slept normally that night. Instruction was resumed in the same room the next day for 3 hours. Although both the classroom and the chemical storeroom were well ventilated, eight of the students who had been affected the previous day again developed headaches, but to a lesser degree. Two of these students stayed away from school for a few days.

Physical examination of one of the students revealed some undescribed changes about the eyes, and, although his liver was palpable, his spleen was not [14]. Protein, erythrocytes, and a few leukocytes found in the urine at that time disappeared within 5-6 weeks; no epithelial cells or casts were observed. The chemical responsible was identified as ethanethiol, about 3 g of which had vaporized in the 325-cu m rooms (approximate concentration 4 ppm or 9 mg/cu m).

Between 1954 and 1956, investigations showed that ethanethiol and closely related compounds had striking antitubercular activity when tested in mice, guinea pigs, and rabbits [39-42]. Only those compounds producing ethanethiol in vivo appeared to be active in that they prolonged the survival time of the test animals injected subcutaneously (sc) or fed orally with a preparation of a strain of human tubercle bacilli. The specificity was related to the presence of the ethyl moiety, and the extent of such activity was altered by the nature of absorption and degradation of the compound [42]. The reduced antitubercular activity of ethanethiol when tested in vitro suggested that a metabolite of ethanethiol might have been the active compound. Kushner et al [41], who studied a series of thiol pyrazinoates for "antitubercular activity," found that the ethyl derivative was significantly active. However, during testing for antitubercular activity in mice, the authors found that animals given this compound, as well as ethanethiol, had an enlarged and cyanotic spleen.

Davies and Driver [43], in 1958, also showed that ethanethiol at a concentration of 10 µg/ml inhibited the growth of tubercle bacilli in monocytes derived from peritoneal exudates of normal guinea pigs, as well as in human monocytes obtained from a leukemia patient. Methanethiol showed no antitubercular activity and, in fact, partially antagonized the effect of ethanethiol. However, diethyldisulfide did have antitubercular activity.

Effects on Humans

The reports described in this section relate to the effects of exposures to methane-, ethane-, and butanethiol resulting from accidents and to human odor threshold studies on C_1-C_6 n-alkane thiols and benzenethiol. Additionally, some controlled experiments that determined the effects of exposure to ethanethiol are also reported.

Shults et al [12], in 1970, gave a detailed description of the methanethiol poisoning of a 53-year-old black male laborer, who, as a result of accidental exposure, manifested acute, severe hemolytic anemia, methemoglobinemia, and deep coma before his death 28 days after the accident. The immediate cause of death was stated to be a massive embolus that occluded both main pulmonary arteries.

The man's job had involved the salvaging of metal cylinders of the type used for storage of gas under pressure [12]. On the day of overexposure, the man apparently had emptied several tanks containing the thiol and had refilled them with water according to instructions. No indication was given that the man used protective equipment in his job. After an hour, he was found in a sitting position, unconscious, against a tank; on the asphalt pavement near him was a vaporizing liquid. The man was admitted to a hospital in a comatose state. His breath and clothes emitted a very strong, obnoxious odor. His health prior to the poisoning episode was reportedly good. On admission, the man had tachycardia (120/minute), a labile blood pressure (188/90-230/130 mmHg), and decerebrate rigidity with suppression of response to painful stimuli and of the deep tendon reflexes.

Within the first few days following admission, evidence of severe intravascular hemolysis appeared [12]. Hemoglobinuria began on the 3rd day and was marked by the 4th day. Profound anemia developed by the 7th day (hemoglobin 5.0 g% and hematocrit 16%) and was accompanied by a concentration of bilirubin in the serum (3.5 mg/100 ml), more than twice the upper limit of normal. After a tranfusion, there was no further evidence of hemolysis, and the concentration of hemoglobin in the patient's blood actually increased during the following days. Decerebrate rigidity accompanied by random myoclonic jerks continued. The patient developed a fever (39.4 C) on the 22nd day of hospitalization and, despite antibiotic and supportive treatment, died of a sudden hypotensive crisis on the 28th day. The apparent immediate cause of death, disclosed at autopsy, was a massive embolus occluding both main pulmonary arteries. The mechanism by which methanethiol caused cerebral dysfunction was not understood. The origin of the pulmonary embolus was not explained by the authors. Erythrocytes obtained on the day before the patient died gave evidence of some deficiency of glucose-6-phosphate dehydrogenase, which the authors considered may have played a part in the hemolytic phenomena in this case. It should be recognized, however, that the percent incidence of glucose-6-phosphate dehydrogenase deficiency is higher in the American Negro than in other ethnic groups [44].

In 1968, Gobbato and Terribile [15] described an episode of acute butanethiol intoxication in seven workers 25-34 years old. These individuals worked in a pilot plant in Italy where polymerization tests with acrylic resins were conducted.

In the course of these tests, the individuals mistakenly used about 1 kg of n-butanethiol, mislabeled as octanethiol, as a stabilizer and

antioxidant for an unstated amount of acrylic resin in an autoclave [15]. The exposure occurred when the workers opened the autoclave in a routine discharge operation. The intense characteristic thiol odor was noted, and the exposure lasted for about an hour. The autoclave apparently had been opened at a temperature of 70-80 C, instead of at the prescribed 50-60 C. Gas chromatographic analysis of an air sample taken 3 hours after the accident revealed that butanethiol rather than octanethiol had been the offending chemical. The exact concentration of butanethiol in the air during the exposure was not known but was surmised to have been between 50 (184.38 mg/cu m) and 500 (1,843.84 mg/cu m) ppm, based on published odor threshold data and the fact that the workers tolerated the odor for about 60 minutes before manifesting signs and proclaiming symptoms of toxicity. Intoxication was severe in one worker, mild in six. All seven workers had asthenia, muscular weakness, and malaise; six had sweating, nausea, retching, and headache; three had neck pains, dizziness, slight inebriation, or confusion; two showed anxiety, agitation, and drowsiness; and one had disturbed vision. One of the individuals lapsed into a coma.

On admission to the hospital, all seven displayed flushing of the face, sweating, increased rate of breathing, and obvious mydriasis [15]. Six of the patients recovered within a day but were held for observation for the next 3 days in the hospital. The most seriously affected patient, a 25-year-old man who remained unconscious for 20 minutes immediately after the exposure, suffered profound weakness, dizziness, nausea and vomiting, drowsiness, and depression.

Gobbato and Terribile [15] stressed the dominance of neurologic effects over the minimal renal or hepatic signs in this episode of acute butanethiol poisoning. In retrospect, they recommended that the then current maximum allowable concentration (MAC) of 10 ppm be respected and that respiratory protection be provided in cases of extended exposure above the MAC.

In 1941, Cristescu [13] described a case of mixed thiol poisoning at an oil refinery in Ploesti, Rumania. A workman descended into a pit to empty a trap containing condensate from a line through which methane-, ethane-, and other volatile thiols from a cracking process passed in transit to a burning stack. Refinery rules for this operation required the use of a gas mask, as well as the presence of a second person to observe from outside the pit, but neither of these regulations was followed. Two hours later, the man was found unconscious at the bottom of the pit sitting on a chair, his head bent over his chest. He was quickly hospitalized.

The patient was admitted in a comatose state, exhaling a very strong odor [13]. His face, lips, and limbs were cold and cyanotic. Generalized tonic contractions were accompanied by trismus and periodic convulsions. His cyanosis disappeared after 5 hours, and he regained consciousness 8 hours after his admission but did not remember when or why he had entered

the pit. Cristescu concluded that the 2-hour exposure to methane- and ethanethiols and others at a "high (but unknown) concentration" led to the following signs in the patient: loss of consciousness followed by amnesia, coma, cyanosis of the face and extremities, skeletal muscle contractions, trismus and clonic movements, paresis of bronchial muscles (as evidenced by rhonchi), fever, leukocytosis, lung abscess, and exhalation of a strong, characteristic odor; urinary abnormalities and erythrocytic changes were not observed. The general health of the worker was improved after he was immediately removed from the contaminated surroundings and placed under medical supervision. After his 2nd day of hospitalization, he was released in good health; however, 2 weeks after release, he returned to the hospital suffering from a severe cough. Medical examination revealed an abscess of his lungs, and treatment was begun immediately. After 2 weeks of treatment, the patient's general state of health improved, and he left the hospital completely cured.

Shibata [45], in 1966, reported the effects of experimental inhalation of ethanethiol on the respiratory and circulatory functions of three men. The inhaled and exhaled gases were analyzed for thiol content by gas chromatography.

For 20 minutes, two subjects inhaled ethanethiol at 50 ppm (127.12 mg/cu m), and one subject inhaled it at 112 ppm (284.58 mg/cu m) [45]. Their frequency of respiration, pulse rate, and blood pressure were measured either continuously or at prescribed intervals for 10 minutes prior to exposure. These measurements continued during the period of inhalation of ethanethiol; a recovery period followed. Exhaled air was sampled every 2 minutes for estimation of the concentration of ethanethiol. To analyze exhaled air for thiol, two subjects inhaled ethanethiol for 35-60 minutes; during this time 5-ml samples of inhaled and exhaled air were collected at known intervals. Average tidal volume was obtained by dividing the average minute volume of expiration by the breathing rate.

In one of the two subjects who inhaled 50 ppm (127.12 mg/cu m) ethanethiol, the breathing frequency decreased as soon as the inhalation started and returned to the preinhalation level following termination of inhalation [45]. The second subject's breathing rate did not change. The breathing rate of the subject exposed at 112 ppm (284.58 mg/cu m) became slightly irregular and decreased slightly. The minute volume of expiration tended to increase in all subjects. The tidal volume usually increased markedly; in one subject exposed at 50 ppm, this change was observed during the initial period of exposure only. The pulse rate showed a slight increase in only one subject inhaling 50 ppm. There were no electrocardiographic abnormalities, and no effect on blood pressure was observed. The only subjective response to ethanethiol was the recognition of the odor during the first few inhalations after the experiment was started; the odor apparently was not objectionable later. Nothing else was mentioned by the subjects during or after exposure to the gas. This study

established that with exposure to ethanethiol at 50-112 ppm, some physiologic changes occurred and the olfactory apparatus became fatigued within minutes of exposure.

The thiol concentration in the exhaled air during the experimental period was 20-40% of that inhaled, with no constant tendency to increase or decrease [45]. In the opinion of the author, 60-80% of the inhaled thiol was absorbed into the blood from the lungs at almost a constant rate. The retention of thiol in the respiratory apparatus, calculated from the minute volume and the thiol concentrations in the inhaled and exhaled air, was 1.2 µliter/minute.

Bagramian et al [46] published an abstract in 1976 on the chromosomal aberrations observed in 11 workers employed by a factory producing latex designated LNT-1 Latex, which was used in the manufacture of footwear. The workers were exposed to a mixture of airborne chloroprene (2-7 mg/cu m), dodecanethiol (1-2.5 mg/cu m), and ammonia (4-10 mg/cu m) during an unspecified length of time. Five workers from a shoe factory served as controls. Lymphocytes from peripheral blood from each individual were cultured, and 100-200 cells were examined at the metaphase stage of cell division. Chromatid breaks were observed more frequently in cells from the workers exposed to the mixture of vapors than in those from the controls. Chromosomal breaks were observed less frequently than chromatid breaks. Other chromosomal lesions, such as rings, dicentrics, and exchanges, were not observed. In the opinion of the authors, humans exposed for a long term to airborne chloroprene, dodecanethiol, and ammonia, in concentrations significantly lower than MAC's for these substances, develop increased chromosomal aberrations.

The effects on humans of inhalation exposures to three thiols and a mixture of two of these compounds are summarized in Table III-2 [12-15,45].

Odor Threshold Studies

The characteristic obnoxious odor of thiols, especially those of lower molecular weight, has been recognized since the initial synthesis of ethanethiol in 1834 [1]. The application of this property for use as a warning agent in industry has been a subject of considerable investigation.

Katz and Talbert [16], in 1930, described an extensive study on the odor thresholds of various substances including certain thiols in humans. Subjects were exposed to odorous substances at various concentrations; in addition to the determination of intensities of odor, nasal and eye irritations were noted. A series of 74 measurements was made with 55 chemicals, among which were methanethiol, ethanethiol, 1-propanethiol, 1-butanethiol, and benzenethiol. An odorometer was used [47] for determining the amount of thiol volatilized and for diluting the vapors with air to various concentrations ranging from 1 part in 10 to 1 part in 1,013. The concentration of a thiol at which odors could be detected was

TABLE III-2

EFFECTS ON HUMANS OF ACUTE INHALATION EXPOSURES TO THIOLS

Thiol	No. Exposed	Duration of Exposure	Concentration	Effects	Reference
Methanethiol	1 M	Up to 8 hr/d for 5 d; approx 1 hr on 1 day	Unknown low; unknown high for the 1 hr	Unconsciousness, offensive odor, coma, pulmonary and neurologic changes, intravascular hemolysis, hemolytic anemia, methemoglobinemia, and hemoglobinuria, death on d 28 (pulmonary artery emboli)	12
Mixed thiols (methane/ethane)	"	2 hr	Unknown high	Unconsciousness, coma, cyanosis, muscular contractions with trismus and clonic movements, exhalation of a strong odor, leukocytosis, lung abscess, recovery	13
Ethanethiol	"	20 min	112 ppm	Breathing rate slightly irregular and decreased, increase in minute volume of expiration, olfactory fatigue	45
"	2 M	"	50 ppm	Slight decrease in breathing rate during inhalation, increase in minute volume of expiration, olfactory fatigue	45
"	28 M, 2 F	1 hr	4 ppm (est)	Varying headaches, gastric discomfort urine changes in about 50%, recovery (6-8 hr)	14
Butanethiol	7 M	"	50-500 ppm	Eye disturbances, gastric discomfort, muscular discomfort, headache, nausea, mydriasis	15

measured by weight loss of the contents of the vaporizer and the total volume of air with which the thiol was mixed.

Six observers, including the operator of the odorometer, were normally employed to test intensities of odor and irritation [16]. Fourteen observers were used for tests with butanethiol that extended for 3 days. The test results are given in Table III-3.

No significant nasal or eye irritation was observed from alkane thiols [16]. However, benzenethiol caused a choking sensation in the throat, mucosal irritation, and headache. The odor of methanethiol was described by the participants as that of decayed cabbage, onions, and garlic; of ethanethiol as that of decayed cabbage, very disagreeable; of 1-propanethiol as that of onions, disagreeable; of 1-butanethiol as skunklike, disagreeable; and of benzenethiol as very disagreeable, repulsive, persistent (eye, nose, and throat irritation immediately after exposure; eyes irritated for hours). The single common physiologic response observed for all these thiols was nausea on exposure at a sufficiently high concentration. Benzenethiol also caused headache in some observers.

Perceiving the need to consider the obnoxious odor of thiols in the formulation of standards for air purity in industrial premises, Blinova [48], in 1965, reported olfactory threshold values for ethanethiol, propanethiol, and butanethiol. The experimental procedure involved having volunteers inhale for 1 minute through a gas mask connected to a 1,000-liter chamber in which a known concentration of thiol had been established. An individual threshold was established for each volunteer. During the intervals between experiments, the chamber was purged of thiols by UV radiation from a quartz lamp and by flushing with air. Nine individuals participated in the ethanethiol experiment that involved a total of 211 tests. The olfactory threshold (minimum perceptible concentration) ranged from 0.6×10^{-5} to 0.3×10^{-4} mg/liter. The maximum imperceptible concentration ranged from 0.5×10^{-5} to 0.2×10^{-4} mg/liter. Ten individuals participated in the propanethiol study in which a total of 208 tests was performed. The minimum perceptible concentration ranged from 0.7×10^{-5} to 0.3×10^{-4} mg/liter, and the maximum imperceptible concentration ranged from 0.6×10^{-5} to 0.2×10^{-4} mg/liter. Ten individuals participated in a total of 220 tests with butanethiol. The range of minimum perceptible concentration was from 0.5×10^{-5} to 0.4×10^{-4} mg/liter. Thus, similar threshold concentration values were obtained for ethane-, propane-, and butanethiol.

Precise information on the olfactory threshold for ethanethiol was acquired by exposing volunteers to ethanethiol at various concentrations below what the author [48] called the resorptive effect, by which he may have meant the dose inducing some symptom or sign of systemic toxicity. The volunteers inhaled the vapor continuously for 3 hours/day for 5-10 days

TABLE III-3

ODOR INTENSITY OF THIOLS IN HUMANS

Thiol	Degrees of Odor Intensity Vs Thiol Concentration in ppm*											
	0		1		2		3		4		5	
Methanethiol	0.003000	(0.0059)	0.04100	(0.081)	0.570	(1.1)	7.90	(16)	110	(220)	1,500	(3,000)
Ethanethiol**	0.000021	(0.000053)	0.00097	(0.0025)	0.045	(0.11)	2.10	(5.3)	97	(250)	4,500	(11,000)
	0.000006	(0.000015)	0.00026	(0.00066)	0.011	(0.028)	0.49	(1.2)	21	(53)	920	(2,300)
1-Propanethiol	0.000110	(0.00034)	0.00160	(0.005)	0.024	(0.075)	0.36	(1.1)	05.4	(17)	81	(250)
1-Butanethiol**	0.002700	(0.0099)	0.04800	(0.19)	0.840	(3.1)	15.00	(55)	260	(960)	4,600	(17,000)
	0.000045	(0.00017)	0.00100	(0.0037)	0.022	(0.081)	0.50	(1.8)	11	(40)	250	(920)
Benzenethiol	0.000005	(0.000023)	0.00025	(0.0012)	0.014	(0.063)	0.72	(3.2)	38	(170)	2,000	(9,000)

*0 = no odor, 1 = detectable, 2 = faint, 3 = quite noticeable, 4 = strong, 5 = very strong;
numbers in parentheses = concentration in mg/cu m
**Results of two tests are presented for ethanethiol and butanethiol.

Adapted from reference 16

from a special device, which was not described. The pulse and respiration rates and blood pressures of the subjects were measured, as were the fatigue response (by an unexplained method), the sensitivity of the olfactory analyzer, and the response of the taste analyzer to sweet and bitter substances. The chronaxie of the visual apparatus of the eye was also measured by use of what was described as an electronic pulsed stimulator that applied weak electric discharges to the eyeball. These measurements were made before and after each exposure to an experimental mixture. The state of fatigue was also estimated during 5 minutes in each of the 1st, 2nd, and 3rd hours of inhaling a mixture. The volunteers were subjected also to a control experiment in which they inhaled pure air. The tests produced no significant changes other than decreases in blood pressure and pulse rate that were considered physiologic responses to forced rest.

In the first experiment with ethanethiol, three volunteers were exposed to the compound at 10 mg/cu m (3.94 ppm) [48]. One of the volunteers, a woman, had a uniform response throughout the 10-day test with no tendency toward either intensification or habituation. Observations on the two men were made, therefore, for only 5 days. The woman's olfactory threshold rose from 6.2 ±0.26 to 12 ±0.18 ml. The corresponding shifts for the two men were from 9.4 ±2.7 to 11.0 ±1.8 ml and from 6.0 ±0.9 to 16.0 ±0 ml. Thus, weakened olfactory responses to ethanethiol were observed after 3-hour inhalation exposures. No changes in taste were reported. The rheobase of the visual apparatus lowered to some extent. For the woman the rheobase before exposure was 4.1 ±0.11 volts (V) and after exposure it was 3.6 ±0.33 V. Corresponding values for the two men were 4.8 ±0.45 V and 30 ±0.73 V before and 3.0 ±0.48 and 2.1 ±0.25 V after exposure. Error analysis indicated some fatigue.

All volunteers recorded, from the beginning of the experiment, a fairly strong smell resembling that of onions, garlic, or gasoline; the intensity of the odor lessened after about 1.5-2 hours [48]. Each person complained of such sensations as periodic nausea, irritation of the mucous membranes of the mouth and lips and, less frequently, the nose, a feeling of head heaviness, and fatigue.

In the second experiment conducted about a month later, the same individuals were exposed to ethanethiol at 1 mg/cu m (0.394 ppm) [48]. Increases in the olfactory threshold, but to a lesser extent than in the first experiment, were observed. The woman had an increase from 5.8 ±0.15 to 7.3 ±0.52 ml, and the corresponding changes for the two men were 6.7 ±0.8 to 7.5 ±0.94 ml and 7.3 ±0.25 to 11.0 ±0.45 ml. Neither a change in taste nor a lowering of the original rheobase of the eye was observed. The three subjects reported a moderate odor, resembling that of onions, that disappeared entirely halfway through the experiment, but no other unpleasant symptoms. In view of the above findings and in consideration of tests of its chronic toxicity in animals, 0.001 mg/liter was tentatively

recommended by Blinova as the maximum permissible concentration of ethanethiol for factories. This study [49] showed that the inhalation of ethanethiol led to an increase in the olfactory threshold more sensitively than it did to any other index studied. No other cumulative effects were noticed during the 5-10 days.

In 1969, Wilby [50] reported on the variability in recognition of odor thresholds by panel members in a study initiated by the Pacific Lighting System of Southern California. The 18 sulfur compounds chosen for the study on the basis of their predominant occurrence in natural gas included methanethiol, ethanethiol, 1-propanethiol, and 1-butanethiol.

The panelists chosen were not previously trained in odor threshold work [50]. All were company employees working in the same building. Comprising the panel were five men (two smokers) and four women (one smoker) aged 18-35; six men (four smokers) and seven women (four smokers) aged 36-55; and seven men (four smokers) and six women (two smokers) aged 56-66. All testing was done outdoors during clement weather when "no ambient odors" were present. A two-step dilution procedure was adopted to obtain threshold concentrations in the ppb range. First, a gas mixture of highly purified methane containing a few ppm of a thiol was confined at 200 psig in a specially constructed and cleaned 1.7-cu ft stainless steel pressure vessel and allowed to equilibrate for 24 hours. The gas mixture was then analyzed for the thiol by hydrogenation followed by estimation of H_2S by the methylene blue method and by gas chromatography. The latter procedure permitted detection of oxidation of the thiol to a disulfide. Second, dilution to the olfactory thresholds was accomplished with special odorometers. For each test, a series of concentrations, in increments of $10^{0.2}$, was presented to the panel in random order. The author estimated that the overall accuracy of estimation of the concentration was ±30%. The panelists walked in single file past three odorometers, pausing at each to take one or two breaths and to note on their test cards whether they detected an odor. The threshold concentration was defined as the lowest concentration the respondent could smell consistently, not necessarily the lowest concentration reported. The ratio of highest to lowest odor threshold concentration was determined for each panelist as a measure of the range of response of the panelists. The odor thresholds were presented in histograms for the different compounds. The histograms yielded estimates for the median and mean threshold concentrations, which are given in Table III-4.

