

NIOSH

**criteria for a recommended standard
occupational exposure to**

CHLOROPRENE



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service Center for Disease Control

National Institute for Occupational Safety and Health

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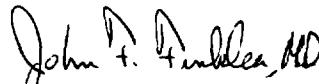
PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on chloroprene by members of the NIOSH staff and the valuable constructive comments by the Review Consultants on Chloroprene, by the ad hoc committees of the Society for Occupational and Environmental Health and the Society of Toxicology, and by Robert B. O'Connor, M.D., NIOSH consultant in

occupational medicine. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on chloroprene. A list of Review Consultants appears on page vi.



John F. Finklea, M.D.
Director, National Institute for
Occupational Safety and Health

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

The Division review of this document was provided by J. Henry Wills, Ph.D., Chairman, Richard A. Rhoden, Ph.D., and Robert L. Roudabush, Ph.D., with Joseph K. Wagoner, S.D.H., and Peter F. Infante, D.P.H. (Division of Surveillance, Hazard Evaluation, and Field Studies), Robert A. Glaser (Division of Physical Science and Engineering), and Harry B. Plotnick, Ph.D. (Division of Biomedical and Behavioral Science).

The views expressed and conclusions reached in this document, together with the recommendations for a standard, are those of NIOSH. These views and conclusions are not necessarily those of the consultants, other federal agencies or professional societies that reviewed the document, or of the contractor.

REVIEW CONSULTANTS ON CHLOROPRENE

Alfio J. Besozzi, Ph.D.
Industrial Hygiene Coordinator
Petro-Tex Chemical Corporation
Houston, Texas 77017

J. Bradford Block, M.D.
Medical Consultant
Division of Occupational Safety and Health
Kentucky Department of Labor
Frankfort, Kentucky 40601

Dennis I. Chamot, Ph.D.
Assistant to the Executive Secretary
Council for Professional Employees, AFL-CIO
Washington, D.C. 20006

Norton Nelson, Ph.D.
Director, Institute of Environmental Medicine
New York University Medical Center
New York, New York 10016

Sidney Pell, Ph.D.
Manager, Epidemiology
Medical Division
E. I. du Pont de Nemours & Company
Wilmington, Delaware 19898

Norman M. Trieff, Ph.D.
Assistant Professor
Department of Preventive Medicine and
Community Health
University of Texas (Galveston Branch)
Galveston, Texas 77550

James G. Wilson, Ph.D.
Professor of Pediatrics
Children's Hospital Research Foundation
Cincinnati, Ohio 45229

CRITERIA DOCUMENT:
RECOMMENDATIONS FOR AN OCCUPATIONAL
EXPOSURE STANDARD FOR CHLOROPRENE

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I. RECOMMENDATIONS FOR A CHLOROPRENE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to chloroprene in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour work shift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of chloroprene on the health of employees and provide for their safety. Sufficient technology exists to permit compliance with the recommended standard. Although NIOSH considers the workplace environmental limit to be a safe level based on current information, the employer should regard it as the upper boundary of exposure and make every effort to maintain the exposure as low as is technically feasible. The criteria and standard will be subject to review and revision as necessary.

These criteria and the recommended standard apply to occupational exposure to the chlorinated hydrocarbon monomer, $\text{CH}_2:\text{C}(\text{Cl})\text{CH}:\text{CH}_2$, hereinafter referred to as chloroprene. Synonyms for chloroprene include 2-chloro-1,3-butadiene, 2-chloroprene, and beta-chloroprene. The monomer is polymerized in a water solution, forming a polychloroprene latex also called neoprene latex. Neoprene historically was the trademark for polychloroprene latex and rubber products; the two names are now synonymous.

The primary hazards in the manufacture of chloroprene arise from inhalation of the vapor and skin contact with the liquid. The most important issues are whether chloroprene is a mutagen, a teratogen, or a

carcinogen in humans. It may cause adverse effects on the central nervous system (CNS), liver, cardiovascular system, and kidneys.

"Occupational exposure to chloroprene" is defined as work in any establishment where chloroprene is manufactured, stored, handled, used, or otherwise present. If exposure to other chemicals is likely, the employer shall also comply with any applicable standards for these other chemicals. "Emergency" is defined as any disruption in work process or practice, such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment, which is likely to result in unexpected exposure to chloroprene in quantities that may cause physical harm. Occupational exposure to chloroprene shall require adherence to all the following sections.

Section 1 - Environmental (Workplace Air)

(a) Concentration

The employer shall control exposure to chloroprene so that no employee is ever exposed at a concentration greater than 3.6 milligrams per cubic meter (mg/cu m) of air (1 ppm), determined as a ceiling concentration for any 15-minute sampling period during a 40-hour workweek. The schedule for such sampling shall be determined by a professional industrial hygienist in accordance with good industrial hygiene practice.

(b) Sampling and Analysis

Samples of workplace air shall be collected and analyzed at least annually as described in Appendices I and II, or by any methods shown to be equivalent in accuracy, precision, and sensitivity to the methods specified.

Section 2 - Medical

(a) Placement examinations shall include at least:

(1) Comprehensive medical and work histories with special emphasis directed towards the skin, the eyes, and the hepatic, pulmonary, renal, and central nervous systems.

(2) Physical examination giving particular attention to the skin, eyes, and CNS function.

(3) Specific clinical tests, including at least urinalysis, a 14- x 17-inch posteroanterior chest roentgenogram, and pulmonary function tests such as the forced vital capacity (FVC) and the forced expiratory volume at one second (FEV 1). In addition, such tests as determination of serum glutamate-pyruvate transaminase (SGPT), electrocardiographs, and any others considered by the responsible physician to be useful in assessing possible deleterious effects on the employee's health should be used at the physician's discretion.

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

(b) Periodic examinations shall be made available on at least an annual basis or at some other, lower frequency to be determined by the responsible physician. These examinations shall include at least:

(1) Interim medical and work histories

(2) Physical examination as outlined in 2(a)(1-3) above.

(c) During preplacement examinations, applicants or employees having medical conditions which would be directly or indirectly aggravated by exposure to chloroprene shall be counseled on the increased risk of impairment of their health from working with this substance. Employees who become pregnant shall be counseled that their continuing to work with chloroprene may have adverse effects on their pregnancies. All employees shall be advised of the value of periodic medical examinations. Workers shall be advised that chloroprene has shown antifertility effects on male rats and that testing with bacteria and fruit flies showed that it induced mutations. The relevance of these studies to male and female workers has not yet been established. High exposures have induced oligospermia in men. These findings indicate that both employers and employees should attempt to minimize exposure to chloroprene whenever possible.

(d) Initial medical examinations shall be made available to all employees as soon as practical after the promulgation of a standard based on these recommendations.

(e) In an emergency involving chloroprene, all affected personnel shall be provided with immediate first-aid services, especially with regard to the lungs and eyes. In the event of contact with chloroprene, any contaminated clothing and shoes shall be immediately removed and the skin washed with soap and water. If chloroprene contacts the eyes, they shall be immediately flushed with water for 15 minutes.

(f) Pertinent medical records shall be kept for all employees exposed to chloroprene in the workplace. Such records shall be kept for at least 30 years after termination of employment. These records shall be made available to the designated medical representatives of the Secretary

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

Section 3 - Labeling and Posting

All the labels and warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Illiterate workers or workers reading languages other than those used on labels and posted signs shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

(a) Labeling

The following warning label shall be affixed in a readily visible location on processing or other equipment and storage tanks or containers which hold chloroprene either alone or as an incidental component of polychloroprene latex:

CHLOROPRENE

DANGER! FLAMMABLE!
BREATHING VAPOR MAY BE HAZARDOUS TO HEALTH

Use only with adequate ventilation.
Avoid breathing vapor.
Avoid contact with skin.
May generate toxic vapors on contact with heat or open flame.
Keep containers closed when not in use.

First Aid: In case of skin contact, wash thoroughly with soap and water for at least 15 minutes. In case of eye contact, flush with water for at least 15 minutes. In case of eye contact or ingestion, consult a physician.

(b) Posting

The following warning sign shall be affixed in a readily visible location at or near entrances to areas in which there may be occupational exposure to chloroprene:

CHLOROPRENE

DANGER! FLAMMABLE!
BREATHING VAPOR MAY BE HAZARDOUS TO HEALTH
LIQUID BURNS SKIN

If respirators are required, the following statement shall be added in large letters to the sign required above:

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

In any workplace or area where there is a likelihood of emergency situations arising, signs required by paragraph (b) of this section shall be supplemented by training sessions giving emergency and first-aid instructions and procedures, the locations of first-aid supplies and emergency equipment, and the locations of emergency showers and eyewash fountains.

Section 4 - Personal Protective Clothing and Equipment

The employer shall use efficient engineering controls and safe work practices to maintain exposure to chloroprene within the limit specified in Section 1(a) and shall provide protective equipment and clothing impervious to chloroprene (ie, vinyl- or rubber-coated material) to prevent skin and

eye contact. Emergency exits shall be located at clearly identified stations within the work area and shall be adequate to permit all employees to escape safely from the area. The employer shall provide eyewash fountains at locations convenient to, but not within, areas of possible exposure to chloroprene.

(a) Protective Clothing

(1) The employer shall provide face shields (8-inch minimum) with goggles and shall ensure that employees wear the protective equipment at any operation which affords a possibility of liquid chloroprene coming into contact with the eyes. Eye protective devices shall conform with 29 CFR 1910.133.

(2) The employer shall provide appropriate protective clothing for use in any operation where the worker has any possibility of coming into direct contact with liquid chloroprene. The clothing shall be both impervious and resistant to chloroprene. Gloves, boots, overshoes, and bib-type aprons that cover boot tops shall be provided when necessary. Impervious supplied-air hoods or suits shall be worn when entering confined spaces, such as pits or tanks, unless they are known to be safe. In situations where heat stress is likely to occur, air-supplied suits shall be used. All protective clothing shall be cleaned, well-aired, and inspected for defects prior to reuse.

(b) Respiratory Protection

(1) Engineering controls shall be used when needed to keep chloroprene concentrations at or below the permissible exposure limit. The only circumstances in which respiratory protective equipment may be used to restrict exposure of workers to chloroprene are:

(A) During the time necessary to install or test the required engineering controls.

(B) For operations such as maintenance and repair activities that may cause brief exposure at concentrations in excess of the occupational exposure limit.

(C) During emergencies when air concentrations of chloroprene may exceed the permissible limit.

(2) When a respirator is permitted by paragraph (b)(1) of this section, it shall be selected and used in accordance with the following requirements:

(A) The employer shall establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134. Employees shall be instructed in the proper use and testing for leakage of respirators assigned to them.

(B) To determine whether a respirator is needed in a nonemergency situation, the employer shall measure the atmospheric concentration of chloroprene in the workplace before it is entered by the appropriate workers and supervisors.

(C) The employer shall provide respirators in accordance with Table I-1 and shall ensure that employees use the respirators provided. The respiratory protective devices provided in conformance with Table I-1 shall be those approved by the Mining Enforcement and Safety Administration and NIOSH as specified under the provisions of 30 CFR 11.

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR
EXPOSURE TO CHLOROPRENE

Self-contained breathing apparatus with
positive pressure in full facepiece

Combination supplied-air respirator,
pressure-demand type, with auxiliary
self-contained air supply

(D) When a self-contained breathing apparatus is selected, the employer shall provide initial training and monthly refresher courses on the use, maintenance, and function of the self-contained breathing apparatus.

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

Section 5 - Informing Employees of Hazards from Chloroprene

(a) Employees to be assigned to work in areas in which exposure to chloroprene is likely shall be informed by the employer prior to employment, and on a semiannual basis thereafter, of the hazards, relevant symptoms of overexposure, appropriate emergency procedures, and proper conditions and precautions to minimize chloroprene exposure. Employees engaged in maintenance and repair activities shall be included in these training programs. All employees shall be instructed about the availability of such information and its location. Records of such training shall be preserved to verify the frequency of training.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience or training, to ensure that all employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator usage. The instructional program shall include a description of the general nature of the medical monitoring procedures and of the advantages to the employee of undergoing these examinations. As a minimum, instruction shall include oral presentation of the information in Appendix III, which shall be kept on file, readily accessible to employees at all places where exposure may occur.

(c) Required information shall be recorded on the "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.

Section 6 - Work Practices

(a) Exhaust Ventilation Systems

Operations having the potential of producing occupational exposure to chloroprene shall be enclosed to the maximal extent practicable and provided with local exhaust ventilation, unless other methods of controlling the workplace airborne chloroprene concentration below the occupational exposure limit have been established. Motors for ventilation equipment and other items requiring external motive power shall be sparkproof. Effluent air shall be treated appropriately to enable it to meet any emission standards that may be promulgated and shall not be recirculated in the workplace.

Enclosures, exhaust hoods, and the associated ductwork shall be kept in good repair to contain vapors and maintain design airflows at hood faces

and within ducts. Airflows shall be measured at hood faces and inlets to ducts at least every 6 months and preferably monthly. Continuous airflow indicators, such as manometers containing light oil or another comparatively nonvolatile fluid, mounted to indicate airflow, are recommended. A record of design airflows and measurements made at least every 6 months at critical points of the exhaust system shall be kept in a permanent record book.

(b) Emergency Procedures

For all work areas where a reasonable potential for emergencies involving chloroprene exists, the employer shall take all necessary steps to ensure that employees are instructed in and follow the procedures specified below and any others appropriate for the specific operation or process and shall instruct employees in their implementation.

(1) Procedures shall include prearranged plans for obtaining emergency medical care and for transportation of injured employees. Employees shall also be trained in administering immediate first aid and shall be prepared to render such assistance when necessary.

(2) Approved eye, skin, and respiratory protection, as specified in Section 4, shall be used by personnel essential to emergency operations. Employees not essential to emergency operations shall be evacuated from hazardous areas where inhalation, ingestion, or direct skin or eye contact may occur. The perimeters of these areas shall be delineated, posted, and secured.

(3) Only personnel properly trained in the procedures and adequately protected against the attendant hazards shall shut off sources of chloroprene, clean up spills, and immediately repair all leaks.

(4) Any spills of chloroprene shall be cleaned up immediately.

(5) Eyewash fountains and emergency showers shall be provided in accordance with 29 CFR 1910.151.

(6) Portable fire extinguishers shall be placed in readily accessible locations and shall meet the requirements of 29 CFR 1910.157.

(7) Fires, if any arise, shall be extinguished with foam, carbon dioxide, dry-chemical, or other smothering devices.

(8) An alarm to signal evacuation of the plant under emergency conditions shall be installed in the plant and shall meet the requirements of 29 CFR 1910.163(a).

(c) Confined Spaces

(1) Entry into confined spaces or into other areas from which egress may be limited shall be controlled by a permit system. Permits shall be signed by an authorized representative of the employer certifying that preparation of the confined space, precautionary measures, personal protective equipment, and procedures to be used are all adequate.

(2) Tanks, pits, tank cars, process vessels, tunnels, sewers, or other confined spaces that have contained chloroprene or polychloroprene (neoprene) shall be thoroughly ventilated to assure an adequate supply of oxygen, tested for chloroprene and other contaminants, and inspected prior to each entry. Ventilation shall be maintained while workers are in the confined space.

(3) Seepage of chloroprene into the confined space while work is in progress inside shall be prevented by disconnecting and blanking off chloroprene or latex supply lines.

(4) Personnel entering a confined space shall be furnished with appropriate personal protective equipment as specified in Section 4 above and protected by a lifeline tended outside the space by another worker who shall also be equipped for entry with approved respiratory, eye, and skin protection and a lifeline. These two workers shall be in constant communication. A third worker shall maintain general surveillance of the activities of the other two and shall be equipped appropriately to be able to enter the confined space if necessary.

(d) Handling and Storage

(1) Storage containers, piping, and valves shall be inspected periodically for leakage. Containers shall be stored in cool, well-ventilated areas and shall be kept away from peroxides and other oxidizing chemicals.

(2) Storage facilities shall be designed and sited to contain spills, to prevent contamination of workroom air, and to lessen the hazard from fire. The applicable provisions of 29 CFR 1910.106 shall be adhered to.

(3) Processes and storage facilities shall not be located near open flames or high-temperature operations.

(4) Where chloroprene is transferred from one metal container to another, the two vessels shall be grounded or electrically interconnected by bonding. This does not apply to transfers through piping. All mechanical equipment shall be of sparkproof construction.

(e) General Work Practices

(1) Prior to maintenance work, sources of chloroprene shall be shut off. The concentration of chloroprene in the air of the work area

shall be reduced to the extent feasible. If concentrations at or below the ceiling environmental air limit cannot be assured, respiratory protective equipment, as described in Section 4 of this chapter, shall be used during such maintenance work.

(2) Employees who have skin contact with chloroprene shall immediately wash or shower with soap and water for at least 15 minutes to remove all traces of chloroprene from the skin. Contaminated clothing shall be removed immediately and disposed of or cleaned before reuse.

Section 7 - Sanitation Practices

(a) Eating, drinking, and food preparation or dispensing (including vending machines) shall be prohibited in chloroprene work areas.

(b) Smoking shall be prohibited in areas where chloroprene is used, transferred, stored, or manufactured. Carrying of lighters, matches, and other sources of ignition into chloroprene-containing work areas shall be prohibited.

(c) Employees who handle chloroprene or equipment contaminated with chloroprene shall be instructed to wash their hands thoroughly with soap and water before using toilet facilities or eating.

(d) Waste material contaminated with chloroprene shall be disposed of in a manner not hazardous to employees. The disposal method must conform with applicable local, state, and federal regulations and must not constitute a hazard to the surrounding population or environment.

Section 8 - Monitoring and Recordkeeping Requirements

As soon as possible after promulgation of a standard based on these recommendations, the employer shall conduct an industrial hygiene survey at each location where chloroprene is released into the workplace air to determine whether exposure to airborne chloroprene is in excess of the occupational exposure limit. The employer shall keep records of these surveys. If the employer concludes that concentrations of airborne chloroprene are at or below the occupational exposure limit, the records must state the basis for this conclusion. Surveys shall be repeated at least quarterly and within 30 days of any process change likely to result in an increase in airborne chloroprene concentrations. If the employer has determined that the environmental concentration of chloroprene in a workplace may exceed the occupational exposure limit, he shall fulfill the following requirements:

(a) Personal Monitoring

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

(2) Routine monitoring of employee exposures shall be conducted at least quarterly.

(3) Samples representative of the exposure in the breathing zone of the employee shall be collected in all personal monitoring. Procedures for sampling, calibration of equipment, and analysis of chloroprene samples shall be as provided in Appendices I and II. Methods of comparable sensitivity, accuracy, precision, reliability, and ease of

performance may be substituted for those described in these appendices.

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

(5) The exposure of affected employees shall be monitored at least once every 3 months. In the event of overexposure, control measures shall be initiated and the employee shall be notified of the overexposure and of the control measures being instituted. Such monitoring shall continue until two determinations, at least 1 week apart, indicate that the employee's exposure no longer exceeds the recommended environmental limit; routine monitoring may then be resumed.

(b) Recordkeeping

Employers or their successors shall keep records of environmental monitoring for each employee for at least 30 years after the individual's employment has terminated. These records shall include the name of the employee being monitored, dates of measurements, duties and job locations within the worksite, sampling and analytical methods used and evidence of their accuracy, number and duration of samples, results of analyses, occupational exposure concentrations based on these samples, and personal protective equipment used by the employee. Records for each employee which indicate date of employment with the company and changes in job assignment shall be kept for the same 30-year duration. The employer shall make these records available on request to authorized representatives of the Assistant Secretary of Labor for Occupational Safety and Health or of the Director of

the National Institute for Occupational Safety and Health. Employees and former employees, or their authorized representatives, shall have access to information on their own exposures, and the employee or the employee's representative shall be given the opportunity to observe any measurement conducted in accordance with this section. Any observer shall have the right to an explanation of the procedures used, of the results of the measurements, and of the meaning of the results for human health and safety.

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 from workplace exposure to chloroprene. 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."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health and to provide for the safety of employees exposed to hazardous chemical and physical agents. Criteria for any recommended standard should enable management and labor to develop better engineering controls and more healthful work practices and should not be regarded as a final goal.

These criteria for a standard for chloroprene are part of a continuing series of documents developed by NIOSH. The recommended standard applies to workplace exposure to chloroprene arising from the processing, manufacture, and use of the substance, as in the production of polychloroprene latex, as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-

large, and any extrapolation beyond occupational exposures is not warranted. It is intended to (1) protect against the development of both systemic effects and local effects on the skin and eyes, (2) be measurable down to the proposed ceiling concentration of chloroprene by techniques that are feasible, reproducible, and available to industry and government agencies, and (3) be attainable by using existing technology.

The primary hazards to health in chloroprene manufacture arise from inhalation of airborne chloroprene vapor and skin contact with the liquid. A major obstacle encountered in the preparation of this document was the paucity of pertinent information on human and animal toxicity. During the development of this criteria document, repeated attempts were made to contact foreign investigators for the purpose of acquiring additional information on their published data. Since these attempts were unsuccessful, it was not possible to confirm the validity of all the data and the significance of the conclusions referred to in this document. Consequently, proper scientific evaluation and interpretation of these articles could not be achieved.

There are many unanswered questions concerning the general toxicity of chloroprene. The mechanisms of the toxicity of chloroprene and its metabolites are unknown and should be investigated. Studies of chloroprene metabolism in the liver and lungs, the organs most susceptible at high exposure concentrations, are also needed. Mutagenic, carcinogenic, and reproductive effects must be further studied to clear up discrepancies in the current literature. Further epidemiologic and primate studies to ascertain a dose-response relationship are required. Validation of sampling and analytical procedures for concentrations of chloroprene below

those at which these methods have been validated by NIOSH will be carried out as soon as possible.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Chloroprene, $\text{CH}_2\text{:C}(\text{Cl})\text{CH:CH}_2$ (formula weight 88.5), is a colorless, flammable, volatile liquid. It has a pungent, ethereal odor. The odor threshold has been reported to range from about 0.1 to several hundred ppm [1,2]. Additional physical and chemical properties are presented in Table XII-1 [3,4].

Chloroprene was first synthesized in 1930 by Carothers et al [5]. Acetylene was bubbled through cuprous chloride/ammonium chloride solution yielding monovinyl acetylene, CH_2CHCCH . This was then chlorinated with hydrochloric acid in cupric chloride/ammonium chloride solution to form 2-chloro-1,3-butadiene, $\text{CH}_2\text{:C}(\text{Cl})\text{CH:CH}_2$ (beta-chloroprene). Byproducts of the reactions were acetaldehyde (3-7%), methyl vinyl ketone (unknown percentage), and vinyl chloride (0.5%). Although this method is still in commercial use throughout the rest of the world, chloroprene has been synthesized from 1,3-butadiene in the United States since 1970 [6].

The butadiene process involves the chlorination of butadiene in the gas phase to 1,4-dichloro-2-butene and 3,4-dichloro-1-butene; the latter, being the precursor of chloroprene, is distilled off, and the 1,4-dichloro-2-butene is isomerized to 3,4-dichloro-1-butene by distillation over copper and cupric chloride [6-8]. The 3,4-dichloro-1-butene is dehydrohalogenated with aqueous sodium hydroxide to yield chloroprene. Chloroprene is removed from the mixture of sodium hydroxide and 3,4-dichloro-1-butene by vacuum distillation. The purified chloroprene is stored at less than -10°C in the presence of antioxidants. Although the butadiene process is cleaner and

less likely to explode than the acetylene process, it introduces a different set of impurities, mainly alpha-chloroprene [6,8].

All the chloroprene produced is subjected to polymerization, usually in an emulsion in the presence of resin, fatty acids, and alkylmercaptans [6]. Polymerization is usually initiated by the addition of a "peroxy" salt, producing neoprene or polychloroprene latex. Unreacted monomeric chloroprene is steam stripped from the latex and recycled. The stripped latex is coagulated by decreasing the pH, precipitated by decreasing the temperature, collected in large sheets, and washed to remove salts. The major worker exposure to chloroprene occurs in the manufacture of the monomer and during the polymerization to neoprene latex. The process, through the steam stripping, is completely enclosed and can be a continuous-flow operation. However, specialty latices are made in batches. Exposure to chloroprene occurs primarily through leakage or accidental spillage during its manufacture and during maintenance [3,7,9,10,11 (pp 7,40)]. The latex may contain 0.01-0.5% free monomeric chloroprene [12]. The air above the latex inside storage vessels can also be a source of worker exposure. Chloroprene vapor may remain in the tank after the latex is removed. Exposure may occur during tank entry if improper work practices are followed [12,13].

In chloroprene manufacture, workers may also be exposed to butadiene, acetylene, chlorobenzenes, calcium carbide, monovinyl acetylene, hydrogen chloride, acetic acid, dichlorobutenes, chlorine, alkyl mercaptans, alkylamines, and antioxidants; other ingredients are proprietary. The toxicity of many of these compounds is not well documented, but 1,4-dichloro-2-butene, which is also an intermediate in the manufacture of

nylon, produced local tumors after intraperitoneal (ip) or subcutaneous injections in female ICR/HA Swiss mice [14], and 3,4 dichloro-2-butene has been shown to be mutagenic in bacteria [15].

Chloroprene is used to manufacture only polychloroprene latex and neoprene rubber. The latex is used in the manufacture of some types of rubber cement. Production figures for chloroprene are not available, but the production of neoprene rubber increased from 112 million pounds in 1950 to 410 million pounds in 1974, an average production increase of about 5-6%/year. In 1974, the manufacture and use of chloroprene was reported by two companies, Du Pont and Petrotex, at four plants. NIOSH estimates that 2,500 workers are potentially exposed to chloroprene during its production and polymerization in the United States [16,17].

Historical Reports

The first study of chloroprene toxicity was reported by Von Oettingen et al [18] in 1936. Acute toxicity was determined in mice, rats, cats, rabbits, and pigeons. Exposures of mice and rats for 30-90 days to airborne chloroprene in the range of 28-98 ppm were also conducted. More detailed information is included in Animal Toxicity.

In 1942, Roubal [19] reported an investigation of the toxicologic and hygienic aspects of the Czechoslovak chloroprene rubber industry. This is believed to be the first report of human exposure. Workers involved in the washing and polymerization operations experienced loss of hair. Other workers complained of a sensation of pressure in the chest with rapid pulse, severe fatigue, and conjunctivitis and necrosis of the corneal epithelium. Albumin was reported to be present in the urine of a small

number of workers who, according to Roubal, presumably had had massive chloroprene exposure. Since blood pressure changes varied, Roubal did not believe that blood pressure change was a good indicator of the early stages of chloroprene poisoning. The exposure duration before the occurrence of symptoms was not reported. No environmental chloroprene concentrations were reported.