Methanethiol and ethanethiol are metabolites of the human body and are excreted in the breath of normal subjects [20,22] and in higher concentrations in the breath as well as the urine [21] of patients suffering from advanced liver disease [22]. In 1975, Solis-Gaffar et al [20] published levels of methanethiol (expressed as elemental sulfur) in the early morning oral breath of normal subjects ranging from 23.4 to 33.9 ng S/ml. In 1955, Challenger and Walshe [21] established the presence of

TABLE III-4

VARIATION IN ODOR THRESHOLDS OF SELECTED THIOLS

Thiol	No. of Observers	Concentration Median (ppb)	Concentration Mean (ppb)	Standard Deviation	Coefficient of Variation	Highest:Lowest Odor Threshold (± SD)
Methane-thiol	34	0.80	0.99	0.71	0.72	3.15 (3.02)
Ethane-thiol	33	0.32	0.40	0.26	0.65	2.80 (1.62)
Propane-thiol	35	0.75	1.20	1.20	0.98	3.20 (2.85)
Butane-thiol	35	0.62	0.72	0.57	0.79	3.25 (2.24)

*Adapted from reference 50

methanethiol in the urine of a patient with fetor hepaticus ("liver breath") by precipitating it as the characteristic mercury mercaptide.

In 1970, Chen et al [22] reported the use of gas chromatography to measure the concentrations of methanethiol, ethanethiol, and dimethyl sulfide in the breath of normal subjects, both fasting and following ingestion of methionine, and of patients with cirrhosis of the liver or in hepatic coma. Methanethiol and ethanethiol levels in the breath of seven normal fasting subjects ranged from 0.1 to 1.3 ng/liter and 1.1 to 12.3 ng/liter, respectively. After daily ingestion of 8-12 g of methionine for 7 days, six subjects showed an average 1.5-fold increase in the concentrations of both methanethiol and ethanethiol in their breaths.

In 10 cirrhotic patients, the concentrations of methanethiol and ethanethiol in their breaths averaged 4.4 and 11.5 ng/liter respectively [22]. Methanethiol constituted on the average about 28% of the total thiols exhaled by these patients as compared with 12% in the controls. After ingesting methionine, the cirrhotic patients had slight increases in the exhaled concentrations of thiols, the percent increase in that of methanethiol being somewhat greater than in that of ethanethiol. The concentrations of ethanethiol did not increase appreciably in the breaths of the cirrhotic patients following ingestion of methionine. The intensity of the breath odor in cirrhotic patients after methionine administration was unrelated to the concentration of thiols but was directly related to the concentration of dimethyl sulfide, which ranged from 33.2 to 0.683 ng/liter in seven patients. The authors believed that the excess methionine fed to these patients was metabolized by intestinal bacteria to form dimethyl sulfide that bypassed the impaired liver to be excreted by the lungs.

The effects of thiols on humans in odor threshold studies are summarized in Table III-5.

Epidemiologic Studies

No report of an epidemiologic study of a population of workers exposed to thiols was found in the literature.

Animal Toxicity

(a) Acute Toxicity

The literature contains information on the acute toxicity of methanethiol, ethanethiol, propanethiol, butanethiol, pentanethiol, hexanethiol, and benzenethiol, but little published information was found on the acute toxicity of the other thiols (heptanethiol through octadecanethiol and cyclohexanethiol).

TABLE III-5

EFFECTS ON HUMANS OF THIOLS IN ODOR THRESHOLD STUDIES

Thiol	No. Exposed	No. or Duration of Exposures	Concentration ppm	Concentration mg/cu m	Effects	Reference
Methanethiol	6	1 inhalation	7.9	15.5	Nauseating odor (cabbage, onion, garlic)	16
"	6	"	41.0*	0.081	Very faint odor	16
"	6	"	3.0*	0.0059	No odor	16
"	34 M and F	1 or 2 inhalations in 3 sequential exposures	Mean ratio 3.15 (SD 3.02)		Highest to lowest odor threshold	50
Ethanethiol	6	1 inhalation	0.49	1.2	Easily noticed, nauseating odor	16
"	6	"	0.26*	0.00066	Very faint odor	16
"	6	"	0.006*	0.000015	No odor	16
"	18 M 17 F	1 or 2 inhalations in 3 sequential exposures	Mean ratio 2.80 (SD 1.62)		Highest to lowest odor threshold	50
"	1 M	20 min	112	284	Breathing rate slightly irregular and decreased, increase in minute vol of expiration, olfactory fatigue	45
"	2 M	"	50	127	Slight increase in breathing rate during inhalation, increase in minute volume of expiration, olfactory fatigue	45
"	9	1-min exhalation x 211 tests	Minimum 10.8-2.2*	0.03-0.006	Perceptible concentration	48
			Maximum 7.2-1.8*	0.02-0.005	Imperceptible concentration	
"	1 F	3 hr/d for 10 d	4	10	Nauseating odor (onion, garlic, gasoline), olfactory fatigue, mucosal irritation	48
"	"	3 hr/d for 10 d, 1 mo after above exposure	0.4	1.0	None	48

TABLE III-5 (CONTINUED)

EFFECTS ON HUMANS OF THIOLS IN ODOR THRESHOLD STUDIES

Thiol	No. Exposed	No. or Duration of Exposures	Concentration ppm	Concentration mg/cu m	Effects	Reference
Ethanethiol	2 M	3 hr/d for 5 d	4.0	10	Nauseating odor (onion, garlic, gasoline); olfactory fatigue; mucosal irritation	48
"	"	3 hr/d for 5 d, 1 mo after above exposure	4.0	10	Same as above but less pronounced	48
"	"	3 hr/d for 5 d	0.4	1.0	None	48
"	"	3 hr/d for 5 d, 1 mo after above exposure	0.4	1.0	"	48
Propanethiol	6	1 inhalation	0.36	1.12	Easily noticed, nauseating odor (onion)	16
"	6	"	1.6*	0.005	Very faint	16
"	6	"	0.11*	0.00034	No odor	16
"	18 M 17 F	1 or 2 inhalations in 3 sequential exposures	Mean ratio 3.2 (SD 2.85)		Highest to lowest odor threshold	50
"	10	1-min inhalation x 208	Minimum 9.6-2.2*	0.03-0.007	Perceptible concentration	48
			Maximum 6.4-1.9*	0.02-0.006	Imperceptible concentration	
Butanethiol	14	1 inhalation	0.5	1.85	Nauseating odor	16
"	14	"	1.00*	0.0037	Very faint odor	16
"	14	"	0.045*	0.00017	No odor	16
"	18 M 17 F	1 or 2 inhalations in 3 sequential exposures	Mean ratio 3.25 (SD 2.24)		Highest to lowest odor threshold	50
"	10	1-min inhalation X 220	Minimum 10.83-1.89*	0.04-0.007	Perceptible concentration	48
			Maximum 5.4-1.3	0.02-0.005	Imperceptible concentration	
Benzenethiol	6	1 inhalation	0.72	3.244	Headache, irritation (throat, eyes, nose), putrid odor	16
"	6	"	0.26*	0.0012	Very faint odor	16
"	6	"	0.005*	0.000022	No odor	16

*ppb

(1) Methanethiol through Hexanethiol; Benzenethiol

The inhalation toxicity of methanethiol was determined by Selyuzhitskii [51] in experiments with mice and rats. The details of exposure were not stated. The 2-hour LC_{50} for mice was 6.53 (5.67-7.5) mg/cu m. The 4-hour LC_{50} for rats was 8.87 (7.64-10.29) mg/cu m. The oral LD_{50} value for methanethiol in mice was 60.67 (52.3-64.31) mg/kg. Overall, the lack of data to support the statements made in the text and the paucity of details about experimental procedures diminish the utility of this report.

In 1978, a report [52] was published on the inhalation toxicity of methanethiol in white rats. Ninety rats were divided into 9 groups, each containing 5 males and 5 females. Each group was placed in a custom-built 75-liter glass chamber prior to a 4-hour exposure period. Eight groups of rats were exposed to methanethiol at eight concentrations ranging from 400 to 800 ppm (788 to 1,576 mg/cu m). The remaining group of rats was sham exposed to check for mortality arising from conditions other than actual gas exposure. After exposure, the rats were separated by sex and observed for the subsequent 14 days. Gross pathologic observations were made on the 2-week survivors as well as on those that died.

The calculated LC_{50} value for methanethiol was 675 ppm (1,338 mg/cu m), with apparent 95% confidence limits of 643-709 ppm (1,265-1,395 mg/cu m) [52]. No gross pathologic changes were observed in the survivors or in those that died. The author stressed that the results are relevant to the understanding of the acute effects and are not applicable to toxic effects produced by chronic exposure to low doses because the mechanism of chronic toxic effects is different from those of acute lethality.

Ljunggren and Norberg [53], in 1943, reported on the inhalation toxicity of methanethiol in white female rats weighing 90-130 g. Methanethiol was introduced into a chamber that had a 7.6-liter capacity and into which one rat was placed. The chamber was then hermetically sealed. At the end of the 30- to 35-minute exposure, the maximum calculated carbon dioxide concentration was 1.8% by volume, which the authors concluded would not affect the experiment. The concentrations at which methanethiol was tested ranged from 500 to 10,000 ppm (985 to 19,700 mg/cu m). Apparently, only one rat was exposed to methanethiol at each of four concentrations. Surviving animals were killed by decapitation after a 24-hour observation period, and their lungs were prepared for microscopic examination.

No physiologic or pathologic changes were observed in the rat exposed to methanethiol at 500 ppm (985 mg/cu m) for 30 minutes [53]. The rat exposed at 700 ppm (1,379 mg/cu m) "appeared tired" during exposure but recovered quickly on removal from the chamber. After 30 minutes, the rat exposed at 1,500 ppm (2,955 mg/cu m) could rise on its legs "only

momentarily" but recovered within 5 minutes after removal from the chamber. Microscopic examination of the lungs of this rat revealed thickened alveolar walls and a hemorrhagic exudate within the alveoli. The rat exposed at 10,000 ppm (19,700 mg/cu m) went into convulsions after 1 minute and died within 14 minutes. Necropsy disclosed small hemorrhagic areas in the lungs, and microscopic examination revealed areas in the alveoli filled with erythrocytes and serous fluid. The evidence suggests that methanethiol, at high concentrations, is a central nervous system (CNS) depressant causing paralysis of the locomotor muscles and irritation of the mucous membranes.

In a 1960 report on the inhalation toxicity of methanethiol in white mice, Horiguchi [54] suggested that methanethiol is a CNS toxicant. Groups of 10 mice (13-17 g) were exposed to methanethiol for up to 4 hours at each of the following concentrations" 1,200 (2,364 mg/cu m), 1,300 (2,561 mg/cu m), 1,500 (2,955 mg/cu m), 1,600 (3,152 mg/cu m), 1,800 (3,546 mg/cu m), and 2,200 ppm (4,334 mg/cu m). Nine mice made up a 2,000-ppm (3,940 mg/cu m) exposure group. Signs of methanethiol poisoning preceding death and the number of deaths occurring during the test were recorded.

The calculated LD_{50} value for methanethiol was 1,664 ppm (3,278 mg/cu m), with apparent 95% confidence limits of 1,577-1,757 ppm (3,107-3,461 mg/cu m) [54]. If signs of toxic effect were present, they consisted of paralysis of all four limbs and convulsions. The initially increased, and later suddenly decreased, respiratory rates in the mice that died indicated to Horiguchi paralysis of the respiratory centers in these animals. Within 10-60 minutes after the first evidence of limb paralysis and general convulsions, all mice manifesting these effects were dead. Approximately 20% of the surviving animals exhibited increased respiratory rates during exposure.

The animals were necropsied either immediately after death or following a 4-hour observation period after the end of the exposure [54]. Minor congestion was found in the lungs, liver, kidneys, and spleen of all mice. With exposure at increasing concentrations of methanethiol, the air content of the lungs decreased, and inflammation was found in the nasal mucosae and lungs. Microscopic examination of fixed and stained sections of organs from mice exposed to methanethiol at 1,200, 1,600, and 2,200 ppm (2,364, 3,152, and 4,334 mg/cu m) revealed fatty degeneration of the liver and congestion of the kidneys and lungs in proportion to the concentration of methanethiol; in addition, hyperemia of the lungs, with some edema perivascularly and within alveoli, and petechiae of the respiratory tract were found in mice exposed to methanethiol at 2,200 ppm (4,334 mg/cu m). No changes were found in their hearts, digestive organs, or brains.

In 1974, Zieve et al [55] reported on the "coma-producing" properties of methanethiol and ethanethiol. Male rats, weighing 285-325 g, were exposed singly for up to 15 minutes to methanethiol or ethanethiol at

concentrations of approximately 600-2,200 ppm (1,182-4,334 mg/cu m) or 27,000-38,000 ppm (68,580-96,520 mg/cu m), respectively. Three to eight rats were exposed at each concentration. For static exposures, the desired thiol concentrations were achieved by injecting the required amount of thiol through a rubber septum in the lid of the chamber into which the rat had been placed. Occasional analysis of chamber air showed that actual concentrations varied by 5% at a 1%-by-volume (10,000 ppm) concentration and by less than 25% at the 0.1%-by-volume (1,000 ppm) concentration. For the determination of dose-response relationships, the animals were observed until they had completely lost the righting reflex or until they had been exposed to the thiol for 15 minutes. The concentration of thiol in the blood was determined after a 4-minute exposure.

The thiol concentration at which 50% of the rats lost their righting reflex was 1,600 ppm (3,152 mg/cu m) for methanethiol and 33,000 ppm (83,820 mg/cu m) for ethanethiol [55]. The rats went through a brief excitement period before they became "groggy and lethargic," and then their righting reflex was lost within the next few minutes. The duration of the phase of excitement and beginning depression varied inversely with the concentration of the thiol inhaled. Methanethiol at 2,000 ppm (3,940 mg/cu m) caused all rats to lose their righting reflex, whereas 1,200 ppm (2,364 mg/cu m) was the highest concentration at which no animal lost the righting reflex. If the animals were removed from the chamber immediately after losing the righting reflex, "consciousness" was regained within 30 minutes. How consciousness was determined was not stated.

The ratio of the concentration of thiol in the blood to that inhaled was determined [55]. Rats exposed to methanethiol at an air concentration of 0.066 millimole/liter had blood levels of the substance that ranged from 0 to 0.5 millimole methanethiol/ml blood. For ethanethiol, a mean concentration of 200 nmol/ml blood was attained in 11 of 15 rats exposed to the substance at an air concentration of 1.32 millimoles/liter. From the data presented, no dose-response relationship could be determined.

Three metabolic studies relating to CNS toxicity [49,56,57] suggest that prolonged exposure and consequent increased concentrations of methanethiol in the brain may affect the brain Na^+,K^+-ATPase system. Foster et al [56] reported a study of the effect of methanethiol and ethanethiol on the Na^+,K^+-ATPase system in rat brains. When concentrations of methanethiol ranging from 0.19 µmol (9.12 µg) to 1.9 µmol (91.2 µg) were added to the system in vitro, 46-74% inhibition of Na^+,K^+-ATPase was produced. The dose-response relationship was characterized as not linear. The concentrations of methanethiol and ethanethiol required to cause 44-45% inhibition were 0.19 µmol and 0.21 µmol, respectively.

In a detailed examination of the kinetics of inhibition of the Na^+,K^+-ATPase system, Quarfoth et al [49], in 1976, indicated that

methanethiol caused a 50% inhibition of rat brain ATPase at a 0.1 mM thiol concentration and that the inhibition increased to 72% at 1.0 mM. Complete inhibition was not achieved. Inhibition was not time dependent, did not increase during 30 minutes, and was determined to be completely reversible when the concentration of the thiol was decreased by dilution of the assay medium.

Pashchenko [57], in 1969, studied in vivo the effect of methanethiol on rat Mg^{++}-ATPase activity. When rats inhaled methanethiol at 2,030-2,538 ppm (4,000-5,000 mg/cu m) for an unspecified period, brain ATPase activity decreased by 15%. When rats inhaled methanethiol at 203-305 ppm (400-600 mg/cu m) for 3 hours/day for 3 weeks, the ATPase activity of brain, lungs, and spleen decreased by 15, 13 and 28%, respectively. However, when the animals were exposed for a longer, unspecified time, the ATPase activities of brain and spleen increased by probably insignificant amounts (5 and 12%, respectively). These results indicate that exposure to methanethiol alters Mg^{++}-ATPase activity.

Shibata [58], in 1966, reported the effect of ethanethiol on respiratory function in six 3-kg male rabbits that inhaled ethanethiol at 10, 100, and 1,000 ppm (25, 254, and 2,540 mg/cu m) for approximately 20 minutes through masks. Both the breathing rate, which was measured by observed movements of the thorax, and the minute expiratory volume, as measured by wet spirometry were monitored throughout the exposure period. The tidal volume then was calculated by dividing the minute expiratory volume by the breathing rate.

All indicators of respiratory function, except the breathing rate, of the rabbits exposed to ethanethiol at 1,000 ppm, returned to control levels by the end of the 35-minute postexposure observation period [58]. The breathing rate of the rabbits exposed at 1,000 ppm remained depressed. For all three concentrations of ethanethiol, a negative correlation was found between the breathing rate and tidal volume during inhalation.

In 1958, Fairchild and Stokinger [59] extensively reported on the acute toxicity of ethanethiol, propanethiol, butanethiol, hexanethiol, and benzenethiol in rats and mice and on the toxicity of benzenethiol in rabbits. Male animals were exposed to the thiols by intraperitoneal (ip) injection, oral intubation, inhalation, and cutaneous application. Rats, weighing an average of 180-220 g, were exposed to the various thiols by each of the four routes of administration. Mice, weighing 25-28 g, were exposed to thiol vapors by inhalation. The experimental groups consisted of from 5 to 10 animals, except that 3 groups of only 2 rabbits each, of unspecified weight, were exposed to benzenethiol applied to the skin on an area of the back from which the hair had been clipped. The dosages administered by each exposure route differed by a factor of either 1.26 or 2.0 in a geometric series. For the ip and oral administration, cumulative mortality was determined on days 1, 2, 3, 5, 10, and 15. In most cases,

the LD_{50} and LC_{50} values were calculated for days 1, 2, and 15. The mortalities of rats and rabbits were closely observed during the 72 hours following a single application of benzenethiol to the skin. Animals were killed either immediately after an experiment or after a 2-week to 1-month observation period.

In the inhalation experiments, groups of 5 rats and 10 mice were exposed for 4 hours [59]. The accuracy of the sampling technique and analytical procedure was such that the recovery was found to be within 2% of the calculated amount taken. For ip and oral administration, the aliphatic thiols were given undiluted. Benzenethiol was administered orally as an 8% V/V solution in ethanol and ip as a 5% V/V solution in ethanol. For estimation of absorption from the skin's surface, areas of skin approximately 3 cm square, or 6 x 10 cm, of the upper midbacks of rats and rabbits, respectively, were clipped as close to the skin as possible without causing abrasions. Measured amounts of undiluted benzenethiol were dropped on the clipped areas of the skin.

Mice were more susceptible to 4-hour inhalation exposures of the various thiols than were rats [59]. Except for benzenethiol, the thiols were approximately twice as toxic to mice as to rats on the basis of comparisons of 15-day postinhalation LC_{50} values. The incidence of delayed toxicity was higher in rats than in mice, but delayed mortality was very marked in both rats and mice exposed to benzenethiol. Table III-6 presents the 4-hour LC_{50} data for rats and mice.

The characteristic signs of toxicity found with maximum sublethal and lethal concentrations of thiols were increased breathing rate and restlessness (hyperactivity in mice), uncoordinated movement and staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of the prone position, and apparently mild to heavy sedation [59].

When administered in single ip doses to rats, as by other routes of administration, ethanethiol was the most toxic of the alkane thiols tested, being surpassed in toxicity by benzenethiol alone. The data are presented in Table III-7.

Fairchild and Stokinger [59] observed that, to some extent, delayed toxicity with intermittent mortality was found for all thiols. The 24-hour ip LD_{50}'s were approximately 1.5-2 times the respective 15-day values. Much of the delayed toxicity occurred subsequent to the 48-hour postinjection period. For all thiols tested, the appearance of the following toxic effects in rats was fairly consistent: restlessness, increased respiratory activity, incoordination, muscular weakness, skeletal muscle paralysis (in most cases), mild to heavy cyanosis, lethargy or sedation or both, respiratory depression followed by coma, and death after lethal doses. Muscle paralysis, when present, affected the hind limbs first. All the aliphatic thiols were found to be apparent central

TABLE III-6

LC_{50} VALUES FOR RATS AND MICE AFTER 4-HOUR INHALATION EXPOSURES TO VAPORS OF SELECTED THIOLS

Thiol	Analyzed Concentration (ppm)	LC_{50} (95% Confidence Limits in ppm)					
		Rats (range of body wt: 180-220 g)			Mice (range of body wt: 25-2 g)		
		24 hr	48 hr	15 d	24 hr	48 hr	15 d
Ethanethiol	2,600-5,125	4,870 (4,783-4,957)	4,565 (4,448-4,682)	4,420 (4,299-4,541)	-	2,770 (2,661-2,879)	-
Propanethiol	3,050-11,260	-	7,300 (Estimate)	-	-	4,950 (Estimate)	4,010 (Estimate)
Butanethiol	2,150-6,000	4,460 (4,132-4,786)	4,280 (3,959-4,601)	4,020 (3,656-4,384)	2,950 (2,824-3,076)	-	2,500 (2,437-2,563)
Hexanethiol	220-1,475	1,200 (1,115-1,285)	1,145 (1,044-1,236)	1,080 (930-1,230)	610 (548-672)	550 (487-613)	528 (470-586)
Benzenethiol	20-132	-	59 (50.7-67.3)	33 (29.6-36.4)	47 (43.4-50.6)	35.5 (32.4-38.6)	28 (24.8-31.2)

Adapted from reference 59

TABLE III-7

LD_{50} VALUES FOR RATS AFTER SINGLE IP DOSES OF SELECTED THIOLS

Thiol	Dose Range* (mg/kg)	LD_{50} (95% Confidence Limits in mg/kg) Day 1	Day 2	Day 15	Day of Last Death
Ethanethiol	105-1,680	450 (359-564)	420 (331-532)	226 (180-283)	5-10
Propanethiol	209-1,672	1,028 (781-1,298)	780 (556-1,096)	515 (390-679)	3-5
Butanethiol	209-1,672	679 (515-896)	-	399 (257-619)	5-10
Hexanethiol	212-1,696	600 (405-887)	-	396 (282-556)	10-15
Benzenethiol	6.7-108.00	25.2 (17.9-35.4)	-	9.8 (7.0-13.7)	5-10

*Altered by factors of 2 (ethanethiol) or of 1.26 (remaining thiols) in geometric series; 5-10 animals at each dose

Adapted from reference 59

depressants, the degree of depression ranging from mild stupor to heavy sedation. Benzenethiol caused only slight sedation.

The acute toxicity data for rats following single oral doses of selected thiols are presented in Table III-8.

The oral toxicity of the thiols was considerably lower than that found after ip injection [59]. Delayed toxic effects, although evident with the alkane thiols, were not seen as frequently in the orally dosed rats as in those injected ip; none was reported for rats given benzenethiol. The signs of acute oral toxicity were essentially the same as those seen after ip administration. The characteristic central depressant action of the alkane thiols was evident, particularly in rats given hexanethiol.

Benzenethiol was applied to the clipped backs of rats at doses ranging from 134 to 538 mg/kg and to the backs of rabbits at doses from 67 to 269 mg/kg [59]. The cutaneous LD_{50}'s, determined 4-8 hours after application, were 300 mg/kg (95% confidence limits 236-384 mg/kg) for rats and 134 mg/kg (estimated) for rabbits. Signs of percutaneous benzenethiol toxicity were similar to those observed after ip and oral administration. Benzenethiol produced some inflammation of the skin a few hours after percutaneous application, but the redness usually disappeared within 24-48 hours after the exposure ended.

When autopsies were performed on animals dying after single ip, oral, or percutaneous doses of thiols, significant gross or microscopic tissue changes were not usually found [59]. Animals that survived near-lethal ip or oral doses of thiols and that were killed 20 days after treatment frequently exhibited microscopic changes indicative of damage to the liver and kidneys. The rats and mice that died several hours after exposure at a high concentration of a thiol vapor had mild to severe hyperemia of the trachea and lungs. Changes seen in mice exposed to thiols at moderate to near-lethal concentrations were greater than those in rats exposed at the same concentrations. Microscopic changes included those called cloudy swelling, fatty degeneration, and necrosis of the liver; capillary engorgement, patchy edema, and occasional hemorrhage in the lungs; and mild to moderate cloudy swelling in the kidneys. Rats had a high incidence of acute pneumonia, and alveolar wall breakage was consistently found in those exposed to benzenethiol.

To determine whether there was a true increase of pneumonia as a result of benzenethiol exposure, the authors exposed 7-10 rats with existing pulmonary infection at "low" concentrations of the thiol for 3 consecutive days [59]. Histologic examination of sections of lung revealed that benzenethiol exacerbated the latent respiratory infection, whereas in nine control rats the latent pulmonary infection had not been activated. Benzenethiol was the only thiol that caused microscopic changes after exposure at low concentrations.

TABLE III-8

LD_{50} VALUES FOR RATS AFTER SINGLE ORAL DOSES OF SELECTED THIOLS

Thiol	Dose Range* (mg/kg)	LD_{50} (95% Confidence Limits in mg/kg) Day 1	Day 2	Day 15	Day of Last Death
Ethanethiol	210-3,360	1,034 (667-1,603)	-	682 (517-900)	10-15
Propanethiol	1,327-3,344	2,362 (2,014-2,770)	2,055 (1,836-2,300)	1,790 (1,632-1,963)	5-10
Butanethiol	1,093-3,344	2,575 (2,145-3,090)	1,683 (1,346-2,105)	1,500 (1,244-1,809)	7
Hexanethiol	848-2,137	-	1,580 (1,347-1,855)	1,254 (1,084-1,451)	3-5
Benzenethiol	21.6-172.5	46.2 (29.8-71.6)	-	-	1

*Altered by factors of 2 (ethanethiol, benzenethiol) or 1.26 (remaining thiols) in a geometric series; five animals at each dose

Adapted from reference 59

In summary, the general signs of acute thiol poisoning exhibited by mice, rats, and rabbits were central depression and respiratory paralysis, with death caused by respiratory failure [59]. Certain thiols were associated with a high incidence of delayed mortality. All the thiols were central depressants, the degree ranging from mild stupor to heavy sedation. Inhalation, ip, and oral administration, at relatively high levels, caused liver and kidney damage. Inhalation of thiols at high concentrations caused slight to severe irritation of the respiratory tract, the degree being dependent on the thiol. Some rats exposed to benzenethiol developed pneumonia, possibly as a result of activation of latent pulmonary infection. Benzenethiol, administered by all routes, also caused significant microscopic changes at low levels of exposure.

Carpenter et al [60] performed range-finding assays, published in 1949, on acute vapor toxicity. Male and female albino rats weighing 100-150 g were exposed to pentanethiol in a 9-liter desiccator. The authors assumed that the calculated pentanethiol concentration was probably slightly higher than an analytically estimated one would have been. Six rats were exposed to pentanethiol at 2,000 ppm (8,520 mg/cu m) for 4 hours. Two, three, or four (exact number not stated) of six rats died during the 14-day observation period. On the basis of these results, the authors concluded that the degree of hazard associated with exposure to pentanethiol is moderate. As mentioned earlier [59], the LC_{50} values on the 15th day following single 4-hour inhalation exposures of rats to butanethiol and hexanethiol were 4,020 ppm (14,834 mg/cu m) and 1,080 ppm (5,227 mg/cu m), respectively. Pentanethiol would thus appear to rank between butanethiol and hexanethiol in inhalation toxicity.

(2) Heptanethiol through Dodecanethiol; Cyclohexanethiol

The intravenous (iv) toxicity of the following thiols was determined in mice: propane-, butane-, hexane-, heptane-, octane-, nonane-, decane-, undecane-, dodecane-, hexadecane-, octadecane-, and cyclohexanethiol (WW Wannamaker, written communication, December 1977). The LD_{50} values for the aliphatic thiols were all greater than 316 mg/kg. The LD_{50} value for cyclohexanethiol was estimated to be 316 mg/kg because one of two mice injected at this concentration died. When present, the signs of toxicity generally were rapid breathing, hunched posture, and decreased activity.

The acute toxicity of dodecanethiol and of a mixture of C_7 through C_{11} thiols to mice and rats was studied by Gizhlaryan [61] in 1966. The intragastric LD_{50} of dodecanethiol was 4,225 mg/kg (range 3,069-5,381) for the mouse, but a dose of 7,000 mg/kg caused no deaths in rats. When a mixture of C_7 through C_{11} thiols was administered, the LD_{50} for rats was 3,300 mg/kg (range 2,842-3,758) and the LD_{50} for mice was 2,025 mg/kg (range 1,579-2,471). Experimental details were not provided. The author indicated that the inhalation of unstated concentrations of dodecanethiol,

or the thiol mixture, for 2 hours caused no lethal effects. Dodecanethiol and the thiol mixture applied to the skin at concentrations of 3.4 ±0.1 mg/liter and 2.9 ±0.12 mg/liter, respectively, caused marked local effects, as well as general poisoning, in both rats and mice; no further information was provided. This study indicates that the higher molecular weight thiols have a low toxicity in comparison with the lower molecular weight thiols.

(3) Ocular Effects

Fairchild and Stokinger [59], in 1958, reported results of tests on the ocular toxicity of ethane-, propane-, butane-, hexane-, or benzenethiol in rabbits. One-tenth of a milliliter of each undiluted thiol was instilled into the conjunctival sac of the right eye of a male rabbit; the whole left eye served as a control. Propanethiol and benzenethiol were later instilled into the control eye, which was washed copiously with water approximately 5 seconds after instillation. Ocular reactions were observed with a hand slit lamp.

Ethanethiol, propanethiol, and butanethiol caused slight to moderate irritation [59]. Hexanethiol was not irritating. Propanethiol was the only alkane thiol that caused an irritation observable 48 hours after exposure ended. Heavy discharge and severe redness of the palpebral conjunctivae were evident at the 24- through 96-hour observations, and chemosis appeared at 48 hours. The same signs of irritation were seen in eyes washed with water after instillation of propanethiol, but, in each case, the conditions gradually improved and disappeared by day 8 after the exposure.

Benzenethiol produced not only severe irritation of the conjunctivae but also injured the cornea [59]. The instillation of undiluted benzenethiol into the conjunctival sac produced moderate to severe redness, chemosis, and a discharge that continued for 3-4 days. The conjunctivae gradually returned to normal by the 16th day. All three benzenethiol-exposed rabbits developed diffuse corneal opacities involving three-quarters of the cornea by the 4th day after instillation. In one, this condition subsided within 3 days, and no sign of injury persisted. In the other two rabbits, the corneal opacities gradually increased in density until the 16th and 19th days, when opalescent areas covered the iris. All evidence of corneal injury disappeared within 2 months following instillation.

The injury caused by benzenethiol seemed to be increased in rabbits whose eyes had been flushed with water approximately 5 seconds after instillation of the thiol [59]. Signs of conjunctival irritation were evident in two such rabbits until the 16th and 21st days after the instillation. By approximately 3 weeks after treatment, opalescent areas of the cornea completely covered the iris in one rabbit, whereas the other had slightly less corneal injury. These conditions persisted for several

weeks before recovery began, but recovery was complete after 3-4 months. The authors found that, if the eye was flushed with 0.5% silver nitrate solution immediately after thiol instillation and then with copious amounts of water to remove the visible silver-sulfhydryl precipitate, both the irritation and corneal injury caused by benzenethiol were minimized. Depilation frequently occurred in areas around and below the eyes, being caused apparently by contact with benzenethiol. Depilation was prominent at 5-6 days after exposure and lasted from 2-3.5 weeks.

(b) Subchronic Toxicity

(1) Methanethiol through Hexanethiol; Benzenethiol

Horiguchi [54], in 1960, reported on the toxicity of methanethiol to mice. Eleven male white mice, weighing 13-17 g, were exposed at 300 ppm (591 mg/cu m) for 2 hours/day, 3 days/week, for 2 months. Horiguchi's methods of exposure were described in Acute Toxicity. All 11 mice were dead after 25 exposures, 6 or more having died after 15 exposures.

In 1972, Selyuzhitskii [51] described the effects in rats of methanethiol inhalation. White rats, in groups of 15 each, were exposed to methanethiol 6 hours/day for 6 months at 0.51, 0.05, and 0.0003 ppm (1.0 ±0.003, 0.1 ±0.002, and 0.0005 ±0.00004 mg/cu m).

Rats that inhaled methanethiol at 0.51 ppm (1.0 mg/cu m) exhibited a reduced growth rate, an increase in the ratio of heart weight to body weight and changes in the distribution of corticosteroids in adrenal tissue [51]. Electroencephalographic (EEG) recordings from rats exposed 6 hours/day for 6 months showed that these animals perceived a concentration of methanethiol of 0.5 µg/cu m but were not distressed by it; a concentration of 5 µg/cu m reportedly caused desynchronization of the EEG, persistent disturbance of breathing, and irregular heartbeats. A concentration of 0.1 mg/cu m caused a number of alterations in the biochemistry of the rats, including increased concentrations of carbon dioxide, SH, cholesterol, and lactic and pyruvic acids in the blood. A concentration of 1 mg/cu m decreased the rate of growth of the rats, increased the relative weight of the heart, and altered the distribution of corticosteroids in adrenal tissues. The effects of the oral administration of methanethiol to mice were not discussed.

Sandage [62] studied physiologic changes in male mice, rats, and monkeys continuously exposed to methanethiol for 90 days. The animals were kept in large, insulated exposure chambers, where the rate of air turnover was 10% of the chamber volume per minute. Methanethiol in cylinders equipped with regulator valves was used to maintain the methanethiol in the chamber at 50 ±5 ppm (98 ±9.8 mg/cu m). Mean body weights for the 10 monkeys, 50 rats, and 100 mice making up the experimental group were 1.7 kg, 175 g, and 25 g, respectively. Various clinical studies were performed

before, and at 30-day intervals during, exposure. Approximately 50% of the animals surviving the 90-day exposure were subjected to a stress test in which the swimming time for the control animals was 45 minutes. The stress-tested animals were necropsied shortly after the stress tests. The remaining animals were observed for 2 weeks and then necropsied. Tissues from the heart, lungs, liver, kidneys, and brain were examined microscopically. The data were summarized with statements that certain changes were statistically significant (95% confidence limits) but without actual values.

Monkeys had a 40% mortality during the exposure period [62]. The experimental monkeys lost significant amounts of weight. However, in the swimming stress tests, they were able to hold their heads above water longer than the control animals. Urinalyses gave normal results. When compared with preexposure values, the only measured index in blood that was significantly altered in the exposed monkeys was the concentration of sodium, which was increased. When compared with control animals kept for 90 days, monkeys exposed to methanethiol showed increases in blood cholinesterase and alkaline phosphatase activity. When necropsies were performed on the monkeys, six were found to have lung changes and two were found to have brain changes consisting of a small softening in the cortex of the right parietal lobe of one monkey and of the left frontal lobe of the other; three of the monkeys had no microscopic changes. Most of the pulmonary effects consisted of mild to moderate edema, often associated with either vascular congestion or an accumulation of polymorphonuclear leukocytes or both. None of the lesions reported accounted for the 40% mortality found in monkeys.

A number of hematologic changes were seen in rats exposed to methanethiol [62]. When compared with values determined before the experiment, reticulocyte counts, hematocrit, hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin values were significantly elevated. When experimental values were compared with the values from the control animals kept for 90 days, there were significant decreases in erthyrocyte and platelet counts and hemoglobin concentration and significant increases in leukocyte and reticulocyte counts. The differences observed in the rats (the 10% mortality, the stress-test results, and weight changes) were not considered statistically significant when compared with those of the control group. In rats, the findings at necropsy were limited to unspecified lung changes in 16% of the animals; 84% showed no organ changes. The changes observed in the blood could have resulted from the stress to which the animals were subjected. The effect of methanethiol on the rats was considered slight by the investigator.

Mice exposed to methanethiol at 50 ppm (98 mg/cu m) had a variety of hematologic and other effects [62]. When compared with preexposure values, the erythrocyte count was decreased and the leukocyte and platelet counts and the mean corpuscular volume were increased in the exposed mice. In

comparison with the control group at 90 days, the experimental group had significantly decreased erythrocyte counts and mean corpuscular hemoglobin concentrations; significant increases were found in the reticulocyte and platelet counts, the mean corpuscular volume, and the concentration of urobilinogen. Mortality at 43% was statistically significant. Methanethiol-exposed mice also demonstrated shorter stress-test swimming times. At necropsy, the percentages of mice showing cellular changes in the various organs were tallied, but not described, as follows: liver, 75%; lung, 26%; kidney, 22%; and heart, 1%. Persistent hepatitis was found in the mice, and there were a "few cases" of bronchopneumonia and pyogenic abscesses of the liver and lungs. The 43% mortality of the mice was most probably caused by hepatitis, pneumonia, and lung and liver abscesses. Methanethiol may have contributed to the morbidity and mortality.

The subchronic toxicity of ethanethiol for rats and rabbits was studied by Wada [63]. Ethanethiol was prepared as either a 10 or 30% solution in peanut oil and injected into groups of rats and rabbits. One group of rats and rabbits was injected sc with 0.01 ml/kg of ethanethiol daily. In another group, some of the rats were injected with 0.09 ml/kg of ethanethiol daily, and others were injected with 0.09 ml/kg of ethanethiol every other day. In one more group, rabbits were injected initially with 0.03 ml/kg of ethanethiol every other day. After an unspecified period of time, the injected volume was changed to 0.01 ml/kg of ethanethiol. The injections were continued for 1 year or until the animal died.

All animals developed localized necrosis at the site of injection, with rabbits generally developing more serious effects [63]. The intensity of the necrosis increased in proportion with the concentration injected. When injection ceased, the necrotic tissue was gradually replaced with scar tissue. Rabbits injected with 0.01 ml/kg of ethanethiol either daily or every other day had reductions in red blood cell counts (RBC's) and hemoglobin. Leukocyte and reticulocyte counts both increased. The degree of change generally was related to the dose. The most marked microscopic changes in both rats and rabbits were found in the spleen. Findings there included hyperemia and dilation of sinusoids, deposits of hemosiderin, fibrosis, red blood cell destruction by white blood cells, and hematopoiesis. Some of these changes were seen also in the control animals. Microscopic changes in the liver, lungs, kidney, testes, and ovaries were minor and were possibly incidental to the debility caused by the injection. The author concluded that many of the red blood cells were destroyed, as reflected in the splenic changes, but offered no further explanation. This and the previous study [62] both indicate that subchronic exposure to methanethiol or ethanethiol may lead to a reduction in the erythrocycte count.

Shibata [58] reported in 1966 on the effects of inhalation of ethanethiol on the blood picture, urinary volume, sulfate excretion, and body weight of rabbits. Four male rabbits each inhaled 10 liters/day of

air containing ethanethiol at 1,000 ppm (2,540 mg/cu m) for 20 minutes/day through masks on their muzzles. Midway through the 10-day experimental period, the animals were given 1 day of rest; the total inhalation period was thus 9 days. Urinary sulfates, blood cell counts, urine amounts, and body weights of the rabbits were determined on days 3, 5, 7, 9, 11, and 13.

Although shortly after the start of the study urinary sulfates were considerably elevated in two of the four exposed rabbits, they had returned to control levels by day 11 [58]. The author concluded that, in general, the rabbits exposed to ethanethiol had no significant increase in urinary sulfates above control values. In the experimental group, the WBC decreased slightly after 5-7 days of exposure to ethanethiol but returned to the control levels by day 11. Erythrocyte counts, urinary excretory volumes, and body weight gains were similar in both the experimental and control groups. Thus, the inhalation of ethanethiol at 1,000 ppm (2,540 mg/cu m) during 20 minutes/day for 9 days did not adversely affect these variables in the rabbits.

In 1975, Szabo and Reynolds [64] as a part of their survey of compounds having a two-carbon atom skeleton for possible ulcerogenic effects, included tests on ethanethiol and butanethiol in rats. Two of five female rats given oral dosages of butanethiol at 20 mg/100 g thrice daily on the 1st and 2nd day and at 40 mg/100 g on the 3rd and 4th day developed adrenal necrosis, apparently in the cortex. The degree of necrosis was not described. None of the rats developed duodenal ulcers. None of the rats given a similar dosage schedule of ethanethiol for only 3 days developed either adrenal necrosis or duodenal ulcers. No other studies have indicated these types of changes.

Fairchild and Stokinger [59], in 1958, reported a study on the subchronic toxicity of benzenethiol in rats. Six male rats, weighing 180-220 g, were injected ip with nine doses of 3.5 mg/kg benzenethiol, ie, one-third the ip LD_{50}, as a 2% V/V solution in ethanol for 3 weeks. One rat died on the 7th day. The remaining rats had no significant weight loss, and no signs of cumulative toxicity were noted. When the rats were necropsied, only minor lesions were found. The repeated irritation of ip injections apparently caused a fibrous thickening of the splenic capsule. Enlargement of the spleen was found in most of the rats, and hyperemia of the adrenal medulla was found in all rats. Some rats had a mild degree of what was called at that time cloudy swelling in the tubules of the kidneys, with hyaline casts in the lumina. These pathologic changes are similar to those noted following acute exposure to benzenethiol, as described previously.

(2) Heptanethiol through Octadecanethiol; Cyclohexanethiol

Gage [65] reported in 1970 on the subchronic inhalation toxicity of many industrial chemicals, including dodecanethiol, in rats. Two male and two female rats, with an average weight of 200 g, were exposed to a

"nearly saturated atmosphere" of dodecanethiol for up to 6 hours/day, 5 days/week, for 4 weeks (a total of 20 exposures). During the 20 exposures, no signs of toxicity were noted. After the last exposure, urine was collected overnight. The following day, samples of lungs, liver, kidneys, spleen, and adrenals were collected for microscopic examination. The heart, jejunum, ileum, and thymus were also assayed for some of the chemicals studied; whether these organs were taken from the rats exposed to dodecanethiol was not stated. Microscopic examination of these tissues revealed all to be normal.

The subchronic inhalation toxicity of dodecanethiol and of a mixture of C_7 through C_{11} thiols to rats was reported by Gizhlaryan [61] in 1966. Thirty-two male and female rats inhaled air saturated with thiols from a 750-liter chamber, 4 times/week for 5.5 months (length of daily exposure unspecified). The saturation level of dodecanethiol was 3,400 mg/cu m (411 ppm) and that for the thiol mixture was 2,900 mg/cu m. No changes in body weight, oxygen consumption, ability of the CNS to summate threshold pulses, blood catalase level, erythrocyte count, -SH group content in the hemolysate, liver function as indicated by hippuric acid excretion in urine after a test dose of benzoic acid, and the duration of hexobarbitol-induced sleep were found after 2 months of exposure to either dodecanethiol or the C_7 through C_{11} thiol mixture. After 5.5 months of exposure, a suppression of body weight gain was accompanied by slight changes in oxygen uptake by the red blood cells and in oxygen usage by the tissues, a slightly increased leukocytosis, a 50% decrease in the functioning of the adrenals as indicated by the number of eosinophils following sc administration of ACTH, reduced liver function as indicated by urinary hippuric acid output following a preliminary loading with sodium benzoate and the duration of hexobarbital-induced sleep. The liver, spleen, brain, and kidneys, but not the blood (hemolysate and serum), of rats exposed to either dodecanethiol or the C_7 through C_{11} thiol mixture had small increases in sulfhydryl content. The ratio of organ weight to body weight was unchanged.

Microscopic examination of the organs of exposed animals showed vascular congestion in all organs, with hemorrhages in the lungs and adrenal medulla, mild bronchitis, slight inflammation of the renal tubules, myocardial fibrosis, slight fatty infiltration of the liver, depletion of lipid in the adrenal cortex, and slight edema of the brain [61]. The author concluded that both dodecanethiol and the C_7 to C_{11} thiol mixture were of low toxicity and that they presented only a slight hazard to industrial workers but noted that the experimental information suggested the possibility of rare cases of low-level chronic intoxications in workers.

(c) Skin Effects

Cirstea [66], in 1972, reported on the contact-sensitizing capacities of butanethiol, octanethiol, and dodecanethiol in guinea pigs. The flanks

of five albino guinea pigs (300-500 g) of either sex were depilated manually 24 hours before commencement of the daily application of 0.2 ml of a 20% solution of each thiol in acetone for 10 days, or until signs of contact dermatitis were evident. Erythema, induration, and eczematous crusts were considered positive indications of contact dermatitis. One month after the final application of the thiol solution, the opposite flank of the animal was shaved and painted with the solution if the animal had exhibited contact dermatitis during the 10-day period of application.

None of the thiols tested had a primary irritating effect as judged by the absence of local changes within 48 hours after the first application [66]. If signs of dermatitis developed within 3 days or more after the first application, the author considered the thiol to have exhibited contact-sensitizing ability. Ordinarily, at least 5 days are considered necessary for development of a sensitization response. The severity of the response was graded according to the intensity of the reaction and the time that had elapsed between the first application and appearance of dermatologic signs. With respect to contact sensitization, dodecanethiol was rated "intense," octanethiol as "moderate," and butanethiol as "absent or negative." When animals were painted with octanethiol and dodecanethiol only once, about half the animals developed dermatitis; when animals were painted again on the opposite flank 1 month later, signs of sensitivity appeared within 24 hours, as compared with control animals (3-5 days). The duration of the dermatitis was not stated, however.