Nystrom [20] described a series of medical studies carried out in Swedish chloroprene plants between 1944 and 1947. These were the first and only studies to include experimental reports of human exposure to airborne chloroprene and to report a human fatality. Experimental exposure of human subjects to chloroprene at 973 ppm led to nausea and giddiness in 15 minutes in resting subjects and in 5-10 minutes in subjects performing light work. Nystrom noted anemia in pilot plant workers who were exposed at air concentrations estimated to be approximately 459 ppm. The range of concentrations of chloroprene in the air was from 56 to greater than 334 ppm in the main chloroprene plant after full operation was achieved. Nystrom stated that, in the pilot plant, air concentrations must have been much higher. Workers, especially those in the fractional distillation department, developed extreme fatigue and unbearable chest pains after exertion about 1 month after starting work. The symptoms were particularly severe by the end of the workday. Because of fatigue and severe chest pains, 90% of the workers often had great difficulty bicycling to their homes after work and had to rest repeatedly. Both pain and fatigue usually subsided by the following morning, returning during the next workday. These workers also noted changes in their personalities towards irritability and quick-tempered behavior. Contact dermatitis (25-30%) and

reversible hair loss were also noted in some workers, especially in the polymerization area, where 90% of the workers showed hair loss. Liver and kidney functions were normal; no albumin was detected in the urine. Lung function tests were normal, and 67/80 had normal lung roentgenograms, 8/80 had sinus obliteration, 2/80 had parenchymatous changes, and no data were presented for 3 workers. The basal metabolic rates of 10 workers and the electrocardiograms in 15 workers were normal. Nystrom stated that exposure at high but unspecified concentrations of chloroprene for short periods of time led to temporary unconsciousness in an unknown number of men. On regaining consciousness, the men were able to resume work immediately.

Nystrom [20] also found a single fatality resulting from occupational exposure to chloroprene in 1948. A worker entered a polymerization vessel containing chloroprene vapor (concentration unspecified) for cleaning purposes without first ventilating it. After 20-30 seconds, the man became unconscious. He was rescued within 3-4 minutes, but resuscitation attempts failed. Pulmonary edema was noted at autopsy. Fluid was also found in the larynx, trachea, and bronchi as well as in the terminal bronchioles and the parenchyma of the lungs. Microscopic examination showed marked hyperemia of the lungs and blood vessels, and large amounts of thin fluid were observed throughout the lung tissue.

In 1948, Ritter and Carter [21] related that synthetically prepared dimers of chloroprene caused rapid hair loss in rodents when applied to the skin. Cyclic dimers and short-chain polymers were prepared by refluxing chloroprene with para-tertiary-butylcatechol. No information was given on the structural nature of the dimers and polymers. Two drops of the resulting solutions were put on the backs of unspecified numbers of mice

and guinea pigs. Within 4-10 days, the hair on the skin exposed to the solutions of the cyclic dimer and of the short-chain polymer fell out. After 6 weeks, the hair had regrown. The authors concluded that, based on the experimental results and their observations that human hair loss occurred exclusively in manufacturing areas where chloroprene was polymerized, chloroprene monomer did not cause hair loss. These findings might also be explained by higher monomer concentrations in the polymerization area.

Effects on Humans

Factory workers exposed to chloroprene have been the subject of extensive study in the USSR. Few studies were found on effects of occupational exposure to chloroprene in other countries.

Sanotskii [22] quoted a study by Fomenko, Katosova, and Davtian (from an unavailable report) who investigated disturbances in spermatogenesis after 6-10 years of worker exposure to chloroprene and morphologic disturbances after 11 years of exposure. In addition, spontaneous abortion was said to occur in the wives of chloroprene workers more than three times as frequently as it did in the general population. The actual data, however, were not presented in this report. Because these observations may have resulted from air contamination with agents other than chloroprene, a detailed clinical and safety inspection was made. The results showed that the main hazard to workers was chloroprene vapor, with concentrations ranging from 1 to 7 mg/cu m (0.28 to 1.94 ppm). Ammonia, in concentrations ranging from 2 to 4 mg/cu m, was the most frequently encountered other volatile substance. Such concentrations of ammonia, however, were within

the maximum permissible concentration (MPC) of 20 mg/cu m and were not considered to be a hazard to health.

In 1967, Lejhancova [23] investigated hair loss resulting from chloroprene exposure at a rubberized fabric factory in a process employing six women. The concentration of airborne chloroprene ranged from 17 to 81 ppm (61 to 292 mg/cu m) inside the factory. Chromatographic analysis of the polychloroprene latex at the end of the study showed 3.88% free chloroprene, but no dichlorobutene or small polymers. Lejhancova mentioned that the monomeric content of the fresh latex supplies may have been much higher, since polymerization continues at room temperature during storage of the latex. A few days after receiving the latex, six female workers complained of headache, nausea, and severe fatigue. After 2 weeks, one woman began to lose her scalp hair, becoming completely bald within 4 weeks. Later, three other women lost their scalp hair, but two were unaffected.

Lejhancova [23] concluded that the loss of hair resulted from exposure to free chloroprene monomer in the polychloroprene latex and that better hygiene practices in the plant should decrease the chloroprene concentrations and, subsequently, the hair loss. After unspecified plant improvements, the women's hair grew back within 6 months.

In 1969, after the opening of a polychloroprene manufacturing plant in France, Malassis and Malassis-Jouve presented, in a section of a paper by Paulet and Malassis [24], the results of a study of a group of workers in the chloroprene industry. The authors reported a high frequency of chemical burns in 100 of 130 workers (77%) exposed to chloroprene. Conjunctivitis was also noted. Hair loss was reported in 34 of 130 workers

(26%). This occurred in the polymerization area where exposure concentrations were unknown. Sexual impotency, involving both libido and sexual dynamics, was reported by workers, but no further details were given. All such disorders disappeared after the workers were relocated. Ventilation of the plant was improved later. No deviations from normal were reported in either bound or free cholinesterase activity in blood samples collected from 54 workers segregated into 4 groups on the basis of probable exposure to chloroprene.

Avakian et al [25], from 1956 to 1958, observed and reported on the health of up to 273 persons with 7-13 years of experience working with chloroprene. No indications of the chloroprene air concentrations or the sex of the workers were given. Disorders of the cardiovascular system were stated to be of primary concern to the authors. Fifteen percent of the workers complained of heaviness in the chest, slow pulse was noted in 48%, fast pulse appeared in 19%, 6.7% showed signs of cardiac neurosis, and hypotension was observed in 15-30%. Capillary permeability was said to be significantly increased in a majority of the 136 workers tested. No frequency of occurrence of these signs and symptoms in control workers was given. Ninety-six workers were subjected to electrocardiographic examination: 27% had decreased heart rates, 33% had signs of myocardial dystrophy, and 15% showed atherosclerosis of the cardiac vessels. In a control group of mechanics (unknown number and sex), myocardial dystrophy was diagnosed in 7.3% and atherosclerosis in 4.8%. Followup examinations on the exposed workers through 1958 showed that the incidence of myocardial dystrophy increased to 39.2% and that of cardiac neurosis increased to 9.2%.

Avakian et al [25] concluded that the toxic influence of chloroprene increased with the length of exposure. Although the authors stated that there were comparatively high concentrations of chloroprene in the production areas, no actual concentrations were given. The authors mentioned the use of prophylactic measures, including periodic medical examinations, vitamin administration, vacations at health resorts, and more balanced nutrition, to increase the working capacity of the workers. The medical significance of these findings is difficult to evaluate because of the authors' imprecise description of the correlation between the abnormal conditions found in workers and cardiac neurosis and myocardial dystrophy.

Immunologic response and reactivity in chloroprene factory workers (Kirov, Armenian SSR) were the subjects of a 1965 study by Mikaelian and Frangulian [26]. Blood samples from 208 workers, said to be mostly male (number of women not given), from 25 to over 50 years of age with extended exposure to chloroprene, were examined for titer of what were called OH agglutinins and the phagocytic index. The durations and concentrations of the workers' exposures were not specified in the paper. The titer of agglutinin and the phagocytic index were determined both before and after immunization against what was described as Typhus abdominalis (perhaps *Salmonella typhosa* or *S. typhi*) and compared with the results of blood samples from 113 workers not exposed to chloroprene.

No specific method was given for determination of the titer of OH agglutinins, but the phagocytic index was determined by incubating serum with either specific (*Typhus abdominalis*) or nonspecific (*Staphylococcus aureus*) organisms [26]. One billion bacterial cells were incubated with citrated blood for 30 minutes at 37 C. Smears of the mixture were

prepared, stained, and observed microscopically. The number of phagocytized bacteria/100 leukocytes was counted, and the average number of phagocytized bacteria/leukocyte (ranging from 0.1 to greater than 10) was considered the phagocytic index.

The increase in titer against Typhus abdominalis was not marked in the exposed workers [26]. After tetravaccine vaccinations (in the United States, by definition, tetravaccine imparts immunity to typhoid, paratyphoid A and B, and cholera), the agglutinin titer did not exceed dilutions of 1:50 or 1:100 in 52% of the individuals. In unexposed workers, 89% of the vaccinated individuals had titers of 1:800 or more, and 45% had titers of 1:3,200 or more.

The phagocytic index showed a similar trend [26]. Prior to the immunizations, the index with Typhus abdominalis ranged from 0.1 to 2.0 for all workers. After vaccinations, this index ranged from 2.1 to 3.0 for only 19% of the workers; the remainder were still in the range of 0.1-2.0. Blood samples from 68 unexposed workers (60%) were in the range of 3.1-10 after immunization, while 27% ranged from 4.1 to 10. The nonspecific phagocytic index for Staphylococcus aureus was not markedly affected by the administration of tetravaccine. The authors [26] concluded that chloroprene exposure depressed the "defense mechanisms" (immune response) of humans. Since the chloroprene concentration in the plant during the study was not determined, no dose-response relationship could be established.

Another approach to studying the effect of chloroprene on human immune capacity was given by Keчек and Semerdzhian [27] in 1962. Blood samples from 39 workers in various chloroprene exposure areas of the Kirov

plant were compared with samples from 10 workers who were not exposed to chloroprene. Total proteins, total albumins, and alpha, beta, and gamma globulins were measured in the serum obtained from each worker. The protein content of each fraction was determined by precipitation with decreasing concentrations of monosubstituted potassium phosphate with subsequent determinations of the proteins in each fraction by comparison of the turbidity of the solutions with that of a calibrated turbidity standard. The authors stated that this method gave results comparable with those obtained by paper electrophoresis. There were no significant changes in total serum protein, albumin, or alpha globulin when control sera were compared with those from exposed workers; however, a significant increase in the beta globulin fraction and a significant decrease in the gamma globulin fraction were noted. The authors implied that some of the gamma globulin fractions had been converted to beta globulin, but no direct evidence for this interconversion was presented.

As part of the State Sanitary Inspection Commission's program to evaluate the Maximal Air Concentration documentation in the USSR, Mnatsakanian [1] studied the range of odor threshold for chloroprene and the effects of chloroprene on the sensitivity of the retina to light during dark adaptation. The odor threshold, based on about 700 total determinations, for 11 persons ranged from 0.11 to 0.56 ppm. The average was 0.25 ppm. The average maximal imperceptible concentration was 0.2 ppm. Three subjects (24, 29, and 30 years of age) were tested for sensitivity of their dark-adapted eyes to light. These three subjects had odor thresholds of 0.25, 0.11, and 0.14 ppm, respectively. No alteration in the sensitivity to light of the dark-adapted eyes was observed with exposure

below the individual's odor threshold. Exposure above the odor threshold decreased dark-adapted light sensitivity. The purity of the chloroprene used in this study was not reported. The neurophysiologic significance of studies of this type is not clear. The findings could indicate an effect on the innervation of the iris, on the retinal receptors, on the statistical conduction of sensory impulses in the optic nerve, or on the central mechanisms of visual perception.

Carcinogenic, mutagenic, teratogenic, and reproductive effects will be discussed in later portions of the document.

Epidemiologic Studies

Epidemiologic data available on the incidence of cancer and other effects in workers exposed to chloroprene are, again, primarily from the USSR.

Khachatryan's [28] investigation of the occurrence of skin cancer in Erevan, USSR, from 1956 to 1970, considered a total of 24,989 persons of both sexes. These people were assigned to one of five groups according to their occupational exposures. The group "chloroprene workers" consisted of 684 employees involved in the production of chloroprene and polychloroprene latex and rubber. The group "chloroprene derivative workers" comprised 2,250 employees, mainly from shoe factories, with exposure to polychloroprene cement. There was thus a total of 2,934 persons with some exposure to chloroprene. The group "chemical workers" included 4,780 employees with no chloroprene exposure but with prolonged contact with lacquers, acetone, benzene, gasoline, and acids (truck drivers and cabinet makers). The last two groups, 8,755 nonchemical workers and 8,520

nonindustrial workers, served as controls. (The text of the article referred to the fourth group as chemical workers, but the accompanying table referred to them as nonchemical.)

Khachatrian [28] diagnosed skin cancer in 137 people from the total of 24,989 persons studied. The exact numbers, percentages of total workers, average ages, and work experiences of the cancer patients in the five groups of workers are listed in Table III-1. Frequencies have been recalculated from the author's data and are also presented in the table.

TABLE III-1

OCCURRENCE OF SKIN CANCER IN RUSSIAN WORKERS
FROM 1956 TO 1970

	Chloroprene Workers	Chloroprene Derivative Workers	Chemical Workers	Nonchemical Workers	Nonindustrial Workers
No. examined	684	2,250	4,780	8,755	8,520
No. of cases	21	38	32	35	11
Reported %	3.00	1.60	0.66	0.40	0.12
Corrected %*	3.07	1.69	0.67	0.40	0.13
Average age of patients	59.6	59.1	64.4	68.9	72.05
Average years of employment	9.5	8.7	13.8	15.4	16.3

*Recalculated from author's data

Adapted from reference 28

The greatest prevalence of skin cancer, 3%, was found in the chloroprene workers. In workers from the nonchemical and nonindustrial situations, the frequencies of skin cancer were 0.40% and 0.12%, respectively. Recalculation of the latter frequency from the data presented in the paper gives a value of 0.13%. Both groups were regarded as controls, but the calculations were based only on the nonindustrial workers. Corrected frequencies and ratios are given below in parentheses after those presented by Khachatryan. Khachatryan reported that, in those workers with extended (undefined) chloroprene contact during manufacture, the frequency of skin cancer was stated to have increased 25-fold (recalculated value 23.1); of workers in contact with chloroprene derivatives (latices, adhesives, and rubber), there was a stated increase of 13.3-fold (13.1). When the chemical workers were considered, the frequency of skin cancer increased by a factor of 5.5 (5.2). This was based on a frequency of 0.12% (0.13%) in the nonindustrial workers.

The neoplasms in the three control populations were found mostly on the face, neck, and hands, and they often occurred at the sites of various birth defects on the skin (moles and birthmarks) [28]. In the case of workers with chloroprene contact, the neoplasms were most frequently located on the skin of the nose and ears. It was stated that in 90% \pm 7% of the workers with tumors, the neoplasms had been preceded by skin changes characterized as chronic dystrophic or inflammatory skin conditions, such as eczema, cracks, and dyskeratoses. The progression of skin lesions in chemical workers was similar to that observed in chloroprene workers. No further information on sex, prior work histories, or durations of exposure was given in the paper. The concentrations of chloroprene and of any other

toxic compounds in the workplace were not presented.

Khachatryan [28] concluded that chloroprene was a carcinogen or cocarcinogen for human skin. The author felt that the observed chronic dystrophic and inflammatory skin ailments, which usually preceded the skin cancer, had a role in the development of eventual neoplasms.

In a second study, Khachatryan [29] observed the prevalence of lung cancer in 19,979 workers in the city of Erevan, USSR. Although there were four groups, rather than five as in the previous paper, the assignment of the workers to groups was similar, except that no distinction was made between workers exposed to chloroprene and those using only chloroprene derivatives. The total number of workers with occupational chloroprene exposure and the number of chemical workers with no chloroprene exposure (4,780) were the same as in the previous study. Chemical workers without chloroprene exposure were defined as those with any exposure to chemicals other than chloroprene (truck drivers, polishers, cabinet workers, painters, gas station attendants, and typesetters). The numbers of nonindustrial (6,045 professionals) and nonchemical (6,220) workers were smaller than those used in the skin cancer epidemiologic study [28]. A total of 87 persons suffering from lung cancer were identified (82 men and 5 women), 16 of whom had formerly been workers in a chromium plant. The individual's career progression, age at which the individual began working, work experience, evidence of contagious lung disease (before and after starting work), and smoking habits were all considered in the study, but detailed information was not provided in the paper. There was no description of the specific types of lung cancer.

Sixty-six (76%) of the workers with lung cancer also suffered from chronic bronchitis, three (3.4%) had tuberculosis, and four (4.5%) had pneumonia [29]. Fifty-seven (66%) of the cancer patients were heavy or long-term smokers. The lung cancer data are listed in Table III-2 [29].

TABLE III-2

OCCURRENCE OF LUNG CANCER IN RUSSIAN WORKERS
FROM 1956 TO 1970

	Chloroprene Workers*	Chemical Workers	Nonchemical Workers	Nonindustrial Workers
No. examined	2,934	4,780	6,045	6,220
No. of cases	34	22	11	4
Reported %	1.24	0.46	0.8	0.064
Corrected %**	1.16	0.46	0.18	0.064
Average age of patients	44.5	54.9	59.3	60.2
Average years of employment	8.7	10.3	14.9	18.5

*Includes chloroprene derivative workers

**Recalculated from author's data

Adapted from reference 29

The methods used for diagnosis were not discussed in the paper. There are inconsistencies between the table and the text regarding percentage of cancer and the number of cancers tabulated as occurring in chloroprene plant workers (18) plus workers from shoe factories (17). The total number of lung cancers in workers exposed to chloroprene was stated to be 34, but

from the percentage stated in the text, it appears to be based on neither 34 nor 35 patients, but on 36 cases of cancer (2,934 x 1.24%). The incidence of lung cancer among workers with extended contact with chloroprene and its derivatives was stated to be 1.24% (actually 1.16%); the average age of these stricken workers was 44.5 years [29].

Khachatrian [29] described 16 additional cases of lung cancer in former maintenance workers, cleaning women, laundry workers, and chemical workers from the plant where chromium compounds had been used in plant processes. The total number of workers in the plant was not given, but there was stated to be a 4.2% frequency of lung cancer among them. All of the 16 former chromium plant workers were found to have perforated nasal septa, which had developed during their employment.

Khachatrian [29] concluded that extended contact with chloroprene and its derivatives led to significant increases in primary lung cancer. In addition, it was stated that chloroprene was as carcinogenic as chromium compounds. The author reported that the chemical workers without chloroprene exposure had a lung cancer frequency 0.37 times that of workers exposed to chloroprene. From the data in Table III-2, the corrected ratio is calculated to be 0.40. The author stated that the frequency in nonchemical workers was 0.16 times, and in nonindustrial workers it was 0.05 times (actually 0.06), that in workers exposed to chloroprene.

It is very difficult to assess the actual risk of lung or skin cancer for the Russian workers exposed to chloroprene. Savelev, Deputy Chief of the Administration of Foreign Relations of the Soviet Ministry of Health [8] has stated in a letter that a panel of Russian experts examined Khachatrian's investigations and found errors in her methods that led to

incorrect conclusions. He stated that the Ministry of Health planned a formal statement on this matter, but none has been forthcoming to date.

Pell [30] recently submitted to NIOSH summaries of preliminary reports of an epidemiologic survey of cancer mortality in male employees engaged in the manufacture of chloroprene and its polymerization to neoprene rubber. There were two study populations, one from the Louisville Works in Kentucky, (1,661 persons) and one from the Chambers Works in Deepwater, New Jersey (243 persons). The Louisville group consisted of those persons on the wage roll who were working at the plant on June 30, 1957. Chloroprene production began at Louisville in 1942, but the routine recording of deaths through life insurance claims did not begin until 1956. The records of the Louisville group were assessed through December 31, 1974. Workers in the Deepwater cohort were employed in the neoprene rubber manufacturing area between 1931 and 1948, and mortality data were analyzed for the period from 1956 through 1974.

Three groups from the 1,661 workers in Louisville were considered to have the highest exposure to chloroprene: 263 maintenance mechanics, 458 chemical operators, and 124 workers in other high-exposure occupations [30]. All persons in the cohort who died during the study period were identified by (1) plant personnel and medical records, (2) the corporate medical division's files of deceased employees and retirees, and (3) a followup on 240 employees missing from these two sources because of short terms of employment. Nineteen of these employees had yet to be traced at the time of reporting. Women (84 at Louisville and 19 at Deepwater) were excluded from the overall study because of little or no exposure at both plants.

The observed number of deaths for each type of cancer was compared with the number expected based on death rates for the various cancers in US men and in male employees and retirees of the company [30]. In the Louisville study, 18 deaths were caused by cancer of the respiratory system (17.1 expected based on US statistics), and 16 of these were the result of lung cancer. Four lung cancer deaths occurred in maintenance mechanics (3.8 expected), three in chemical operators (3.2 expected), and two in other high-exposure occupations (1.6 expected). The exact nature of these job classifications was not indicated. The differences between the mortalities due to lung cancer in the worker population and in the US male population were judged to be insignificant. Incidence of skin cancer was not considered.

Four maintenance mechanics with lung cancer were still alive and were so identified at the end of the study [30]. If these four cases are added to the four deaths due to lung cancer in the same group of workers, the total of eight cases of lung cancer in the maintenance mechanics would account for 40% of the reported cases of lung cancer; however, maintenance mechanics constituted only 17% of the population studied. Pell felt that this excess risk of lung cancer might "be the result of... [another] chemical carcinogen in the plant, ...cigarette smoking [smoking at work is permitted in this group], ...or a fortuitously high concentration of [cancer] cases." Seven of the eight affected maintenance mechanics were known cigarette smokers.

At Deepwater, three deaths from lung cancer were observed (3.5 expected) [30]. None of the three who died was a maintenance mechanic, but one mechanic who died from myocardial infarction had lung cancer. The

mortality from bladder cancer was 10 times the expected value (3 observed, 0.3 expected); however, these workers had also had significant exposure to beta-naphthylamine, a known bladder carcinogen to which these deaths were attributed.

The reports by Khachatryan [28,29] suggest an excess of skin and lung cancer in chloroprene-exposed workers, while the report by Pell [30] concludes that there was no significant excess of cancer in chloroprene workers except in maintenance mechanics. However, limitations in methodology and study design of these investigations preclude an assessment of the carcinogenic risk.

None of these epidemiologic studies give adequate consideration to environmental concentrations, job classification, intensity or duration of exposure, or latency--all factors known to influence the risk of cancer. In each of these studies, the investigator did not analyze the data separately for chloroprene polymerization workers. (The greatest risk in the vinyl chloride industry was in polymerization workers, not in monomer production workers.) The Pell [30] and Khachatryan [28,29] studies do not mention the criteria by which the cancers were diagnosed, nor are the cell types for skin and lung cancer indicated.

In the Khachatryan reports [28,29], adjustments for age and sex also are not mentioned. The difference of 40-50 years between mean age of cancer patients and mean length of employment for these patients suggests that total employment histories appear to be lacking.

In the Pell study [30], past information indicates that some causes of death indicated on the death certificates were classified for the chloroprene-exposed workers, but not for the control group. This procedure

may have introduced bias. Pell used industrial controls that were composed of subsets of workers exposed to multiple industrial agents known or suspected to be carcinogenic. Such an approach underestimates the true carcinogenic risk. In the Pell report, cases of cancer were identified through life insurance claims. Since skin cancer may be a nonfatal disease, this method would only identify fatal skin cancer cases and result in an underestimate of the skin cancer risk.

Pell [30] also suggests an excessive risk of lung cancer among maintenance mechanics, a group expected to have high exposure to chloroprene. However, the ages of the lung cancer patients among the maintenance mechanics are not compared with those of the lung cancer patients in the other study groups. Thus, definitive evaluation of this observation of pulmonary cancer is not possible, although the observation does suggest an excess of lung cancer in maintenance mechanics exposed to chloroprene.

Two human studies carried out between 1950 and 1954 in the Kirov chloroprene plant in Soviet Armenia were described by Mkhitarian [31,32]. In the first of these, 110 workers (sex unspecified) were studied. In the second study [32], data for an additional four workers were considered. In the following discussion, whenever a range of numbers of persons is given, the smaller number refers to the earlier study [31] and the larger to the later one [32]. Three groups of workers were selected according to the shop they worked in, and five professions were identified: shop A (highest exposure), where 30-31 cleaners and loaders worked; shop B (intermediate exposure concentration), where 33-35 equipment operators worked; and shop C (negligible chloroprene exposures), where 18-19 persons worked as rollers

and packers. It was not stated directly that these workers handled the latex sheet. The actual exposure concentrations were not given. Of the 110-114 workers considered in the studies, data were presented for 81-85 of them, the rest apparently having been control groups from other shops.

Work experience was broken down in the following manner: 28 workers had more than 10 years' service, 20 had between 5 and 10 years' service, and 33-37 had 5 years' service or less [31,32]. No further breakdown into job groupings was done. Blood samples from the workers were tested for the following: glucose, cholesterol, total protein, albumin, total globulins, glutathione (oxidized and reduced), fibrinogen, carbonic anhydrase, catalase, calcium, chloride, and reserve alkalinity (the tendency toward acidosis). The assays used were not clearly defined. Blood pressure also was measured. The author stated that exposure to chloroprene led to hypoglycemia, hypocholesterolemia, decreased carbonic anhydrase activity, decreased reserve alkalinity, hypotension, and decreased blood clotting time in some or all of the worker groups. Data supporting the last two statements were not presented. There was no significant change in catalase activity, total globulins, or total glutathione. Increases were noted in total protein, albumin, calcium, oxidized glutathione, fibrinogen, and chloride. No statistical considerations were presented, but the author stated that most data had been statistically processed and were reliable. No data from control subjects were given, but normal values for several of the quantities measured were stated. Concentrations and exposure durations for individuals were also not presented.

In 1964, Mnatsakanian and Mushegian [33] studied the influence of chloroprene on porphyrin metabolism in Armenian children living near the

Kirov plant. Three groups of children of both sexes between the ages of 5 and 8 years were selected from schools located at various distances from the chloroprene plant. Average concentrations of chloroprene in the air during May and September ranged from 0.08 to 0.13, from 0.07 to 0.12, and from 0.04 to 0.05 ppm in schools located at distances of 100, 500, and 700 meters from the plant, respectively. The May through September values were averages of 10 daily assays by microcombustion [34]. Between May and September, urine was collected during each schoolday (5-6 hours), and total coproporphyrin was measured spectrophotometrically by the method of Gusev and Smirnov [35]. The authors [33] stated that the quantity of coproporphyrin varied little according to age and sex, so that the data were analyzed as functions of the distance from the chloroprene source and the air concentration, with no further breakdown.