Brooks et al [67], in 1957, reported some effects of a number of compounds, including octanethiol, dodecanethiol, and octadecanethiol, on mouse skin. Male albino mice 7-10 weeks old were used in the tests. Either pure liquids or solutions in ether were applied in 0.2-ml quantities to a shaved area on the backs of mice either on the 1st, 3rd, and 5th days of the experiment or on 6 days over a 2-week period. The skin was removed on the 6th or the 14th day and cut into 1.5- x 2-cm sample patches. The epidermis was isolated from the dermis, the epidermal patches were dried and weighed, and cholesterol and delta-7-cholestenol (D7-cholestenol) in the epidermal patches were determined. The results are shown in Table III-9.

The application of undiluted octadecanethiol to mouse skin produced within 6 days degeneration of the sebaceous glands, hyperplasia of the follicles, hyperkeratinization of the epidermal surface and the follicles, and, as shown in Table III-9, a decrease in the delta-7-cholestenol concentration in the skin and an increase in that of cholesterol [67]. These changes are similar to those found after dermal application of methylcholanthrene that eventually induced dermal carcinomas. The authors suggested, therefore, that prolonged contact of undiluted octadecanethiol with human skin may result in cancer.

Although no evidence was found in the available literature suggesting that thiols affect human skin, the animal data presented, although not

TABLE III-9

EFFECTS OF HIGHER MOLECULAR WEIGHT ALKANE THIOLS ON MOUSE SKIN

Thiol	Total Dose (mg)	Epidermal Weight (mg/sq cm)	Cholesterol Level (µg/sq cm)	D7-Cholestenol Level (µg/sq cm)	Epidermal Thickness (cells)	Sebaceous Glands	Hair Follicles
Control	-	2.4	51	50	2-3	-	-
Octane-thiol	3	2.2	46	48	2-3	-	-
	500	-	-	Normal	-	Normal	-
Dodecane-thiol	3	6.1	101	46	4-5	"	Elongated and swollen
	500	-	-	Normal	-	"	
Octadecane-thiol	3	4.2	78	23	4-5	Atrophied slightly	Normal
	6	2.5	51	23	3-4	Normal	Elongated
	500	19.3	291	30	8-10	Absent	Hyperplasia and hyperkeratinization

Adapted from reference 67

conclusive, indicate that a delayed dermatitis is possible. The effects on animals of acute and subchronic exposures to thiols are summarized in Tables III-10 and III-11 [51,53-55,58-62,64-67].

Bagramian and associates [46] and Bagramian and Babaian [68] reported on the mutagenic potential of dodecanethiol, chloroprene, and ammonia in rats. Six to eight white rats, weighing 180-250 g, inhaled a combination of chloroprene, dodecanethiol, and ammonia for up to 4 months. Chromosomal aberrations in bone marrow cells in both the anaphase and telophase stages of cell division were determined using acetocarmine. A relative increase in the number of chromosomal aberrations in the exposed animals over that in the control animals was observed in both experiments. In one experiment [68], after approximately 24 hours of inhalation of chloroprene (1.96 ±1.04 mg/cu m), dodecanethiol (5.02 ±1.96 mg/cu m), and ammonia (19.8 mg/cu m), the production of abnormal chromosomal aberrations increased from 5.5% in the controls to 8.8% in the test animals. After weekly exposure to chloroprene, dodecanethiol, and ammonia at the above concentrations for 4 months, the number of chromosomal aberrations was 11.1% above that of the control animals ($P < 0.05$).

In another experiment [46], at the end of 120 days of exposure (daily exposure period not specified) to chloroprene (0.89 ± 0.9 mg/cu m), dodecanethiol (0.12 ±0.03 mg/cu m), and ammonia (2.07 ±0.27 mg/cu m), the test group had 10.1% chromosomal aberrations, whereas the control group had 5.3% ($P = 0.01$). The increase in aberrations consisted mainly of an increase in the number of chromosomal fragments.

The mutagenic studies on Drosophila by Garrett and Fuerst [69] mention methanethiol as one of the six gases investigated. No experimental evidence was presented other than that treatment with this thiol resulted in an LD_{100} at a flowrate of 22 ml/minute.

Metabolic Studies

In their 1953 report, Canellakis and Tarver [70] showed that methanethiol was rapidly oxidized in the rat, yielding carbon dioxide and sulfate. A series of four experiments was carried out. In the first, one 180-g male rat was given 0.3 mg ^{14}C-labeled methanethiol ip, and the distributions of ^{14}C in tissues and excretory products were determined. The exhaled methanethiol and carbon dioxide were trapped and separated by reaction with isatin in concentrated sulfuric acid. During the 1st hour following injection, 29.2% of the dose was excreted as ^{14}C-labeled carbon dioxide, and 6.4% was exhaled as volatile sulfur-containing compounds. During the 2nd hour, no ^{14}C-methanethiol was detected in the exhaled air, and no further determinations were made of exhaled ^{14}C-labeled methanethiol. The exhalation of ^{14}C-labeled carbon dioxide was as follows:

TABLE III-10

SUMMARY OF EFFECTS ON ANIMALS OF SINGLE EXPOSURES TO THIOLS

Thiol	Species	No. of Animals	Duration and/or Route of Exposure	Concentration or Dose	Effects	Reference
Methanethiol	Rat	1	30-35 min, respiratory	500-10,000 ppm (985-19,700 mg/cu m)	At 10,000 ppm (19,700 mg/cu m), neurologic and respiratory changes, lung changes, death (14 min)	53
"	"	3-8	up to 15 min, respiratory	600-2,200 ppm (1,182-4,334 mg/cu m)	At 1,600 ppm (3,152 mg/cu m), 50% lost righting reflex	55
"	Mouse	10	up to 4 hr, respiratory	1,200-2,200 ppm (2,364-4,334 mg/cu m)	LC_{50} = 1,664 ppm (3,278 mg/cu m); neurologic and liver changes	54
Ethanethiol	Rat	5 or 6	4 hr, respiratory	2,600-5,125 ppm (6,606-13,021 mg/cu m)	LC_{50} = 4,870 ppm (12,370 mg/cu m) at 24 hr, 4,420 ppm (11,227 mg/cu m) at d 15; some latent toxicity	59
"	"	3-8	up to 15 min, respiratory	27,000-38,000 ppm (68,603-96,552 mg/cu m)	At 33,000 ppm (83,820 mg/cu m), 50% lost righting reflex	55
"	"	5	oral	210-3,360 mg/kg	LD_{50} = 1,034 mg/kg at d 1, and 682 mg/kg at d 15; some latent toxicity	59
"	"	5 or 10	ip	105-1,680 mg/kg	LD_{50} = 450 mg/kg at d 1, and 226 mg/kg at d 15; some latent toxicity	59
"	Mouse	10	4 hr, respiratory	2,600-4,832 ppm (6,606-12,277 mg/cu m)	LC_{50} = 2,770 ppm (7,038 mg/cu m) at 48 hr	59
"	Rabbit	2	20 min, respiratory	1,000 ppm (2,540 mg/cu m) 100 ppm (254 mg/cu m) 10 ppm (25 mg/cu m)	Respiratory change Temporary respiratory changes Brief respiratory fluctuations	58
Propanethiol	Rat	6	4 hr, respiratory	3,050-11,260 ppm (9,499-35,066 mg/cu m)	Estimated 48-hr LC_{50} = 7,300 (22,734 mg/cu m)	59
"	"	5	oral	1,327-3,344 mg/kg	LD_{50} = 2,362 mg/kg at d 1, 1,790 mg/kg at d 15; some delayed toxicity	59
"	"	5	ip	209-1,672 mg/kg	LD_{50} = 1,028 mg/kg at d 1, 515 mg/kg at d 15; delayed toxicity	59
"	Mouse	20	4 hr, respiratory	3,050-11,260 ppm (9,499-35,066 mg/cu m)	Estimated LC_{50} = 4,950 ppm (15,415 mg/cu m) at 48 hr, 4,010 ppm (12,488 mg/cu m) at d 15	59
Butanethiol	Rat	5	"	2,150-6,000 ppm (7,929-22,126 mg/cu m)	LC_{50} = 4,460 ppm (16,447 mg/cu m) at 24 hr, and 4,020 ppm (14,824 mg/cu m) at d 15	59

TABLE III-10 (CONTINUED)

SUMMARY OF EFFECTS ON ANIMALS OF SINGLE EXPOSURES TO THIOLS

Thiol	Species	No. of Animals	Duration and/or Route of Exposure	Concentration or Dose	Effects	Reference
Butanethiol	Rat	5	oral	1,093-3,344 mg/kg	LD_{50} = 2,575 mg/kg at d 1, 1,500 mg/kg at d 15; some delayed toxicity	59
"	"	5	ip	209-1,672 mg/kg	LD_{50} = 679 mg/kg at d 1, 399 mg/kg at d 15; delayed toxicity	59
"	Mouse	10 or 12	"	2,150-6,000 ppm (7,929-22,126 mg/cu m)	LC_{50} = 2,950 ppm, (10,879 mg/cu m) at 24 hr, 2,500 ppm (9,219 mg/cu m) at d 15	59
Pentanethiol	Rat	6	4 hr, respiratory	2,000 ppm (8,520 mg/cu m)	Mortality in 2-4 of 6 by d 14	60
Hexanethiol	"	5 or 6	"	456-1,475 ppm (2,205-7,131 mg/cu m)	LC_{50} = 1,200 ppm (5,808 mg/cu m) at 24 hr, 1,080 ppm (5,227 mg/cu m) at d 15	59
"	"	5	oral	848-2,137 mg/kg	LD_{50} = 1,580 mg/kg at d 2, 1,254 mg/kg at d 15; some delayed toxicity	59
"	"	5	ip	212-1,696 mg/kg	LD_{50} = 600 mg/kg at d 1, and 396 mg/kg at d 15; delayed toxicity	59
"	Mouse	10 or 12	4 hr, respiratory	220-1,475 ppm (1,064-7,131 mg/cu m)	LC_{50} = 610 ppm (2,950 mg/cu m) at 24 hr, 528 ppm (2,553 mg/cu m) at d 15	59
Thiols (C_3, C_4, C_{6-12}, C_{16}, C_{18})	"	2	iv	31.6-316 mg/kg	All LD_{50}'s > 316 mg/kg	*
Thiols (mixture C_7-C_{11})	Rat	Unspecified	intragastric	Unspecified	LD_{50} = 3,300 mg/kg	61
"	Mouse	"	"	"	LD_{50} = 2,025 mg/kg	61
Dodecanethiol	Rat	"	"	"	7,000 mg/kg caused no deaths	61
"	Mouse	"	"	"	LD_{50} = 4,225 mg/kg	61
Cyclohexanethiol	"	2	iv	31.6-316 mg/kg	LD_{50} approximately 316 mg/kg	*
"	"	10	cutaneous	100 mg/kg	Median lethal time 50 min	*
Benzenethiol	Rat	5, 6, or 10	4 hr, respiratory	20-132 ppm (90-595 mg/cu m)	LC_{50} = 59 ppm (266 mg/cu m) at 48 hr, 33 ppm (149 mg/cu m) at d 15; latent toxicity	59
"	"	5	oral	21.6-172.5 mg/kg	LD_{50} = 46.2 mg/kg at d 1	59

TABLE III-10 (CONTINUED)

SUMMARY OF EFFECTS ON ANIMALS OF SINGLE EXPOSURES TO THIOLS

Thiol	Species	No. of Animals	Duration and/or Route of Exposure	Concentration or Dose	Effects	Reference
Benzenethiol	Rat	5	ip	6.7-108.0 mg/kg	LD_{50} = 25.2 mg/kg at d 1, 9.8 mg/kg at d 15; latent toxicity	59
"	"	5 or 10	cutaneous	134-538 mg/kg	LD_{50} = 300 mg/kg at 4-8 hr	59
"	Mouse	10	4 hr, respiratory	20-79 ppm (90-356 mg/cu m)	LC_{50} = 47 ppm (212 mg/cu m) at 24 hr, 28 ppm (126 mg/cu m) at d 15; latent toxicity	59
"	Rabbit	3	cutaneous	67-269 mg/kg	Estimated LD_{50} = 134 mg/kg	59

* WW Wannamaker III, written communication, December 1977

TABLE III-11

SUMMARY OF EFFECTS ON ANIMALS OF SUBCHRONIC EXPOSURES TO THIOLS

Thiol	Species	No. of Animals	Duration and/or Route of Exposure	Concentration or Dose	Effects	Reference
Methanethiol	Rat	15	2 hr/d x 6 mo, respiratory	0.003-0.5 ppm (0.006-0.985 mg/cu m)	At 0.5 ppm (1 mg/cu m) reduced growth rate; heart and adrenal changes	51
"	"	50	90 d, respiratory	50 ppm (.45 mg/cu m)	Mortality 10%; blood changes; lung changes	62
"	Mouse	11	2 hr/d, 3 d/wk for 2 mo, respiratory	300 ppm (590.72 mg/cu m)	Mortality 100% after 25 exposures	54
"	"	100	90 d, respiratory	50 ppm (.45 mg/cu m)	Mortality 43%; blood changes; lung, liver, and kidney changes	62
"	Rhesus monkey	10	"	"	Mortality 40%; significant body weight loss; lung and brain changes	62
Ethanethiol	Rabbit	4	10 d* respiratory	1,000 ppm (2,543.31 mg/cu m)	No urine or blood changes	58
Propanethiol	"	1	ocular	0.1 ml	Severe eye irritation	59
1-Butanethiol	Rat	5	oral	20 mg/100 g, 3/d, d 1-2 40 mg/100 g, 3/d, d 3-4	Cortical or medullary changes	64
"	Guinea pig	5	10 d, cutaneous	0.04 ml/d	No dermal changes	66
1-Octanethiol	"	5	"	"	Moderated contact sensitization	66
"	Mouse	**	5 d, cutaneous	500 or 3 mg	No dermal changes	67
Thiols (mixture C_7-C_{11})	Rat	32	4 d/wk x 5.5 mo, respiratory	2,900 mg/cu m	Slightly reduced growth rate, slight decrease in liver and adrenal function	61
1-Dodecanethiol	"	32	"	411 ppm (3,400 mg/cu m) saturated atm	"	61
"	"	4	6 hr/d, 5 d/wk x 4 wk, respiratory		No changes	65
"	Mouse	**	5 d, cutaneous	500 mg	Changes in epidermis and hair follicles	67
"	"	"	"	3 mg	Changes in epidermis	67
1-Dodecanethiol	Guinea pig	5	10 d, cutaneous	0.04 ml/d	Intense contact sensitization	66
1-Octadecanethiol	Mouse	**	5 d, cutaneous	500 mg	Moderate to severe changes in epidermis, hair follicles, sebaceous glands	67
"	"	"	"	3 mg	Slight changes in epidermis and sebaceous glands	67
"	"	"	13 d, cutaneous	6 mg	Slight to moderate changes in epidermis and hair follicles	67
Benzenethiol	Rat	6	3 wk, ip	3.5 mg/kg, 3 x/wk	Mortality of 1 at d 7; no other changes	59
"	Rabbit	3	ocular	0.1 ml	Severe eye changes	59

*Animals not exposed on d 4 or 5
**Unspecified

Fraction of Dose Excreted (%)	Period (hr)
29.2	0-1
6.2	1-2
3.8	2-4
1.6	4-6

Extrapolation of the curve constructed with these values indicates that the excretion of isotopic carbon through the lungs as carbon dioxide would become essentially zero between 6 and 7 hours after the injection [70]. This means that about 60% of the methyl moiety of methanethiol must be used in some other way within the body than by oxidation to carbon dioxide. When analyzed, the tissues contained considerable amounts of radioactive label, in counts/minute/mg tissue as follows: liver, 17.8; kidneys, 11.4; spleen, 9.8; lungs, 11.5; testes, 8.5; plasma protein, 22.7; erythrocytes, 0; muscle, 2.2; and intestinal mucosa, 16.7. Canellakis and Tarver concluded that all the ^{14}C-methanethiol may have been oxidized to a one-carbon fragment and sulfate by the 6th hour after its administration.

In the second experiment, one 200-g male rat was given 1.4 mg ^{14}C-methanethiol ip in nine fractions at 1-hour intervals [70]. The animal was killed 2 hours after the last dose; the liver proteins were isolated, and the amino acid contents were identified and determined by column radiography. Most of the activity was present in the serine peak. A small fraction of the methanethiol appeared as the sulfoxide, approximately in the same location as alanine. Two other small peaks, which could not be identified, also appeared. The authors thought that one of these peaks may have been due to aspartic acid. Very little radioactivity was found in the cystine peak; this may have been due to loss during isolation of the amino acids. Differing amounts of radioactivity were found in tissue choline, creatine, and serine.

For the third experiment, one 200-mg male rat was given a total of 2 mg of ^{35}S-labeled methanethiol in four ip doses, given at 2-hour intervals; 92% of the administered dose was excreted in the urine within 8 hours [70]. Of the total 1.33-mg dose of sulfur, 33.7% was excreted as total sulfur; 96.7% of this sulfur was in the form of sulfates, of which 90.5% was inorganic sulfate. There appeared to be no relationship between the methanethiol oxidized to carbon dioxide (experiment 1) and the sulfate appearing in the urine (experiment 3). The authors attributed this to the fact that in one case methanethiol was given as a single dose, and in the other the dose was given during an 8-hour period.

The authors [70] concluded that both the carbon and the sulfur of methanethiol were rapidly oxidized to carbon dioxide and sulfate, respectively. The methyl group of methanethiol was also incorporated into serine at the beta-carbon and into the methyl groups of methionine, choline, and creatine. It is presumably these labeled methyl groups that

account for the radioactivity found in the tissues that were sampled for activity.

McBain and Menn [71] studied the metabolic products excreted in the urine of adult rats fed ^{35}S-labeled benzenethiol, methylphenyl sulfide (MPS), and methylphenyl sulfone ($MPSO_2$) at doses of 6 mg/kg, 2.5 mg/kg, and 2.5 mg/kg, respectively. One hour after administration, excreted urine was extracted with benzene and the aqueous layer was acidified with sulfuric acid and extracted with ether. The benzene- and water-soluble products were analyzed by thin-layer chromatography and gas-liquid chromatography. Urine from rats not fed the above compounds was treated with labeled thiols to detect any in vitro decomposition products. The only benzene-soluble product isolated from the urine was $MPSO_2$. The water-soluble products appeared to consist of p- and o-hydroxy $MPSO_2$ in all cases. In the control urine, 30% of the added benzenethiol was converted to diphenyl disulfide (DPDS), and no $MPSO_2$ was recovered. Based on these findings, it appeared that ^{35}S-labeled benzenethiol readily underwent S-methylation in vivo followed by oxidation to MPS and then to $MPSO_2$. Similarly, guinea pigs and mice dosed with ethanethiol excreted ethylmethyl sulfone [72].

Snow [72] studied the kinetics of distribution of radioactivity in the tissues and excreta of mice and guinea pigs injected sc with ^{35}S-labeled diethyl disulfide and ethyl ^{35}S-thiobenzoate, two derivatives of ethanethiol with antitubercular activity. About 50% of the radioactivity was excreted in the urine of the guinea pig in 10 hours. Considerable radioactivity was present in the breath and very little in the feces. Inorganic sulfate contained about 80-90% of the radioactivity in urine, and organic sulfur metabolites accounted for about 10-20% of the radioactivity. Two organic sulfur metabolites were detected; only one of them, ethyl methyl sulfone, was identified.

Bremer and Greenberg [73] identified an enzyme in the microsomal fraction of several tissues of the rat and in the liver of mammals (mice, rats, rabbits, guinea pigs, cattle, and sheep) capable of catalyzing the transfer of a methyl group from S-adenosylmethionine to produce nonphysiologic sulfhydryl compounds that included methanethiol. With S-adenosylethionine, a transethylation was found to take place.

These investigators [73] showed that the incubation of sodium sulfide, S-adenosylmethionine, and rat liver microsomal protein in tris-HCl buffer, pH 8.0, for 2 hours, led to the formation of methanethiol and dimethyl sulfide. This was demonstrated by acidifying the reaction mixture after incubation and capturing the liberated gas in mercuric chloride solution. The authors surmised that methanethiol and dimethyl sulfide could well be metabolic products of hydrogen sulfide in vivo. They further argued that the increased formation of methanethiol in liver disease could be due to blockage of the oxidation of cysteine to sulfate and taurine, leading to an increase in hydrogen sulfide formation. This investigation suggested a

mechanism for the in vivo formation of methanethiol under normal metabolic conditions.

The limited information found on the metabolism of alkane thiols and benzenethiol, as shown in Figure III-1, has led NIOSH to construct the following scheme:

(a) The sulfur atom of thiols is metabolized by oxidation and is excreted almost entirely as urinary inorganic sulfate, as in the case of methanethiol [70], or for the major part, as in the cases of ethanethiol [72] and benzenethiol [71]. In addition, methylation of the thiol followed by oxidation leads to excretion of some of the sulfur as the sulfone of the methylated thiol. This metabolic pathway seems to become more important in the thiols of larger molecular weight.

(b) The sulfur atom of the thiol group is not incorporated into the cysteine or methionine sulfur in mammals [70].

(c) The carbon atom of methanethiol is eliminated to a significant extent as respiratory CO_2 and is found in the beta-carbon of serine and in a methyl group of methionine, choline, and creatine, as indicated by the study by Canellakis and Tarver [70].

(d) Although thiols are easily oxidized in vitro to disulfides, no evidence was found demonstrating the conversion of thiols to their corresponding disulfides in vivo. It is possible that the thiols, as well as disulfides, are maintained in vivo in a reduced state. Such a reaction may be brought about by transhydrogenation [6,7] via a thiol-disulfide system such as the one mediated by glutathione reductase. Thiols in a reduced state could then be either oxidized directly or methylated first by an enzyme, such as the one catalyzing the transfer of the methyl group of S-adenosyl methionine [73], and subsequently oxidized. Snow's study [72] of the metabolism of diethyl disulfide serves as an example.

(e) Oxidation of dimethyl sulfide to dimethyl sulfone was suggested by a study [76] in which dimethyl sulfide administered orally or injected into rats did not lead to the urinary excretion of excess inorganic sulfate.

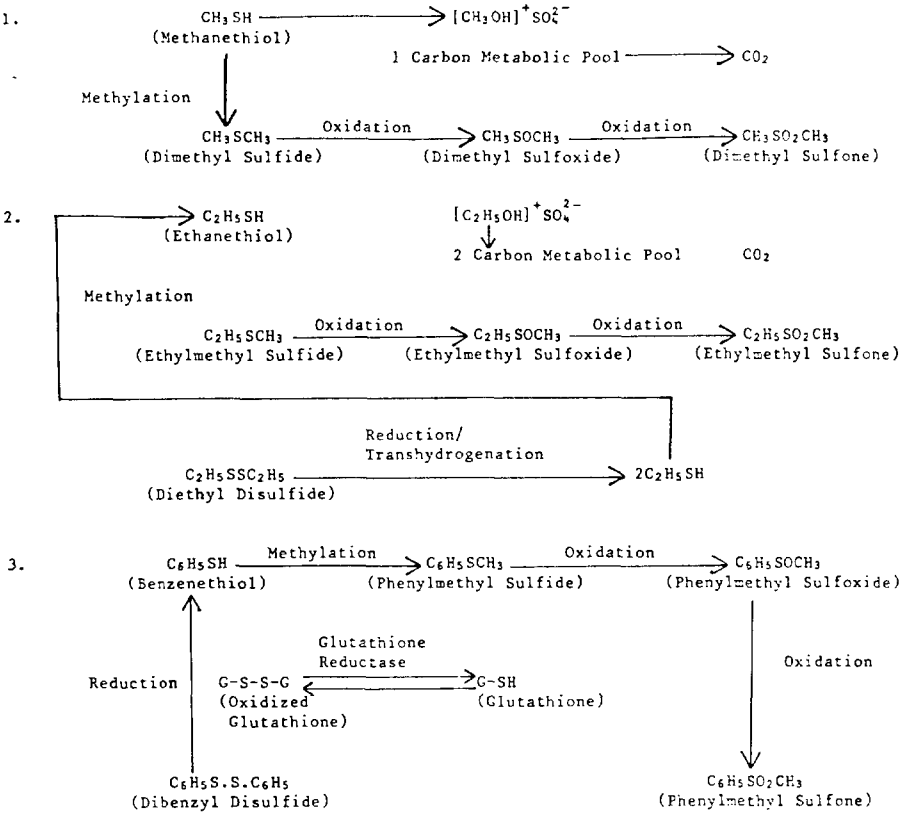
(f) Although enzymatic sulfhydryl-disulfide interchange leading to the formation of mixed sulfides may occur between substances containing -SH groups in the cell [74,77], no studies designed to evaluate the importance of these reactions and their relationship to the toxicities of the alkane thiols, cyclohexanethiol, or benzenethiol were located.

Correlation of Exposure and Effect

The data on the effects of exposure of humans and experimental animals to thiols demonstrate the following dose-effect relationship: Acute

FIGURE III-1

METABOLISM OF THIOLS AND SULFIDES



Adapted from references 5,6,8,70-72,74-76

exposure at high concentrations of thiols in humans [12-15] as well as in mice, rats, and rabbits [51,53,54,58,59] caused narcosis, apparent decerebrate rigidity, bronchospasm, uremia, hematuria, and proteinuria. The available human studies on exposure to methane-, ethane-, and butanethiols are on essentially short-term exposures designed to measure odor thresholds. Data indicate that human exposure to the lower molecular weight thiols (C_1-C_6) can produce severe CNS depression [12-14]. A worker exposed to methanethiol at extremely high concentrations died, without recovering from coma, approximately 1 month following exposure [12]. Another worker exposed to both methanethiol and ethanethiol at high concentrations for 2 hours was also found in a comatose condition [13].

In an experimental odor threshold study [48], inhalation of ethanethiol at 0.01 mg/liter (4 ppm) for 3 hours/day for 5-10 days, caused some rise in olfactory threshold and fatigue, periodic nausea, irritation of mucous membranes, and head heaviness. Inhalation of ethanethiol at 0.001 mg/liter (0.4 ppm) caused relatively less increase in the olfactory threshold and no other of the signs mentioned above.

In another controlled experiment to determine the effects of exposure to ethanethiol at 50 ppm (120 mg/cu m) and 112 ppm (270 mg/cu m) for 20 minutes, the investigator [45] observed no significant adverse effects in three volunteers. There were changes in respiratory frequency, which returned to normal after exposure ended. In contrast, an accidental exposure of high school students to ethanethiol at an estimated concentration of 3.6 ppm (9 mg/cu m) for 1 hour produced general symptoms of headache, discomfort, and abdominal pain and vomiting and diarrhea [14]. Recovery was apparently complete in a few hours. The above complaints could have resulted from mass hysteria and anxiety rather than from the specific effects of the thiol. Ten persons complained only of headache. One of the students studied in detail had unspecified changes around the eyes, a palpable liver, a spleen described as nonpalpable, and protein and red and white blood cells in the urine.

Signs and symptoms of CNS toxicity occurred in seven workers exposed to butanethiol for 1 hour at an estimated concentration of 50-500 ppm (180-1,800 mg/cu m) [15]. The workers exhibited asthenia, muscular weakness, and malaise. When humans were exposed to methane-, ethane-, and butanethiols to establish odor thresholds, odors in the concentration range of 0.5-7.6 ppm were noticed quite readily.

The LC_{50} and LD_{50} data on mice and rats for ethanethiol, propanethiol, butanethiol, hexanethiol, and benzenethiol as reported by Fairchild and Stokinger [59] suggest that there is similarity in toxicity among the n-alkane thiols via the ip and oral routes of administration. However, via the inhalation route hexanethiol was four and five times as toxic as ethanethiol to rats and mice, respectively. The 48-hour LC_{50} of ethanethiol after a 4-hour inhalation period was 2,770 ppm. Horiguchi [54]

reported a LC_{50} of 1,664 ppm (3,261 mg/cu m) for methanethiol in mice exposed for up to 24 hours. Carpenter et al [60] reported that 33-67% of the rats exposed to pentanethiol at 2,000 ppm for 4 hours died within 15 days. Taken together, these results indicate that methane-, ethane-, propane-, butane-, pentane-, and hexanethiols may be grouped together on the basis of acute toxicities. Furthermore, the intragastric LD_{50} values for higher molecular weight n-alkane thiols (C_7-C_{12}) are in the same range [61] as the LD_{50} values found for the lower molecular weight n-alkane thiols in rats [59].

The toxicity of inhaled benzenethiol was 77- and 78-fold greater than that of ethanethiol in mice and rats, respectively [59]. By oral and ip administrations to rats, the toxicity of benzenethiol was 22- and 23-fold greater, respectively, than that for ethanethiol. The ratios of LC_{50} and LD_{50} values for these species suggest that benzenethiol is from 22- to 78-fold as toxic as ethanethiol, depending upon the route of exposure. Instillation of benzenethiol (0.1 ml in the conjunctival sac) into the conjunctival sacs of rabbits caused severe irritation, corneal injury lasting 3 weeks to 2 months, and depilation of skin around the orbit when the exposed eye was washed with water.

Several subchronic toxicity studies have been conducted on the C_1-C_6 alkane thiols [54,58,62]. Exposures to methanethiol at 300 ppm for 2 hours/day, 3 days/week for 2 months killed 50% of mice after 15 exposures, and 100% after 25 exposures [54]. Inhalation exposures of monkeys, rats, and mice to methanethiol at 50 ppm continuously for 90 days caused 40% mortality in monkeys, 10% mortality in rats, and 43% mortality in mice [62]. Subjecting rabbits to inhalation of ethanethiol at 1,000 ppm (2,541 mg/cu m) for 9 days produced no notable effects [58].

The intragastric LD_{50} values for mice and rats administered a mixture of C_7 through C_{11} thiols were 2,025 mg/kg and 3,300 mg/kg, respectively [61]. The intragastric LD_{50} value for mice administered dodecanethiol was 4,225 mg/kg, and an intragastric dose of 7,000 mg/kg caused no deaths in rats. Gage [65] exposed rats to air saturated with dodecanethiol for up to 6 hours/day, 5 days/week for 4 weeks and found no signs or microscopic evidence of toxicity. Rats exposed to dodecanethiol at the saturation level of 3,400 mg/cu m or to a mixture of C_7 through C_{11} thiols four times weekly for 2 months showed no signs of toxicity [61]. After 5.5 months of exposure, there was a small decrement of weight increase, a slight degree of leukocytosis, a 50% decrease in the functioning of the adrenals as measured by the number of eosinophils released following the sc administration of adrenocorticotropic hormone, and reduced liver function as demonstrated by both the amount of hippuric acid produced following a preliminary loading with sodium benzoate and the duration of hexobarbital-induced sleep.

The only available toxicity data on cyclohexanethiol suggested that the iv LD_{50} for mice is approximately 316 mg/kg (WW Wannamaker III, written

communication, December 1977). The application of 100 mg/kg cyclohexanethiol to the skin of mice resulted in the death of two out of two animals in 24 hours. Higher molecular weight alkane thiols (C_7-C_{12}, C_{16}, C_{18}) and cyclohexanethiol do not appear to represent a substantial inhalation hazard; the main effect is on the skin [61,66,67].

No information on the acute dermal or subchronic effects of thiols in humans was found. However, when 0.04 ml of octanethiol was applied daily for 10 days to the depilated flanks of guinea pigs, there was no irritation of the skin, but contact sensitization resulted [66]. A total dose of 3 mg of dodecanethiol applied to the clipped backs of mice for 1 week caused an increase in the dry weight of the epidermis, an increase in the concentration of epidermal cholesterol, and a possible decrease in the amount of epidermal delta-7-cholestenol [67]. Microscopic examination of the skin revealed slight thickening of the epidermis, and the hair follicles were elongated and swollen. The sebaceous glands were described as normal. When a total dose of 500 mg was applied to the skin of mice, the epidermal delta-7-cholestenol concentration was not affected, and the sebaceous glands were not damaged. Cyclohexanethiol (WW Wannamaker III, written communication, December 1977) when applied to the skin of mice at a dose of 100 mg/kg killed all the animals in 24 hours. No other data on skin sensitization in animals were found.

In summary, all thiols behave as weak acids, their chemical reactivity being due essentially to the -SH group. The predominant biologic effect of exposure to thiol vapors is on the CNS. Toxicity via the inhalation route of administration is of importance in the case of the C_1-C_6 group of alkane thiols and the dermal route in the case of C_7-C_{12}, C_{16}, and C_{18} alkane thiols and cyclohexanethiol, the former group being more volatile than the latter. Such a distinction, however, does not apply when ocular exposure is considered. Benzenethiol is the most toxic of all the thiols included in this document. It is pertinent to recognize that all the thiols have strong odor that constitute a nuisance at concentrations far lower than those at which they cause signs and symptoms of toxicity. In general, the low molecular weight thiols have a more obnoxious odor than the high molecular weight thiols at comparable concentrations. On the basis of similarity in the toxicity, the n-alkane thiols C_1-C_{12}, C_{16}, and C_{18} and cyclohexanethiol can be considered together as a group whereas benzenethiol needs to be considered separately because of its relatively higher toxicity.

Carcinogenicity, Mutagenicity, Teratogenicity and Effects on Reproduction

No data on teratogenicity or effects on reproduction have been found. There are, however, a few reports dealing with the mutagenic and carcinogenic potential of thiols.

Bagramian and associates [46] and Bagramian and Babaian [68] reported on the mutagenic potential of dodecanethiol admixed with chloroprene and

ammonia. Rats were exposed to the combined vapors of the three substances. These three substances are components of "LNT-1 Latex." The incidence of aberrations was found to be increased in experimental rats compared with that in the controls. Eleven workers employed in a "LNT-1 Latex" factory were also studied [46]. The peripheral blood lymphocytes obtained from each individual were cultured and examined. More chromatid breaks were found in the lymphocytes of these individuals than in those of a group of five employees from a shoe factory who served as controls.

Based on the information presented in these studies it is difficult to assess the mutagenic potential of dodecanethiol, since the experimental animals as well as workers were exposed simultaneously to chloroprene, a compound that reportedly causes chromosomal aberrations [78]. Furthermore, in the human study [46], insufficient numbers of cells were examined and the control group used in the study was not clearly defined.

The application of 500 mg of undiluted 1-octadecanethiol to the shaved backs of mice resulted in epidermal changes similar to those found after applications of doses of methylcholanthrene known to produce tumors [67]. This response is not considered to be necessarily indicative of carcinogenesis. Such observations leave unsettled the carcinogenicity of octadecanethiol. No other indication that thiols may be carcinogenic has been found in the literature.

Garrett and Fuerst [69] reported that all six gases, including methanethiol, in their study were significantly mutagenic in Drosophila. However, no data on mutagenicity by methanethiol per se were presented in the paper.

IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

Environmental Data

Thiols constitute a class of organic sulfur compounds whose chemistry has been well studied [9,17]. Only limited quantitative data are found on air concentrations of thiols in occupational environments, probably since they are easily detectable by their odor at the ppb or ppm levels [16,45,48,50,79-81]. Indeed, odors of sulfur-containing components are readily discernible near plants that manufacture and use thiols [82].

Sampling and Analytical Methods

(a) Sampling

A variety of techniques has been used to collect airborne thiols. Collection systems are required to be more effective for lower molecular weight thiols than for those with higher molecular weights in order to sample with optimal collection efficiency because of the greater volatility of the first group [83].

Methanethiol has been collected in an aqueous solution of mercuric acetate-acetic acid [84,85], in an aqueous solution of mercuric cyanide [86], with the use of refrigerated solvents at -78 C [87,88], or in a Porasil D trap at -80 C [89]. With direct gas-chromatographic analysis, the air sample was either first collected into a gas sampling bottle [90] or picked up with an inert sampling line connected to the chromatograph [91,92]. Aqueous collection is essentially complete [84], but some losses can be expected if the thiol is to be freed for the analytical step. The refrigerated solvent systems do provide at least 94% collection [87]. However, no information is found on the sampling efficiency with the Porasil D trap. Direct injection into a gas chromatograph will collect 100% of the methanethiol present in air, if transient reactions are blocked.

Similarly, ethanethiol has been collected in an aqueous solution of mercuric acetate-acetic acid [84], in an aqueous solution of mercuric cyanide [86], or in a sorbent tube containing Chromosorb 104 [93]. Complete absorption was obtained in six tests with the mercuric acetate, but results with the mercuric cyanide were not reported. The Chromosorb 104 sorbent did not provide satisfactory recoveries, even after ethyl acetate was substituted as a desorbing solvent. Only 80% recovery was obtained after 3 days and less than 10% after 8 days.

With propanethiol, only two reports indicate methods of collection: absorption in mercuric cyanide solution [86] and direct gas chromatography from a gas sampling bottle [90]. Neither report has information concerning the efficiency of these methods.

Collection of butanethiol in an aqueous mercuric acetate-acetic acid solution has been described, with 97% collection efficiency and a coefficient of variation of 0.6% on the basis of six tests [84]. Absorption in mercuric cyanide solution also has been used, but the collection efficiency was not reported [86]. Butanethiol is the only thiol for which a NIOSH-validated method has been approved [94]. This method uses a sorbent tube containing Chromosorb 104 and achieves effective adsorption and desorption in the range required. The Chromosorb 104 method offers convenience and reliability. This recommended method for lower molecular weight thiols is described in Appendix I.

No mention of a specific method for pentanethiol collection was found in the literature, but the mercuric acetate-acetic acid method should be applicable. Hexanethiol collection has had about a 94% efficiency with this absorbing system and a coefficient of variation of 0.6% on the basis of six tests [84]. Specific methods for higher molecular weight thiols were not reported in the literature.

In conclusion, the use of sorbent tubes containing the proper type of adsorbent, such as Chromosorb 104 for butanethiol, is the most efficient and convenient method of collection for thiols and is the method recommended in Appendix I. The use of refrigerated solvents, particularly ethylbenzene, which provides good separation in the gas chromatographic analytical stage, should be considered as a second choice. The lower molecular weight thiols (C_1-C_3) can be collected in ethylbenzene at -78 C, and the higher molecular weight thiols (C_6-C_{18}) are retained in the same solvent at 0 C [87,88].

(b) Analysis

Ryland and Tamele [95] published an extensive review on the application of titrimetric, polarographic, spectrophotometric, gas-liquid chromatographic, mass spectrometric, and radiometric methods to thiol determinations.

One report [96] described potentiometric titration, with a silver wire coated with silver sulfide as the indicating electrode, in an alkaline medium with silver nitrate solution for the determination of thiols and hydrogen sulfide. This method applies directly to lower molecular weight thiols (C_1-C_3) and also to hexanethiol and heptanethiol, provided any hydrogen sulfide present is first removed. The method is useful for rapid analysis of a large number of samples.

Spectrophotometric methods for the determination of lower molecular weight alkane thiols in industrial air also have been described [84,85]. Collected in mercuric acetate solution, thiols reacted with N,N-dimethyl-p-phenylenediamine to form a red complex, with an absorption maximum at 500 nm. Hydrogen sulfide, sulfur dioxide, and nitrogen dioxide did not interfere with the reaction. The method applied to the determination of total thiols only and did not differentiate among individual thiols. Methanethiol at concentrations ranging from 0.5 to 25 ppm was readily detected.

A titrimetric method for determination of thiol sulfur in gases or distillates containing more than 0.001% (wt) of thiol sulfur has been reported [97]. Thiols are converted to silver mercaptides by reaction with silver nitrate, the excess of which is determined by titration with ammonium thiocyanate with ferric alum as the indicator. When hydrogen sulfide is present in the test sample, it is precipitated with cadmium sulfate, and the clear aqueous layer is titrated as above. Acetylenes interfere with this method, and this limitation should be considered when this method is used in monitoring thiols.

A simple and accurate colorimetric method for measurement of odorant levels and isopropylthiol and tert-butylthiol mixtures in natural gas was developed by Knight and Verma [98]. The test was based on the reaction of alkane thiol with N-ethylmaleimide; the color developed immediately and was stable for 10 minutes. Under field conditions, when a spectrophotometer was not available, a visual comparison with a standard color chart was used. A linear response was obtained with 1-9 μmol of thiols.

Analytical methods aimed at measuring methanethiol in the atmosphere of kraft paper mills take into account the presence of other sulfur compounds such as dimethyl sulfide, dimethyl disulfide, hydrogen sulfide, and sulfur dioxide; these compounds usually occur at concentrations higher than that of methanethiol. Analysis of kraft mill gases containing sulfur by titrimetric [99-102], polarographic [103], and gas chromatographic methods, which include flame-ionization detection [104,105] and flame-photometric detection [106,107], has been extensively studied.

The alkane thiols, especially those with lower molecular weights (C_1-C_5), have high vapor pressures; at concentrations detectable by their odor, in the ppb range, gas chromatographic methods have been the most effective because such methods are highly sensitive and allow clear separation and precise measurement of thiols. Feldstein et al [86] reported on the gas chromatographic determination of a number of organic sulfur compounds, including methanethiol, ethanethiol, and propanethiol, using a variety of partitioning agents.

Stevens et al [108] described an automated gas chromatographic system for measuring ambient air concentrations as low as 2 ppb for sulfur

dioxide, hydrogen sulfide, methanethiol, and dimethyl sulfide. They found fluorinated ethylene-propylene (Teflon) tubing to be better than stainless steel, soft glass, or borosilicate glass, in that no undesirable retention of sulfur dioxide at levels below 10 ppm occurred. Powdered Teflon coated with polyphenyl ether (5-ring variety) and orthophosphoric acid was the best column packing. A flame-photometric detection system was used. Following essentially the same procedure, Bremner and Banwart [109] identified and separated methane-, ethane-, propane-, and butanethiol as well as hydrogen sulfide, dimethyl sulfide, carbon disulfide, diethyl sulfide, and diethyl disulfide from soils. Many of these compounds may occur in the atmosphere surrounding manufacturing processes or industrial operations.

Additional experimental modifications include graphitized carbon black, treated with phosphoric acid and Dexsil-300, as packing material, and, for calibration, an exponential dilution flask constructed entirely of Teflon [110]; cyanosilicone coating material (XE-60) instead of Dexsil and a double detection system with a combination of flame-ionization and flame-photometric detectors [111]; a stainless steel column packed with Triton X-305 on Chromosorb G for the separation of ethanethiol and dimethyl sulfide [112]; an all stainless steel column and connections and Porapak QS treated with 5% QF-1 Chromosorb G treated with polyphenyl ether to overcome problems associated with low concentrations of individual thiols in natural gas that have a tendency to absorb on column walls and are readily oxidized in the presence of traces of oxygen and Porapak QS column treated with acetone [113,114].

Recently, Vitenberg et al [115] described another possible gas chromatographic method (combining gas chromatographic head space analysis and microcoulometric detection) for the determination of trace sulfur compounds in industrial effluents. In addition to the gain in sensitivity, this method improves the quality of the separation and the accuracy of the quantitative values obtained. Water solutions of methanethiol and ethanethiol can be measured at the ppm level with less than 10% analytical error.

Although a variety of techniques can be applied to the analysis of thiols in occupational environments, most of them are nonspecific and rely upon the reactions of the thiol group. Gas chromatographic and mass spectroscopic methods allow the separation, detection, and quantitative determination of individual thiols in the presence of other sulfur-containing substances encountered in industrial environments. In summary, gas chromatographic techniques using flame-photometric detection are available and provide a specific quantitative analytic method for thiols [106,107,109,111,112,114]. Resolution of interferences from various compounds, such as H_2S, sulfides, or alkanes, has been accomplished by selection of the appropriate stationary phases [86]. Other columns that have been used successfully to quantitatively analyze thiols are reported in a number of publications [108,110-114].

A gas chromatographic method with flame-photometric detection [94] is recommended for analysis of samples of thiols collected from the workplace environment. It has the ability to separate and quantitatively determine thiols from mixtures containing structually similar compounds. This method is precise, accurate, and sensitive and is described in detail in Appendix I. It has been tested and validated by NIOSH.

Engineering and Administrative Controls

Industrial methods for the production of thiols are described in the literature [116-124]. These methods indicate the nature of raw materials, waste products, physical characteristics of the various processes, and products that may be encountered in occupational environments where thiols are manufactured and used.

Raw materials, products, and sulfur-containing byproducts from the production of thiols are potentially hazardous in the occupational environment. In general, thiols, carbon disulfide, hydrogen sulfide, and related materials should be contained in closed systems and vented to flare or scrubber systems to prevent inadvertent discharge of these odorous compounds into occupational and community environments [82].