In the first school (average exposure range of 0.08-0.13 ppm of chloroprene), 42 children excreted an average of $6.36 \pm 0.46 \mu\text{g}$ of coproporphyrin [33]. In 99 children in the second school, the average coproporphyrin excretion was $5.51 \pm 0.36 \mu\text{g}$ (average exposure range of 0.07-0.12 ppm). In the third school, 105 students exposed to chloroprene at 0.04-0.05 ppm excreted $4.11 \pm 0.23 \mu\text{g}$ of coproporphyrin. Whether these values were related to daily excretion or excretion for each liter of urine was not stated. The authors stated that the increase in coproporphyrin excretion was statistically significant and attributed it to the increasing air concentration of chloroprene, but no quantitative statistical reliance was assigned. The normal range of urinary coproporphyrin in children is 0-80 $\mu\text{g}/24$ hours [36], and all the above data are within this range.

Mnatsakanian [37] measured urinary 17-ketosteroids as an evaluation of adrenal function in the same groups of children during the same time period as in the study by Mnatsakanian and Mushegian [33]. Five hundred urine specimens were collected over a 5- to 6-hour period and the volumes recorded. The concentration of 17-ketosteroids in each sample was determined spectrophotometrically by the method of Uvarovskaia [38]. Steroid content was reported as total milligrams/urine sample. The control value was 0.73 ± 0.045 mg. At chloroprene concentrations in the air of 0.07-0.12 and 0.08-0.13 ppm, urinary 17-ketosteroid excretions were observed to be 0.919 ± 0.086 and 1.021 ± 0.086 mg, respectively. Total urine volume for each child was not reported. From these studies, the author claimed a statistically significant increase in urine volume and in 17-ketosteroid excretion as a function of the chloroprene concentration. He concluded that there was an effect on adrenal function in children at chloroprene concentrations of about 0.11 ppm. The normal excretion of 17-ketosteroids for children under 12 years old is less than 5 mg in a 24-hour period [36]. All the observed values are within the normal range.

Vanuni [39,40] investigated the effect of chloroprene in the air on human milk production near the Kirov chloroprene works in Erevan, Armenia. Four groups of 30 pregnant women each were examined: group I worked in the plant (25.94 \pm 0.34 years old, 4.07 \pm 0.47 years of working exposure), group II lived 500 meters distant, group III lived in a village 1,500 meters distant, and group IV lived 3,000 meters from the plant. Data on average age and exposure of groups II, III, and IV were not specified. On the 8th day after parturition, a milk sample was taken, and total protein and individual amino acid composition were measured by paper chromatography

(method not given in detail). Two control groups of 25 women each, one from a village 25 km distant and the other from the northern portion of the city of Erevan (distance not specified), were selected and examined in a similar manner.

A significant increase was noted in total milk protein concentration as a function of distance from the plant [39,40]. Milk protein concentrations from mothers working in the plant were 964 ± 9 mg/100 ml ($P < 0.001$). Total protein concentrations were $1,049 \pm 15$ mg/100 ml ($P < 0.001$), $1,074 \pm 24$ mg/100 ml ($P < 0.01$), and $1,140 \pm 24$ mg/100 ml ($P < 0.001$) for groups at 500, 1,500, and 3,000 meters, respectively. Control concentrations of milk protein averaged $1,321 \pm 22$ mg/100 ml in women from the northern section of the city and $1,289 \pm 17$ mg/100 ml for mothers 25 km away. Mothers from the plant had milk protein concentrations that were 73% of those of the Erevan controls.

Concentrations of some individual amino acids in milk were significantly decreased when samples from mothers who worked in the plant were compared with those from the two control groups [39,40]. Cysteine concentrations were 90% of the controls ($P < 0.05$), lysine was 66.3% ($P < 0.001$), arginine was 58.8% ($P < 0.001$), valine plus methionine was 75.7% ($P < 0.001$), and leucine plus isoleucine was 93.0% of the controls ($P < 0.05$). The decrease in lysine and valine plus methionine appeared to be distance dependent, whereas decreases in cysteine, arginine, and leucine plus isoleucine were not.

Since the mothers had similar diets and lived under the same climatic conditions, Vanuni [39,40] concluded that depression of the quantity of amino acids in the milk, and hence of its nutritional value, apparently

depends on the depressed lactation function of the mammary glands due to chloroprene intoxication. This argument appears to be spurious, since depressed lactation reduces milk volume (quantity) but does not necessarily affect the nutritional value (quality). Chloroprene was not reported to have been found in the mothers' milk, and the concentration of chloroprene in the plant air was not reported. The chloroprene concentrations at the various distances from the plant were also not indicated. Therefore, a precise dose-reponse relationship cannot be determined.

In 1976, Volkova et al [41] surveyed conditions in a Soviet plant manufacturing rubber gloves from polychloroprene latex. A total of 65 workers were examined: 43 had less than 5 years of exposure to chloroprene latex, 15 had worked for from 10 to 20 years, and the exposures of the other 7 are not clear. Most (no number specified) of the 65 persons worked as dippers. This job was not described in any detail. The concentration of chloroprene in the air in the dipping area varied between 0.8 and 1.95 ppm. The authors stated that they observed an increase in the frequency of complaints of fatigue, headache, and chest pain with increasing time of service. No quantitative data were presented. Nineteen percent of the workers had chronic tonsillitis (the control frequency was not presented). Of the women in the study group, 47% (the total number of women was not given) had menstrual disorders versus 10% in a control population. The major menstrual disorder observed was decreased blood flow, and the frequency of the disorder increased with length of service.

Volkova et al [41] concluded that concentrations of chloroprene near the maximum allowed in air in the USSR at that time (0.56 ppm) adversely affected the workers' health. However, in an operation using

polychloroprene latex, there is concomitant exposure to many substances besides chloroprene [42]. The significance of the symptoms described is difficult to assign. Fatigue and chest pain have usually been reported only at much higher concentrations [20].

Recently, cytogenetic analysis of lymphocytes from the blood of persons working in chloroprene manufacture was carried out by Katosova [43] in the USSR. Of three groups of employees with chloroprene exposure studied, subjects in group A were also exposed to chlorine, acetylene, ammonia, mercaptans, and monovinyl acetylene; those in group B were exposed to essentially pure chloroprene (mercaptan and ammonia below the MPC); and those in group C were exposed to chloroprene only. Since no significant differences between the percentages of chromosomal aberrations in the exposed groups were observed, the data from the three groups were combined. Blood samples were taken from 18 healthy workers (13 men and 5 women), and lymphocytes were cultured. The lymphocyte cultures were coded, and all available metaphase cells that met certain unstated requirements were analyzed for aberrations and gaps. Blood samples from nine workers not exposed to chloroprene were used to obtain control lymphocytes. The average air concentration of chloroprene was 5 ppm (nine times the 1975 USSR standard). Data presented for each examined worker included age, sex, number of cells in metaphase studied, and the frequencies of aberrations and gaps. The author stated that the maximum frequencies of cells in metaphase with aberrations were observed in the blood cells of cleaners, manual laborers, and loaders, but no breakdown by occupation was shown in the tabular data presented. Chromosomal aberrations were mainly paired

fragments, while chromatid-type aberrations (68% of total aberrations) were individual fragments.

There was no relationship between the frequency of aberrations and the number of years of service, but the average frequency of aberrations in the occupationally exposed group was $4.77 \pm 0.57\%$, versus $0.65 \pm 0.56\%$ in the controls ($P < 0.001$) [43]. The frequency of cells in metaphase with gaps was also significantly ($P < 0.01$) higher in the exposed group, $3.71 \pm 0.59\%$ versus $1.14 \pm 0.43\%$. The author concluded that, since the number of chromosomal aberrations in the workers exposed to chloroprene was significantly increased in comparison with both that for the control group and that reported for spontaneous change (1.6%), the cytogenetic effect was probably related to the influence of chloroprene. However, the author suggested that further experimental studies were necessary because this study did not demonstrate directly that chloroprene was mutagenic.

In 1975, further study of chromosomal aberrations in lymphocytes from workers exposed to chloroprene was reported by Bochkov (written communication, March 1976) at an International Symposium on New Developments in Mutagenicity Testing. Control subjects (437) had a mean of 1.19% of chromosomal aberrations in lymphocytes, whereas 57 workers exposed to chloroprene had a mean of 2.90%. No measures of variability in these two populations were given, so that the significance of the differences between these two percentages cannot be judged.

In 1976, Volkova et al [41], as part of a survey of working conditions in a Soviet polychloroprene rubber glove manufacturing plant, studied 20 women, 19-23 years old, with 2-4 years of service. These women worked in the dipping area, where the chloroprene air concentration varied

between 0.8 and 1.95 ppm. They had blood pressures and olfactory sensitivities below normal and short attention spans. In 16 of 20 subjects, the frequency of chromosomal aberrations in lymphocytes was greater than normal (1.5-9%). The average frequency of occurrence of aberrant cells in the blood of exposed women, $3.49 \pm 0.51\%$, was significantly higher than that reported by Bochkov et al [44] in 1972, $1.19 \pm 0.06\%$. The authors concluded that these cytogenetic changes indicated that chloroprene at concentrations of 0.8-1.95 ppm had mutagenic properties. Since there are other compounds emitted by Russian polychloroprene latex besides chloroprene, eg, ammonia, dodecylmercaptan, and methacrylate [42], the study did not demonstrate conclusively that chloroprene was mutagenic. Data on the control group were gathered from previously reported studies [44] that were not conducted under similar conditions.

Fomenko et al [45] stated that, although cytogenetic analysis of blood cultures of workers is a promising technique for detecting occupationally induced chromosomal aberrations, the interpretation of results from such studies is difficult because of the many other environmental factors in and around the plant.

In 1965, Gasparian and Arutiunian [46] reported on chloroprene-induced changes in the electroencephalographs (EEG's) of 70 workers involved in the production of chloroprene. Twenty persons with no chloroprene exposure were studied as controls. The age, sex, work history, location, and chloroprene exposure of each worker were not presented. The authors did state, however, that young and middle-aged men with 5-15 years of experience predominated in the occupationally exposed group. The

authors stated that chloroprene caused a sense of drunkenness, sleepiness, suppression of memory, dizziness, and increased reflex excitability. Early in a series of repeated occupational exposures, toxic neurasthenia was evident. In later stages, encephalopathy with epileptiform seizures may have occurred.

The authors [46] stated that chloroprene exposure for 5-15 years led to five different types of abnormal EEG's. The three most common of these types were (1) deflections of low voltage and frequency, (2) deflections of low frequency but long duration (delta-type), and (3) inconsistent wave patterns with alternating alpha-, beta-, and delta-activities and occasional spikes. In workers with comparatively short durations of exposure to chloroprene, the predominant EEG changes were disruption of the alpha-rhythm or predominance of beta- or delta-activity. When the exposed workers were subjected to a flashing light during recording of the EEG, 82.8% (11.4% high, 14.3% moderate, 57.1% low) reacted, while 17.2% were completely unreactive. In the control group, 100% of the subjects reacted (50% high, 40% moderate, 10% low) to the flashing light, and none were completely unreactive. Of the workers, 78.6% did not synchronize with the frequency of the visual stimulus or only synchronized at comparatively low frequencies, whereas only 25% in the control group failed to synchronize. The authors concluded that the EEG changes induced by chloroprene exposure may have been either functional or partially organic in nature, and that the balance between functional and organic abnormalities of the brain was related to the length of contact of the workers with chloroprene.

The significance of these data [46] is difficult to assess. Chloroprene can cause CNS effects, but it was not convincingly demonstrated

in this paper. Comparison of the EEG's taken on the workers with similar recordings made prior to exposure would have been much more meaningful. The methods of recording and analysis were not described in sufficient detail in the text.

Animal Toxicity

The general toxicity of chloroprene in various species of animals has been evaluated by several routes of exposure. Effects of chloroprene exposure on reproduction have been studied extensively in rats and mice. A smaller number of studies has been found on the carcinogenic and mutagenic effects of chloroprene exposure in these animals. Bacteria and *Drosophila* have also been used to evaluate the mutagenicity of chloroprene.

In 1936, Von Oettingen et al [18] first examined chloroprene toxicity and the resulting adverse effects. Their report described a large number of studies, but involved a small number of animals, thus making statistical evaluation difficult. The minimum fatal oral dose, resulting in (by the authors' definition) 70-100% deaths, was determined for chloroprene using a total of 39 rats of unspecified strain, 3-15 rats at each dose. At chloroprene doses of 0.4 ml/rat or greater (body weight not given), 75% or more of the rats died. Lung edema, internal bleeding, liver necrosis, and gastric inflammation were found upon autopsy. The investigators did not report the relationship between toxic signs and specific dose. Doses/unit of body weight cannot be calculated, because the latter values were not given.

The minimum fatal concentration (defined as the concentration killing at least 70% of a group of exposed animals) for mice via inhalation for 1

hour was 278-834 ppm [18]. In another experiment, mice, rats, cats, and rabbits were exposed to chloroprene at varying concentrations in air from 40 to 43,800 mg/cu m for 8 hours. At each individual chloroprene concentration, three to nine mice, two to four rats, one cat, and one rabbit were exposed. The minimum fatal concentrations for these animals were 167 ppm for mice, 4,170-5,860 ppm for rats, 695 ppm for cats, and 2,085 ppm for rabbits.

Von Oettingen et al [18] also investigated the effect of nutritional states on susceptibility to chloroprene and skin toxicity. Three fed rats were exposed to chloroprene at an air concentration of 3,030 ppm for 8 hours. This exposure was not lethal. A second group of three rats was starved for 120 hours prior to exposure at 3,030 ppm for 8 hours. Two of these rats died on the day of exposure and the third on the following day. Similar results were observed when two rats, starved for 24 hours, were exposed to concentrations of chloroprene in the air of 4,114 ppm. Both fed and starved rats were equally susceptible to chloroprene at concentrations of 5,778 ppm (20,800 mg/cu m).

Skin-painting studies were described in which 0.5 ml of chloroprene was applied to the unshaved backs of seven rats for 1 week [18]. The rats then had the hair removed from their backs with barium sulfide and were rested for 2 weeks. After that, a dose of 1.5 ml of chloroprene was applied daily to the bare skin for up to 55 days. Administration of chloroprene to one of the seven experimental rats was discontinued on day 49. After each daily application of chloroprene, the rats showed some signs of local irritation and later developed a state of depression that continued for about 2 hours.

After the higher dose of chloroprene had been applied to their skin for about 2 weeks, the exposed rats gained weight less rapidly than the controls [18]. The rat that had the chloroprene application terminated on the 49th day regained practically all its deficit of gain of weight by the 71st day. Four of the six rats that had applications of chloroprene up to the 55th day regained some of their deficit of gain of weight by the 71st day, one continued to lose weight, and the remaining rat maintained an approximately constant body weight from day 55 to day 71.

Three rats were killed for examination on day 74. The skin of all the experimental rats was normal in structure, although the hair shafts appeared to have been dissolved partially by the chloroprene. The internal organs were normal in gross appearance, but there were mild nephroses, hyperemic spleens, and slight degeneration and calcification of the testes. The livers of two rats showed signs of scattered hydropic degeneration and lysis of the nuclei of the hepatocytes.

The authors [18] concluded that chloroprene was a toxic material that should be handled with great caution, that contamination of the skin should be avoided, and that inhalation of the vapor at concentrations as low as 83 ppm could cause toxic symptoms. However, adverse reproductive effects in male mice were observed below this level and are discussed further in part (c) of this section, Teratogenicity and Effects on Reproduction. These studies are difficult to evaluate quantitatively because the number of animals in each experiment was small and the authors did not report the purity of the chloroprene.

Roubal [19], in 1942, conducted experiments on five cats, five rabbits, and one dog that were administered chloroprene by inhalation,

injection, or skin application. In one experiment, a single cat (2.6 kg) was given a 5-cc dose of chloroprene subcutaneously. Respiratory changes were noted within a few minutes; after about 0.5 hour, breathing stopped. Blood pressure, after an initial increase, dropped gradually until the heart stopped. The total elapsed time between injection and heart stoppage was 41 minutes. A second cat (2.6 kg) was anesthetized and made to inhale chloroprene vapor for 7.5 minutes through a mask saturated with 10 cc of the liquid. Irregularity of breathing was observed at first, but, after 7 minutes, respiration returned to normal. Blood pressure initially rose and then fell rapidly after an additional 5 cc of chloroprene were applied to the mask. The mask was left in place until death occurred. The total time elapsing until death was not given.

A rabbit of unspecified strain (2.3 kg) was injected subcutaneously with distilled chloroprene at a dose of 1 cc. Although it died after 20 hours, Roubal [19] found no physical changes in the rabbit after the injection. Another rabbit (2.7 kg) received four separate subcutaneous injections of chloroprene at a dose of 1 cc on days 1, 5, 13, and 27. The rabbit died 26 hours after the last injection.

The unshaven skin of a dog was painted daily with chloroprene on an area 10 x 10 cm for 12 days [19]. Hair fell out of the painted area for 3 days after the application, leaving the area bare. Twenty days after the start of hair loss and 8 days after the last application of chloroprene, hair was observed to be growing back.

An experiment was also conducted by Roubal [19] with a cat exposed to chloroprene in an inhalation chamber. Twice-distilled chloroprene was administered at an unspecified concentration and duration of time. Loss of

muscle coordination developed first, followed by difficulty in breathing. The cat died 6 weeks later. On post-mortem examination, Roubal [19] observed the following in one cat and in all rabbits: edema, degenerative changes in the liver, some kidney and adrenal tissue degeneration, and hair loss.

Nystrom [20] presented a comprehensive study of chloroprene toxicity carried out between 1944 and 1948. The author examined the differences in toxicity between pure, freshly distilled chloroprene and oxidized material stabilized against polymerization with pyrocatechol but exposed to the air for several days. Using 280 rats, strain and sex not specified, Nystrom calculated the LD50's after subcutaneous administration to be 0.002 ml/g of body weight (1,916 mg/kg) for pure chloroprene and 0.0005 ml/g of body weight for the oxidized material, a fourfold difference. Twenty rats were exposed at each of seven doses. The mean survival time was stated to be distinctly shorter for animals exposed to oxidized chloroprene than for those exposed at similar doses of pure material. It was stated that the lungs showed a greater extent of hyperemia and edema when rats were administered the oxidized chloroprene above the LD50. Administration of similar doses of pure chloroprene resulted in less extensive changes. This was the first report to describe and examine the two types of chloroprene. The author made no statements on the chemical nature of the oxidized chloroprene.

Exposure of 10 rats to chloroprene at air concentrations of 334 ppm for 8 hours each day for 5 months resulted in the deaths of half the rats by the end of the 13th week of exposure [20]. This exposure led to significant decreases in body weight, red blood cell count, and hemoglobin

concentrations, but blood leukocyte levels increased. The rats ate and drank little during the first 10-14 days of the exposure, but thereafter ate and drank about as much as the controls. Despite this increased appetite and thirst, a continuous loss of weight occurred throughout the exposure. Statistical analysis of these changes is not possible, since only mean values were given. Exposure of a second group of 10 rats at a chloroprene concentration of 56 ppm for 8 hours each day for 5 months resulted in no deaths. No changes were observed in body weight and red blood cell, leukocyte, or hemoglobin levels in these rats. Changes observed at autopsy were described by the author as "inconsiderable."

Nystrom [20], in an attempt to delineate physiologic changes at unspecified "high" concentrations of oxidized chloroprene, measured the volume of plasma in the blood, the oxygen content and oxygen capacity of the blood, and blood coagulation time; both rats and rabbits were used. After 20 minutes of inhalation of air bubbled through chloroprene, Nystrom observed decreases in blood plasma content in 10 rats, $55.8\% \pm 0.77$ before exposure versus $49.3\% \pm 0.42$ after exposure. After 30 minutes of exposure, the mean coagulation time of the blood in 40 rats was reduced, 2.36 minutes before exposure versus 1.67 minutes after exposure. The mean value of the ratios of the coagulation times after exposure to those before exposure was 0.738 ± 0.018 . After unspecified exposures to chloroprene, arterial blood of 15 rats showed a mean decrease of 17% in oxygen content, and that of 6 rabbits showed mean decreases of 8.3% in oxygen content and 10.1% in oxygen capacity.

A striking finding in this series of experiments with rats is that from the changes in the percent of plasma in whole blood, the blood of a

rat can be calculated to lose about 1 g of plasma, and the weights of the lungs of exposed and unexposed rats indicated that exposed lungs could gain up to 1.25 g of fluid. Nystrom suggested, therefore, that transudation of plasma from pulmonary capillaries explains both the increased concentration of the blood and the pulmonary edema found after heavy exposures to oxidized chloroprene. The increase in weight of the lungs after exposure of the rat to oxidized chloroprene was not reproduced by exposure to unoxidized chloroprene. No comparison of the effects of oxidized and unoxidized chloroprene on the percent of plasma in whole blood was made.

In 1969, Paulet and Malassis [24] investigated chloroprene toxicity in Wistar rats. Rats of unspecified sex (10 at each dose) were injected ip with chloroprene in an unspecified type of polyethylene glycol at 300, 500, 800, 1,000, 1,200, or 1,500 mg/kg. The LD50 was reported to be 520 mg/kg.

In 1971, Asmangulian and Badalian [47] studied the oral toxicity of chloroprene to rats and mice. Sixty white mice (20-24 g) of unspecified strain and sex were given chloroprene in sunflower oil at single oral doses (10 mice/dose) of 50, 100, 200, 300, 400, or 500 mg/kg. The LD50 was reported to be 260 mg/kg. A total of 54 white rats of unspecified sex and strain (180-200 g) were also given single oral doses of chloroprene in sunflower oil; the actual amounts were not specified. The LD50 was reported to be 251 mg/kg. The authors [47] stated that acute (single-dose) poisoning was characterized by signs of CNS depression; the animals were listless and sluggish. After 2 weeks of recovery, no abnormal behavior was observed in surviving animals. The criteria for this were not discussed. Autopsy of dead animals showed vascular congestion and edema in the lungs, liver, brain, spleen, and epicardial region. The stomach showed signs of

inflammation, and myocardial degeneration was evident.

A second group of rats (number and sex unknown) was exposed to chloroprene for 5 months at a daily oral dose of 15 mg/kg [47]. Although this is cumulatively over four times the LD100 (400 mg/kg for rats and 500 mg/kg for mice), none of these animals died. No information was presented on possible sublethal toxic effects. The authors concluded that chloroprene was a strongly toxic substance but not a cumulative poison by the oral route.

Jaeger et al [48] have reported that single 4-hour exposures to concentrations of 500, 1,000, or 2,000 ppm of airborne chloroprene did not cause an elevation of the activity of alanine alpha-ketoglutarate transaminase in the serum of fed rats, but did have this action in rats fasted for about 18 hours before exposure and caused death in the fasted rats exposed at each of these concentrations. The difference between the responses of fed and fasted rats exposed to chloroprene vapor disappeared at a concentration of 10,000 ppm. The hepatotoxic effect of chloroprene, evidenced by an increase in the activity of alanine alpha-ketoglutarate transaminase in the serum, increased progressively from 12 to 24 hours after exposure. The difference between fasted and fed rats was thought to be related to the lower concentrations of glutathione found in the liver of the fasted rats.

(a) Carcinogenicity

Khachatrian [49] subjected 10 groups of mice and rats (a total of 210 mice and 180 rats) to repeated subcutaneous injections, cutaneous applications, or intratracheal administrations of preparations of chloroprene latex and nonpolymerized chloroprene, alone or mixed with other

materials. Presumably, the latex was primarily polymerized chloroprene. The number of doses was stated in only 5 of the experiments and was 1, 16, or 40. Although it is unclear what form of the chemical was given, Khachatrian observed that high percentages of the animals that survived the series of administrations developed toxic hepatitis with extensive necrosis, hemorrhages in the liver, lungs, gastrointestinal tract, and kidneys, leukosis, and tumors in various sites.

Khachatrian [49] stated that malignant tumors were found in the internal organs following skin application or subcutaneous injection, but not at sites of either injection or application to the skin, but she gave no quantitative information about the types of tumors and their sites of occurrence. The development of more than one tumor in a single animal was said to be a common result of exposure to chloroprene; one example of this response included a pulmonary adenoma, sarcomatosis of the skin, and intestinal tumors.

Leukosis appeared rapidly in animals whose skins were painted with a solution of chloroprene in acetone [49]. In some experiments, mixtures of chloroprene latex and shellac or of chloroprene latex, shellac, and oil paint were applied to the skins of the experimental animals; myeloid leukosis occurred. All 11 surviving animals (from an unspecified number) exposed to the two-part mixture and 7 of 11 surviving animals (from an unspecified number) exposed to the three-part mixture had tumors of unspecified origin and type. The author concluded that both nonpolymerized chloroprene and chloroprene latex were carcinogens. Evaluation of these data are particularly difficult because the descriptions of the methods used to generate the data are incomplete. Moreover, the absence of control

studies prevents NIOSH from making dependable conclusions from these data.

In 1972, Zilfian and Fichidjian [50] published the results of a study investigating the effect of chloroprene on the growth of implanted Crocker's murine sarcoma. Thirty mixed-breed mice, 18-20 g, were injected subcutaneously with chloroprene in peach oil (0.1 g/kg of body weight) five times prior to inoculation with Crocker murine sarcoma suspension. Six additional subcutaneous injections of chloroprene were given after the tumor inoculation. Thirty mixed-breed mice, 18-20 g, were injected with peach oil and the Crocker's tumor suspension in the same manner and kept as controls. The frequency and spacing of chloroprene and peach oil injections were not specified, but the doses are presumed to have been given at intervals of 1-2 days because the experiment was said to have been terminated on the 12th day after the sarcoma cell suspension was injected into the mice.

The authors [50] observed that the mice injected with chloroprene exhibited palpable tumors 1-2 days earlier than mice in the control group. The number of mice in each group developing tumors and the latent period were unspecified. Autopsies were carried out 12 days after inoculation of the tumor suspension. Tumors in the mice injected with chloroprene were almost twice as large and 4.5 times as heavy as tumors in the control mice. The authors suggested that chloroprene depressed the immune system of the mice, allowing the tumors to grow more rapidly.

A brief report describing a 2-year carcinogenicity study was published by Zilfian et al [51] in 1975. A total of 290 mice were exposed to chloroprene, 9,10-dimethyl-1,2-benzanthracene (DMBA), or both by skin painting. Benzene was used as the solvent for all skin-painting studies.

Fifty percent chloroprene (100 mice), 0.1% DMBA (80 mice), or 50% chloroprene plus 0.01% DMBA (number not stated) was painted on shaved shoulder regions of each mouse. Chloroprene or DMBA was applied (the amount/application was not stated) twice weekly for 25 weeks, while the chloroprene-DMBA mixture was applied five times in all. The exposure duration and frequency for chloroprene-DMBA administration were not stated.

After skin painting, 42 of 100 mice painted with chloroprene died within 6 months [51]. In addition, 20 of 80 exposed to DMBA alone died, while 38 died after application of the mixture (total number not stated). Examination of an unspecified number of mice surviving to the end of the experiment found no tumors in animals painted with chloroprene alone or with the mixture of chloroprene and DMBA. However, 92% of the mice painted with 0.1% DMBA developed skin tumors. No data on the overall frequency of tumors or the causes of death in the mice expiring before the end of the study were given. It is difficult to assess the significance of the consequences of painting the skin with chloroprene when the exact dose for each animal is unknown.

In a second section of the study [51], 390 rats were given subcutaneous injections of chloroprene or DMBA in sunflower oil. Four groups of rats were used: the first group (110 rats) was given 10 injections of chloroprene at 400 mg/kg, the second group (number not specified) received 50 injections of chloroprene at 200 mg/kg, the third group (60 rats) received DMBA at a single dose of 0.5 mg, and the fourth group (number unspecified) was given 50 injections of chloroprene at 200 mg/kg plus a single dose of 0.5 mg of DMBA. The timing and frequency of the injections were not given. The rats were observed for a 2-year period.

Sarcomas of the subcutaneous cellular tissue developed in rats exposed to DMBA, a known carcinogen. With DMBA alone, the first tumor appeared after 3.5 months. Of 60 rats, 50 survived the injections, but only 32 (64%) developed sarcomas. With the mixture of chloroprene and DMBA, the first tumor appeared at 4 months. Surviving the 6-month injection period were 42 rats (the total number exposed was not mentioned), 24 (57%) of which developed sarcomas. No malignant tumors were observed in any of the chloroprene-treated rats over the entire 2-year observation period. Deaths were noted after 6 months (ie, during the period of injections). Twenty percent of the rats died at the 400 mg/kg chloroprene dosage, and 46 rats (unknown percentage) died at the 200 mg/kg dosage. The authors concluded that chloroprene was not a carcinogen. When chloroprene was given in combination with DMBA, the formation and growth of tumors were decreased and the tumor growth appeared to be somewhat delayed. Therefore, the authors concluded that chloroprene may suppress the growth of DMBA-induced tumor cells.

(b) Mutagenicity

In 1975, Bartsch et al [52] described a mutagenic study of chloroprene in the *Salmonella typhimurium* strain TA-100 histidine auxotroph. Bacteria were exposed to chloroprene at 0.5, 2, or 8% concentrations in air (v/v) for 4 hours at 37 C in the presence of an NADPH-generating system and a 9,000 G liver supernatant from a homogenate of liver from male mice. The chloroprene, manufactured from acetylene, was 98.94% pure. Contaminants were alpha-chloroprene (0.98%), butadiene (370 ppm), vinyl acetylene (280 ppm), and tertiary-butyl-catechol (250 ppm added as a stabilizer). The number of plates incubated was not given.

Chloroprene in air caused back mutations as a linear function of the chloroprene concentration to which the bacteria had been exposed. At 8% chloroprene, mutation rates were approximately three times the spontaneous rate. An additional two- or threefold increase in mutagenic response was observed when postmitochondria supernatant from phenobarbital-treated or control male mice was added. The results are summarized in Table III-3. Bartsch et al concluded that chloroprene was mutagenic with or without microsomal activation.

In 1976, Bartsch et al [15] published an abstract of data presented at the 67th annual meeting of The American Association for Cancer Research. The authors investigated the mutagenicity of several airborne compounds using the *Salmonella typhimurium* TA-100 tester strain in the presence or absence of a microsomal enzyme activation system. Mutation rates were calculated from linear regions of dose and time-dependent plots and were expressed as revertant colonies/ μ mol/hour/plate. The plots were not presented; as a consequence dose ranges could not be ascertained.

Vinyl chloride exposure resulted in 6 reversions/ μ mol/hour/plate (2 without mouse microsomal activation), 2-chloroprene exposure resulted in 51 reversions (9 without activation), 1-chloroprene exposure resulted in 157 reversions (81 without activation), and 3,4-dichlorobutene exposure resulted in 490 reversions (345 without activation). The authors [15] also stated that human liver fractions activated vinyl chloride and 2-chloroprene to compounds with mutagenicities comparable to those induced by activation by the mouse liver microsomal system.

TABLE III-3

SUMMARY OF MUTAGENIC TESTS WITH CHLOROPRENE VAPOR

Air Exposure (% v/v)	Microsomal Activation	Salmonella typhimurium Strain				Ref- erence
		TA-1535*	TA-1537*	TA-1538*	TA-100**	
8	None	-	-	-	117 ± 6	52
8	Liver	-	-	-	306 ± 25	52
2	None	-	-	-	70 ± 4	52
2	Liver	-	-	-	154 ± 15	52
1.26	None	2.25	8.56	10.20	-	***
0.63	"	3.15	8.65	12.69	-	***
0.63	Lung	3.92	2.09	8.45	-	***
0.63	Liver	1.85	3.83	10.69	-	***
0.5	None	-	-	-	49 ± 3	52
0.5	Liver	-	-	-	101 ± 4	52
0.30	None	2.56	14.09	5.54	-	***
0.30	Lung	2.22	1.91	9.84	-	***
0.30	Liver	7.70	2.02	8.77	-	***
0	None	2.34	11.84	8.48	-	***
0	"	1.36	9.68	8.57	-	***
0	"	-	-	-	35 ± 2	52
0	Liver	-	-	-	35 ± 3	52

*Revertants/100 million survivors, unspecified exposure duration

**Revertants/plate, 4-hr exposures

***Adapted from RS Barrows (personal communication, August 1976)

Bartsch et al [15] reported that 2-chloroprene was activated to an alkylating agent as measured by trapping with 4-nitro-(4-benzyl-pyridine). No details were provided on this aspect of the study. Although the authors stated that this work demonstrated the conversion of 2-chloroprene to potentially carcinogenic metabolites, extrapolation from mutagenicity to potential carcinogenicity may or may not be warranted.

Recently, RS Barrows (written communication, August 1976) transmitted to NIOSH results of Litton Bionetics' testing of the mutagenicity of chloroprene in *Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 using the Ames procedure [53,54]. These mutagenicity tests were carried out in 1974 and 1975. Mutagenicity was measured with and without microsomal activation, apparently by using single plates, ie, no replication of data. Known mutagens including dimethylnitrosoamine, 2-acetylaminofluorene, 7,12-dimethylbenzanthracene, ethyl methanesulfonate, 2-nitrofluorene, and quinacrine mustard were also tested. Saline was used as the control. Cells were exposed to liquid chloroprene at 0.1, 1, 10, or 100 μ l/plate and to chloroprene vapor at 0.30, 0.63, or 1.26% (v/v). In the first series of tests, microsomally activated and nonactivated plates showed no reversions above the spontaneous levels with atmospheric chloroprene exposure in TA-1535, TA-1537, or TA-1538. In activated and nonactivated suspension tests, Barrows (written communication, August 1976) reported that no mutagenic response was observed. The data can also be interpreted as showing a weak mutagenic response in only strain TA-1535. The results are presented in Table III-3.

When activated and nonactivated plate tests were repeated in 1975, using liquid chloroprene and strains TA-98 and TA-100 in addition to TA-

1535, TA-1537, and TA-1538, moderately positive results were obtained in strain TA-1535. In contrast to the results of Bartsch et al [15,52], mutagenicity was not observed in TA-100 (RS Barrows, written communication, August 1976). The results are presented in Table III-4. Bartsch et al [52]

TABLE III-4

SUMMARY OF MUTAGENIC TESTS WITH LIQUID CHLOROPRENE

Exposure Concentration (μ l)	Microsomal Activation	Salmonella typhimurium Strain*				
		TA-1535	TA-1537	TA-1538	TA-98	TA-100
100	None	11	12	22	19	14
100	Liver	115	12	23	44	102
100	"	175	-	-	-	-
10	None	14	11	23	21	45
10	Liver	53	15	25	24	105
10	"	21	-	-	-	-
1	None	13	9	20	22	24
1	Liver	23	12	19	18	102
1	"	23	-	-	-	-
0	None	10	11	23	21	42
0	Liver	34	15	16	30	85
0	"	18	-	-	-	-

*Revertants/plate, unspecified exposure duration

Adapted from RS Barrows (personal communication, August 1976)

used only TA-100, but reported a response that increased linearly with increasing concentrations of chloroprene, whereas the study by Barrows (written communication, August 1976) found variable responses to increasing concentrations of chloroprene.

Using the Berlin K strain of *Drosophila melanogaster*, a strain that has been found to be especially susceptible to mutagenic activity by ethyl methanesulfonate and 1-(2,4,6-trichlorophenyl)-3, 3-dimethyltriazine, E Vogel (written communication, July 1976) found that chloroprene fed to adult males for 3 days at a concentration of either 5.7 or 11.4 millimolar resulted in increases in the percent of X-linked recessive lethal mutations from $0.18\% \pm 0.04$ to $0.58\% \pm 0.3$ or $1.0\% \pm 0.4$, respectively. The last value is clearly significant evidence of potential mutagenic activity in other species. It is noteworthy that the recessive lethal mutations produced in *Drosophila* include the small deletions that are the most important type of genetic damage indicating a potential hazard to man.

A brief study of chromosomal aberrations in bone marrow cells from male rats of unspecified strain exposed over a period of 4 months to chloroprene vapor and other substances present in latex was presented by Bagramian and Babaian [42]. Six rats were used in each exposure group and six were kept as controls. The frequency of chromosomal aberrations was determined using histochemical methods (no method specified) and was reported to be 5.5% in the controls. Inhalation of chloroprene at 0.54 ± 0.29 ppm in conjunction with dodecyl mercaptan at 5.02 ± 1.96 mg/cu m and ammonia at 19.8 mg/cu m for 1 day produced 8.8% chromosomal aberrations in rat bone marrow cells. When methylmethacrylate at 4.0 ± 0.25 mg/cu m was combined with chloroprene at 2.8 ± 2.0 mg/cu m, 10.7% of the chromosomes

were altered after 1 day. Controls exposed to only dodecyl mercaptan, chloroprene, or methyl methacrylate were not run in this study. The authors concluded that the mixture tested caused a mutagenic effect in rats.

In 1976, Volkova et al [41] presented a brief study of metaphase configurations in bone marrow cells of mice exposed to chloroprene. Separate groups of 6-10 mice were exposed for 2 months to airborne chloroprene at each of the following six concentrations: 0.054, 0.064, 0.13, 0.32, 1.85, and 3.5 mg/cu m. Two groups of six and eight unexposed mice served as controls. Chromosomal disorders of an undefined nature were measured and appeared with increasing frequency as the chloroprene concentration was increased (units are percent of occurrence): 3.05 ± 0.46 and 2.0 ± 0.58 (in the two control groups), 3.4 ± 0.7 , 2.8 ± 0.33 , 4.65 ± 0.89 ($P < 0.05$), 6.07 ± 0.4 ($P < 0.001$), 10.9 ± 1.34 ($P < 0.001$), and 10 ± 0.68 ($P < 0.001$). Volkova and coworkers stated that this was an increased frequency of cell aberration. The types of marrow cells examined were not indicated, making evaluation of the data difficult. The authors also stated that chloroprene induced what were called dominant lethal mutations in mouse reproductive cells at the two highest air concentrations, 1.85 and 3.5 mg/cu m.

Davtian et al [55] measured mutagenicity in bone marrow cells of 36 male rats exposed to airborne chloroprene at 1.1 and 11 ppm (3.8 and 39 mg/cu m) using a cytogenetic anaphase-telophase analysis. The authors stated that the number of chromosomal aberrations was increased above the control level at both 1.1 and 11 ppm; no data were given to support this conclusion.

(c) Teratogenicity and Effects on Reproduction

In 1936, Von Oettingen et al [18] investigated the action of chloroprene on male reproductive processes in the rat. A total of 18 male rats of unknown strain were exposed to chloroprene in air for 8 hours at concentrations of 121-6,227 ppm. Five control males were unexposed. After 0-30 days of isolation, the males were mated with normal female rats, and the frequency of successful matings was determined. Only 6 of 19 matings produced pregnancies, with an average of 6.8 offspring/liter. Unproductive matings occurred at all exposure concentrations of chloroprene. The five control rats mated successfully, producing an average of 6.4 offspring/liter.

The chloroprene inhalation experiment was repeated with a total of 14 male mice exposed to chloroprene at air concentrations of 12, 75, 115, 119, 121, 150, or 152 ppm for 8 hours [18]. The exposed males were mated with females 1 to 9 days after exposure. Only 6 of the 14 matings produced pregnancies, with an average of 6 offspring/litter. Five of six control mice reproduced normally, producing seven offspring/litter.

Five female mice were also exposed for 8 hours to chloroprene at air concentrations of 151 ppm [18]. All these animals reproduced normally when mated 1 day after the exposure, producing an average of 4.8 offspring/litter. No degenerative changes in the female sexual organs were observed microscopically.

The authors [18] concluded that chloroprene interfered with reproductive processes in male rats and mice; testicular atrophy was demonstrated in the rat. On the other hand, female mice exposed at similar concentrations reproduced normally when mated.

There have been several recent publications on the effect of chloroprene on the reproductive capacities of male and female rats. Davtian et al [55] exposed a total of 36 male rats to airborne chloroprene for 4 hours/day over a 48-day period at concentrations of approximately 1.1 or 11 ppm. The animals were subsequently observed for overall toxic effects and for specific effects on reproductive function. Weight gain, oxygen requirement, detoxification by the liver (sodium benzoate loading followed by measurement of hippuric acid excretion), total serum albumin and sulfhydryl content, diuresis, total urinary albumin and chloride, and the relative weights of the internal organs were measured. Male reproductive function was determined by measurement of fertilizing ability, spermatozoic motility, testicular atrophy, and preimplantation and postimplantation mortality. Each male was mated with two females (strain unspecified). The males were killed after mating; some females were killed on day 21 and the fetuses were examined. The development of the offspring of some females was also followed after birth.

The only reported indices of toxicity to the males were increased concentrations of chloride in the urine and decreased concentrations of what were called stable intermediate products [55]. The nature of this latter index was not given. It was, however, observed to decrease significantly ($P < 0.1$), from 5.8 to approximately 4.5 units (units not defined) at both 1.1 and 11 ppm. Urinary chlorides increased only at 11 ppm from 1.14 ± 0.21 to 1.74 ± 0.16 mg/ml ($P < 0.05$). No other significant changes were observed in the other parameters measured, except that both exposure concentrations were said to have increased the number of chromosomal aberrations in the cells of the bone marrow; no data to support

this statement were included.

Davtian et al [55] observed no effects of inhaled chloroprene on spermatozoal motility or fertilizing ability. The effect on postimplantation embryonic death increased at chloroprene concentrations of 1.1 and 11 ppm, from 2.2 ± 1.1 in the offspring of controls to 4.7 ± 1.5 in offspring of animals exposed to the lower concentration, and to 8.4 ± 3.4 in offspring of animals exposed to the higher concentration (no units specified), but these changes were not significant ($P > 0.05$) in any case. Preimplantation losses were increased significantly ($P < 0.02$) when compared with those of the control dams, at both exposures to chloroprene. Total embryonic mortality was demonstrated to increase significantly ($P < 0.05$), from 12.9 ± 2.7 in the offspring of control rats to 30.7 ± 5.7 and 32.0 ± 7.4 in those of rats exposed at 1.1 and 11 ppm, respectively.

Davtian et al [55] suggested that sex and somatic cells had identical sensitivities to chloroprene and concluded that embryonic death was apparently linked to the mutagenic activity of chloroprene. Although the two exposure concentrations of chloroprene apparently had no graded effects on either preimplantation or total embryonic mortality, they seemed to have graded effects on postimplantation mortality. The authors noted the need to study the effects of still lower concentrations of chloroprene.

Davtian [56] described the effects of chloroprene on the reproductive function of male rats. A total of 100 rats of unspecified strain was exposed to chloroprene at concentrations of 0.47, 0.042, or 0.014 ppm by inhalation. The animals were exposed 4 hours/day for periods up to 5.5 months. Unspecified numbers of animals were killed after 1.5, 2.5, 3.5, and 4.5 months of exposure, and spermatozoa were examined microscopically

with respect to duration of motility, vitality (percentage of live sperm), and resistance to hypertonic and acid solutions. Testicular weight coefficients (percentage of total body weight) were also determined. Liver function was determined after 5.5 months of exposure by sodium benzoate loading experiments; results were reported as milligrams of hippuric acid excreted. Oxygen uptake was also measured. No details were given on how these indices were determined. After 2.5 months of exposure, eight males at each exposure concentration were mated with virgin female rats of unspecified strain to determine fertilization efficiency. The females were killed after the 20th day, and the preimplantation and postimplantation losses, overall embryonic mortality, and fetal size were determined.

Oxygen uptake decreased significantly, as did hippuric acid excretion, after chloroprene exposure at the concentration of 0.47 ppm for 5.5 months [56]. Neither the number of rats nor the collection interval was reported. Atrophy of the testicles and decreased vitality, motility, and acid resistance of spermatozoa were found in some of the males exposed to chloroprene at 0.47 ppm; similar changes also occurred in some male rats exposed at 0.042 ppm. No effects were reported at 0.014 ppm; however, no data were presented. Davtian [56] found that untreated females mated to males exposed at 0.042 ppm showed significant increases in total embryonic mortality and preimplantation deaths.

Davtian [56] concluded from this study that the threshold for general toxicity (oxygen consumption and liver function, both poorly defined) was approximately 0.56 ppm, but that the thresholds for interferences with reproductive function were one order of magnitude lower. He also stated that the increases in embryonic death were the result of increased

preimplantation deaths; however, preimplantation death may not be a good indication of genetic damage [57,58]. Postimplantation losses were not reported.

Volkova et al [41] described an inhalation study in which chloroprene-induced reproductive effects were examined. Randomly bred male rats and C57BL/6 mice were exposed to chloroprene in air at concentrations of 0.14-0.47 ppm for 4.5 months. The numbers of rats and mice exposed at each concentration were not given. The number of hours of exposure each day was not given. The authors stated that the highest concentration of chloroprene caused a decrease in rat spermatozoal motility and acid resistance, atrophy of the testicles in five of eight rats, and an increase in the number of dead spermatozoa. Tabular data were presented for "animals"; the tabular material did not distinguish between rats and mice, but the discussion implied that clearly it was limited to rats. Without more specific information, the significance of this study is difficult to assess.

In 1968, Salnikova [59] first discussed the combined embryotoxic effects of volatile chloroprene and ammonia, derived from polychloroprene latex, on pregnant rats and mice of randomly bred strains. Neither the method of generating the vapors nor the identities of volatile dimers and contaminants were described, but the concentrations of chloroprene and ammonia were 4 ppm (14.4 mg/cu m) and 4.8 ± 0.3 mg/cu m, respectively. The analytical methods were not described. Thirteen mice and 11 rats were exposed to chloroprene and ammonia for 4 hours/day for the first 18 or 19 days of pregnancy, respectively. Two control groups were used in the study, one exposed to ammonia alone at 58 ± 6 mg/cu m (10 mice and 7 rats)

and the other exposed to air alone (11 mice and 9 rats). The following measurements were made on day 17 of treatment: body weight, hemoglobin content, and red and white blood cell counts. No actual values were given, but the author reported that there were no significant changes from normal physiologic limits.

On the last day of exposure, day 18 or 19, the females were killed and autopsied [59]. The following variables were measured: liver and kidney weights, urinary albumin and chloride concentrations, numbers of corpora lutea, sites of implantation, postimplantation deaths, and living fetuses, and the weights of the fetuses. Preimplantation deaths were defined as the difference between the number of corpora lutea and the number of implantation sites.

The only physiologic changes observed that could be attributed to chloroprene alone were slight, but significant ($P=0.01$), increases of liver and kidney weights (no units were given) of the female mice compared with those of the controls, 6.18 ± 0.03 versus 5.64 ± 0.18 and 1.65 ± 0.06 versus 1.16 ± 0.03 , respectively [59]. The kidney weights of female rats were also increased, 0.65 ± 0.02 versus 0.57 ± 0.02 ($P=0.05$). In the mice exposed to both chloroprene and ammonia, the average number of postimplantation deaths was significantly ($P<0.001$) increased, 8.1 ± 1.1 versus 1.47 ± 0.43 for the air controls and 1.9 ± 0.79 for the ammonia-inhalation controls. There was a complete loss of all litters in the pregnant mice exposed to vapors derived from latex. Female rats exposed to both chloroprene and ammonia vapors under the same conditions showed no significant ($P>0.05$) change in the number of postimplantation embryonic deaths when compared with rats exposed to ammonia and with rats exposed

only to air. After exposure of the dams to latex fumes, the number of rat fetuses with hematomas or cyanoses was elevated, 2.50 ± 1.04 versus 0.40 ± 0.29 ; however, this was not significant (P between 0.05 and 0.1). The mean number of normal rat fetuses/litter was 52% below that of the controls ($P < 0.01$, 4.70 ± 1.24 versus 9.80 ± 1.76). No criteria for distinguishing abnormal fetuses from normal ones were presented.

Salnikova [59] concluded that the polychloroprene latex studied liberated volatile substances that possessed considerable embryotoxic action. The effect was not attributed to ammonia, since a tenfold higher exposure to ammonia alone did not have comparable embryotoxicity. However, the possibility of ammonia and chloroprene acting together to cause embryotoxicity cannot be entirely ruled out, as a chloroprene control was not included in the study. The amounts of oxidized chloroprene and other contaminants released from the latex were also not determined, making the assignment of toxic activity to chloroprene somewhat difficult. The composition of the latex and the method for generation of fume from it were not described. Complete reliance on the data presented is impossible without this information.

In 1973, Salnikova and Fomenko [60] published the results of an investigation of chloroprene's influence on embryogenesis in pregnant rats. In these studies, 205 rats in groups of 22 to 30 were exposed to chloroprene, via inhalation, at 1 of 5 concentrations for 4 hours/day during the entire period of pregnancy, and the results were compared with those from control groups. The concentrations were 1.11, 0.83, 0.17, 0.036, and 0.016 ppm of chloroprene. The purity of the chloroprene was not indicated. The experimental protocol was not outlined.

The embryotoxicity experiments were done at three different times; consequently, three sets of control animals were examined [60]. Variables considered for embryos and fetuses were total mortality (no breakdown into preimplantation and postimplantation embryonic losses), liver weight, femoral and fibular diaphysis lengths, and disturbances in vascular permeability. Variables considered in the study of 2-month-old weanlings included urinary proteins, cholinesterase (no tissue specified), oxygen requirement, serum sulfhydryl content (no method described), urinary hippuric acid after benzoate loading, weight gain, and weight ratios of brain, lung, liver, and kidney. No data were supplied on organ weights. The additional gain in liver weight after further hepatotoxic stress with alcohol was measured, but the results were not indicated.

In dams exposed at 0.83 and 1.11 ppm, total embryonic mortality was significantly increased by 273% ($P < 0.01$) and by 193% ($P < 0.05$), respectively. Exposure of dams to chloroprene at 0.17, 0.036, or 0.016 ppm led to nonsignificant increases in embryonic and fetal mortalities of 76, 71, and 14%, respectively, over those of the controls. The weight of fetuses was stated to be significantly ($P < 0.001$) below that of those from controls, 1.8 ± 0.18 versus 2.3 ± 0.2 g, when dams were exposed at 1 ppm. Disturbances in the vascular permeability and decreases in the lengths of long bones (femur and fibula) also occurred at around 1 ppm (no data were presented).

The mortalities during the 3 weeks after birth of progeny from dams exposed at 0.17 and 0.036 ppm were increased more markedly than embryonic mortality, $34.1\% \pm 12.0$ versus $2.2\% \pm 1.5$ ($P = 0.05$) and $26.0\% \pm 3.4$ versus $11.2\% \pm 4.2$ ($P < 0.02$), respectively [60]. The documenting of physiologic

changes observed during the study of first-generation progeny was incomplete and variable. Some effects seen with low-exposure concentrations were not observed at higher concentrations, so no dose-response relation was derived. Because of the varying statistical results and incomplete details of the study, interpretation of the physiologic effects is not possible. In addition, the lack of information on the purity of the chloroprene affects the overall value of this study.

A rather novel approach to studies of the effects of industrially produced chloroprene vapor on pregnant rats was described by Apoian [61]. Four groups of pregnant rats were housed in, or at various distances from, the Kirov chloroprene complex. The lengths of exposures and numbers of rats were not indicated for the teratogenicity portion of the study. Chloroprene concentrations (detection method not specified) were determined to be as high as 61 ppm within the plant (average not given) and means of 0.2 (range 0.056-0.44), 0.14 (range 0.039-0.52), and 0.05 (range 0.038-0.11) ppm were observed at distances of 500, 1,500, and 7,000 meters from the plant, respectively. Rats housed at these distances were identified as groups 1-4, respectively. Group 4 was used as a control. Data were reported on 15 rats (highest number only listed in the tables) exposed in the plant (group 1), 23 exposed at 500 meters (group 2), 9 at 1,500 meters (group 3), and 14 controls at 7,000 meters (group 4) for 20 days. The author stated that increased fetal mortality was noted particularly in the preimplantation period (no specific chloroprene concentration or location was mentioned), and that there were reductions in placental weight. For rats housed at the highest exposure concentration (group 1), the weights of livers of 20-day fetuses were lower, and the period of pregnancy in dams

was lengthened, when compared with those of groups 2-4. This elongation led to an increased number of prenatal (23.2%) and neonatal (38.2%) deaths.

Apoian [61] measured placental weight in all four groups and fetal liver weight in groups 1 and 3. He also measured vitamin C content in the brain, liver, adrenals, and placenta of all the dams and in the brain and liver of 20-day-old fetuses. A significant (no P value) decrease in placental weights in all exposed groups was reported when compared with those of control dams housed at 7,000 meters, but the decreases were not dose dependent: group 1, 625.6 ± 22.3 mg; group 2, 563.8 ± 12.9 mg; group 3, 521.5 ± 14.1 mg; and control group 4, 690.8 ± 13.3 mg. Decreases described as reliable were also observed in embryonic liver weights of groups 1 and 3: 251.3 ± 7.9 mg and 231.6 ± 9.4 mg, respectively, versus 273.8 ± 7.8 mg in control group 4; the response again was not dose dependent. There was no significant change in the concentration of vitamin C in any tissue of either the dams or the fetuses in which it was measured.