All systems should be designed, operated, and maintained to prevent spills or release of thiols, particularly during the transfer of products (shipping and receiving) or in the collection of samples. An example of good design was observed in a plant where the drum and tank car transfer stations had return lines vented to flares. When the thiol was pumped into drum or tank, the displaced atmosphere (diluted with nitrogen or another inert gas) was not released into the environment [82]. For fast and safe intervention in routine (and emergency) operations, systems handling thiols should have adequate instrumentation, such as levels indicators, pressure gauges and thermometers, volumetric flow recorders, etc. In addition, remote controls are recommended so that operators are sheltered from accidental spills and overflows, since they can work at a safe distance from systems they are controlling. The two techniques, instrumentation and remote controls, are found in the most recent plant installations. A closed system to prevent the release of materials is recommended. An engineering control program, providing for frequent inspections, preventive maintenance, and prompt repair of any faulty equipment, is essential. In tank-car or drum-filling operations, submerged transfer lines and return vent lines, or vent lines connected to flares, with provision for line flushing before disconnection, should be used [82].

Because hydrogen sulfide is a raw material generated, or used, in thiol manufacturing plants, special precautions are necessary to avoid its release in hazardous concentrations. As specified in the NIOSH criteria document on hydrogen sulfide, remote sensors at fixed locations to detect

hydrogen sulfide [125] or other sulfur-containing gases should be integrated into plant warning systems [82]. The design and operation of the plant should provide for rapid evacuation of employees, preferably by sufficient egress routes to allow employees to take advantage of the wind direction by moving away from the buildings either upwind or crosswind as indicated by the location of the release site. Wind direction indicators, such as wind socks, should be installed so as to be clearly visible from all the plant work areas [82].

Where closed systems are not practical or when leaks develop, occupational exposure to thiols becomes possible, and the likelihood of exposure increases for operations that require handling, transferring, or sampling of thiols. In addition, an employee can become exposed during routine maintenance and repair of equipment by entering tanks, vessels, or other confined spaces or when an emergency or nonroutine situation develops. Ventilation systems, such as hood, glove box, or local exhaust systems, are necessary when thiols are handled in an open system. In addition, a ventilation system is desirable as a standby, should a closed system fail. Guidance for the selection of ventilation systems is provided in NIOSH's Recommended Industrial Ventilation Guidelines [126] and Industrial Ventilation--A Manual of Recommended Practice [127] and in Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971 [128]. Proper control of atmospheric concentrations and capture of released thiols during those operations when exposure is possible should be based on the principles set forth in those publications.

Ventilation systems require regular inspection and maintenance to ensure effective operation. Routine inspections should include face velocity measurements of the hood and examination of the air mover and the collection or dispersion system. Any changes in the process or equipment that may affect the ventilation system must be promptly evaluated to ensure that control measures provide adequate protection for employees. Measurements of atmospheric concentrations of thiols in the work environment are needed to evaluate the efficiency of the ventilation system.

Because hydrogen sulfide, which may be present, is extremely corrosive in the presence of moisture, all facilities require frequent inspection and preventive maintenance to ensure that leaks are readily detected and repaired. Thiols in general are corrosive, and systems must be composed of corrosion-resistant materials, such as stainless steel or passivated metal. All exhaust gases from ventilation systems should pass through a sulfur recovery system or be exhausted to a scrubber or flare for oxidation. Alternatively, UV light, which can destroy ethanethiol in a scrubber application, may be considered [129].

Contingency planning for emergencies, the inadvertent release of materials, and equipment breakdown is vital; planned procedures should be

supported by the availability of appropriate equipment at strategic locations and by trained personnel. In addition to overall contingency planning for the entire plant site, written departmental plans, updated as necessary, and well understood by the department's personnel, are required. They should include:

(a) Reporting requirements--how and whom to notify for help; how to document the incident later.

(b) Steps to prevent spilled chemical from reaching a waterway, overloading a waste-water treatment system, or creating an airborne cloud.

(c) Toxicity, solubility, flammability, and reactivity data on materials being handled.

(d) Inventory and location of spill contingency equipment.

(e) Procedures for handling water-soluble, insoluble, and other chemicals requiring special consideration.

In addition to having knowledge of internal reporting procedures, plant management personnel should understand the need for keeping good records to fulfill the reporting obligations established by various regulatory agencies. With such organized logging of every aspect of their operations, plant operators should also be able to answer any legitimate questions that may be raised by other interested groups. Information on the proper way to satisfy these requirements should be readily accessible to plant supervisors, along with lists of other company officials to help them with the necessary data.

As a general approach, the employer should review material handling operations, maintenance and repair procedures, and process operations in order to identify areas and job locations where employees may come in contact with thiols. Where the process is continuous, an analysis of the hazardous operations should be performed once a year at a minimum; where production is intermittent, a similar analysis should be performed at the start of each separate campaign. Factors to be considered include, but are not limited to, the following:

(a) Transfer, loading, and unloading facilities, including procedures for moving chemicals to and from drums, storage tanks, trucks, railcars, and marine equipment; procedures to secure equipment during loading or unloading; equipment design; instrumentation; and employee monitoring of operations.

(b) Sources of process upsets (startup, shutdown, and cleanup procedures).

(c) Equipment and storage tank diking, surface drainage routing, and sewer system layout.

(d) History of individual departments--spills, current operating procedures, and contingency plans.

(e) Mooring practices, together with booming, dock design, hose systems, catch or drip pans, collection systems, curbing, spill contingency equipment, preferred valve types, equipment blanking practices, barge design, loading logs, and communication systems for marine facilities.

(f) Operating procedures in piping--valve identification, capping or plugging of drain valves, vent valves, hose connection design, and winterizing practices for in-plant process and transfer equipment.

Administrative control through selective assignment of employees may be necessary to protect hypersensitive or sensitized individuals. Sensitive individuals may experience adverse reactions to thiols and related materials at lower concentrations than those tolerated by most other employees.

V. WORK PRACTICES

Work practices appropriate to the manufacture, handling, storage, and use of thiols are primarily concerned with preventing inhalation of, and skin and eye contact with, liquids, aerosols, and vapors of thiols. There is limited evidence from animal studies that thiols may be absorbed through the intact skin (WW Wannamaker III, written communication, December 1977). Inhaled methane- and ethanethiol are exhaled unchanged to some extent, but most thiols appear to be detoxified by metabolic oxidation [70]. Early recognition that an exposure has occurred, together with immediate countermeasures, should prevent adverse effects.

Good industrial hygiene practice requires that all reasonable effort be made to prevent contact of thiols with the skin or eyes and to prevent the inhalation of thiols. Areas of potential exposure by inhalation or skin or eye contact should be posted as restricted areas, and access should be limited to designated employees. If skin contact with a thiol occurs, the affected area should be washed immediately with soap and water. Evaporation of low molecular weight thiols can cause rapid cooling and frostbite. Organic solvents should not be applied to the affected area because defatting of the skin or absorption of the solvent may result. Organic solvents may also enhance absorption of the thiols. Emergency showers and soap should be available where exposures may occur. Where contact of thiols with the eyes is possible, emergency eyewash stations should be provided.

Washrooms and showers should be located conveniently, and employees should be urged to wash or shower after each workshift. To minimize exposure time, whenever employees are exposed through skin contact, they should be required to clean up immediately and change their work clothes.

Work practices and procedures for the use of personal protective devices to minimize contact with thiols should be developed. Personal protective equipment is necessary for additional positive protection in situations where exposures occur in spite of other precautions.

Training

In all areas where thiols are handled, written instructions informing employees of the particular hazards of the compounds, methods for handling the material, procedures for cleaning up spills, personal protective equipment requirements, and procedures for emergencies should be on file and readily available to employees. Employers should establish programs of instruction to familiarize all potentially exposed employees with these procedures. A Material Safety Data Sheet described in Appendix III should

be used as a guide by employers in providing the necessary information; but this should be supplemented with specific instruction and training in work operations involving potential contact with, or inhalation exposure to, hydrogen sulfide, carbon disulfide, other raw materials, and waste products, as well as thiols.

In addition, a continuing education program should be established. Such a program could include, but not be limited to, the following:

(a) Adoption of standardized written procedures, with appropriate personnel training and periodic review, for all routine phases of plant operations.

(b) Job procedures analysis for identification of spill potential.

(c) Encouragement of employees to report unsafe conditions.

(d) Development of a reporting form for all leaks and spills, whether or not they reach a waterway; investigation and review of all significant leaks and spills with the objective of preventing recurrence.

(e) Periodic inspections of dikes and transfer station valves, and review of work practices.

(f) Drills in containing spills.

(g) Bulletins to publicize "near miss" incidents or unsafe conditions.

(h) Communication of new ideas on health and safety aspects of the job.

(i) Use of slogans, posters, etc, to maintain employee interest.

(j) Publicizing of plant and department health and safety performances.

(k) Use of editorials by the plant manager in plant newspaper or bulletins, and regular emphasis on importance at employees' and supervisors' meetings.

Only individuals properly trained in the use of respirators and other protective equipment (including selection, fitting and checking, use, and care) should be permitted access to areas in which exposures to thiols as a result of spills or other accidents are likely. This is particularly important in areas, or during operations, where hydrogen sulfide, carbon disulfide, or low molecular weight thiols (C_1 through C_6) may be released. All such areas and operations should be clearly identified by appropriate posted warnings.

The effective use of recommended work practices to prevent exposures depends on the knowledge and cooperation of employers and employees. Employees must be thoroughly trained in all work operations and emergency procedures and in the use of required equipment and protective devices. They should be provided with the proper tools, equipment, and personal protective clothing or devices and receive adequate, responsible supervision to ensure that all safety requirements and practices are followed. Periodically, at least annually, refresher sessions and drills should be conducted to maintain a high level of competence in safe work practices and emergency procedures.

Protective Clothing and Equipment

Gloves, boots, aprons, goggles, face shields, and other personal protective devices should be made available for employee use. This equipment must be correctly fitted and kept in good condition. Respiratory protective devices must be kept clean and in good working order (29 CFR 1910.134) and must be cleaned and inspected after each use. Respirator canister/cartridges must be changed periodically and at least when the odors of thiols are detected within the mask. Adequate supervision must be exercised to ensure that respirators are worn regularly and properly. Cleanliness of respirators is important because of the hazard associated with skin exposure to thiols, particularly the low molecular weight compounds. Respirators will often restrict the wearer's field of vision and perhaps mobility. This may pose additional safety hazards, so that safety procedures appropriate to the job must be developed also. All personal protective equipment should be cleaned frequently, inspected regularly, and repaired or replaced as necessary. This equipment must be stored in appropriately designated containers or locations when not in use.

Each employee potentially exposed to thiol vapor, or likely to come in contact with solutions of these compounds, must be provided with, and required to wear, adequate protective clothing, such as cotton coveralls, splash-resistant aprons, etc, and equipment appropriate to the tasks and area of work. Adequate supervision must be exercised to ensure that the protective clothing and equipment are regularly and properly worn. All personal protective devices must be cleaned thoroughly after each wearing and before being reused. If any such item becomes contaminated with a thiol, raw material, or waste product during the workshift, it should be flushed with large amounts of water; when such flushing makes the item unsuitable for continued wear, it must be removed and replaced by a clean one.

Eye protection is of particular importance because of the irritant effects of thiols [59], raw materials, and waste products [125,130]. Well-fitted chemical safety goggles must be worn in posted areas as protection from irritating concentrations of thiol mists and splashes.

When using a respirator, employees also should have a full facepiece to provide the necessary eye protection. Full-length, plastic face shields may be worn to protect the face from splashes and spills, but chemical safety goggles are still necessary to protect the eyes from vapor, mists, and splashes that can enter behind the edge of the shield.

Emergency and First-Aid Practices

Each employer should establish a program to meet any emergency that can reasonably be anticipated. Employees assigned to emergency teams should be thoroughly informed of and trained in their responsibilities. First-aid supplies and oxygen resuscitation equipment, approved respiratory protective devices, protective garments, and other equipment that may be needed should be maintained in readiness at emergency stations close to areas of likely emergencies.

Respiratory protective devices approved for escape or evacuation from areas of excessive exposure to a thiol should either be provided to every employee in areas of potential emergency or be readily available at prominently and clearly identified locations throughout such areas.

In emergencies or other operations where airborne concentrations are unknown, respiratory protection must be provided to employees. The type of respirator required is described in Tables I-1 and I-2.

When employees are required to enter any confined space suspected of, or possibly subject to, contamination by a thiol, tests should be made to determine the safety of the atmosphere before entering. The odor of thiols and other sulfur-containing materials may warn of the presence of these compounds but does not necessarily indicate the extent of respiratory protection required.

Eye-flushing stations and safety showers should be available in plant areas where splashes or spills of thiols are possible. If contact with any thiol occurs, the affected skin areas and eyes should be flushed immediately with a copious flow of water. In case of eye contact with benzenethiol or with a mixture including benzenethiol, the affected eye shall be treated with not more than two drops of a 0.5% solution of silver nitrate ($AgNO_3$), applied from a bougie or other previously sealed container, and then flushed with copious quantities of water. When eye contact with any thiol has taken place, the affected person should be referred to a physician after eyewashing has been completed.

Material Handling

Employers must establish material-handling procedures to ensure that employees are not exposed at hazardous concentrations or amounts of thiols.

The following practices and procedures should be observed by all employees who handle thiols, raw materials, and wastes:

(a) Containers of thiols, raw materials, and wastes should be properly labeled and securely closed during transport.

(b) Thiols should be transported or stored in sealed, intact containers. A sealed container is one that has been closed and kept closed so that there is no release of thiols. An intact container is one that has not deteriorated or been damaged to the extent that the contained thiol is released. Because sealed, intact containers would pose no threat of exposure to employers, it should not be necessary to comply with required monitoring and medical surveillance requirements in operations involving only such containers. If, however, containers are opened or broken so that the contained thiols are released, then all provisions of the recommended standard should apply.

(c) Large containers (carboys, drums, and others) should be moved and handled by mechanical equipment of appropriate design and construction.

(d) The transfer of thiols from bulk containers should be done by pumping through a hermetically sealed system of lines. These lines must be vented to a scrubber, flare, or other recovery or destructive process to prevent release of material to both the occupational and community environment.

(e) The transfer of thiols, raw materials, and wastes or solutions from tank cars or tank trucks should be done only by specially trained employees under responsible supervision.

(f) Enclosed process machinery and containers of thiols or solutions thereof should be kept closed or covered, except when operations require otherwise.

(g) Tanks, machines, pumps, valves, and lines should be drained and residual thiols removed by steam followed by an oxidizing solution and before maintenance or repair work. Care must be exercised to avoid contact with the drained or flushed fluids. Containers and lines must be purged of thiols, raw materials for their production, and wastes before performance of any external welding, grinding, or other operation that might offer a source of ignition for flammable vapor.

(h) No individual should enter any tank or equipment until it has been flushed free of thiols, raw materials, and wastes, the atmosphere therein has been determined to be safe, and a permit has been issued by a responsible supervisor.

(i) No individual should be permitted to enter any tank or confined space whose entrance is not large enough to admit an individual fitted with safety harness, lifeline, and an emergency respiratory protective device.

(j) An individual may work in a tank or confined space only with another person outside in constant contact and with rescue equipment and assistance available.

(k) Pipelines and hoses should be blanked off or disconnected to prevent inadvertent entry of thiols, raw materials, and wastes into a confined space in which an individual is working.

(l) Spills and leaks of thiols should be immediately contained, absorbed, or neutralized with household bleach solution and flushed with an abundant flow of water. Employees should wear appropriate respiratory protective equipment and clothing during cleanup of spills.

(m) Eyes and skin surfaces coming into contact with thiols should be immediately flushed with large amounts of water. In the case of contact with the eyes, a physician should be consulted as soon as possible.

(n) Respirators and protective clothing and equipment should be worn in accordance with recommendations and requirements. Employees should exercise care not to transfer thiols, raw materials used in the production of thiols, and waste products from contaminated gloves or other protective garments to unprotected eye or skin surfaces.

(o) Employees should comply with occupational safety and health provisions and all rules and regulations applicable to their own actions and conduct.

Sanitation

Appropriate locker rooms should be provided for changing into required protective clothing in accordance with 29 CFR 1910.141(e). To prevent and limit contact dermatitis from, and skin absorption of, thiols, employees should practice good personal hygiene. Employers should encourage employees to shower at the end of the workshift.

Food should not be stored, prepared, dispensed (including vending machines), or eaten in areas where thiols are manufactured, stored, or used. Lunchroom or lounge areas, if provided, should be separated from work areas and protected from contamination by thiols, raw materials, or wastes.

Wastes containing thiols, raw materials for the production of thiols, or byproducts should not be flushed into a community sewer system unless such action will not interfere with sewage treatment. Organic components of waste water may be treated by either chemical or biologic oxidation processes. The latter processes usually involve impounding the waste liquor, in which case precautions must be taken to ensure that seepage of effluent from the impoundment does not contaminate ground water or adjacent watercourses. Recycling spilled material back into the process should be considered.

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1954, the American Conference of Governmental Industrial Hygenists (ACGIH) proposed tentative threshold limit values (TLV's) of 50 ppm for methyl mercaptan (methanethiol), 250 ppm for ethyl mercaptan (ethanethiol), and 10 ppm for butyl mercaptan (butanethiol) [128], expressed as time-weighted average (TWA) concentrations for an 8-hour day. All three of these values were adopted in 1962. In 1963, the TLV's, defined as TWA concentrations except when designated as ceiling concentrations, for both ethyl mercaptan and methyl mercaptan were changed to ceiling concentrations of 20 ppm.

In 1964, the ACGIH proposed a reduced TLV of 10 ppm for methyl mercaptan, which was adopted in 1966. In 1965, the ACGIH proposed a ceiling value of 10 ppm for ethyl mercaptan. This was adopted in 1967. The ACGIH established the TLV's by analogy with the toxicity of hydrogen sulfide [131]. Methyl mercaptan was regarded as having an acute toxicity similar to, but less than, that of hydrogen sulfide, according to studies by de Rekowski [132] and Frankel [133]. This analogy was supported by citing the Ljunggren and Norberg report [53], and a TLV of 10 ppm was recommended. By a similar analogy, ethyl mercaptan was regarded as being only one-tenth as toxic as hydrogen sulfide. The inhalation studies by Fairchild and Stokinger [59] on mice and rats were cited, with 4-hour LC_{50}'s for ethyl mercaptan of 2,770 and 4,420 ppm, respectively. These values were considered to be similar to values obtained for butyl mercaptan. Reports of headache, nausea, and irritation experienced by humans at levels approaching 10 ppm led the ACGIH to propose and adopt a ceiling concentration of 10 ppm for ethyl mercaptan. In contrast, butyl mercaptan at 10 ppm was considered to be odorous, but not sufficiently so to be seriously objectionable. In addition, the odor of butyl mercaptan was considered to be similar to that of hydrogen sulfide, and a TLV of 10 ppm was recommended. In the notice of intended changes for the 1968 TLV list, the ACGIH stated values of 0.5 ppm as the proposed TLV's for butyl, ethyl, and methyl mercaptans. These TLV's were adopted as TWA limits in 1970, and no further changes have been made in the recommended values for these thiols through the 1977 TLV listing. In 1977, the ACGIH [134] proposed a TLV for phenyl mercaptan (benzenethiol) of 0.5 ppm (2 mg/cu m), expressed as a TWA concentration.

The justification for the change respecting methanethiol was presented in the 1976 edition of Documentation of the Threshold Limit Values for Substances in Workroom Air [131]. Methanethiol was cited as being similar to hydrogen sulfide in toxicity but with a stronger, more disagreeable odor; the latter statement was not supported. The 0.5 ppm TLV is the

equivalent (approximately) of 0.98 mg methanethiol/cu m. For ethanethiol, the TLV of 0.5 ppm (approximately 1.3 mg/cu m) was based on the effects in humans--headache, nausea, and irritation--of exposure to the chemical at 4 ppm for 3 hours/day [48]. For butanethiol, the TLV of 0.5 ppm (approximately 2 mg/cu m) just noted and from its readily noticeable odor at 0.1-1.0 ppm (approximately 0.4-4.0 mg/cu m of air).

In 1968, Mississippi had TWA limits of 50 ppm for methyl mercaptan and 10 ppm for butyl mercaptan [135], and Massachusetts listed a TWA limit of 250 ppm for ethyl mercaptan. Pennsylvania listed a TWA limit of 5 ppm for methyl mercaptan in 1968; earlier TWA limits were 20 ppm for ethyl mercaptan and 10 ppm for butyl mercaptan.

The current Occupational Safety and Health Administration limits, stated in 29 CFR 1910.1000, based on the ACGIH-adopted values for 1968, are 10 ppm for butyl mercaptan, expressed as a TWA concentration, and a ceiling value of 10 ppm for methyl and ethyl mercaptans.

Austria, Belgium, Finland, Switzerland, and Yugoslavia have established limits for methyl, ethyl, and butyl mercaptans at 0.5 ppm. The Netherlands has limits for only methyl and butyl mercaptans at 0.5 ppm, and the Federal Republic of Germany lists a limit for ethyl mercaptan at 0.5 ppm. The USSR limit is 0.8 ppm for ethyl mercaptan. Rumania has limits of 30, 50, and 30 ppm for methyl, ethyl, and butyl mercaptans, respectively [135].

Basis for the Recommended Standard

(a) Environmental Concentration Limits

There is no definitive study that allows derivation of a dose-effect relationship for thiols in humans or in animals. Human studies are available for methane-, ethane-, and butanethiol, but these are essentially acute exposures designed to measure odor thresholds. The human exposure data presented in Chapter III indicated that exposure to thiols can produce CNS depression [12-14], and one death has been reported [12] following overwhelming exposure. In an experimental study [15], human exposure to ethanethiol at 4 ppm (1 mg/cu m) for 3 hours/day for 5 days caused olfactory fatigue and mucosal irritation. These effects returned to normal after cessation of exposure. Furthermore, exposure at 0.4 ppm under the same conditions did not cause the effects mentioned above. In another controlled experiment with volunteers [45], no significant adverse effects were noted after exposure to ethanethiol at 50 ppm (120 mg/cu m) or 112 ppm (270 mg/cu m) for 20 minutes, except for increases in breathing rate, which returned to normal after cessation of exposure. Signs and symptoms of CNS toxicity occurred in workers exposed for 1 hour to butanethiol at concentrations guessed to lie within the range of 50-500 ppm (180-1,800 mg/cu m) [15]. The workers exhibited asthenia, muscular weakness, and malaise.

Based on the animal toxicity data presented in Chapter III, the thiols can be categorized into two classes according to the degree of toxicity: (1) C_1-C_{12}, C_{16}, and C_{18} alkane thiols and cyclohexanethiol; and (2) benzenethiol. The inhalation toxicity data presented suggest that ethanethiol and butanethiol were equitoxic in rats and mice. Propanethiol was slightly less toxic than ethanethiol when inhaled or when administered orally and ip. Hexanethiol was four to five times as toxic as ethanethiol by inhalation but was only slightly more toxic than ethanethiol to rats and mice when given orally or ip [59]. Other acute inhalation studies in animals [54,60] indicated that methanethiol and pentanethiol are of approximately the same order of toxicity as ethanethiol. Therefore, the C_1-C_6 thiols can be grouped together as approximately equitoxic.