The author [61] also examined the effect of chloroprene on DNA and RNA concentrations in tissues of pregnant rats handled in the manner described in the preceding paragraphs. In the Kirov plant, chloroprene daily mean air concentrations ranged from 4.1 to 14.8 ppm. When RNA and DNA concentrations were determined in the brain, liver, and placenta of dams and in the brain and liver of 20-day-old fetuses, the only significant change in group 1 was a decrease in the mean concentration of RNA in the liver of the fetuses [61]. In group 2, the mean concentrations of RNA in the placenta and liver of the dams and of DNA in the brain and liver of the fetuses were decreased with at least 95% reliability. In group 3, the only change stated to be reliable at the 95% level was a decrease in the

concentration of RNA in the liver of the dams. Apoian explained the predominance of significant alterations in the nucleic acid concentrations in various organs of the dams and fetuses of group 2 by supposing that comparatively large concentrations of chloroprene have general toxic effects that are more apparent than the biochemical ones, and that an intermediate concentration has more apparent biochemical effects because it has less general toxic effect. He asserts that Gofmekler, Pushkina, and Klevtsova have reported a similar situation in pregnant rats exposed to formaldehyde vapor. With the dearth of experimental detail and data and the possibility of mixed exposure, interpretation of this paper is not possible.

In 1971, Mnatsakanian et al [62] published a brief, preliminary report of a study similar to that of Apoian [61] and in the following year published a more detailed paper [63] on this research. In the preliminary report [62], four groups of pregnant rats were caged in apparently the same locations used by Apoian [61]. The animals in these two studies [61,62] may have been the same. In the later paper of Mnatsakanian et al [63], the results of caging at locations 1 and 2 were compared with those of caging at location 4. The rats caged at location 4 were used as control animals; the group caged at location 3 was not discussed. The three groups of pregnant white rats were exposed to chloroprene at three concentration ranges: 4.1-14.8 ppm in the plant, 0.056-0.44 ppm at 500 meters away, and 0.033-0.11 ppm at 7,000 meters away from the plant (considered as controls). The total number of females exposed at each concentration was not stated. Prenatal deaths were stated to occur in 20.93% of the embryos in 9 females of the first group (4.1-14.8 ppm), in 6.38% in 5 females of

the second group (0.056-0.44 ppm), and in 10.88% in 15 females in the control group (0.033-0.11 ppm). Prenatal deaths were determined by comparing the number of points of uterine-placental attachment to the number of fetuses within a few days after giving birth.

Neonatal deaths were also considered [63]. At the highest concentration of chloroprene in air, 38.2% of the offspring from nine rats were stillborn or died immediately after birth. No deaths were observed at the lower exposure concentration, and 2.3% of the offspring from 30 females studied in the control group died. The only postnatal deaths (two) were observed in the group exposed at 0.056-0.44 ppm. A study of weight gain during the first 6 months of offspring growth (the number was unstated) showed some deviation from the controls at various times but no general trends.

Mnatsakanian et al [63] concluded that, on exposure to vapors freed during production of polychloroprene, the course of pregnancy in the rat was disrupted, labor was prolonged, and neonatal deaths were increased. They stated that the embryotoxic effect of chloroprene was characterized by early embryonic death in both exposed groups; however, the data to demonstrate this were not presented. No distinction was made between early and late embryonic deaths (preimplant and postimplant), and the methodology described would not have allowed such a distinction. In addition, the group exposed to chloroprene at 0.056-0.44 ppm had a smaller proportion of prenatal deaths than the control group, 6.4% versus 10.9%. It also had a smaller proportion of unviable offspring than the control group, 0 versus 2.3%.

In 1975, Salnikova and Fomenko [64] studied the embryotoxic and teratogenic effect of chloroprene administered orally and by inhalation. Each group of pregnant white rats (no particular strain specified) contained 8-15 rats. Six groups were given daily oral doses of 0.5 mg/kg for 2-day periods through the 14th day of pregnancy, ie, days 3 and 4, 5 and 6, etc. One group was given the same dose every day for the entire 14-day period, and a control group was left unexposed. Paralleling the oral regimen, eight other groups of pregnant rats were exposed to airborne chloroprene at 1.1 ppm for staggered 2-day periods to the 18th day of pregnancy, and one group was exposed on days 1 through 20. The number of hours of exposure each day was not stated. The fetuses of all rats were examined on the 20th day of pregnancy. This procedure included examination for teratogenic effects as well as quantification of total embryonic and fetal toxicity. Preimplantation and postimplantation embryonic deaths were determined separately but reported only as total embryonic deaths.

Embryonic deaths in rats receiving oral chloroprene doses were significantly ($P < 0.001$) increased for rats exposed for 14 days, 9.4 (about 92%) versus 0.4 (about 5%) for the controls [64]. The authors stated that deaths were primarily preimplantation. The total number of embryonic and fetal deaths was elevated in those rats given chloroprene on days 3 and 4 (7.7%) and on days 11 and 12 (5%). All fetuses from rats given chloroprene orally for 14 days showed hydrocephalus and internal bleeding.

Total deaths of concepta in dams inhaling 1.1 ppm of airborne chloroprene were approximately 20% for those exposed on days 1 and 2, 3 and 4, 9 and 10, 11 and 12, or 1 through 20, versus 8% for the controls [64]. Dams exposed at periods other than those listed above had lower embryonal

mortalities, that for dams exposed on days 7 and 8 actually being below that for unexposed dams. No teratogenic effects were observed in offspring of controls or of those animals exposed by inhalation throughout pregnancy. Internal bleeding was found in 70% of the fetuses of the dams exposed throughout pregnancy versus 16% in those of the controls. Internal bleeding, hydrocephalus, and cerebral herniations were also observed in fetuses from dams exposed for the 2-day periods after day 5, the frequencies being 34-47%, 6-34%, and 1.6-23.5%, respectively. The only effect classified by the authors as teratogenic was hydrocephalus with cerebral herniation. The largest number of cerebral hernias was seen in fetuses from dams exposed to chloroprene on days 5 and 6 of pregnancy.

In 1976, Melik-Alaverdian et al [65] presented the results of a three-generation study of reproductive function and sexual maturation in female rats. Ninety female rats (150-180 g, no strain identification given) were exposed at concentrations of airborne chloroprene of 8.34 ppm for 5 hours each day, 6 days each week, during 6 months. Thirty-six females were not exposed to chloroprene and served as controls. At the end of the exposure period, the rats were mated with nonexposed males. The percentage of females giving birth to progeny, number of progeny/litter, intrauterine development of fetuses, and fetal weights were all determined.

The first generation of exposed animals had the same percentage of fertility (62.2 versus 63.8%) and average fetal weight (4.76 ± 0.09 versus 4.61 ± 0.05 g) as the control group [65]. Intrauterine development was normal; no stillbirths or deformities were observed in either group. The average number of fetuses/litter was decreased in the exposed dams to 3, versus 5.2 in the control group. The authors also stated that the estrus

cycle was altered in the 3rd month of exposure at 30 mg/cu m. The length of the heat period was significantly ($P<0.05$) increased in the exposed rats, 1.3 versus 1.1 days in the control group. A significant ($P<0.001$) decrease in the length of anestrus was also observed, 3.4 days in exposed rats versus 5.1 in the controls.

Female offspring were chosen from the second generation, 60 from exposed dams and 65 from control dams [65]. These females were mated with nonexposed males. None of the second-generation animals were exposed to chloroprene. Fertility in the female rats derived from exposed dams was decreased, 56.6% versus 66% in the second-generation control animals. Intrauterine development and pregnancy duration were normal in both groups, and average fetal weight was unchanged, 4.69 ± 0.05 in experimental progeny versus 4.50 ± 0.06 in control progeny.

In the 3rd month of a 6-month observation period, experimental dams showed significant ($P<0.001$) decreases in the duration of anestrus, 3.5 versus 5.1 days, and in the number of estrus cycles, 6.13 versus 7.9 in the control group [65].

Sixty-one female offspring of the third generation and 65 females of the same generation of controls were chosen and mated with unexposed males [65]. Nearly all the reproductive indices were normal. Fertility was unchanged, 60.6 versus 63% in controls, but the average litter size was decreased, 3.3 versus 4.1. No stillbirths or deformities were observed, but fetal weights were decreased significantly: 4.48 ± 0.07 versus 5.03 ± 0.08 in the control progeny. The duration of estrus was significantly ($P<0.05$) increased, 4.56 days in the experimental group versus 3.5 days in the controls.

The authors [65] concluded that 8.34 ppm of chloroprene caused decreased litter size in the first and third generations and a decrease in the frequency of conception in the second generation. No substantial changes were observed in estrus or other indices of development.

Culik et al [66] described the exposure of pregnant Charles River-CD rats to freshly distilled chloroprene at nominal concentrations of 25, 10, and 1 ppm in inhalation chambers for 4 hours/day. In the embryotoxic study, 50 pregnant rats at each concentration and 50 control rats were observed after exposure from day 1 through day 12 of pregnancy; the rats were killed on day 17. For determination of teratogenicity, 25 rats were exposed at each concentration (along with 25 control rats) from day 3 through day 20 before being killed on day 21. Resorptions and preimplantation and postimplantation losses were measured in addition to the examination of surviving fetuses for viability and teratogenic effects. Chloroprene concentrations in the chambers were analyzed every 30 minutes by gas chromatography using methods similar to those described in Appendix II. The nominal concentrations of 1, 10, and 25 ppm were determined to average 0.8, 8.6, and 22.7 ppm, respectively. The chloroprene was freshly distilled from antioxidant-stabilized solutions and was protected from exposure to air until injection into the airstream of the chamber.

Culik et al [66] stated that there were no embryotoxic or teratogenic effects at any of the concentrations of chloroprene tested. They also stated that chloroprene did not affect the body weight or gravid uterus weights of the dams. No gross abnormal changes were noted in the uterine horns, ovaries, or other organ systems at any of the test concentrations. The only effect seen in the teratogenic study was a tendency toward

increased size and weight of the fetuses from dams exposed at a nominal concentration of 25 ppm; however, the increase was not significant and the number of fetuses was not decreased. Although 21.1% of the litters of the dams exposed at 25 ppm had bipartite thoracic centra, compared with 9.5% of those of the control dams, the authors stated that this difference was not significant by Fisher's exact probability test. Pregnancy outcome, as measured by preimplantation and postimplantation losses of fertilized ova and number of live fetuses in each litter, was not significantly different from that of the controls. Median preimplantation loss in control dams was 20%; at 25 ppm, this loss was 16%. Fifty-one percent of the control litters showed early resorptions, compared with fifty percent of those exposed at 25 ppm. In terms of absolute preimplantation losses, there were 168/653 (25.7%) in controls and 144/637 (22.6%) in dams exposed at 25 ppm. Control dams had an absolute number of 39/485 (8.0%) early resorptions versus 34/493 (6.9%) in animals exposed at 25 ppm. Total postimplantation fetal loss was 39/485 (8%) in control litters and 34/493 (6.9%) in litters from dams exposed at 25 ppm. No changes were observed at 1 or 10 ppm.

A second portion of the study [66] addressed the effects of pure chloroprene on fertility of male rats. Five male Charles River-CD rats (150-200 g) were exposed for 4 hours daily for 22 consecutive days to chloroprene vapor at 25 ppm. Five males were kept as controls. On day 23, eight sequential mating trials were initiated with five test and five control rats. In each trial, a male was housed with three unexposed virgin females for a total of 7 days. After mating, the females were housed separately and allowed to deliver and raise their pups to weaning. The number of pups in each litter and their average body weight at weaning were

calculated along with the percentage of successful matings, the percentage of pups surviving 4 days or longer after birth, and the percentage of pups surviving through weaning. After the eighth mating trial, the males were killed and their reproductive organs examined microscopically after staining. No clinical signs of toxicity were observed during the test. Gross and microscopic examination showed no changes attributable to chloroprene. There were no significant differences between test and control animals for any of the reproductive variables measured.

This study [66] shares with others [55,56,60,64] one principal shortcoming limiting its applicability to occupational exposures to chloroprene: daily 4-hour exposures for 7 days/week are not representative of actual industrial situations. Further, many of the findings are stated as means or medians without any indication of the variability of the quantity measured within the various groups of rats. Although the authors concluded that no embryotoxic or teratogenic effects were seen at the exposure concentrations used, NIOSH believes that the data may justify a conclusion that the highest concentration to which the pregnant females were exposed may have increased significantly the incidence of abnormal centra in the thoracic vertabrae of the pups, which could be considered a teratogenic action. This abnormality appeared in the fetuses of the various groups with the following frequencies: control, 2/126; 0.8 ppm, 3/122; 8.6 ppm, 2/112; and 22.7 ppm 8/122. None of the exposed groups, when compared individually with the control group, had a significantly increased incidence of abnormal vertebral centra in the pups. It is apparent, however, that the group of dams exposed to the highest concentration of chloroprene produced pups that had a different incidence

of abnormal centra than did pups of the other three groups of dams. If the control groups and the groups of pregnant females exposed to the two lowest concentrations of chloroprene are lumped together, the incidence of abnormal vertebral centra in the pups of the group of pregnant female rats exposed to the highest concentration of chloroprene is statistically significant. NIOSH believes, therefore, that the highest concentration of chloroprene used by Culik et al may have had a teratogenic effect on the offspring of the female rats exposed to it.

Correlation of Exposure and Effect

No well-documented epidemiologic studies correlating occupational environmental concentrations of chloroprene with observed toxic effects have been found in the literature. The few epidemiologic studies of long-term, low-level occupational exposure have been reviewed, but these give no indication of the chloroprene air concentrations in the occupational environment [28-30].

Occupational exposure to chloroprene occurs chiefly by inhalation and skin contact. Chemical burns resulting from contact with chloroprene have been reported [11,24,67]. Few details are available, but the severity of the burns was dependent on the duration of contact. Dermal application of chloroprene has been found by several investigators [18,20,51] to cause damage to the skin and induce systemic poisoning in rats or mice as well.

There are few reports concerning the toxic effects of chloroprene inhalation on humans where the airborne concentrations were known. Observed signs and symptoms include CNS effects [1,20,46], chest pains [19,20,25,41], loss of scalp hair [23,24,68-70], hypotension [19,20],

conjunctivitis [19,24], extreme fatigue [19,20,41], slow pulse rate [25,41], fast pulse rate [25], and irritability [20]. These reports are summarized in Table III-5. Since nearly all these human effects involve mixed exposure, it is difficult to assign every one of these signs and symptoms to chloroprene alone. From Table III-5, the lowest occupational concentration of chloroprene reported to produce definite symptoms is given as a range of 1.95-0.8 ppm. Although these symptoms are nonspecific, they are in part the same as those produced by much larger concentrations of chloroprene.

Inhalation of chloroprene by animals has been reported to lead to CNS depression [19,20], primary irritation of the respiratory tract [19], and hypotension [19]. The results of the animal studies are summarized in Table III-6.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Khachatryan [28,29] reported that working where exposure to chloroprene was likely increased the risk of developing lung and skin cancer. Such information as work history, dietary and hygiene practices, exposure concentrations, smoking habits, and other compounds in the air are lacking in particular instances. The very high probability of mixed exposure at the Kirov Synthetic Rubber Complex renders interpretation of these data difficult. Volek et al [71], using gas-liquid chromatography, detected more than 25 compounds, mostly chlorinated hydrocarbons, in technical grade chloroprene manufactured from acetylene.

The study reported by Pell [30] suggests an excess of lung cancer in maintenance mechanics in a chloroprene manufacturing facility. Since the

task of the maintenance mechanics is to replace leaking pipefittings, to install equipment, and to do general maintenance in reactor areas, this group of workers would be expected to have relatively high exposures to chloroprene. Because the mean age of the lung cancer patients among maintenance mechanics is not compared with that of lung cancer patients among other types of employees at the plant, the lung cancer data for the maintenance mechanics are difficult to interpret.

Zilfian et al [51] reported that chloroprene did not induce tumors in mice when administered alone or in conjunction with dimethyl-1,2-benzanthracene by skin painting or by subcutaneous injection. This demonstrated that chloroprene was neither carcinogenic nor cocarcinogenic in an unspecified number of surviving mice or rats.

Results of mutagenicity testing of chloroprene by Litton Bionetics (RS Barrows, written communication, August 1976) were negative in *Saccharomyces cerevisiae* and in some *Salmonella* tester strains, but positive in TA 1535. In two studies [15,52], investigators demonstrated a dose-dependent mutagenic response to chloroprene in TA-100, both with and without metabolic activation. Bartsch [72] has reported that chloroprene is mutagenic in *S. typhimurium* TA-1530 also. The chloroprene used by Bartsch et al [15,52] was manufactured from acetylene, whereas that used by Litton Bionetics was made from butadiene. Different contaminants or testing methods and procedures may explain the differences between experimental results with different samples of chloroprene.

Further, in regard to mutagenicity, E Vogel (written communication, July 1976) has demonstrated sex-linked recessive lethal mutations in *Drosophila*. Several investigators [22,41,43] have demonstrated a

significant excess of chromosomal aberrations in blood cells of workers exposed to chloroprene in comparison with those of controls. Although one could speculate that the excess of chromosomal aberrations in chloroprene-exposed workers may be the result of air contamination with other agents, the study by Katosova [43] demonstrated no significant differences in the percentages of chromosomal aberrations in the blood cells of workers exposed to essentially pure chloroprene or chloroprene only and in those of workers exposed to chloroprene mixed with several other starting materials and byproducts. Sanotskii [22] has reported morphologic disturbances in sperm of workers exposed to chloroprene, as well as a threefold excess of miscarriages in the wives of chloroprene workers. No reports clearly attributing mutagenic effects on mammalian cells to chloroprene have been found.

Reports of experimental attempts to induce the formation of birth defects by exposing pregnant female animals to chloroprene have been described [64,66]. Oral administration resulted in teratogenic effects in rats [64]. Inhalation of chloroprene during the full period of pregnancy at nominal air concentrations of 1.0, 1.1, 10, or 25 ppm led to no clearly teratogenic effects [64,66], although there is a possibility that the highest concentration used by Culik et al [66] may have increased the incidence of abnormal vertebral centra in pups of the exposed pregnant rats. Inhalation at 1.1 ppm for 2 days between the 5th and 14th days of pregnancy did lead to greater incidence of hydrocephalus and cerebral herniation in fetuses [64]. The greatest incidence of cerebral herniation was found in the offspring of rats that inhaled chloroprene on days 5 and 6 of pregnancy. The greatest incidence of hydrocephalus occurred in

offspring of dams that inhaled chloroprene on days 11 and 12. Inhalation of chloroprene throughout pregnancy did not produce these effects, leading the authors to suggest that under this condition, the fetus adapts to chloroprene in some way and remains unaffected.

Experimental attempts to induce postimplantation embryonic deaths by chloroprene exposure in pregnant rats were not successful [56,59,64]. Some increases of preimplantation embryonic deaths by exposure of dams at concentrations of chloroprene below 2 ppm (as low as 0.04 ppm) have been reported [55,56,61] and have been contradicted [66] by results showing no effect at higher chloroprene concentrations of 1, 10, or 25 ppm. Many of the papers claiming to demonstrate chloroprene-induced preimplantation deaths lacked controls or reported exposures to other compounds in addition to chloroprene. The implication presented was that preimplantation death is a strong indication of a dominant-lethal genetic change. However, only postimplantation embryonic death is a sound indicator of a dominant-lethal effect [57,58]. Preimplantation deaths are quite variable, even in control populations, due in part to the imprecise basis on which they are calculated. For this reason, apparent changes in the incidence of preimplantation deaths are not reliable indications of mutational activity.

Effects on the male reproductive process in rats and mice, including testicular atrophy and decreased reproductive functions, have been found by Von Oettingen et al [18] to occur between 75 and 6,232 ppm. Davtian [56] observed a significant excess of total embryonic mortality following exposure of male rats to concentrations of airborne chloroprene as low as 0.042 ppm. With exposures to 1 and 11 ppm, Davtian [56] found testicular atrophy but no effect on male reproductive function. At 0.04 and 0.5 ppm,

Volkova et al [41] reported testicular atrophy and decreased spermatozoal motility. In contrast, Culik et al [66] could not demonstrate changes in male reproductive success at 25 ppm and found no histologic changes in the reproductive organs.

Recently, a confirmed case of angiosarcoma of the liver in a worker who had extensive exposure to finished polychloroprene (Neoprene) has been identified (PF Infante, written communication, March 1977). The worker had been employed as a roll builder during the period 1952-1962 when he applied neoprene to metal cylinders, which were then vulcanized. After this procedure, the material often would be cut to the desired size with a metal saw. The worker did not wear a mask, but an attempt to control dust by water sprays was made. Data for atmospheric levels of chloroprene were not available. A history of exposure indicated that this worker had never had occupational exposure to vinyl chloride, nor had he ever received Thorotrast, a diagnostic preparation also associated with the induction of angiosarcoma of the liver. Because of the chemical similarity between vinyl chloride and chloroprene, this observation may be important. On the other hand, this case of angiosarcoma of the liver could be one of the rare spontaneous tumors of this type and location.

In summary, the presently available data appear to be insufficient to formulate firm conclusions on the carcinogenicity of chloroprene. However, chloroprene is mutagenic in Salmonella [15,52]. Likewise, sex-linked recessive lethal mutations have been induced in Drosophila (E Vogel, written communication, July 1976). Infertility has been reported following exposure of male mice and rats to chloroprene [18]. Administration of chloroprene to male rats has also been associated with embryonic mortality

[55,56], testicular atrophy [41], and reduced numbers and motility of live spermatozoa in animals with nonatrophied testicles [41,56]. Although exposure of humans to chloroprene has not produced all the effects summarized above, male workers have had decreased numbers and motility of viable spermatozoa after exposure to chloroprene [22]. A threefold excess of miscarriages in wives of chloroprene workers has been reported [22]. Most investigators have found no apparent teratogenic risk from inhalation of chloroprene by rats and mice, although one study [64] reported hydrocephalus and cerebral herniation, and another [66] reported some increased, but statistically nonsignificant, skeletal abnormalities in offspring of exposed dams. The transplacental effects of chloroprene on embryos are somewhat less clear cut. There have been several studies on this subject [55,56,61,63,64], and some have indicated increased preimplantation deaths in rats [55,56,61]. Chloroprene has also been associated with increased chromosomal aberrations in bone marrow cells of rats [42,55] and mice [41]. Likewise, two studies have reported a significant excess of chromosomal aberrations in blood cells of chloroprene-exposed workers in comparison with those of controls [41,43]. NIOSH believes that, although any single study cited in this document may not allow definite conclusion that chloroprene is mutagenic, the consistency of positive mutagenic responses in various test systems and the number of systems yielding them, as well as additional observations indicating that chloroprene may affect the spermatozoa, testicles, and male reproductive function, establish a clear need to control chloroprene as a mutagenic agent.

TABLE III-5

EFFECTS OF CHLOROPRENE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory	-	973 ppm - 15 min	Nausea and giddiness	20
"	30 persons	334 - 56 ppm -	Fatigue, chest pains, heart palpitations, giddiness, irritability, dermatitis, hair loss	20
"	6 women	80.6 - 16.7 ppm -	Hair loss in 4	23
"	5 women and 13 men	1 5 ppm - 15 yr	Increased chromosomal aberrations in blood lymphocytes	43
"	65 men and women	1.95 - 0.8 ppm Up to 20 yr	Fatigue, headache, chest pains, chronic tonsillitis, menstrual disorders	41
"	246 boys and girls	0.13 - 0.04 ppm 9 mon	Increased steroid hormones in urine, diuresis	37
"	148 boys and girls	0.13 - 0.04 ppm 9 mon	Increased coproporphyrin in urine	33
"	155 persons	1 Unknown - 15 yr	Hypoglycemia, hypocholesterolemia, decreased carbonic anhydrase and reserve alkalinity in blood, decreased clotting time; increased total proteins, albumin, calcium, oxidized glutathione, fibrinogen, and chlorides in blood; hypotension	31, 32

TABLE III-5 (CONTINUED)

EFFECTS OF CHLOROPRENE ON HUMANS

Routes of Exposure	Subjects	Exposure Concentration and Duration	Effects	Reference
Respiratory	273 men and women	7 Unknown - 13 yr	Chest pains, variable pulse rate, hypotension, increased capillary permeability, myocardial dystrophy	25
"	2,934 men and women	Unknown 9.1 yr	59 cases of skin cancer	28
"	"	Unknown 8.7 yr	34 cases of lung cancer (2 expected)	29
"	120 women	Unknown	Decreased protein, cystine, lysine, arginine, valine plus methionine, leucine, and isoleucine in milk	39 40
"	208 men and women	"	Increased titer of "OH" agglutins and phagocytic index, decreased immune response	26
"	39 persons	"	Increased gamma globulins, decreased beta globulins	27
"	130 men and women	"	Chemical burns, hair loss, conjunctivitis, sexual impotency	24

TABLE III-6

EFFECTS OF CHLOROPRENE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Rats	13 M	6,227-121 ppm 8 hr	Reproductive failure	18
"	"	10	470 ppm 8 hr/d x 13 wk	Decreased body weight, red blood cells, and hemoglobin value	20
"	"	-	Up to 60 ppm -	Increased preimplantation deaths, reduction in placental weight	61
"	Mice	14 M 152	- 12 ppm 8 hr	Reproductive failure	18
"	Rats	-	14.8- 4 ppm -	Increased prenatal and neonatal death	63
"	"	36 M	10 ppm 4 hr/d x 48 d	Increased chlorides in urine, increased embryonic mortality	55
"	"	73 F	8.6- 0.14 ppm Up to 21 d	Increased embryonic deaths	62
"	"	11 F	4.1 ppm with 1.3 ppm ammonia 4 hr/d 18 - 19 d	Increased liver weights	59
"	"	-	1.1 ppm 2 - 14 d	Internal bleeding, hydrocephalus, cerebral herniations, and death of fetuses	64
"	"	205 F	1.11- 0.16 ppm 4 hr/d on d 1 - 21 of gestation	Increased embryonic mortality with increased concentration, decreased fetal weights and long bone lengths	60

TABLE III-6 (CONTINUED)

EFFECTS OF CHLOROPRENE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Rats	36 M	1 ppm 4 hr/d x 48 d	Decreased chlorides in urine	55
"	Rats Mice	- -	0.47- 0.14 ppm 4.5 mon	Testicular atrophy, decreased spermatozoal motility and resistance to acid, chromosomal disorders, increased dead spermatozoa	41
"	Rats	6 M	0.78 ±0.56 ppm 4 mon	Chromosomal aberrations in bone marrow cells	42
"	"	100 M	0.47 ±0.02 - 0.04 ±0.002 ppm 5 hr/d up to 5.5 mon	Increased embryonic mortality and preimplantation deaths in mated females, decreased spermatozoal vitality, motility, and acid resistance	56
"	"	100 M	0.014±0.0008 ppm 5 hr/d up to 5.5 mon	No effects	56
"	Mice	13 F	4.1 ppm with 1.3 ppm ammonia 4 hr/d 18 - 19 d	Increased liver and kidney weights and increased embryonic mortality	59
"	Cats	1	10 cc* 7.5 min	Irregular breathing, returning to normal after 7 min, lung edema, liver and kidney degeneration, hair loss	19

TABLE III-6 (CONTINUED)

EFFECTS OF CHLOROPRENE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Respiratory	Cats	1	Unknown	Difficult breathing, loss of muscular coordination, lung edema, liver and kidney degeneration, hair loss, death in 6 wk	19
Dermal	Mice	100	50% in benzene twice/wk x 25 wk	No skin tumors, 42 deaths	51
Oral	Rats Mice	54 60	500 - 50 mg/kg 1 dose	CNS depression, listlessness, sluggishness, vascular congestion; lung, liver, brain, spleen, and epicardial edema; inflammation of stomach, myocardial degeneration	47
"	Rats	100	200 mg/kg twice/wk x 25 wk	No tumors, 60 deaths	51
"	"	-	0.5 mg/kg x 14 d	Increased preimplantation and embryonic deaths	64
Subcutaneous	"	280	1,916 mg/kg -	LD50, pulmonary edema, hyperemia	20
"	"	110	400 mg/kg x 10 doses**	No connective tissue tumors, 22 deaths after 6 mon	51
"	"	-	200 mg/kg x 50 doses**	No connective tissue tumors	51
"	Rabbits	1	684 mg/kg on d 1, 5, 13, and 27	Lung edema, liver and kidney degeneration, hair loss, death on d 28	19

TABLE III-6 (CONTINUED)

EFFECTS OF CHLOROPRENE ON ANIMALS

Routes of Exposure	Species	No.	Exposure Concentration and Duration	Effects	Reference
Subcutaneous	Rabbits	1	417 mg/kg	No physical changes initially, death after 20 hr, lung edema, liver and kidney degeneration, hair loss	19
"	Cats	1	1,843 mg/kg	Initial increase in blood pressure, then gradual decrease until death in 41 min	19
ip	Rats	50	520 mg/kg 1 dose	LD50	24

*Liquid poured onto a mask

**Interval between doses not specified

IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

Sampling and Analysis

Airborne chloroprene concentrations can be measured directly with chemical indicator (Draeger) tubes by passing a known volume of air through the sampling tube, thus producing a stained zone on the indicator portion of the tube; the length of the stained zone is a measure of the concentration [73]. These tubes have been found to be satisfactory for concentrations in the range of 5-90 ppm, provided other organic vapors with double bonds (propene, butene, butadiene, vinyl chloride, etc) are not present [73]. The tube contains permanganate, which is reduced to manganese dioxide in the presence of a double bond, resulting in a yellow-brown stain. E. I. du Pont de Nemours & Company [11] reported that in the absence of olefinic compounds, Draeger tubes gave "very good agreement" when tested against a gas-chromatographic method (the coefficient of variation of the ratio is 10-15%) [73].

In 1954, Senderikhina [34] reported a method of microcombustion, which has since been used for analysis of airborne chloroprene samples in the USSR. The air samples were collected in ethanol and burned, liberating hydrogen chloride, which was then trapped in ammonium hydroxide and measured by turbidometric means, titrating the chloride ion. The presence of other chlorinated hydrocarbons interferes with the method, as it is nonspecific for chloroprene.

Babina [74], in 1969, described a colorimetric method using adsorption on silica gel, desorption with heat, and trapping of evolved chloroprene in acetic acid. Desorption from silica was nearly complete

within 5 minutes when 0.05-0.5 mg of chloroprene had been adsorbed. This sampling method was reported to be five times faster than collection in ethanol. The desorbed chloroprene was coupled with a paranitrophenyl diazonium salt [74]. The absorption at 380 nm was determined. The sensitivity was 0.005 mg, but ammonia interfered with the assay.

In 1971, Apoian et al [75] described an ultraviolet spectrophotometric method for chloroprene analysis. The authors described the construction of standard curves and the range (0.5-50 mg of chloroprene/10 ml of alcohol) of chloroprene sensitivity, but neither graphic presentation nor description of linearity within this range was presented. Sampling required the use of four impingers in series, each filled with 10 ml of 96% alcohol and immersed in ice. The type of alcohol was not stated. Air was drawn through the impingers at a flowrate of up to 5 liters/hour. Ultraviolet spectra were taken, and the absorption maxima at 222.6 nm were recorded. The method was described as five times more sensitive than microcombustion. The method is inconvenient because it requires keeping the impingers in ice and is impractical for personal sampling.

Hollis and Hayes [76], in 1962, described a gas-liquid chromatographic method of chloroprene analysis using 100-foot squalane capillary columns with triode argon detection. Using this system, 2-chloroprene was separated from the monochloro isomers of butene and 1-chloro-1,3-butadiene (alpha-chloroprene) at 30 C. The method was presented merely as a means of separating isomers, but the authors stated that, for precise work, exact calibration for each compound in the particular chromatograph being used would be necessary. No sampling method was

employed; known standards were injected directly into the chromatograph columns.

In 1974, NIOSH published its Manual of Analytical Methods [77]. E. I. du Pont de Nemours & Company [78] modified the general method, Organic Solvents in Air (P & CAM 127) [77], to separate and analyze 2-chloro-1,3-butadiene, 1-chloro-1,3-butadiene, 2,3-dichloro-1,3-butadiene, and toluene; 1,4-dichloro-2-butene was not tested. The method used adsorption on commercial charcoal tubes, sampling volumes as large as 10 liters, and two 12-foot x 1/8-inch stainless steel columns. The first column contained 10% silicon rubber U C W98 on Chromosorb W 80-100 mesh (Hewlett-Packard), and the second contained 20% Carbowax 20 M on Chromosorb P. Using conditions of helium carrier gas at 50 psig, 200 C injection port, 300 C detector, and 100 C oven, the following retention times were obtained: carbon disulfide, 225 seconds; 2-chloroprene, 300 seconds; 1-chloroprene, 360 seconds; 2,3-dichloro-1,3-butadiene, 660 seconds; and toluene, 790 seconds. The acceptable range of concentration for all compounds tested was 0.3-300 ppm. Recovery of chloroprene from the charcoal tubes ranged from 92% at 5 ppm to 100% at 86 ppm. Desorption efficiency ranged from 92% at 25 ppm to 98% at 390 ppm. A 10-liter air sample was used. Up to 280 ppm of chloroprene can be adsorbed onto charcoal from dry air, prior to breakthrough, using a 10-liter air sample.

A second analytical method for chloroprene alone was also described by Du Pont [78]. This procedure involved the use of the second column only, Carbowax 20 M on Chromosorb P. One-milliliter air samples were injected directly into the column. Chloroprene had a retention time of 150 seconds under the following conditions: column temperature, 100 C;

injection port, 200 C; detector, 200 C; helium flow, 25 ml/minute at 50 psig; hydrogen flow, 30 ml/minute at 10 psig; and airflow, 200 ml/minute at 30 psig. This method gave a linear response from 1 to 800 ppm.

Petrotex Chemical Corporation uses a very similar gas-chromatographic method with 6-foot columns packed with Carbowax 400 on Porasil S. The method is also satisfactory [11].

Hervin and Polakoff [79] used a Gastech halide meter in 1972 during a Health Hazard Evaluation of polychloroprene cement usage by a garage door manufacturer. How well such a halide meter functions in chloroprene detection and quantitation cannot be determined from this report because no chloroprene was detected in the trial.

The NIOSH method for chloroprene [80], using conditions validated for general organic solvents [77] (P & CAM 127, 10% FFAP on Chromosorb W), failed the validation test for chloroprene. The proper conditions were not used in the evaluation of desorption of chloroprene from activated charcoal tubes [80]. A second validation was carried out [81] using a 4-ft long, 1/3-in O.D. stainless steel column packed with 50/80 mesh Porapak Q. This method was validated for the range 12.3-47.5 ppm and is described in Appendix II. It has not been validated at the proposed occupational exposure limit, nor has the column been tested for identification of other compounds suspected to be present in the air of chloroprene manufacturing and polymerizing plants.

Although the method developed by Du Pont is claimed to have a greater sensitivity than the NIOSH method, NIOSH has not tested or validated the Du Pont method. NIOSH believes that its own method may be satisfactory for validation at a lower concentration than that at which its current

validation has been made.

Adsorption on charcoal tubes is a satisfactory method for chloroprene sampling, as desorption efficiencies range from 92% to more than 98% depending on the amount of chloroprene adsorbed. This is the product of the duration of sampling and the concentration in the air. Draeger tubes are acceptable for quick sampling. If olefins are present, the results obtained with these tubes will be high, and verification of the results by charcoal adsorption, carbon disulfide elution, and Carbowax gas chromatography is recommended. In this method, the sampling device is small and portable; thus it is useful for both personal and area monitoring. Chloroprene can be identified in combination with many other compounds. The sampling tubes, personal pumps, and gas-chromatographic columns required for this method are all commercially available.

Environmental Levels

Little information has been found concerning levels of atmospheric chloroprene. The first available sampling data were taken in 1948 by Nystrom [20]. Air concentrations of 56-334 ppm were measured at a Swedish chloroprene factory using an iodometric titration method. Lejhancova [23], in 1968, reported chloroprene air concentrations of 17-81 ppm (60-290 mg/cu m) in a plant manufacturing rubberized fabric in Czechoslovakia. No methods for sampling or analysis were described.

In 1954, Mnatsakanian presented data that had been included in the report by Apoian [75] on chloroprene air concentrations taken 500 and 7,000 meters from the chloroprene plant in Erevan, USSR. Mean diurnal levels were 0.5 and 0.04 ppm (1.8 and 0.14 mg/cu m), respectively. Chloroprene

air concentrations at the same distances were also determined between 1963 and 1964 to be 0.11 and 0.04 ppm, respectively. The methods of collection and analysis were not specified. Using a newly developed ultraviolet detection method, Apoian et al [75] reported in 1971 that the mean diurnal chloroprene air concentration in the Erevan plant was 7.9 ppm (28.4 mg/cu m), while the peak concentration was approximately 62 ppm (223 mg/cu m). Mean airborne chloroprene concentrations at 500 and 7,000 meters were 0.2 and 0.056 ppm, respectively. Katosova [43], in 1973, noted that the chloroprene air concentration in the Erevan plant was 5 ppm.

In 1975, Volkova et al [82] stated that chloroprene air concentrations ranged from 2.3 to 14.1 ppm in the Moscow Chemical Products Plant, where polychloroprene latex was used in the manufacture of rubber goods. At the Kazan Rubber Products Plant, the concentration of chloroprene in the air of the working zone averaged 2.2-2.8 ppm. These authors reported also, that, in the shoe industry, which used a polychloroprene latex containing about 0.1% free chloroprene, the work areas around shoe-gluing machines with local exhaust ventilation had a mean concentration of chloroprene in air of 1.7 ppm (6.1 mg/cu m). When the exhaust system was not working, the concentration of chloroprene in the air might rise to 20-30 mg/cu m. In 1976, Volkova et al [41] investigated the health of workers in a plant manufacturing gloves from polychloroprene latex. The use of latex in this operation gave rise to concentrations of chloroprene in air of 0.3 to 2.2 ppm.

At one chloroprene polymerization facility, preliminary air monitoring conducted in 1973 showed chloroprene emission sources in the workplace with levels as high as 6,760 ppm (WE Egan, written communication,

May 1975). These levels were peak levels obtained by collection in glass sampling flasks and analysis by gas chromatography. The data are shown in Table IV-1. Eight-hour time-weighted average exposure levels found at the same plant in 1975 ranged from 0.51-39.18 ppm (Table IV-1), which were considerably below those found in 1973. The 1975 survey was carried out using charcoal tube collection of the samples with subsequent gas-chromatographic analysis. No information on the individual assay methods was supplied. More recently (1976), average air concentrations of 2-9 ppm were reported in US chloroprene manufacturing plants, including the one from which the previous data were obtained [11 (pp 9,41,51)]. Investigation by Hervin and Polakoff [79] of a factory using polychloroprene rubber cement found no detectable chloroprene with the Gastech halide meter.

TABLE IV-1
ATMOSPHERIC CHLOROPRENE CONCENTRATIONS
AT A POLYMERIZATION PLANT

Area	No. of Samples	Mean Concentration* (Range)	No. of Samples	Mean 8-hour TWA Concentration** (Range)
Make-up	10	554 (14 - 1,420)	17	12.0 (1.6 - 39.2)
Reactor	21	1,015 (130 - 6,760)	-	-
Monomer Recovery	2	223 (6 - 440)	4	2.0 (0.2 - 6.8)
Latex	2	205 (113 - 252)	6	0.7 (0.5 - 1.7)

* All values in ppm, 1973 sampling

**All values in ppm, 1975 sampling

From WE Egan (written communication, May 1975)

Engineering Controls

Engineering controls must be designed and operated to reduce the inhalation of chloroprene vapors and limit skin contact with chloroprene liquid. Closed systems of production should be used wherever possible to limit possible exposure of employees to chloroprene. Closed systems are effective only when their integrity is maintained by frequent inspection for, and prompt repair of, any leaks. Where the use of closed systems is not compatible with the process, local exhaust ventilation must be provided to direct the hazardous chemical away from the employee. Guidance for designing ventilation systems can be found in Industrial Ventilation--A Manual of Recommended Practice [83] and in the American National Standards Institute's Fundamentals Governing the Design and Operation of Local Exhaust Systems (Z9.2-1971) [84].

Enclosures, ductwork, and exhaust hoods must be kept in good repair so that design velocities are maintained. Airflow measurements must be taken at each exhaust hood at least every 6 months, and preferably monthly. Continuous airflow indicators (such as simple oil or water manometers) are recommended; they should be properly mounted and marked to show design airflows.

Because any monomer in the polymerized latex will be volatilized during the drying of films, coatings, foam, and other products, it is necessary to provide ventilation for drying ovens and other process equipment [12]. Other areas where ventilation may be necessary include open latex drums, open transfer points, dipping machines, spray units, and tanks [12].

Biologic Evaluation

No literature on biologic evaluation and biologic monitoring has been found.

V. WORK PRACTICES AND SANITATION

In the manufacture and use of chloroprene, work practices and sanitation must be designed to minimize ingestion, inhalation, and contact with skin and eyes. Good work practices are a primary means of controlling certain exposures and will often supplement other control measures. Enclosure of manufacturing processes and operations is effective in controlling exposure only when the integrity of the system is maintained. Systems should be closed whenever possible. Closed systems should be inspected frequently for leaks, and any leaks found should be promptly repaired. Special attention should be given to the condition of seals and joints, access ports, pumps, and possibly hazardous locations, such as polymerization areas and the vicinity of latex-storage tanks.

Ventilation systems require annual inspection and maintenance to ensure their effective operation. The effects of any changes or additions to the ventilation systems or to the operations being ventilated should be assessed promptly, including measurements of airflow and of environmental concentrations of chloroprene. Work practices should not introduce obstructions or interferences that would reduce the effectiveness of the ventilation. Further protective measures include the use of personal protective equipment and clothing and purging of appropriate equipment prior to and during servicing and maintenance operations.

The handling of chloroprene should follow appropriate guidelines for flammable liquids as specified in 29 CFR 1910.106 (a-e). Large spills represent a fire hazard; therefore, special precautions must be taken to prevent spills. Large spills may be handled by containment, evacuation,

and disposal. Storage tanks must be diked to contain the contents of tanks. Areas where major spills are likely to occur should be constructed so that they may be closed off until properly protected personnel can ventilate, enter, and clean the area. Chloroprene spills should be cleaned up immediately. Large spills should be pumped from the diked area to another tank. Because the main danger from large spills is fire, all operations that may be a source of ignition must be stopped until the spill is cleared. Also, precautions should be taken to prevent polymerization, eg, add antioxidants and cover with foam [11 (p 18)], since uncontrolled polymerization can generate sufficient heat to initiate combustion. Firefighters should be equipped with self-contained breathing apparatus operating in the pressure-demand mode and an impervious suit. Firefighters and other personnel should be warned that chloroprene combustion products may include noxious gases such as hydrogen chloride.

Small spills should be absorbed with rags, vermiculite, sand, etc, and the area should be flushed with water. Workers should wear appropriate respirators and protective clothing during cleanup. Contaminated rags should be stored in metal containers with tight-fitting lids prior to disposal. Disposal of chloroprene and polychloroprene wastes shall be done in compliance with local, state, and federal waste disposal regulations. Liquid waste should be burned completely, with concomitant entrapment of evolved hydrogen chloride. Solid waste should be burned or disposed of in a landfill.

In areas and at operation sites where the use of respiratory protective devices is required, the employee entering and working in such areas should wear the appropriate type of respirator as specified in

Chapter I. In addition, the employee must observe and participate in the respiratory protective program. Since respirators may fail as a result of many factors, the employee should be made aware of the need for cleanliness and maintenance of respirators on a continuing basis.

Because there is evidence that chloroprene is a mutagen in lower organisms, that it has effects on reproduction, and that it may be a carcinogen, NIOSH recommends that only self-contained or supplied-air respirators be used to prevent respiratory exposure to chloroprene during the situations in which respirators are required. Such respirators provide maximal protection against inhalation of toxic agents when properly fitted and donned, with testing for leakage after donning. Respirators provided by employers for use by employees should meet the requirements of 29 CFR 1910.134.

A major hazard of handling chloroprene that can be minimized by good work practices is skin and eye contact. Studies with animals indicate that systemic poisoning may result from skin contact with chloroprene [18,20,51]. Skin contact causes chemical burns; the severe effects are increased by the penetration of chloroprene into the clothing and shoes, which act as reservoirs and intensify the contact. Clothing contaminated with chloroprene must be removed immediately [11 (pp 18,19)] and thoroughly laundered before reuse. Care should be exercised to keep contaminated clothing away from street clothes. Shoes on which chloroprene has been spilled are to be rendered useless and discarded. Protective clothing must be made of material impermeable to chloroprene. When it is necessary to work with liquid chloroprene, the following special handling techniques should be employed routinely. All body surfaces should be protected

against contact with the liquid by the use of gloves, aprons, face shields, rubber boots, and other protective equipment or clothing. The liquid should be placed in closed containers. When exposure to liquid dichlorobutenes is possible, acid suits with supplied air should be used.

In the event of skin contact, the exposed area should be thoroughly washed with soap and water and a physician contacted. If the eyes are contaminated with chloroprene, they must be flushed with water for 15 minutes. Medical attention should be obtained as quickly as possible.

The flashpoint of chloroprene is -20 C (-4 F) [4]. It is classified as a flammable liquid of Class 1 B as defined in 29 CFR 1910.106(a)(19)(ii). The explosive limits in air at 20 C range from 4 to 20% (Table XII-1). Because chloroprene's flashpoint is -20 C, fire is a serious potential hazard, especially during spills. Work practices should be followed that ensure that no flames or other sources of ignition, such as cigars, cigarettes, pipes, lighters, and matches, are permitted in the area where chloroprene is stored, handled, or manufactured.

Safety showers, eyewash fountains, and fire extinguishers shall be located in or near areas where chloroprene exposure is likely to occur and shall be properly maintained. Handwashing facilities, soap, and water must be available to the employees. As good hygiene practices, eating in chloroprene manufacturing and polymerization work areas shall be prohibited, and hands should be washed before eating. Medical and first-aid facilities should be available as prescribed in 29 CFR 1910.151 (a-c). Selective assignment of employees may have to be practiced to protect individuals who display hypersensitivity to chloroprene.

The present method for the manufacture of chloroprene in the United States involves the chlorination of butadiene [6], so suitable controls for safe use of butadiene and chlorine should be used. Engineering controls required for the safe handling of chlorine are discussed in the NIOSH criteria document on occupational exposure to chlorine [87] and the Manufacturing Chemists' Association's (MCA) Safety Data Sheet SD-80 [88]; handling of butadiene is discussed in MCA Safety Data Sheet SD-55 [89]. The major hazards from butadiene are its flammability and explosive characteristics. Dichlorobutenes are intermediates in chloroprene manufacture, and caution must be taken to avoid exposure to these substances as well.

In summary, precautions must be exercised against overexposure to chloroprene. It is important that employees be informed of hazards associated with the use of chloroprene before job placement and when any process changes are made that may alter their exposure. Appropriate emergency procedures should be prominently displayed. The US Department of Labor "Material Safety Data Sheet" shown in Appendix III, or a similar form approved by the Occupational Safety and Health Administration, must be filled out. In addition, all employees in the chloroprene manufacturing and polymerization areas shall be instructed on the location of the safety sheet. If all of these work practices are observed and good engineering controls are installed, employees working with chloroprene should be adequately protected from associated hazards.

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The present federal standard (29 CFR 1910.1000) for chloroprene is an 8-hour time-weighted average (TWA) concentration of 25 ppm (90 mg/cu m). This standard was adopted from the listing published in 1968 by the American Conference of Governmental Industrial Hygienists (ACGIH) [86].

This 25-ppm value has remained unchanged since it was first recommended as a maximal allowable concentration (MAC) by Cook [90] in 1945. The MAC of 25 ppm was based on the report of Von Oettingen et al [18] in 1936. In this study, inhalation of chloroprene for up to 91 days at a mean concentration of 56 ppm, with a range from 28 to 98 ppm, produced signs of toxicity in male rats and mice. The mice were more susceptible; 9 of 20 mice versus 2 of 10 rats died during the course of the study. Some deaths may have resulted from bacterial infection. In their summary, the authors [18] stated that "with continued exposure, 0.3 mg/liter (300 mg/cu m) [of chloroprene] and less, may cause toxic effects" (0.3 mg/liter = 83 ppm). Cook [90] suggested the establishment of a "25 ppm level (for humans) until further data are available as to effects on man on prolonged exposure."

Cook's suggestion for an MAC of 25 ppm was adopted by the ACGIH in 1946 [91]. In 1948, the nomenclature for permissible concentrations of toxic substances in the air was changed from an MAC to a threshold limit value (TLV) to avoid confusion about the word "allowable" in the MAC concept [92]. This in essence, however, changed the standard from a ceiling concentration not ever to be exceeded to an average concentration

that could be exceeded for comparatively short times. The definition of a TLV as a TWA concentration was formulated in 1953 by the ACGIH, thus changing the standard for chloroprene to a TLV of 25 ppm as an 8-hour TWA concentration. The 1966 ACGIH listing [93] included the notation "skin" along with the recommended 25-ppm TLV to indicate that liquid chloroprene could be absorbed through the skin and cause systemic effects. The 1971 ACGIH Documentation of Threshold Limit Values for Substances in Workroom Air [94] gave the basis for the 25-ppm TWA value for chloroprene. Cited in the Documentation were the studies by Von Oettingen et al [18] (see above); by Nystrom [20], who stated that a tolerated limit for humans in occupational environments should be below 300 mg/cu m (83 ppm) even though rats tolerated this concentration for 13 weeks; and by Ritter and Carter [21], who reported that occupational hair loss resulted from small intermediate chloroprene polymers and not from chloroprene itself. The list of TLV's for 1976 added a tentative short-term environmental limit (STEL) of 35 ppm (135 mg/cu m); however, no basis for it has been given [95].

The International Labour Office (ILO) published Permissible Levels of Toxic Substances in the Working Environment [96] for several countries in 1970. The standards for chloroprene in the USSR, Bulgaria, Poland, and German Democratic Republic are maximal air concentrations, ie, absolute limits never to be exceeded [96]. They are concentrations that may be expected to produce no detectable physical deviations from normal in any exposed person. In the USSR, harmful concentrations have been defined loosely as levels that cause any type of aberration [96,97]. Other Eastern European countries have tended to use the USSR's values as guidelines [96].

Some countries tend to follow the concept of maximal air concentrations in setting their standards, while others follow the guidelines and values of the ACGIH [96]. Table VI-1 shows the present international chloroprene standards.

TABLE VI-1

LISTING OF INTERNATIONAL CHLOROPRENE STANDARDS

Country	mg/cu m	ppm
Bulgaria	2	0.56
Czechoslovakia	50* 100**	14* 28**
Federal Republic of Germany	36	10
Finland	90	25
German Democratic Republic	10	2.8
Great Britain	92	25
Poland	4***	1.1
Rumania	50	14
Soviet Union	0.05	0.014
Sweden	90	25
United States	90	25
Yugoslavia	90	25

*Mean concentration

**For brief exposures (peak)

***Was 2 until 1974

Adapted from references 96,99,102

The USSR standard of 2 mg/cu m (0.56 ppm) reportedly was based on scientific papers spanning three decades. Sanotskii [22] stated that the 2-mg/cu m maximal air concentration for chloroprene was set in the USSR in the 1940's on the basis of calculations and data in the literature; no further information was given. The International Labour Office [96] reported that the 1970 Russian standard for chloroprene was 2 mg/cu m. In 1975, the standard was still reported as 2 mg/cu m by Winell [98] and Volkova et al [82]. Although the Russian standard was quoted as 2 mg/cu m as recently as March 1976 [41], Sanotskii [22] has since recommended that the maximal air concentration allowed in the Russian workplace be 0.05 mg/cu m (0.014 ppm). This change was stated to be based on the toxic effects observed in rats and on the results of some human studies carried out in the USSR by Volkova et al [41]. Increased numbers of chromosomal aberrations were observed in the lymphocytes of women employed in a plant using polychloroprene latex and in bone marrow cells from mice exposed to chloroprene vapor. Reproductive effects in male rats, which included testicular atrophy and decreases in spermatozoic motility and acid resistance, were also reported.

The Czechoslovak Committee of Maximal Air Concentration [99] addressed the lack of a published basis for the Soviet standard in 1968. The Czechoslovak standard was a mean of 100 mg/cu m (27 ppm), based on the work of Von Oettingen et al [18] and Roubal [19], but was lowered to a mean of 50 mg/cu m (13.6 ppm), with a peak of 100 mg/cu m, in 1967 after private consultation of the Committee with Roubal [99]. In 1942, Roubal [19] had reported chloroprene-induced loss of scalp hair and chest pains in humans exposed at workplace concentrations of approximately 76 ppm.

The West German standard had been 90 mg/cu m (25 ppm) until 1975, when the maximal workplace concentration (MAK) was dropped to 36 mg/cu m (10 ppm). The reason for this change, given in the 1975 MAK Documentation [2], was uneasiness over the findings of Davtian et al [55] and Khachatryan [28,29]. The Documentation [2] reiterated the view that the Khachatryan papers were ambiguous and difficult to evaluate.