Several studies demonstrate subchronic toxicity of thiols in animal species [54,62]. Twenty-five exposures to methanethiol at 300 ppm (591 mg/cu m) killed all the mice [54]. Inhalation exposures of monkeys, rats, and mice to methanethiol at 50 ppm (98.5 mg/cu m) continuously for 90 days caused morbidity and mortality [62] in all three species.

Although the LD_{50} values for a mixture of C_7-C_{11} thiols and for dodecanethiol suggest a lower order of acute toxicity [61], subchronic inhalation exposure to these thiols does produce some organ changes suggestive of those seen in animals intoxicated with the lower molecular weight thiols. Therefore, these thiols are grouped with the C_1-C_6 thiols on the basis of their subchronic effects. Single exposure of mice by iv route for thiols C_3, C_4, C_6-C_{12}, C_{16}, C_{18}, and cyclohexanethiol resulted in similar LD_{50}'s (WW Wannamaker III, written communication, December 1977). Thus, available toxicity data presented in Chapter III for cyclohexanethiol as well as the information available on skin sensitization in guinea pigs and rats for higher molecular weight thiols indicate that this compound and the C_{16} and C_{18} thiols should all be grouped with the C_1-C_{12} thiols [59,61,66,67].

Both the human and animal toxicity data show adverse effects resulting from relatively short-term inhalation exposure to thiols at 50 ppm. These findings indicate that workplace concentrations of thiols should be kept well below this concentration. The minimal effects of olfactory fatigue and mucosal irritation [15] observed when individuals were exposed to 4 ppm ethanethiol ceased when the inhalation exposure was stopped, and no effects were observed at 0.4 ppm exposure. Because there is no evidence that adherence to the TLV of 0.5 ppm has resulted in any cases of toxicity, NIOSH recommends that the concentration of C_1-C_{12}, C_{16}, C_{18} alkane thiols, or cyclohexanethiol, or any combination of these thiols, in the workplace air should not exceed 0.5 ppm as a ceiling concentration for any 15-minute period. Since the toxic action of thiols, on short term-exposure, is expressed largely by reversible mucosal irritation [12,13,15,16], a ceiling

concentration limit is deemed more appropriate than a TWA concentration limit. The use of a ceiling concentration instead of a TWA has the effect of increasing the protection provided to the worker about twofold. NIOSH believes that adherence to the proposed ceiling concentration would prevent both irritative and systemic effects arising from occupational exposure to the aliphatic thiols.

Because C_1-C_{12}, C_{16}, C_{18} alkane thiols, or cyclohexanethiol can cause respiratory changes leading to respiratory failure, muscular weakness leading to paralysis, mild to severe cyanosis, and coma leading to death [12,15,53], exposure to several of them, even at or below the recommended workplace environmental concentration, may produce additive effects. These possibly additive effects should be considered when simultaneous exposure to several thiols occurs. The formula stated in 29 CFR 1910.1000(d)(2)(i) can be used to calculate the equivalent exposure limit (E_m) for the mixture when such plural exposures may occur:

$$E_m = \frac{C_1}{L_1} + \frac{C_2}{L_2} + \ldots\ldots \frac{C_n}{L_n}$$

where:

C = the concentration of a thiol
L = the permissible exposure limit of the thiol

Table VI-1 gives the mg/cu m equivalent to 0.5 ppm for each of these thiols.

Because benzenethiol is not only more toxic than the other thiols [59] but also has a comparatively marked potential for causing eye and organ damage, eg, at 0.72 ppm, at one-third the concentration of ethanethiol (2.1 ppm), as indicated by Katz and Talbert [16] (Table VI-2), NIOSH recommends that the concentration of benzenethiol in the workplace air should not exceed 0.1 ppm (0.45 mg/cu m) as a ceiling concentration for any 15-minute period.

(b) Sampling and Analysis

The technology is currently available to sample and analyze thiols at the recommended environmental limits and to allow institution of the required engineering controls. As discussed in Chapter IV and presented in greater detail in Appendix I, use of a sampling kit containing freeze-out traps and ethyl benzene at -78 C is recommended for collection of lower molecular weight thiols (C_1-C_3), and adsorption on Chromosorb 104 is recommended for personal breathing zone air sampling of higher molecular weight thiols (C_4-C_{18}). A possible solution to the problem would be the application of thermal desorption techniques. With the use of such methods, the entire sample adsorbed on a solid sorbent can be delivered to

TABLE VI-1

NIOSH RECOMMENDED EXPOSURE LIMITS FOR THIOLS

Thiol	Ceiling Concentration Limits*	
	mg/cu m	Approximate ppm Equivalents
Methanethiol	1.0	0.5
Ethanethiol	1.3	0.5
1-Propanethiol	1.6	0.5
1-Butanethiol	1.8	0.5
1-Pentanethiol	2.1	0.5
1-Hexanethiol	2.4	0.5
1-Heptanethiol	2.7	0.5
1-Octanethiol	3.0	0.5
1-Nonanethiol	3.3	0.5
1-Decanethiol	3.6	0.5
1-Undecanethiol	3.9	0.5
1-Dodecanethiol	4.1	0.5
1-Hexadecanethiol	5.3	0.5
1-Octadecanethiol	5.9	0.5
Cyclohexanethiol	2.4	0.5
Benzenethiol	0.5	0.1

*Limit not to exceed 0.5 ppm when more than one thiol is present except for benzenethiol

TABLE VI-2

ODOR INTENSITY OF THIOLS IN HUMANS

Thiol	Degrees of Odor Intensity Vs Thiol Concentration in ppm*											
	0		1		2		3		4		5	
Methanethiol	0.003000	(0.0059)	0.04100	(0.081)	0.570	(1.1)	7.90	(16)	110	(220)	1,500	(3,000)
Ethanethiol**	0.000021	(0.000053)	0.00097	(0.0025)	0.045	(0.11)	2.10	(5.3)	97	(250)	4,500	(11,000)
	0.000006	(0.000015)	0.00026	(0.00066)	0.011	(0.028)	0.49	(1.2)	21	(53)	920	(2,300)
1-Propanethiol	0.000110	(0.00034)	0.00160	(0.005)	0.024	(0.075)	0.36	(1.1)	05.4	(17)	81	(250)
1-Butanethiol**	0.002700	(0.0099)	0.04800	(0.19)	0.840	(3.1)	15.00	(55)	260	(960)	4,600	(17,000)
	0.000045	(0.00017)	0.00100	(0.0037)	0.022	(0.081)	0.50	(1.8)	11	(40)	250	(920)
Benzenethiol	0.000005	(0.000023)	0.00025	(0.0012)	0.014	(0.063)	0.72	(3.2)	38	(170)	2,000	(9,000)

*0 = no odor, 1 = detectable, 2 = faint, 3 = quite noticeable, 4 = strong, 5 = very strong;
numbers in parentheses = concentration in mg/cu m
**Results of two tests are presented for ethanethiol and butanethiol.

Adapted from reference 16

the gas chromatograph for analysis, reducing the amount of sample that must be collected. Before such methods can be used with confidence, however, it must be established that these smaller samples can be desorbed efficiently. Gas-liquid chromatography is recommended for analyzing the desorbed thiols; the proposed method allows the separation, detection, and quantitative determination of alkane thiols, aliphatic cyclic thiols, and aromatic thiols in mixtures and in the presence of other sulfur-containing derivatives.

(c) Medical Surveillance and Recordkeeping

Medical surveillance, including preplacement and periodic medical examinations, should be made available to all workers who are occupationally exposed to thiols. Because percutaneous absorption, inhalation, and ingestion of thiols have resulted in CNS depression, lesions in the liver, kidneys, spleen, and lungs, and irritation of skin, eye, or respiratory tract [12,59,62,66], special attention should be given to identifying by history and physical examination individuals with any preexisting disorders of these organs and systems. Newly hired, existing, or transferred employees should be informed about possible increased risk of health impairment as a result of workplace exposure to thiols. Blood tests, urinalyses, and other tests considered necessary by the attending physician should also be included. Periodic medical examinations should be made annually.

In an emergency involving eye contact with benzenethiol or mixtures of thiols that contain benzenethiol, the affected personnel shall be provided with immediate first aid, followed by prompt medical evaluation and care. The affected eye shall be treated with not more than two drops of a 0.5% solution of silver nitrate ($AgNO_3$), applied from a bougie or other previously sealed container, and then flushed with copious quantities of water (see Appendix II).

Medical and other pertinent records for all employees exposed to thiols should be retained for at least 30 years after employment ends.

(d) Personal Protective Equipment and Clothing

Percutaneous absorption experiments [66,67] using butanethiol, octanethiol, dodecanethiol, or octadecanethiol have indicated no remarkable effects in mice, rabbits, rats, and guinea pigs. Instillation of propanethiol (0.1 ml in the conjunctival sac) in the eyes of rabbits caused severe irritation, heavy discharge, redness, and chemosis [59]. A similar experiment with benzenethiol (0.1 ml instilled in the conjunctival sac) caused severe irritation, corneal injury lasting 3-4 months, and depilation of skin around the eye socket by the resultant solution when the exposed eye was washed with water [59]. Therefore, care must be exercised to ensure adequate protection against eye contact with thiols, raw materials for their production, and sulfur-containing wastes. Personal protective

equipment, including eye protectors should be available and worn where exposure to liquid thiols is likely. Leather is not recommended for use in protective equipment and clothing against thiols. Splash-resistant clothing is preferred in most operations; however, ordinary clothing can be more easily cleaned and the odors of thiols removed by household bleach [82]. Work practices that prevent skin and eye contact must be followed. Showers and eyewash fountains must be available for immediate use if accidental contact occurs.

All employees assigned to areas where there may be occupational exposure to thiols should wear clean long-sleeved shirts, splash-resistant shoe and head coverings, and penetration-resistant gloves. Respirators may be needed by employees engaged in nonroutine maintenance or repair operations that require opening of usually closed systems. Employees working in posted areas should wear goggles with side guards to protect the eyes. Contaminated shoes and clothing should be removed immediately to prevent skin absorption. Clothing that cannot be decontaminated and contaminated leather should be discarded or destroyed to prevent reuse.

(e) Informing Employees of Hazards

At the beginning of employment where possible exposure to thiols exists, all employees must be informed of the hazards from such exposure and those to raw materials for their synthesis and sulfur-containing wastes. Brochures and pamphlets may be effective as aids in informing employees of hazards. In addition, signs warning of the danger of exposure must be posted in any work area where there is a likelihood of occupational exposure to these compounds.

A continuing education program is an important part of an industrial hygiene program for employees potentially exposed to hazardous materials such as thiols and related sulfur-containing materials. Such a continuing education program, which includes training in the use of protective equipment, emergency procedures, first aid, and information about the advantages of participation in the medical surveillance program, should be available to the employees. Qualified persons should periodically inform employees of possible sources of exposure to thiols, the adverse health effects possibly associated with such exposure, the engineering controls and work practices in use to limit exposure and those being planned, and the environmental monitoring and medical surveillance procedures used to check control procedures and to evaluate the health status of employees. Personnel potentially exposed to any of these thiols, raw materials, and sulfur-containing wastes associated with manufacturing, material handling, or uses must be warned of the adverse effects of accidental exposure and must be informed of the signs and symptoms that may occur. Employees should be warned that the onset of these symptoms may be delayed, particularly with exposures to higher molecular weight thiols [59]. Although thiols have a characteristic odor, employees should be informed that odor alone does not indicate the degree of protection required.

(f) Work Practices

The likelihood of exposure to thiols can best be reduced by implementing appropriate work practices. Since toxic effects from exposure to thiols have been produced by skin and eye contact [59,65,82] and inhalation [59], work practices must protect against exposure by these routes. The effects produced by exposure to thiols by inhalation, skin, and eye contact have been discussed in Sections (a) and (d) of this chapter.

Operations should be performed so as to minimize and prevent leaks of hazardous substances and to prevent spills during material handling, transfer, storage, and sampling. If thiols are handled or stored in intact, sealed containers, compliance with the recommended requirements contained in this chapter, except for Sections (e) and (f), should not be necessary. However, if intact, sealed containers are opened or damaged, then all requirements of the recommended standard should apply. For operations that may increase the concentration of airborne thiols in the work environment, adequate ventilation must be used at all times. In case of an accidental leak or spill, anyone entering the area should be protectively clothed to prevent accidental contacts with the skin or eyes and must wear appropriate respiratory protective devices if needed.

(g) Engineering Controls

Engineering controls must be used whenever possible to maintain concentrations of airborne thiols within the recommended environmental concentration limits. A closed system or local scrubber system should be used when any of the thiols is present. During the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance operations, or to make emergency repairs, exposure to the thiols described can be minimized by the use of respirators and protective clothing. However, respirators should not be used as a substitute for engineering controls during routine operations. The employer should prepare contingency plans for nonroutine and cold-weather operations, process upset, and emergencies. Facilities for emergencies should be evaluated on a regular basis. Appropriate equipment and supplies should be available at proper locations to meet any unusual operating conditions and emergencies. All contingency plans should be prepared in writing, understood by operating personnel and managers, and updated as required.

(h) Monitoring and Recordkeeping Requirements

To ensure that workers are not exposed to thiols at concentrations that exceed the recommended environmental limit, concentrations in the workplace should be monitored at least annually and, if found to be necessary by an industrial hygiene survey, quarterly. If changes in production or

processes are likely to increase air concentrations, the workplace should be monitored within 10 days after these changes. If the concentration exceeds the recommended workplace environmental limit, personal monitoring should be performed at least weekly. Such monitoring should continue until two consecutive determinations, at least 1 week apart, show that workplace air levels no longer exceed the recommended ceiling limits. Quarterly monitoring should then be resumed. Records of environmental measurements should be retained for at least 30 years after employment ends.

VII. RESEARCH NEEDS

Sampling and analytical methods specific for individual thiols are needed to provide accurate and routine measurement of thiols in occupational environments. For protection of the workers, the areas of engineering controls and monitoring need to be developed. Definitive toxicologic investigations and epidemiologic studies are required for the evaluation of the potential occupational hazard of thiols.

Sampling and Analytical Studies

A perusal of the available literature and an assessment of the discussions held and observations made during plant visits have clearly shown a need for a continuous monitoring of the concentration of thiols in the workplace and on the personal sampling of air for thiols in the occupational environment. Area sampling for methanethiol has been extensively studied because of the prevalence of this thiol as a byproduct in the kraft paper industry, and several sampling kits [86-88,98,106] have been suggested. However, a suitable, uncomplicated sampling kit still needs to be developed for sampling other thiols. Additionally, a personal sampling device based on polymeric absorbents such as Chromosorb and cooling devices for such absorbent systems to increase collecting efficiency should also be developed. Analytical methods for the estimation of thiols, based on a number of physicochemical principles, have been described adequately in the scientific literature [84,95,97,103,136,137]. The separation, identification, and estimation of parts per billion quantities of thiols, by a number of gas chromatography procedures, also have been described [86,87,94,104-114]. With this available technical information, suitable analytical methods should be developed with the capability for adaptation to the routine analysis of samples obtained for occupational environment studies.

Epidemiologic Studies

A retrospective cohort or cross-sectional morbidity study of a population with occupational exposure to monofunctional organic thiols would provide valuable information. The former type of study would be possible if suitable medical and personnel records were available for workers employed either in thiol manufacturing plants or in the industrial plants using thiols for the production of synthetic rubber, plastics, agricultural chemicals, or other products. Such studies should be accompanied by industrial hygiene surveys and by appropriately timed analysis of the air in the workplace.

Long-Term Animal Exposure Studies

There is considerable information on the effects of short-term exposure to C_1-C_6 alkane thiols and benzenethiol in humans as well as in experimental animals [12-16,45,48,51,53,54,58-60, and WW Wannamaker III, written communication, December 1977]. Although there are similar data [53-55,58-60] for C_7-C_{18} alkane thiols, information on the long-term effects of these thiols is inadequate [51,58,59,61,62,64-67]. Studies on the effects of long-term exposure of experimental animals to thiols under occupational exposure conditions are needed. The inclusion of higher mammalian species and a greater emphasis on inhalation, dermal, and ocular routes of exposure would be most meaningful to human occupational exposure.

Carcinogenicity Studies

Microscopic examination of the epidermis and determinations of the levels of epidermal cholesterol and epidermal delta-7-cholestenol has shown, according to one report [67], that octadecanethiol when applied to mouse skin had effects similar to those of methylcholanthrene, a known carcinogen. However, similar effects were not found for octanethiol or dodecanethiol. A more elaborate and in-depth study of the carcinogenic potentials of monofunctional organic thiols, and especially of octadecanethiol, is indicated. Studies using two or more mammalian species for both the inhalation and the dermal routes of exposure should be conducted. The duration of exposure and the dosage of thiols should simulate as far as possible the conditions of occupational exposure.

Mutagenicity Studies

The results of a few studies [46,68,69] have indicated some mutagenic potential for methanethiol and dodecanethiol. Although the mutagenic effects have not been established unequivocally, these studies nevertheless point out the need to examine critically the mutagenic potential of n-alkane mono thiols. Such studies should include lower organisms and mammalian species and should consider the occupational environment when designing experimental conditions such as route, dose, and duration of exposure. The studies should also include specific locus tests, heritable translocations, multigeneration tests, and characterization of chromosomal lesions.

Teratogenic and Related Reproductive Effects

Information indicating teratogenic and related reproductive effects on any of the monofunctional organic thiols included in the recommended standard has not been found. Thus, a research effort is needed to evaluate this potential in different species.

Electroencephalographic Studies

Electroencephalographic (EEG) studies in volunteers should be conducted to determine whether significant stress may result from exposure to thiols. Concentrations of thiols required to significantly change the EEG pattern should be determined and compared with the odor threshold concentrations [16,45,48,50].

Skin Effects

The skin-sensitizing effects of butane-, octane-, dodecane-, hexadecane-, and octadecanethiols have been studied in guinea pigs and mice [66,67]. The data suggest correlation between the skin effect and the chain length of the higher molecular weight thiols (C_8-C_{18}). Although no skin effect was observed following exposure to butanethiol, dodecanethiol and octadecanethiol caused intense and moderate dermatitis, respectively, and caused definite delayed effects. These studies emphasize the need for a more thorough evaluation of the skin effects for all the thiols. Experiments using two or more mammalian species with a skin structure similar to that of humans would be valuable, and experimental conditions such as duration of exposure and dose should simulate occupational exposures.

Metabolic Studies

Studies on the influence of alkyl, cycloalkyl, and aryl groups on the rate and character of metabolic degradation of thiols may lead to the identification of unique products that might serve as marker metabolites for occupational and environmental monitoring of thiols.

Although enzymatic sulfhydryl-disulfide interchange is possible between SH-group-containing substances within the cell [74,77] leading to the formation of mixed sulfides, no information is available in this regard for monofunctional thiols. The effect of glutathione transferases on thiols and the effect of such reactions on the activities of proteins such as insulin [138,139] should be investigated.

Personal Protective Equipment

Thiols have obnoxious odors and are absorbed tenaciously into wearing apparel, especially apparel made of synthetic materials. Some of the thiols may cause skin sensitization. It is essential therefore to identify materials impervious to thiols for use in protective clothing, boots, gloves, and air-supplied hoods. Finally, better respirator sorbent materials must be identified for removing thiols from respirable air.

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IX. APPENDIX I

ANALYTICAL METHOD FOR BUTANETHIOL

The following sampling and analytical method has been validated, as Method No. S350, for 1-butanethiol [94]. It is the only NIOSH-validated method for a thiol that is included in this recommended standard. Although the method has not yet been validated at 0.5 ppm, it shows promise of being usable for determining n-alkane thiols at this concentration. This analytical method has been also considered feasible for the determination of benzenethiol in air.

Principle of the Method

(a) A known volume of air is drawn through a tube containing 60/80 mesh Chromosorb 104 to trap the 1-butanethiol vapor present.

(b) The thiol is desorbed with acetone, and the solution analyzed in a gas chromatograph with a flame-photometric detector.

(c) The area of the resulting peak is determined and compared with areas obtained from the injection of standard solutions.

Range and Sensitivity

(a) This method has been validated over the range of 16.8-74.2 mg/cu m at an atmospheric temperature of 22 C and atmospheric pressure of 759 mmHg, using a 1.5-liter sample. This sample size is based on the capacity of the Chromosorb 104 to collect the vapor of 1-butanethiol in air at high relative humidity.

(b) The method may be capable of measuring smaller amounts if the desorption efficiency is adequate. Desorption efficiency must be determined over the range used.

(c) The upper limit of the range of the method depends on the adsorptive capacity of the Chromosorb 104. This capacity may vary with the concentrations of 1-butanethiol and other substances in the air.

(d) Breakthrough is defined as the time that the effluent concentration from the collection tube (containing 150 mg of Chromosorb 104) reaches 5% of the concentration in the test gas mixture. Breakthrough

occurs after sampling for 2.9 hours at an average sampling rate of 0.023 liter/minute and relative humidity of 94% and temperature of 25 C. The breakthrough test was conducted at a concentration of 74.2 mg/cu m.

Interferences

(a) Any compound that has the same retention time as 1-butanethiol at the operating conditions described in this method is an interference. Retention time data on a single column cannot be considered proof of chemical identity.

(b) When other compounds are known or suspected to be present in the air, such information, including their suspected identities, should be transmitted with the sample.

Precision and Accuracy

(a) The coefficient of variation for the total analytical and sampling method ranging from 16.8 to 74.2 mg/cu m was 0.062. This value corresponds to a 2.2 mg/cu m standard deviation at the Federal standard level.

(b) On the average, the concentrations obtained in the laboratory validation study, at 0.5X, 1X, and 2X the Federal standard level, were 2% lower than the "true" concentrations for 18 samples. Any difference between the "found" and "true" concentrations may not represent a bias in the sampling and analytical method but rather a random variation from the experimentally determined "true" concentration. Therefore, the method has no bias.

(c) The coefficient of variation is a good measure of the accuracy of the method since the recoveries and storage stability were good. Storage stability studies on samples collected from a test atmosphere at a concentration of 35.9 mg/cu m indicate that collected samples were stable for at least 7 days.

Advantages and Disadvantages

(a) The sampling device is small and portable and involves no liquids. Interferences are minimal, and most of those that do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick, instrumental method.

(b) One disadvantage of the method is that the amount of sample that can be taken is limited by the number of milligrams that the sorbent will hold before overloading. When the amount of 1-butanethiol found on the backup section of the sorbent tube exceeds 25% of that found on the front section, the probability of sample loss exists.

(c) The precision of the method is limited by the reproducibility of the pressure drop across the tubes. Because the pump is usually calibrated for one tube only, this drop will affect the flowrate and cause the volume to be imprecise.