Basis for the Recommended Standard

(a) Permissible Exposure Limit

From the review of the literature presented on the biologic effects of chloroprene in Chapter III, it is apparent that, excluding reproductive and questionable carcinogenic effects, little toxicologic data from human and animal exposures are available to justify altering the standard for chloroprene in the work environment. Most of the reported effects occurred above 25 ppm. Chloroprene produces a wide array of effects, so that identification of primary target organs or systems at low concentrations is difficult. No information on chloroprene pharmacokinetics in animals or humans has been found. Mnatsakanian's [100] attempts to identify a mechanism of action for chloroprene required such high exposure concentrations for rats, from 556 to above 5,560 ppm, that consideration of his results for setting human exposure limits is not possible.

The major toxic effects on workers from chloroprene worker exposure are abnormalities in CNS function [1,20,46] and skin and eye irritation [19,24]. With respect to effects on CNS function, chloroprene is similar to other chlorinated hydrocarbons. Further, it produces changes regarded as typical of chlorinated hydrocarbon toxicosis, including degenerative

changes in the liver, resembling those produced by methylene chloride, dichloroethane, and chloroform. Complaints commonly reported in the past by workers using chloroprene include headache [41], impairment of memory [46], irritability [20], decreased pulse rate [25,41], increased pulse rate [25], chest pains [19,20,25,41], sleepiness [46], extreme fatigue [19,20,41], loss of scalp hair [21,23,68,69], and irritation of the conjunctiva [19,24]. Symptoms of severe fatigue and chest pains disappeared and scalp hair returned when workers were removed from exposure to chloroprene; however, chest pains recurred on intensified activity [20]. In most instances, the air concentrations at which these effects occurred are unknown.

Nystrom [20] reported that exposure to chloroprene at air concentrations of 3,500 mg/cu m (about 972 ppm) led to nausea and giddiness after 15 minutes; exposures from 56 ppm to more than 334 ppm led to narcosis and, at what was judged to be a very high concentration, death in a worker. Hair loss in women, after exposure to concentrations of 17-81 ppm, was described by Lejhancova [23]. Exposure at lower concentrations has given rise to toxic signs, the significance of which is difficult to judge. For example, chloroprene at air concentrations of 0.08-0.14 ppm has been reported to cause parallel increases in urinary excretion of 17-ketosteroids and coproporphyrin and increased micturition [33,100]. Excretion was observed to increase with increased exposure, but all quantities were within the normal ranges. Other symptoms and signs of exposure to chloroprene in humans have not been linked to specific air concentrations and are therefore unsuitable for development of an environmental limit.

There is no question that chloroprene is toxic at high concentrations. Von Oettingen et al [18] reported that exposure of rats to chloroprene at air concentrations of 6,227 ppm killed all animals within 1 hour. Exposure at air concentrations of 1,751 or 612 ppm for 8 hours killed all animals within 3-5 days; exposure at 278 ppm killed 25% of the exposed rats. Nystrom [20] reported that exposure of rats to chloroprene at air concentrations of 334 ppm for 8 hours/day resulted in the death of 50% of the rats by the 13th week. This exposure led to significant decreases in body weight, red blood cell count, and blood hemoglobin concentration, but increased the leukocyte count. Exposure at 56 ppm for 8 hours/day for 5 months caused no deaths. None of the changes seen at 334 ppm were observed at 56 ppm, and changes found in post-mortem examinations were described by the author as "inconsiderable." Von Oettingen et al [18] found enlarged spleens and edema of the lungs, brain, and liver when rats were exposed to chloroprene at air concentrations ranging from 27 to 97 ppm (the average was 56 ppm), but no deaths resulted. However, the chloroprene used in the study by Von Oettingen et al [18] was not stated to have been protected from air oxidation. Nystrom [20] has shown that the oxidized form of chloroprene was about four times as toxic to rats as pure chloroprene; LD50's for subcutaneous injection were 2 μ l/g versus 0.5 μ l/g of body weight for pure and oxidized chloroprene, respectively. Mnatsakanian [101] has stated that peroxides of chloroprene play a key role in chloroprene's toxic effects.

The study by Culik et al [66] demonstrated the lack of embryotoxicity to rats at chloroprene concentrations of 25 ppm and below. Deleterious effects on male fertility were not reported to have been observed in this

study. Questionable evidence of teratology (skeletal abnormalities) were found with the highest exposure of the dams. Investigations have reported the results of studies on embryotoxicity after exposure to chloroprene vapor concentrations of less than 1 to 4 ppm [59-61,62]. It is not possible to evaluate these studies adequately for several reasons. Proper controls were not always included. Animal exposure was sometimes carried out in the chloroprene manufacturing plant where many other compounds in addition to chloroprene were found in the air. Total embryonic mortality was neither defined nor broken down into preimplantation and postimplantation deaths; mortality only was given as a percentage. As no litter size or number of affected litters was indicated in many instances, the significance of a percentage of total embryonic mortality is difficult to interpret.

Salnikova and Fomenko [64] reported the appearance of hydrocephalus and cerebral herniation in all fetuses from rat dams given chloroprene in oral doses of 0.5 mg/kg during 14 days of pregnancy. Inhalation of 1.11 ppm chloroprene vapor between the 5th and 14th days of pregnancy also resulted in percentages of hydrocephalus ranging from 6 to 34 in several series of experiments, while no cases of hydrocephalus were observed in controls. These data suggest that chloroprene may be teratogenic in animals.

No adequate data on which to base a firm judgment on the carcinogenicity of chloroprene are available at this time. A number of studies (listed in Chapter III) have been initiated after a great deal of publicity about two papers published by Khachatryan [28,29]. These papers suggested that working in plants manufacturing polychloroprene synthetic

rubber from acetylene or in shoe factories in which concomitant exposure to chloroprene and many organic solvents occurs may increase the risk of skin and lung cancer. Surveys in the same manufacturing plant in 1968 had found air concentrations of chloroprene ranging from 0.04 to 61 ppm [75]. The mean daily concentrations were as high as 15 ppm (average 7.7 ppm). There are many shortcomings and inconsistencies in these papers that preclude a firm judgment that occupational exposure to chloroprene may cause cancer.

Pell [30] has suggested that a 25-ppm workplace environmental limit for chloroprene is safe despite the fact that he noted a disproportionately high incidence of lung cancer in maintenance workers, a group expected to have relatively high exposure to chloroprene. The frequency of occurrence of lung cancer in chloroprene workers was the same as expected when compared with the US male population.

The presently available data appear to be insufficient to formulate firm conclusions on the carcinogenicity of chloroprene. However, chloroprene is mutagenic in *Salmonella* [15,52]. Likewise, sex-linked recessive lethal mutations have been induced in *Drosophila* (E Vogel, written communication, July 1976). Infertility has been reported after chloroprene exposure of male mice and rats [18]. Administration of chloroprene to male rats has also been associated with embryonic mortality [18,41], testicular atrophy [41], and reduced numbers and motility of live spermatozoa in animals with nonatrophied testicles [41,56]. Although exposure of humans to chloroprene has not produced all the effects summarized above, male workers have had decreased numbers and motility of viable spermatozoa after occupational exposure to chloroprene [22]. A threefold excess of miscarriages by wives of chloroprene workers has been

reported [22]. There seems to be no great risk of teratogenicity from inhalation of chloroprene by rats and mice, although one study [64] reported hydrocephalus and cerebral herniation, and another [66] found some skeletal abnormalities. The lethal effects of chloroprene on embryos are somewhat less clear cut. There have been several studies on this subject that may indicate increased preimplantation death in rats [55,56,61,62]. Chloroprene has also been associated with increased chromosomal aberrations in blood cells of chloroprene-exposed workers as compared with those of controls [41,43].

Several investigators have reported adverse effects on reproduction or reproductive function following exposure of males to chloroprene. Von Oettingen et al [18] reported interference with reproduction in male rats from skin applications of 0.5-1.5 ml of chloroprene (20 applications during 34 days). Exposure of male rats at concentrations of 120-6,227 ppm (434-22,419 mg/cu m) and of male mice at concentrations of 12-152 ppm (42-548 mg/cu m) for 8 hours resulted in sterility or impotence in 13/19 rats and in 8/14 mice. Unexposed male rats (five) and mice (five) were both potent and fertile. Five female mice exposed to chloroprene at a concentration of 151 ppm (594 mg/cu m) for 8 hours all became pregnant on mating with unexposed males. Degenerative changes in the testes were observed in some of the animals exposed by inhalation. Davtian et al [55] observed that chloroprene inhalation at 1 ppm to male rats did not affect fertilization capacity; however, mating of these animals resulted in a significant excess of embryonic mortality. The investigators reported that this same low concentration of chloroprene induced chromosomal aberrations in bone marrow cells in these animals. The study suggests that germinal and somatic cells

are identically sensitive to low-level (1 ppm) exposure to chloroprene. Davtian [56] reported a significant excess of embryonic mortality following exposure of male rats to chloroprene at a concentration of 0.04 ppm (0.15 mg/cu m). At the same exposure level, testicular atrophy and a reduction in the numbers and motility of sperm in animals with nonatrophied testes also were reported. Consistent with the above-mentioned mutagenic and adverse reproductive effects in animals is the report by E Vogel (written communication, July 1976) demonstrating chloroprene-induced, recessive lethal mutations in *Drosophila*. In this assay system, genetic damage is observed two generations subsequent to exposure of the male fruit fly. Further evidence for the mutagenicity of chloroprene has been demonstrated in *Salmonella typhimurium* strains by Bartsch et al [15,52] and by the report from Litton Bionetics (RS Barrows, written communication, August 1976).

Observations in humans are consistent with findings in animal experimental systems. Three studies have indicated a significant excess of chromosomal aberrations in blood cells of workers exposed to chloroprene as compared with those in controls [41,43, and NP Bochkov, written communication, March 1976]. In one study [43], the chloroprene concentration was reported to be 5 ppm. In a second study [41], the concentration in air ranged between 0.8 and 1.95 ppm. No environmental data were reported in the third study. In addition, morphologic disturbances in the sperm of workers exposed to chloroprene levels ranging from 0.28 to 1.94 ppm have been reported [22]; a threefold increase of spontaneous abortion in the wives of chloroprene-exposed workers also was reported.

Because there are indications that occupational exposure to chloroprene may increase the incidence of cancer of the lungs, may exert embryotoxic and fetotoxic effects, and may interfere with reproductive processes, particularly in the male, as well as produce chromosomal aberrations in peripheral lymphocytes [41-43], NIOSH believes that it is prudent to limit occupational exposure to chloroprene to concentrations in the air of the workplace no greater than 1 ppm, determined in samples collected from the worker's breathing zone during 15-minute periods. Scheduling of sampling should be performed by a qualified industrial hygienist to conform with good industrial hygiene practice.

Because no threshold is known to exist for mutagens and the epidemiologic method for detecting inherited mutations in humans is at best limited and insensitive, the standard must necessarily be based on testing in animals species. The adverse risk of genetic abnormalities being transmitted to subsequent generations by an agent with the mutagenic properties of chloroprene is the main reason for NIOSH's recommendation that the occupational exposure limit for chloroprene be lowered from its current value. The change in the standard is not necessarily based on the position that, from presently available information, the 1-ppm level is absolutely safe for protection against genetic damage. Rather, the 1-ppm standard is based upon a lower concentration that can be measured readily under field conditions by the analytic methods currently available.

Studies should be undertaken to elucidate the metabolic fate of chloroprene. Additional studies of chloroprene's toxic effects, including carcinogenesis, in various species are needed. Some of the work presently

underway may provide some of this information, but more effort in these directions is needed.

It is recognized that many workers handle neoprene latex in work situations where there is, at present, relatively low-level exposure to chloroprene monomer. These concentrations could be reduced to well within the proposed standard through process change directed toward increased recovery of unreacted monomer from the polymer. Under these conditions, it should not be necessary to comply with some of the provisions of this recommended standard. The standard has been prepared primarily to protect worker health from genetic damage during chloroprene manufacture, polymerization, and use. Concern for genetic damage requires that protective measures be instituted below the enforceable limit to ensure that exposure of workers to chloroprene stays below 1 ppm.

(b) Sampling and Analysis

Charcoal tube sampling is recommended for collection of airborne chloroprene vapors because it is an efficient, inexpensive method and is widely used for other chlorinated and nonchlorinated organic vapors. Gas chromatography is recommended for the analysis of chloroprene samples because it has been shown to be accurate and precise, and variations of the method are used for organic compounds in many industries both for sampling and for quality control. The recommended methods are presented in Appendices I and II, although other methods of comparable reliability and accuracy are acceptable. The relative merits of other sampling and analytical methods are discussed in Chapter IV.

(c) Medical Surveillance and Recordkeeping

In view of the documented effects of human exposure to acetylene-derived chloroprene and other compounds produced concomitantly with chloroprene manufacture and use, NIOSH recommends comprehensive preplacement and periodic medical examinations. Detection of respiratory and hepatic abnormalities and of cutaneous conditions that might be aggravated by exposure to an irritant chemical is especially important. Medical records, with supporting documentation, must be retained for the duration of employment plus 30 years.

(d) Personal Protective Equipment and Clothing

Impervious protective equipment, used in accordance with 29 CFR 1910, Subpart I, is recommended to minimize the risk of chemical burns and of eye and throat irritation. This equipment should include face shields, boots, aprons, gloves, and protective clothing. Clothing that has been contaminated with chloroprene must be immediately replaced to prevent burns. Respiratory protection, in accordance with Table I-1, should be used by employees who must work in concentrations of chloroprene vapor that exceed the recommended environmental limit.

(e) Informing Employees of Hazards

Continuing education is an important part of a preventive hygiene program for employees. Workers should be periodically instructed by properly trained persons about the possible sources of exposure, the adverse health effects associated with exposure to chloroprene, the engineering and work practice controls in use or being planned to limit exposure, the danger of fire or explosion from chloroprene, and environmental and medical monitoring procedures used to check on control

procedures. The functioning of monitoring equipment, such as personal samplers, should be explained so that employees understand their part in environmental monitoring. Medical monitoring procedures, especially the use of chest X-ray films and pulmonary function tests, and their importance in detecting possible adverse health effects should be explained.

(f) Work Practices

The flammability and toxicity of chloroprene necessitate conformance to proper work practices. Work practices that diminish contact with or inhalation of chloroprene, such as those discussed in Chapter V, should be followed. Procedures for emergency situations, control of airborne chloroprene, sanitation, and maintenance must be understood and followed by employees occupationally exposed to chloroprene. Employee entry into confined spaces must be controlled by a permit system or equivalent, and these areas should not be entered until the atmosphere has been tested for oxygen deficiency and chloroprene contamination. When necessary, however, proper respiratory protection should be used in entering these areas.

Engineering controls must be used when needed to keep concentrations of airborne chloroprene within the recommended concentration limit. These controls are discussed in Chapter V. During the time required to install adequate controls and equipment, make process changes, perform routine maintenance operations, or make repairs, exposure to airborne chloroprene at concentrations above the recommended environmental limit must be prevented by the use of respirators and protective clothing or, in some cases, by administrative controls.

(g) Monitoring and Recordkeeping Requirements

Industrial hygiene surveys as soon as possible after the promulgation of the recommended standard and within 30 days of any process change are necessary to determine whether exposure to chloroprene at concentrations above the recommended environmental limit may occur.

Records of environmental and industrial hygiene surveys must be kept for the duration of employment and for 30 years afterward to enable the estimation of exposures during the employee's working lifetime.

VII. RESEARCH NEEDS

This review of the toxicity of chloroprene reveals several areas requiring further research. Epidemiologic studies of industrial workers in contact with chloroprene must be undertaken. Considering the number of compounds to which these persons may be exposed, the concentrations of each of these compounds in the workplace air should also be determined. Eating, drinking, and smoking habits and past working experiences must also be considered in these studies.

Studies should be undertaken to determine the factors that make some individuals especially susceptible to the toxic actions of chloroprene. Mechanisms of adaptation to toxic effects by chloroprene need study. Experimental study of the interplay between the effects of chloroprene and those of other chemicals and drugs should be undertaken. Further teratologic studies should be done to clarify the inconsistencies observed by various investigators. Studies should also be undertaken to elucidate the metabolic fate of chloroprene. Additional carcinogenicity studies in various species are needed to clearly prove or disprove the suggestion that chloroprene may be a carcinogen or a cocarcinogen. Some of the work presently underway, listed below, may answer some of these questions, but more effort is needed.

Epidemiology

One of the most pressing research needs for chloroprene is updated information concerning worker exposures and corresponding health effects,

if any, in the contemporary working environment. A carefully designed and meticulously executed epidemiologic study of industrial workers with chloroprene contact should be undertaken. Since chloroprene workers are exposed to other toxic substances, the air concentrations of these other compounds should also be determined. Personal habits, such as eating, drinking, and smoking, should be noted and these activities weighed in the interpretation of the study's morbidity and mortality data. The incidences of various types of cancer should be recorded, as well as those of elevated blood cholesterol, atherosclerosis, abnormalities of liver and kidney functions, reproductive abnormalities, and disorders of the nervous system.

The retrospective study by Pell [30] has dealt adequately with the problems of persons initially lost to observation. However, there is a complete lack of information on exposure concentrations, and the longest exposure period occurred during manufacture by a process no longer in use in the United States. Investigators should be encouraged to monitor worker morbidity and mortality along with measurements of the exposures of the employees studied. T Norseth (written communication, November 1976) has indicated that the Norwegian government is initiating an epidemiologic study of rubber workers. Chloroprene is not manufactured in Norway but is used there, so this study may afford some useful information about the effects of chloroprene on human health.

Mutagenicity

The mutagenicity of chloroprene should be examined in greater detail. Because of the inconsistent results obtained previously with the Ames screening test, these studies should be expanded, running each plate in

triplicate to clarify the significance of small increases in mutation rate and using a larger variety of tester strains. When single plates are used, the significance of a spuriously high number of revertants is often difficult to assess. Mutagenicity should be tested in cultured mammalian cell lines also. Studies of the in vitro effects of airborne chloroprene on cultured human lymphocytes are also suggested.

The question of mutagenicity in vivo in mammals must also be addressed. Standardized techniques of mutagenicity testing are desirable. For further information, the Department of Health, Education, and Welfare's Draft Document on Methods for Determining the Mutagenic Properties of Chemicals, (DHEW Subcommittee on Environmental Mutagenesis, personal communication, March 1977) should be consulted.

Long-term Animal Toxicity

Inhalation exposure of various species of animals (in connection with the mutagenicity study perhaps) at several concentrations of pure and oxidized chloroprene up to 250 ppm, 8 hours/day, 5 days/week, for up to 2 years is suggested. These experiments should include measurement of important biochemical and physiologic parameters. Similar studies after application of chloroprene to the skin of animals of both sexes of various species are desirable also.

The National Cancer Institute's Bioassay Program screen for chloroprene carcinogenicity is monitoring studies now in progress concerning chloroprene: a bioassay screening study underway at the International Agency for Research on Cancer (IARC) in Lyon, France, a lifetime inhalation toxicity study in rats by the Central Institute for

Nutrition and Food Research in Zeist, Holland, begun in February 1976, and a Soviet-sponsored 2-year inhalation study (already half completed).

The IARC study involves oral administration of chloroprene to pregnant rats at doses of 100 mg/kg and observation of the offspring through 120 weeks of age (H Bartsch, written communication, October 1976). The Central Institute for Nutrition and Food Research's study proposal [8,103] involves a 1-year inhalation exposure of rats to chloroprene with observation continuing through a 2nd year. The study will also address mutagenicity in bone marrow cells, spermatozoic mortality, and chloroprene elimination from the body. One hundred rats of each sex will be exposed to chloroprene at concentrations of 50 and 10 ppm.

Metabolism

The metabolic conversion of chloroprene within the animal body and the effects of chloroprene on normal metabolism should be studied. Studies to determine the rates and routes of absorption and excretion of chloroprene and its metabolites should be undertaken also.

Immune Response

The literature indicates that chloroprene interferes with the body's immune response [26,27,50]. It is therefore important to investigate the effects of chloroprene on the immune system directly. Parts of this study could be carried out on the same animals used in studying long-term animal toxicity ie, the responses of control animals may be compared with those of animals exposed to chloroprene. It is suggested that lymphocytes from

individual spleens or thymuses be cultured after the animals are killed for necropsy. The rate of cellular DNA synthesis with and without the addition of a mitogen should be measured by incorporation of ³H-thymidine into acid-insoluble material. Millipore filtration of 24-hour cultures is the most convenient assay method. This serves as a measurement of lymphocyte cell stimulation and response.

Delayed hypersensitivity reaction tests should be performed with a contact-sensitizing agent, such as oxazolone (4-ethoxy-methylene-2-phenyl-2-oxazolone). Animals should be sensitized by painting both ears two or three times at 3-day intervals with a 3-5% solution of oxazolone. About 14 days after the last sensitization, the animals should be injected ip with ³H-thymidine. Twenty-four hours later, one ear should be painted with a 1% solution of the possible sensitizing agent under examination in oil, the other with oil alone. After 24 hours, the animals should be killed and plugs taken from each ear. The increased localization of tritium in the ear exposed to the compound in comparison with that in the control ear is a measure of the ability of the compound applied to induce delayed hypersensitivity.

The effect of chloroprene on humoral antibody response should also be measured. A suitable immunogen should be selected and injected ip with complete Freund's adjuvant. A second injection should follow 14 days later. Serum samples should be collected at weekly intervals and antibody titers determined by passive hemagglutination. The antigen should be coupled to sheep red blood cells for the assay. The titers in controls and animals exposed to chloroprene should be determined.

Sampling and Analysis

More sensitive and easily performed methods of sampling and analysis for chloroprene are needed.

VIII. REFERENCES

1. Mnatsakanian AV: [Experimental data on the maximum permissible concentration of chloroprene in the atmosphere.] *Predelno Dopustimye Konts Atmos Zagryaz* 5:110-17, 1961 (Rus)
2. Henschler D (ed): [Substances Hazardous to Health--Toxicological and Occupational Medical Criteria for MAC Values, 4th supplement.] Weinheim, Federal Republic of Germany, Henschler D Verlag, 1975, pp 45-50 (Ger)
3. Bauchwitz PS, Finlay JB, Stewart CA: Chloroprene, in *High Polymers* 24 (Vinyl and Diene Monomers-2). Wilmington, Del, EI du Pont de Nemours and Co, 1971, pp 1149-83
4. Irish DD: Chloroprene--Aliphatic halogenated hydrocarbons, in Patty FA (ed): *Industrial Hygiene and Toxicology*, ed 2 rev; Toxicology (Fassett DW, Irish DD, eds). New York, Interscience Publishers, 1963, vol 2, pp 1319-21
5. Carothers WH, Williams I, Collins AM, Kirby JE: Acetylene polymers and their derivatives--II. A new synthetic rubber--Chloroprene and its polymers. *J Am Chem Soc* 53:4203-25, 1931
6. Prescott JH: Butadiene to neoprene process makes US debut. *Chem Eng* 78:47-49, 1971
7. Besozzi AJ, Taylor WH, Capp CW: Commercial production of chloroprene via butadiene. *Am Chem Soc Div Pet Chem Prepr* 17:E15-34, 1972
8. Background Information on Chloroprene. Unpublished report submitted to NIOSH by EI du Pont de Nemours and Co, Wilmington, Del, January 1976, 46 pp
9. Hollis CE: Chloroprene and polychloroprene rubbers. *Chem Ind (London)* 47:1030-41, 1969
10. Bellringer FJ, Hollis CE: Make chloroprene from butadiene. *Hydrocarbon Process* 47:127-30, 1968
11. Plant observation reports and evaluation. Menlo Park, Calif, SRI International, December 1976, 80 pp (submitted to NIOSH under contract No. CDC-99-74-31)
12. Neoprene Latex--Toxicity and Safe Handling of Neoprene Latexes, publication No. N1110.1. Wilmington, Del, EI du Pont de Nemours and Co, 1976, 4 pp
13. Neoprene Latex--Tank Entry Procedure, publication No. NL-110.2. Wilmington, Del, EI du Pont de Nemours and Co, 1976, 3 pp

14. Van Duuren BL, Goldschmidt BM, Seidman I: Carcinogenic activity of di- and trifunctional alpha-chloroethers and of 1,4-dichlorobutene-2 in ICR/HA Swiss mice. *Cancer Res* 35:2553-57, 1975
15. Bartsch H, Malaveille C, Barbin A, Planche G, Montesano R: Alkylating and mutagenic metabolites of halogenated olefins produced by human and animal tissue. *Proc Am Assoc Cancer Res* 17:17, 1976
16. Chloroprene is latest cancer scare. *Chem Eng News* 53:4-5, 1975
17. Lloyd JW, Decoufle P, Moore RM: Background information on chloroprene. *J Occup Med* 17:263-65, 1975
18. Von Oettingen WF, Hueper WC, Deichmann-Gruebler W, Wiley FH: 2-Chloro-butadiene (chloroprene)--Its toxicity and pathology and the mechanism of its action. *J Ind Toxicol* 18:240-70, 1936
19. Roubal J: [Manufacture of synthetic chloroprene rubber, from the toxicologic and hygienic viewpoint.] *Sb Lek* 44:63-88, 1942 (Cze)
20. Nystrom AE: Health hazards in the chloroprene industry and their prevention. *Acta Med Scand Suppl* 132:5-125, 1948
21. Ritter WL, Carter AS: Hair loss in neoprene manufacture. *J Ind Hyg Toxicol* 30:192-95, 1948
22. Sanotskii IV: Aspects of the toxicology of chloroprene--Immediate and Long-Term effects. *Environ Health Perspect* 17:85-93, 1976
23. Lejhancova G: [Occupational alopecia due to chloroprene.] *Berufs-Dermatosen* 15:280-87, 1967 (Ger)
24. Paulet G, Malassis D: [Chloroprene--An experimental, biological and clinical study of its toxicity], in *Dixiemes Journees Nationales de Medecine de Travail, Societe de Medecine du Travail Dauphine-Savoie, La Tronche, France, 1969*, pp 677-689 (Fre)
25. Avakian VN, Gasparian YI, Avetisian NO, Grigorian YM: [Dynamics of study of the cardiovascular system in workers of chloroprene group shops.] *Tr Erevan Med Inst* 11:237-39, 1960 (Rus)
26. Mikaelian VG, Frangulian LA: [Effect of chloroprene on immunologic reactivity of organism in persons vaccinated against typhus adominalis.] *Tr Erevan Med Inst* 14:239-44, 1965 (Rus)
27. Keчек YA, Semerdzhian LV: [Dynamics of protein fractions in blood serum upon chloroprene intoxication.] *Izv Akad Nauk Arm SSR Biokhim* 15:63-70, 1962 (Rus)
28. Khachatrian EA: [The role of chloroprene compounds in the process of skin neoplasm formation.] *Gig Tr Prof Zabol* 16:54-55, 1972 (Rus)