Apparatus

(a) Personal sampling pump: Calibrated personal sampling pump, the flowrate of which can be determined within 5% at the recommended flowrate.

(b) Chromosorb 104 tubes: Glass tubes with both ends unsealed, 8.5 cm long with a 6-mm OD and a 4-mm ID, containing two sections of 60/80 mesh Chromosorb 104 separated by a 2-mm portion of urethane foam. The adsorbing section of the tube contains 150 mg of Chromosorb 104, and the backup section contains 75 mg of Chromosorb 104. A plug of silylated glass wool is placed at the ends of the tube. The pressure drop across the tube must be less than 10 mmHg at a flowrate of 0.025 liter/minute. (Chromosorb 104 is a polymeric solid adsorbent manufactured by the Johns-Manville Company and is commonly used as a gas chromatographic column-packing material. Its conditioning and the preparation of the adsorbing tubes are described in Procedure.)

(c) Gas chromatograph: Gas chromatograph equipped with a flame-photometric detector with a sulfur filter. The gas chromatograph should be equipped with a valve to vent the solvent to the air before it reaches the detector.

(d) Chromatography column: Glass tubing (4-foot x 1/4-inch OD) packed with 60/80 mesh Chromosorb 104.

(e) Peak integrator: Electronic integrator or some other suitable method of determining peak areas.

(f) Sample containers: 2-ml glass sample containers with glass stoppers or Teflon-lined caps.

(g) Microliter syringes: 10 µl and other convenient sizes for preparing standards.

(h) Pipets: Delivery type, 1.0 ml, and other convenient sizes.

(i) Volumetric flasks: 10 ml and other convenient sizes for preparing standard solutions.

Reagents

(a) Acetone, reagent grade.

(b) 1-Butanethiol, reagent grade.

(c) n-Hexane.

(d) Nitrogen, purified.

(e) Hydrogen, prepurified.

(f) Oxygen, purified.

(g) Air, filtered, compressed.

Procedure

(a) Sorbent washing procedure: Prior to usage, Chromosorb 104 is washed and dried to reduce or eliminate the effects of unreacted monomers, solvents, and manufacturer's batch-to-batch differences in production. A quantity of Chromosorb 104 is placed in a sintered glass filter fitted to a large vacuum flask. Reagent grade acetone equal to twice the volume of sorbent is added to the sorbent and mixed, and a vacuum is applied. The wash-mix-vacuum sequence is repeated six times. The sorbent is then transferred to an evaporating dish and dried in a vacuum oven at 120 C under 25 inches mercury vacuum for 4 hours. Immediately prior to packing, the tubes are rinsed in acetone and dried at room temperature to eliminate the problem of Chromosorb 104 adhering to the walls of the glass tubes. The Chromosorb 104 tubes are capped with plastic caps at each end.

(b) Cleaning of equipment: All glassware used for the laboratory analysis are detergent washed, thoroughly rinsed with tapwater and distilled water, and dried.

(c) Calibration of sampling pumps: Each personal sampling pump is calibrated with a representative Chromosorb 104 tube in the line to minimize errors associated with uncertainties in the volume sampled.

Collection and Shipping of Samples

(a) Immediately before sampling, remove the caps from the ends of the Chromosorb 104 tube. In each sampling period, all tubes used are to be packed with Chromosorb 104 from the same manufacturer's lot.

(b) The smaller section of Chromosorb 104 is used as a backup and should be positioned nearer the sampling pump.

(c) The tube should be placed in a vertical position during sampling to minimize channeling through the Chromosorb 104.

(d) Air being sampled should not be passed through any hose or tubing before entering the Chromosorb 104 tube.

(e) A sample size of 1.5 liters is recommended. Sample at a flowrate between 0.010 and 0.025 liter/minute. Do not sample at a flowrate less than 0.010 liter/minute. Record sampling time, flowrate, and type of sampling pump used.

(f) The temperature, pressure, and relative humidity of the atmosphere being sampled are recorded. If pressure reading is not available, record the elevation.

(g) The Chromosorb 104 tube should be capped with plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(h) With each batch of 10 samples, submit one tube from the same lot of tubes used for sample collection. This tube is subjected to exactly the same handling as the samples except that no air is drawn through it. This tube should be labeled as the "blank."

(i) Capped tubes should be packed tightly and padded before they are shipped to minimize tube breakage during shipping.

(j) A sample of the bulk material should be submitted to the laboratory in a glass container with a Teflon-lined cap. This sample should not be transported in the same container as the Chromosorb 104 tubes. Because of postal and Department of Transportation regulations, the bulk sample should be shipped by surface mail. A minimum of 18 extra Chromosorb 104 tubes should be provided to the analyst for desorption efficiency determinations.

Analysis of Samples

(a) Preparation of samples: Remove the plastic cap from the inlet end of the Chromosorb 104 tube. Remove the glass wool plug and transfer the first (larger) section of Chromosorb 104 to a 2-ml stoppered sample container. Remove the separating section of urethane foam and transfer the backup section of Chromosorb 104 to another stoppered container. Analyze these two sections separately. Firm tapping of the tube may be necessary to effect complete transfer of the Chromosorb 104.

(b) Desorption of samples: Prior to analysis, pipet 1.0 ml of acetone into each sample container. Cap and shake the sample vigorously. Desorption is complete in 15 minutes. Analyses should be completed within 1 day after the thiol is desorbed.

(c) Gas chromatograph conditions: The following are typical operating conditions for the gas chromatograph:

(1) 50 ml/minute (60 psig) nitrogen carrier gas flow.

(2) 150 ml/minute (30 psig) hydrogen gas flow to detector.

(3) 20 ml/minute (20 psig) oxygen gas flow to detector.

(4) 30 ml/minute (20 psig) air flow to detector.

(5) 150 C injector manifold temperature.

(6) 200 C detector manifold temperature.

(7) 140 C column temperature.

(A) A retention time of about 5 minutes is to be expected for 1-butanethiol under these conditions and with the use of the glass column recommended in Apparatus. The acetone will elute from the column before the 1-butanethiol.

(B) Injection: The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blow back or evaporation of solvent within the syringe needle, one should employ the solvent flush injection technique. The 10-µl syringe is first flushed with solvent several times to wet the barrel and plunger. Three microliters of solvent are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 µl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-µl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle is completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back 1.2 µl to minimize evaporation of the sample from the tip of the needle. Observe that the sample occupies 4.9-5.0 µl in the barrel of the syringe. Duplicate injections of each sample and standard are made. No more than a 3% difference in area is expected. Venting of the acetone solvent for 60 seconds after injection is required at the prescribed gas chromatographic conditions. If the solvent

is not vented, the flame may be extinguished and the detector may temporarily malfunction. It is not advisable to use an automatic sample injector because of possible plugging of the syringe needle with Chromosorb 104.

(C) The area of the sample peak is measured with an electronic integrator or some other suitable device for area measurement, and results are read from a standard curve prepared as discussed in the following section.

Determination of Desorption Efficiency

(a) The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of Chromosorb 104 to another. Thus, it is necessary to determine the fraction of the specific compound that is removed in the desorption process for a particular batch of Chromosorb 104.

(b) Chromosorb 104 equivalent to the amount in the first section of the sampling tube (150 mg) is measured into a 64-mm, 4-mm ID glass tube flame sealed at one end. This Chromosorb 104 is from the same batch as that used in obtaining the samples. The Chromosorb 104 is prewashed with acetone as previously described. The open end is capped with Parafilm. A known amount of a hexane solution of analyte containing 13.73 mg/ml is injected directly into the Chromosorb 104 with a microliter syringe, and the tube is capped with more Parafilm. The amount injected is equivalent to that present in a 1.5-liter air sample at the selected level. It is not practical to inject the neat liquid directly onto the Chromosorb 104 because the amounts to be added would be too small to measure accurately.

(c) Six tubes at each of three levels (0.5X, 1X, and 2X the standard) are prepared in this manner and allowed to stand at least overnight to assure complete adsorption of the 1-butanethiol onto the Chromosorb 104. These tubes are referred to as the "samples." A parallel blank tube should be treated in the same manner except that no sample is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube described in Analysis of Samples.

(d) Since the response of the flame-photometric detector is nonlinear, a series of standards is prepared to cover variations over each of the three levels (0.5X, 1X, and 2X the standard), as in Calibration and Standards. These are analyzed with the samples. The standards are used to confirm the calibration of the gas chromatograph.

(e) The desorption efficiency equals the average weight in mg recovered from the tube divided by the weight in mg added to the tube.

(f) The desorption efficiency is dependent on the amount of 1-butanethiol collected on the Chromosorb 104. Plot the desorption efficiency vs weight of thiol found. This curve is used in Calculations to correct for adsorption losses.

Calibration and Standards

(a) A series of standards, varying in concentration over the range corresponding to approximately 0.1-3 times the standard for the sample under study, is prepared and analyzed under the same gas chromatograph conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/1.0 ml vs square root of peak area.

Note: Since no internal standard is used in this method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the flame-photometric detector response.

(1) Prepare a stock standard solution containing 13.73 mg/ml 1-butanethiol in acetone.

(2) From the above stock solution, appropriate aliquots are withdrawn and dilutions are made in acetone. Prepare at least five working standards to cover the range of 0.0055-0.165 mg/1.0 ml. This range is based on a 1.5-liter sample. Prepare a standard calibration curve by plotting concentration of 1-butanethiol in mg/1.0 ml vs square root of peak area.

Calculations

(a) Read the weight, in mg, corresponding to each peak area from the standard curve. No volume corrections are needed because the standard curve is based on mg/1.0 ml acetone, and the volume of sample injected is identical to the volume of the standards injected.

Corrections for the blank must be made for each sample:

$$mg = mg\ sample - mg\ blank$$

where:

mg sample = mg found in front section of sample tube
mg blank = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

(b) Add the weights found in the front and backup sections to determine the total weight of the sample.

(c) Read the desorption efficiency from the curve (see Determination of Desorption Efficiency) for the amount found in the front section. Divide the total weight by this desorption efficiency to obtain the corrected mg/sample.

For personal sampling pumps with rotameters only, the following correction should be made:

$$\text{Corrected volume} = f \times t \left(\sqrt{\frac{P_1}{P_2} \times \frac{P_2}{T_1}} \right)$$

where:

f	=	flowrate sampled
t	=	sampling time
P_1	=	pressure during calibration of sampling pump (mmHg)
P_2	=	pressure of air sampled (mmHg)
T_1	=	temperature during calibration of sampling pump (K)
T_2	=	temperature of air sampled (K)

The concentration of 1-butanethiol in the air sampled can be expressed in mg/cu m.

$$\text{mg/cu m} = \frac{\text{corrected mg} \times 1{,}000 \text{ (liter/cu m)}}{\text{corrected air volume sampled (liters)}}$$

Another method of expressing concentration is ppm.

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{MW} \quad \frac{760}{P} \quad \frac{T + 273}{298}$$

where:

P	=	pressure (mmHg) of air sampled
T	=	temperature (C) of air sampled
24.45	=	molar volume (liters/mole) at 25 C and 760 mmHg
MW	=	molecular weight (g/mole) of 1-butanethiol
760	=	standard pressure (mmHg)
298	=	standard temperature (K)

Thiols Other Than Butanethiol

Attempts were made by NIOSH to extend the above method to the determination of methanethiol [140] and ethanethiol [93] in air. These failed either because retention on Chromosorb 104 was not adequate or because recovery was unsatisfactory.

Accordingly, until a definitive procedure can be recommended by NIOSH, a number of related methods based on the published reports previously discussed can be suggested for sampling the other thiols.

Adsorption of the higher molecular weight thiols (C_5-C_{18}), cyclohexanethiol, and benzenethiol on Chromosorb 104 remains the method of choice to collect breathing zone samples by personal sampling, if feasible. The confirmation that the NIOSH-validated method for butanethiol can be extended to this group needs to be obtained in the laboratory.

Area samples can be collected by capture of the thiols in traps filled with solvents and refrigerated. Absorption of methanethiol in ethylbenzene at -78 C, with other traps to remove interfering substances [88,144], would be appropriate. Based on their physical properties (see Tables XII-1 and XII-2), the collection of the other lower molecular weight thiols (ethanethiol and propanethiol) would also be feasible in such a system. Higher molecular weight thiols (alkane thiols C_7 to C_{12}, C_{16}, and C_{18}) may also be trapped in this system, in this case at 0 C [88].

Because of the low level recommended, benzenethiol would also require that a larger volume of air be sampled, coupled with an efficient collection system. The ethylbenzene trap at -78 C may provide it, or it may be necessary to use chemical absorption in a midget impinger.

X. APPENDIX II

FIRST AID FOR EYES CONTAMINATED WITH BENZENETHIOL

About 1884, KSF Crede at the Leipzig University Clinic and Polyclinic for Obstetrics and Gynecology and School for Midwives introduced the use of salts of silver to prevent ophthalmia neonatorum, using as a justification statements that 10.8% of 2,897 babies born before initiation of instillation of an isotonic solution of 2% silver acetate into the eyes of newborn infants developed ocular infections, whereas only 0.1 to 0.2% of 1,160 infants born after adoption of routine application of silver acetate to the eyes at birth developed such infections. The use of silver salts, usually silver nitrate, for prophylaxis of ophthalmia neonatorum became common during succeeding years and indeed was required by 44 states of this country until antibiotics displaced it in the late 1940's. Even thereafter, silver salts have been used for topical antisepsis of burns [142]. Silver salts have, therefore, a comparatively long history of safe and beneficial application to skin and eyes.

Silver had almost as great an affinity for the sulfur atom of the sulfhydryl group as mercury and is less likely to damage the epithelium. Solutions of 0.2-0.6% concentrations have been used as eye lotions; solutions of 2% concentration are likely to induce conjunctival irritation if left in contact with the conjunctivae for 30 or more seconds. NIOSH recommends a 0.5% solution of silver nitrate for instillation into the conjunctival sacs of eyes contaminated with benzenethiol before irrigation of the eyes. The solution of silver nitrate should be approximately isotonic, should be sterilized, and should be in containers that protect it from visible light. The containers should be sealed but able to be opened readily; the solution can be dispensed from the container into the conjunctival sacs of an individual. A collapsible bougie, made of an appropriate plastic, with a snippable snout should serve well. Each bougie should contain about 0.3 ml of 0.5% solution of silver nitrate, so that two drops are available for application to each eye of a worker.

When such a device is used, it is important that the tip of the snout not be allowed to touch either the cornea, the surface of the epithelium of the conjunctivae, or the skin surrounding the orbit. If the silver nitrate solution is observed to wet the skin, it should be washed off promptly. Personnel to be responsible for use of the silver nitrate solution should be trained by the responsible physician in procedures for applying solutions to the eye.

Drops to be instilled into a conjunctival sac usually are placed into the lower cul-de-sac, formed by downward traction on the skin below the

lower lid just over the lower rim of the orbit. If the affected person is recumbent, or if the head is tilted back when the person sits or stands, the lids of the eye may be simply spread apart with the first and second fingers of a hand while two drops of the silver nitrate solution are allowed to fall directly on the cornea of the eye. The eye should be irrigated with normal saline solution or water after the silver nitrate has been given a few seconds to react with benzenethiol.

XI. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information that 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 that 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 that 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 and another component because of its flammability; 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) that 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 LC_{50}-rat," "25 mg/kg LD_{50}-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 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 LD_{50} 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, some irritation likely; prolonged or repeated contact, possibly strong irritation.

Eye Contact--some pain, transient irritation; corneal scarring if prolonged contact.

"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 that 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 Mine Safety and Health Administration approval class, ie, "supplied air," "organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

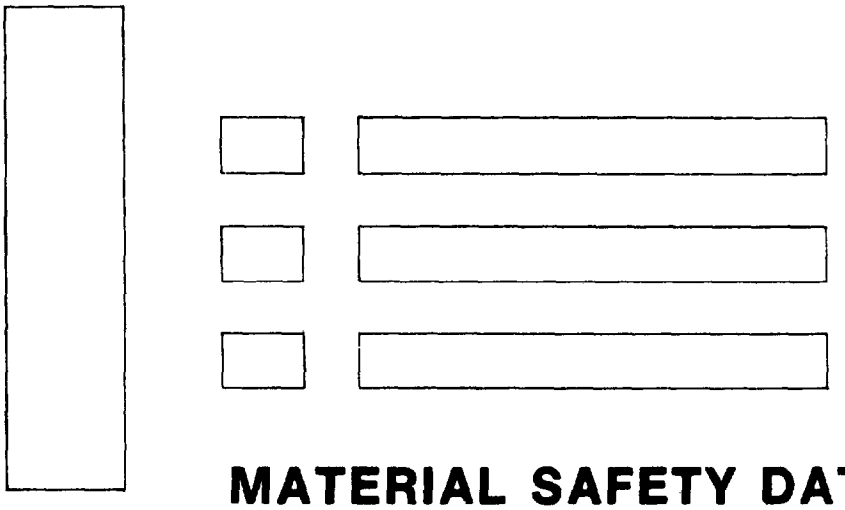
(i) Section IX. Special Precautions

"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 _____

TABLE XII-1

PHYSICAL AND CHEMICAL PROPERTIES OF ALKANE THIOLS, CYCLOHEXANETHIOL, AND BENZENETHIOL

Thiol	Molecular Formula	Molecular Weight	Refractive Index n_D^{20}	Density or Specific Gravity	Melting Point (C)	Boiling Point (C)	Boiling Point (mmHg)	Vapor Pressure (mmHg)	Vapor Pressure (C)	Flash Point (F)*	Conversion Factors** (mg/cu m for 1 ppm)
Methanethiol	CH_3SH	48.11	-	0.8665_4^{20}	-123	6.2	-	2,259	37.8	<0	1.97
Ethanethiol	C_2H_5SH	62.13	1.4310	0.8391_4^{20}	-144.4	35	760	442	20	<0	2.54
1-Propanethiol	C_3H_7SH	76.17	1.4380	0.8411_4^{20}	-113.3	67-68	760	155	25	<0	3.12
1-Butanethiol	C_4H_9SH	90.19	1.4440	0.8337_4^{20}	-115.67	98.46	760	98.2	37.8	55	3.69
1-Pentanethiol	$C_5H_{11}SH$	104.22	1.4469	0.8421_4^{20}	-75.7	126.638 19.505	760 10	13.8 -	25	80	4.69
1-Hexanethiol	$C_6H_{13}SH$	118.24	1.4496	0.8424_4^{20}	-81	151	760	-	-	-	4.84
1-Heptanethiol	$C_7H_{15}SH$	132.27	1.4521	0.8427_4^{20}	-43	177	760	-	-	-	5.41
1-Octanethiol	$C_8H_{17}SH$	146.30	1.4540	0.8433_4^{20}	-49.2	199.1	760	3.0	100	175	5.98
1-Nonanethiol	$C_9H_{19}SH$	160.32	-	-	-	-	-	-	-	-	6.56
1-Decanethiol	$C_{10}H_{21}SH$	174.35	1.4569	0.8443_4^{20}	-26	240.6	760	-	-	-	7.13
1-Undecanethiol	$C_{11}H_{23}SH$	188.37	-	-	-	-	-	-	-	-	7.69
1-Dodecanethiol	$C_{12}H_{25}SH$	202.41	1.4589	0.8450_{20}^{20}	-	142.5	15	2.5	25	190	8.28
1-Hexadecanethiol	$C_{16}H_{33}SH$	258.52	-	-	18-20	123-128	0.5	0.1	-	275	10.57
1-Octadecanethiol	$C_{18}H_{37}SH$	286.57	1.4645	0.8475_4^{20}	24-26 28	188	1-2	-	-	-	11.72
Cyclohexanethiol	$C_6H_{11}SH$	116.23	1.4921	0.9782_4^{20}	-	158 1	760 12	10 -	-	120	4.75
Benzenethiol	C_6H_5SH	110.18	1.5893	1.0766_4^{20}	-14.8	168.7 46.4	760 10	1.0	18.6	-	4.51

*Temperature determined for all substances except propanethiol by open cup method

**ppm = mg/cu m x $\frac{24.45}{MW}$ at 760 mmHg and 25 C

Adapted from references 83,143

TABLE XII-2

SOLUBILITY OF ALKANE THIOLS, CYCLOHEXANETHIOL, AND BENZENETHIOL

Thiol	Solvents			
	Water	Alcohol	Ether	Other
Methanethiol	Soluble	Soluble	Soluble	-
Ethanethiol	"	"	"	Soluble in dilute alkali, acetone
1-Propanethiol	"	"	"	Soluble in acetone and benzene
1-Butanethiol	"	"	"	-
-Pentanethiol	Insoluble	"	"	-
1-Hexanethiol	"	Very soluble	Very soluble	-
1-Octanethiol	-	"	-	-
1-Nonanethiol	-	-	-	-
1-Decanethiol	Insoluble	Soluble	Soluble	-
1-Undecanethiol	-	-	-	-
Dodecanethiol	Insoluble	Soluble	Soluble	-
1-Hexadecanethiol	"	Slightly soluble	"	-
1-Octadecanethiol	"	"	"	-
Cyclohexanethiol	"	Soluble	"	Soluble in acetone, benzene, chloroform
Benzenethiol	"	"	"	Soluble in benzene

Adapted from references 83,143

TABLE XII-3
SYNONYMS FOR 16 THIOLS

Thiol Nomenclature	Synonyms
Methanethiol	Mercaptomethane, methylmercaptan, methylsulfhydrate, thiomethylalcohol
Ethanethiol	Ethylmercaptan, ethylsulfhydrate, ethylthioalcohol, mercaptoethane, thioethanol, thioethylalcohol
1-Propanethiol	3-Mercaptopropane, propane-1-thiol, n-propylmercaptan
1-Butanethiol	1-Butylmercaptan, n-butylthioalcohol, 1-mercaptobutane, thiolbutylalcohol
1-Pentanethiol	Amylhydrosulfide, amylmercaptan, amylsulfhydrate, amylthioalcohol, pentylmercaptan
1-Hexanethiol	n-Hexylmercaptan, n-hexylthiol
1-Heptanethiol	n-Heptylmercaptan
1-Octanethiol	1-Mercaptooctane, n-octylmercaptan, octylthiol
1-Nonanethiol	n-Nonylmercaptan, nonylthiol
1-Decanethiol	Decylmercaptan, 1-mercaptodecane
1-Undecanethiol	-
1-Dodecanethiol	Dodecylmercaptan, laurylmercaptan
1-Hexadecanethiol	Cetylmercaptan, hexadecylmercaptan
1-Octadecanethiol	1-Mercaptooctadecane, octadecylmercaptan, stearylmercaptan
Cyclohexanethiol	Cyclohexylmercaptan, cyclohexylthiol
Benzenethiol	Phenylmercaptan, thiophenol

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