29. Khachatrian EA: [The occurrence of lung cancer among people working with chloroprene.] *Vopr Onkol* 28:85-86, 1972 (Rus)
30. Pell S: Mortality of Workers Exposed to Chloroprene at the Louisville Works, 1957-1974--A Preliminary Study. Wilmington, Del, EI du Pont de Nemours and Co, Medical Division, 1976, 34 pp
31. Mkhitarian VG: [The action of chloroprene on metabolism--Biochemical changes in the blood of workers chronically exposed to chloroprene.] *Izv Akad Nauk Arm SSR, Biol Nauki* 13:27-39, 1960 (Rus)
32. Mkhitarian VG: [The effect of chloroprene on the content of protein and protein fractions, cholesterol and glucose in the blood of workers.] *Izv Akad Nauk Arm SSR, Biol Nauki* 13:65-74, 1960 (Rus)
33. Mnatsakanian AV, Mushegian AV: The influence of small concentrations of chloroprene on the porphyrin metabolism of children. *Hyg Sanit* 29:97-98, 1964
34. Senderikhina DP: [Determination of chlorinated hydrocarbons of microcombustion.] *Gig Sanit* 8:43-45, 1954 (Rus)
35. Gusev MI, Smirnov Yuk: [Spectrophotometric determination of coproporphyrin excreted with the urine.] *Predelno Dopustimye Konts Almos Zagryaz* 4:139-42, 1960 (Rus)
36. Stedmans Medical Dictionary, ed 22. Baltimore, Williams and Wilkins Co, 1975, pp 1460-62
37. Mnatsakanian AV: [Influence of microconcentrations of chloroprene in the air on the function of the adrenal glands of children.] *Gig Sanit* 31:98-100, 1966 (Rus)
38. Uvarovskaia OM: [A precipitation method for identifying neutral urinary 17-ketosteroids (androgens).] *Probl Endokrinol* 11:110-12, 1956 (Rus)
39. Vanuni SO: [Concerning certain problems of the chemical composition of the milk of puerperants working in the synthetic rubber plant and living in nearby residences.] *Zh Eksp Klin Med* 13:111-14, 1973 (Arm)
40. Vanuni SO: [Comparative characteristics of individual and total amino acids in breast milk of working mothers living in villages at various distances from a synthetic chloroprene rubber combine.] *Zh Eksp Klin Med* 14:96-101, 1974 (Arm)
41. Volkova ZA, Fomenko VN, Bagdinov YM, Bialko NK, Katosova LD, Ponomareva NI, Tolcheva EI, Davtian RM, Zilfian ZN, Gurdzhiyev TI, Khaprullina AS: [Determination of the maximum permissible concentrations of chloroprene in the air of working areas.] *Gig Tr Prof Zabol* 20:31-36, 1976 (Rus)

42. Bagramian SB, Babaian EA: [Cytogenetic study of the mutagenic activity of chemical substances isolated from the narit latexes MKH and LNT-1.] Biol Zh Arm 27:102-03, 1974 (Arm)
43. Katosova LD: [Cytogenetic analysis of the peripheral blood of workers engaged in the production of chloroprene.] Gig Tr Prof Zabol 17:30-32, 1973 (Rus)
44. Bochkov NP, Kuleshov NP, Zhurkov VS: [Analysis of spontaneous chromosomal aberrations in a human leukocyte culture.] Zh Tsitol 14:1267-72, 1972, (Rus)
45. Fomenko VN, Sanotskii IV, Strekalova EE, Katosova LD: The problem of hygienic standardization of industrial poisons possessing mutagenic activity. Mutat Res Sect Environ Mutagenesis Relat Subj 21:31-32, 1973
46. Gasparian YI, Arutiunian RK: [Electroencephalographic investigations in chronic chloroprene poisoning.] Gig Tr Prof Zabol 9:51-54, 1965 (Rus)
47. Asmangulian TA, Badalian SO: [Toxicity of chloroprene in an acute test during oral administration.] Tr Erevan Med Inst 15:461-65, 1971 (Rus)
48. Jaeger RJ, Conolly RB, Reynolds ES, Murphy SD: Biochemical toxicology of unsaturated halogenated monomers. Environ Health Perspect 11:121-28, 1975
49. Khachatryan EA: [The blastomogenic properties of chloroprene compounds administered to laboratory animals.] Tr Leningr Nauchnogo Ova Pathoanat 15:174-77, 1974 (Rus)
50. Zilfian ZN, Fichidjian BS: [Effect of chloroprene on the development of Crocker's murine sarcoma], in Materials of the Scientific Conference Celebrating the Fiftieth Anniversary of the Formation of the USSR and the Twenty-Fifth Anniversary of the Organization of the Armenian Institute of Roentgenology and Oncology. Yerevan, USSR, Armyanskii Institut Rentgenologii i Onkologii, 1972, pp 105-06 (Rus)
51. Zilfian VN, Fichidjian BS, Pogosova AM: [Results of studies on chloroprene as carcinogen.] Zh Eksp Klin Med 15:54-57, 1975 (Rus)
52. Bartsch H, Malaveille C, Montesano R, Tomatis L: Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in salmonella typhimuriam. Nature 255:641-43, 1975
53. McCann J, Spingarn NE, Kobori J, Ames BN: Detection of carcinogens as mutagens--Bacterial tester strains with R factor plasmids. Proc Nat Acad Sci USA 72:979-83, 1975

54. Ames BN, Durston WE, Yamasaki E, Lee FD: Carcinogens are mutagens--A simple test system combining liver homogenates for activation and bacteria for detection. Proc Nat Acad Sci USA 70:2281-85, 1973
55. Davtian RM, Fomenko VN, Andreyeva GP: [On the question of the effect of chloroprene on the generating function of mammals (males).] Toksikol Nov Prom Khim Veschestv 13:58-62, 1973 (Rus)
56. Davtian RM: [Toxicological characteristics of the action of chloroprene on the reproductive function of male rats], in Reports of Toxicology and Hygiene of the Products of Petroleum Chemistry and Petrochemical Productions, All Union Conference. Yaroslave, USSR, Yaroslavskii Meditsinakii Institut, 1972, pp 95-97 (Rus)
57. Bateman AJ: Mutagenic sensitivity of maturing germ cells in the male mouse. Heredity 12:213-32, 1958
58. Epstein SS, Arnold E, Steinberg K, Mackintosh D, Shafner D, Bishop Y: Mutagenic and antifertility effects of TEPA and METEPA in mice. Toxicol Appl Pharmacol 17:23-40, 1970
59. Salnikova LS: [Embryotropic effect of volatile substances given off by polychloroprene latices.] Toksikol Nov Prom Khim Veschestv 11:106-11, 1968 (Rus)
60. Salnikova LS, Fomenko VN: [Experimental study of the effects of chloroprene on embryogenesis.] Gig Tr Prof Zabol 17:23-26, 1973 (Rus)
61. Apoian KK: [Biochemical changes in animals in studies of the embryotropic effect of synthetic chloroprene rubber wastes.] Zh Eksp Klin Med 10:36-42, 1970 (Rus)
62. Mnatsakanian AV, Pogosian UG, Apoian KK, Gofmekler VA, Avoian AO, Andikian MS: Certain aspects of the embryotoxic effect of chloroprene in a field experiment. Hyg Sanit 36:140-41, 1971
63. Mnatsakanian AV, Pogosian UG, Apoian KK, Gofmekler VA, Kanaian AS: [Embryotoxic influence of chloroprene synthetic production waste based on materials from the study of the progeny (first generation) of white rats.] Tr Erevan Gos Inst Uoversh Vrachey 5:155-58, 1972 (Rus)
64. Salnikova LS, Fomenko VN: [Comparative characteristics of the embryotropic effect of chloroprene as a function of the mode of its action with various routes of entry into the body.] Gig Tr Prof Zabol 19:30-33, 1975 (Rus)
65. Melik-Alaverdian NO, Kagramanian RG, Kalantarova YG, Krupskaia NK: Reproductive function, and sexual maturation in third generation rats born from mothers intoxicated with chloroprene. Zh Eksp Klin Med 16:54-59, 1976

66. Culik R, Kelly DP, Clary JJ: Beta-chloroprene (2-Chlorobutadiene-1,3)--Embryotoxic and Teratogenic Studies in Rats. Wilmington, Del, EI du Pont de Nemours and Co, Haskell Laboratory for Toxicology and Industrial Medicine, 1976, 18 pp
67. Schwartz L: Skin hazards in the manufacture and processing of synthetic rubber. JAMA 127:389-91, 1945
68. Flesch P, Goldstone SB: Depilatory action of the intermediary polymers of chloroprene. Science 113:126-27, 1951
69. Amblard P, Faure J, Martel J, Fillon JP, Garna A: [Alopecia in a factory making polychloroprene elastomers.] Bull Soc Fr Dermatol Syphiligr 81:114-15, 1974 (Fre)
70. Flesch P, Goldstone SB: Local depilatory action on unsaturated compounds--The effect of human sebum on hair growth. J Invest Dermatol 18:267-87, 1952
71. Volek J, Hrivnak J, Sojak L: [Gas chromatography for analysis of impurities in chloroprene obtained from pyrolysis of acetylene.] Rav Roc 15:375-81, 1973 (Rus)
72. Bartsch H: Mutagenicity test in chemical carcinogenesis. IARC Sci Publ 13:229-240, 1976
73. Leichnitz K (ed): Detector Tube Handbook--Air Investigations with Drager Tubes in the Threshold Limit Value Range, ed 2. Lubeck, Germany, Dragerwerk AG Lubeck, 1973, pp 12-13,18-32,44-45
74. Babina MD: [Determination of volatile substances released into the air by footwear factories.] Nov Obl Prom-Sanit Khim 1:227-32, 1969 (Rus)
75. Apoian KK, Abeshian MM, Golfmekler VA, Mnatsakanian AV, Mutafian GA, Pogosian UG, Tarverdian AK: Spectrophotometric determination of chloroprene in air. Hyg Sanit 36:419-22, 1971
76. Hollis OL, Hayes WV: Gas liquid chromatographic analysis of chlorinated hydrocarbons with capillary columns and ionization detectors. Anal Chem 34:1223-26, 1962
77. National Institute for Occupational Safety and Health, Division of Laboratories and Criteria Development: Organic Solvents in Air--Physical and Chemical Analysis Branch method No. 127, in NIOSH Manual of Analytical Methods, HEW publication No. (NIOSH) 75-121. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, NIOSH, 1974, pp 127-1 to 127-11
78. Air Determination of Chloroprene and Other Volatile Organics--Charcoal Tube Methods, code No. 340.1400S. Wilmington, Del, EI du Pont de Nemours and Co, Elastomer Chemicals Dept, 1975, 10 pp

79. Hervin RL, Polakoff PL: Barcol Overdoor Company Incorporated, Sheffield, Illinois, Health Hazard Evaluation/Toxicity Determination report No. 72-48-35. Cincinnati, US Dept of Health, Education, and Welfare, National Institute for Occupational Safety and Health, Hazard Evaluation Services Branch, Division of Technical Services, 1973, 25 pp
80. Failure Report. Standards Completion Program. US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Laboratories and Criteria Development, 1975, pp S112-1 to S112-6 (unpublished)
81. Chloroprene, method No. S112. Standards Completion Program. US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Laboratories and Criteria Development, 1976, pp S112-1 to S112-10 (unpublished)
82. Volkova JA, Duyeve LA, Zilfian ZN: [Data for hygienic standardization of chloroprene latexes.] Gig Sanit 4:45-48, 1975 (Rus)
83. American Conference of Governmental Industrial Hygienists, Committee on Industrial Ventilation: Industrial Ventilation--A Manual of Recommended Practice, ed 14. Lansing, Mich, ACGIH, 1976, pp 1-1 to 14-8
84. American National Standards Institute Inc: Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971. New York, ANSI, 1971, 63 pp
85. Balance foreseen for butadiene--New ethylene capacity based on heavy feeds will yield more co-product material, but growth in use will soak it up. Chem Week 119:70,72, 1976
86. American Conference of Governmental Industrial Hygienists: Threshold Limit Values of Air-Borne Contaminents [sic] for 1968--Recommended and Intended Values. Cincinnati, ACGIH, 1968, pp 5,6
87. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard...Occupational Exposure to Chlorine, HEW publication No. (NIOSH) 76-170. Rockville, Md, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, NIOSH, 1976, pp 1-155
88. Properties and Essential Information for Safe Handling and Use of Chlorine, Chemical Safety Data Sheet SD-80, rev. Washington, DC, Manufacturing Chemists' Association, Safety and Fire Protection Committee, 1970, 33 pp

89. Properties and Essential Information for Safe Handling and Use of Butadiene, Chemical Safety Data Sheet SD-55, rev. Washington, DC, Manufacturing Chemists' Association, Safety and Fire Protection Committee, 1974, 19 pp
90. Cook WA: Maximum allowable concentrations of industrial atmospheric contaminants. Ind Med 14:936,939, 1945
91. American Conference of Governmental Industrial Hygienists: Maximum Allowable Concentration Values. Cincinnati, ACGIH, 1946, 2 pp
92. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1948. Cincinnati, ACGIH, 1948, 3 pp
93. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for 1966. Cincinnati, ACGIH, 1966, pp 1,6-7
94. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3, 1971. Cincinnati, ACGIH, 2nd printing, 1974, pp 54-55
95. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1976. Cincinnati, ACGIH, 1976, pp 2-3,12-13
96. Permissible Levels of Toxic Substances in the Working Environment--Sixth Session of the Joint ILO/WHO Committee on Occupational Health, Geneva, 4-10 June 1968. Geneva, International Labor Office, 1970, pp 182-87,189,197,200,231,245,269, 278,291,295,296
97. Riasanov AV: New data on maximum allowable concentrations of pollutants in the air in the USSR, in Marsh A (ed): Proceedings of the Diamond Jubilee International Clean Air Conference. London, National Society for Clean Air, 1960, pp 175-76
98. Winell M: An international comparison of hygienic standards for chemicals in the work environment. Ambio 4:34-36, 1975
99. Bardodej Z: Chloroprene, in Documentation of MAC in Czechoslovakia. Praha, Czechoslovak Committee of MAC, 1969, pp 54-55
100. Mnatsakanian AV: [Data for substantiation of the permissible concentration of chloroprene in the atmospheric air.] Gig Sanit 29:14-18, 1964 (Rus)
101. Mnatsakanian AV: [New experimental materials for determination of the mean daily maximum permissible concentration of chloroprene in the atmosphere.] Predelno Dopustimye Konts Atmos Zagryaz 8:89-118, 1964 (Rus)

102. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1972. Cincinnati, ACGIH, 1972 pp 1,12-13
103. Feron VJ, Clary JJ: A long-term inhalation study of beta-chloroprene to rats--Notice of research project. Washington, DC, Smithsonian Science Information Exchange Inc, 1976, 1 p
104. Criteria for a Recommended Standard...Occupational Exposure to Carbon Disulfide. To be published by US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health

IX. APPENDIX I

METHOD FOR SAMPLING CHLOROPRENE IN AIR

The sampling and analytic methods presented in Appendices I and II are based on those described in draft method No. S112 of the Physical and Chemical Analysis Branch of NIOSH [81].

General Requirements

Collect breathing zone or personal samples representative of the individual employee's exposure. At the time of sample collection, record on sampling data sheets the time and date of collection, the flowrate, duration of sampling, a description of the sampling location and conditions, and other pertinent information, such as temperature and pressure.

Recommended Method

The following method of sampling is recommended. If other methods can be proven to be equivalent, they may be used.

(a) Personal samples shall be collected in the breathing zone of the employee without interfering with freedom of movement and shall characterize the exposure for each job or specific operation in each production area.

(b) A portable, battery-operated personal sampling pump whose flowrate can be accurately controlled to within 5% at 50 ml/minute and an

activated charcoal tube are used to collect the samples.

(c) The activated charcoal tube should be attached to the employee's clothing. The shirt collar or jacket lapel is convenient for this purpose.

(d) The sampler should be operated at a flowrate of 10-50 ml/minute. Because some pumps are designed for high flowrates and some for low, care should be taken to use the proper pump with proper flowrate, eg, up to 50 ml/minute.

(e) Breathing zone samples shall be collected to permit determination of a 15-minute exposure for every operation where high-level exposure to chloroprene is expected.

(f) At least one unused activated charcoal tube from the same batch shall be provided to the analytical laboratory to determine the blank correction.

Equipment

(a) Battery-operated personal sampling pump: It should have a clip for attachment to the employee's clothing. All pumps and flowmeters must be calibrated with a calibrated test meter or other reference, as described in Calibration of Equipment.

(b) Charcoal tubes: Glass tubes, with both ends flame-sealed, 7-cm long with a 6-mm outer diameter and a 4-mm internal diameter, containing two sections of 20/40 mesh activated coconut-shell charcoal separated by a 2-mm portion of polyurethane foam. The charcoal is fired at 600 C prior to packing. The adsorbing section contains 100 mg of charcoal, the backup section 50 mg. A 3-mm portion of the polyurethane foam is placed between

the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section.

Calibration of Equipment

Since the accuracy of an analysis can be no greater than the accuracy of the volume of air which is measured, the accurate calibration of a sampling pump is essential for the correct interpretation of the volume indicated. The frequency of calibration is dependent on the use, care, and handling to which the pump is subjected. Pumps should also be recalibrated if they have been misused or if they have just been repaired or received from a manufacturer. If the pump receives hard usage, it should be calibrated more frequently. Regardless of use, maintenance and calibration should be performed on a regular schedule and records of these should be kept for a reasonable period of time.

Ordinarily, pumps should be calibrated in the laboratory both before and after they have been used to collect a large number of field samples. The accuracy of calibration is dependent on the type of instrument used as a reference. The choice of calibration instrument will depend largely on where the calibration is to be performed. For laboratory testing, primary standards, such as a spirometer or soapbubble meter, are recommended, although other standard calibration instruments, such as a wet-test meter or dry gas meter, can be used. The actual setups will be similar for all instruments.

The calibration setup for personal sampling pumps with a charcoal tube is as shown in Figure XII-1. If another calibration device is selected, equivalent procedures should be used. Since the flowrate given

by a pump is dependent on the pressure drop of the sampling device, in this case a charcoal tube, the pump must be calibrated while operating with a representative charcoal tube in the line. Instructions for calibration with the soapbubble meter are as follows:

(a) Check the voltage of the pump battery with a voltmeter to ensure adequate voltage for calibration. Charge the battery if necessary.

(b) Break the tips of a charcoal tube to produce openings of at least 2 mm in diameter.

(c) Assemble the sampling train as shown in Figure XII-1.

(d) Turn the pump on and moisten the inside of the soapbubble meter by immersing the buret in the soap solution, and draw bubbles up the inside until they are able to travel the entire length of the buret without bursting.

(e) Adjust the pump flow controller to provide the desired flowrate.

(f) Check the water manometer to ensure that the pressure drop across the sampling train does not exceed 2.5 inches of water at 50 ml/minute.

(g) Start a soapbubble up the buret and measure with a stopwatch the time required for it to move between calibration marks.

(h) Repeat the procedure in (g) at least twice, average the results, and calculate the flowrate by dividing the volume between the preselected marks by the time required for the soapbubble to traverse the distance. If, for the pump being calibrated, the volume of air sampled is the product of the number of strokes times a stroke factor (given in units of volume/stroke), the stroke factor is the quotient of the volume between

the two preselected marks divided by the number of strokes.

(i) Record the data for the calibration, including the volume measured, elapsed time or number of strokes, pressure drop, air temperature, atmospheric pressure, relative humidity of the air sampled, serial number of the pump, and name of the person performing the calibration.

Sampling Procedure

(a) Break both ends of the charcoal tube to provide openings of at least 2 mm, which is half of the internal diameter of the tube. A smaller opening causes a limiting orifice effect which reduces the flow through the tube. The smaller section of charcoal in the tube is used as a backup section and therefore is placed nearest the sampling pump. Use tubing to connect the back of the tube to the pump, but tubing must never be put in front of the charcoal tube. Support the tube in a vertical position for sampling to prevent channeling.

(b) The recommended sampling flowrate is 10-50 ml/minute. Collect a 15-minute sample. Set the calibrated flowrate as accurately as possible ($\pm 5\%$) using the manufacturer's directions. Record the temperature, pressure, and relative humidity of the atmosphere being sampled. If the pressure reading is not available, record the elevation above sea level.

(c) Record the initial and final counter readings. The sample volume can be obtained by multiplying the number of counter strokes times the volume cc/stroke factor.

(d) Immediately after sampling, seal the charcoal tubes with the plastic caps supplied by the manufacturer. Masking tape is the only

suitable substitute for sealing the tubes. Rubber caps must never be used.

(e) Treat one charcoal tube in the same manner (break, seal) as the sample tubes, except draw no air through it. This tube serves as a blank.

(f) Pack capped charcoal tubes tightly and pad before they are shipped to minimize tube breakage during transport. Bulk samples of the suspected compound must be submitted in glass containers with teflon-lined caps in addition to charcoal tubes. Bulk samples and charcoal tubes must be shipped in separate containers.

Special Considerations

(a) Where two or more compounds are known or suspected to be present in the air, convey such information, including their suspected identities, with the sample.

(b) Do not operate the sampling pump for more than 10 hours without recharging the battery.

(c) If high humidity or water mist is present, breakthrough volume can be severely reduced. If condensation of water occurs in the tube, chloroprene will not be trapped quantitatively. Therefore, in high humidity, reduce the volume sampled.

(d) The desorption efficiency of charcoal varies from batch to batch. Therefore, all the tubes used to collect a set of samples must contain charcoal from the same batch. Several unused charcoal tubes should accompany the samples. Information on the batch number of the charcoal must be supplied.

(e) One disadvantage of the method is that the amount of sample which can be taken is limited by the number of milligrams the tube will hold before overloading [81]. Testing this has demonstrated that the first charcoal tube has held at least 8.2 mg of chloroprene without breakthrough occurring. The concentration of chloroprene in the effluent was less than 2% of that in the influent. The loading of the tube is generally not a limiting factor for a 15-minute sample.

X. APPENDIX II

ANALYTICAL METHOD FOR CHLOROPRENE

The following analytical method for chloroprene is adapted from the Documentation of NIOSH Validation Tests draft [81].

Principle of the Method

A known volume of air is drawn through a charcoal tube to trap the chloroprene vapor present. The charcoal in the tube is transferred to a small, stoppered sample container, and the chloroprene is desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas-liquid chromatograph. The area of the resulting peak is determined and compared with those areas obtained from the injection of standards.

Range and Sensitivity

This method was validated over a range of 44.2-173.9 mg/cu m at an atmospheric temperature and pressure of 21 C and 760 mmHg, using a 3-liter sample. A maximum sample size of 3 liters is recommended. Sample at a flowrate between 10 and 50 ml/minute. Do not sample at a flowrate less than 10 ml/minute. The method is capable of measuring much smaller amounts if the desorption efficiency is adequate. Desorption efficiency must be determined over the range used.

The upper limit of the range of the method is dependent on the adsorptive capacity of the charcoal tube. This capacity varies with the

concentrations of chloroprene and other substances in the air. The charcoal tube consists of two sections of activated charcoal separated by a section of urethane foam (see Apparatus). If a particular atmosphere is suspected of containing a large amount of contaminant, a smaller sampling volume should be taken.

When the amount of water in the air is so great that condensation actually occurs in the tube, organic vapor will not be trapped efficiently. Preliminary experiments with toluene [81] indicated that high humidity severely decreased the breakthrough volume. At a relative humidity of 91% (25 C), breakthrough did not occur after sampling for 4 hours at an average sampling rate of 0.045 liter/minute. The test was conducted at a concentration of 197 mg/cu m.

Interferences

It must be emphasized that any compound which has the same retention time as the chloroprene at the operating conditions described in this method constitutes an interference. Retention time data on a single column cannot be considered as proof of chemical identity. If the possibility of interference exists, separation conditions (column packing, temperature, etc) might be changed to circumvent the problem.

Precision and Accuracy

The Coefficient of Variation (CVT) for the total analytical and sampling method in the range of 44.2-173.9 mg/cu m (12.3-48.3 ppm) was 0.071. This value corresponds to a standard deviation of 6.4 mg/cu m at

the present standard level. Statistical information and details of the validation and experimental test procedures can be found in Documentation of NIOSH Validation Tests [81]. The average values obtained using the overall sampling and analytical method were 1.2% less than the "true" value at one-half, one, and two times the standard level. Storage stability studies [81] on samples collected from an atmosphere containing chloroprene at 86.0 mg/cu m indicated that collected samples were stable for at least 7 days at room temperature.

Advantages and Disadvantages of the Method

The sampling device is small, portable, and involves no liquids. Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick, instrumental method, eg, gas-liquid chromatography. The method can also be used for the simultaneous analysis of two or more compounds suspected to be present in the same sample by simply changing gas-chromatographic conditions from isothermal to a temperature-programmed mode of operation, and determining relative retention times for all compounds under consideration.

One disadvantage of the method is that the amount of sample which can be taken is limited by the number of milligrams the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal tube exceeds 25% of that found on the front section, the possibility of sample loss exists.

Furthermore, the precision of the method is limited by the reproducibility of the pressure drop across the tubes. This drop will

affect the flowrate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only.

Apparatus

(a) Gas-liquid chromatograph equipped with a flame ionization detector.

(b) Stainless-steel column (4 feet x 1/4 inch) packed with 50/80 mesh Porapak Q.

(c) Electronic integrator or some other suitable method of determining peak size areas.

(d) Glass sample containers: 2-ml, with glass stoppers or Teflon-lined caps. If an automatic sample injector is used, the sample injector vials can be used.

(e) Microliter syringes: 10- μ l, and other convenient sizes for making standards.

(f) Pipets: 1.0-ml delivery type.

(g) Volumetric flasks: 10-ml or convenient sizes for making standard solutions.

(h) Microdistillation apparatus with provision for fractional vacuum distillation of pure chloroprene (for making standards).

(i) A stopwatch.

(j) A manometer.

Reagents

- (a) Carbon disulfide, chromatographic grade.
- (b) Chloroprene, distilled from xylene solution (31 C at 354 mmHg), in pentane solution.
- (c) n-Pentane, reagent grade.
- (d) n-Hexane, reagent grade.
- (e) Nitrogen, purified.
- (f) Hydrogen, prepurified.
- (g) Compressed air, filtered.

Analysis of Samples

(a) All glassware used for the analysis should be detergent-washed, thoroughly rinsed with tap water and distilled water, and dried.

(b) Preparation: Score each charcoal tube with a file in front of the first section of charcoal and break open. Remove and discard the glass wool. Transfer the charcoal in the first (larger) section to a 2-ml stoppered sample container or automatic sample injector vial. Remove and discard the separating section of foam and transfer the second section to another sample container or vial. Analyze these two sections separately.

(c) Desorption of samples: Prior to analysis, pipet 1.0 ml of carbon disulfide into each sample container.

PERFORM ALL WORK WITH CARBON DISULFIDE IN A HOOD BECAUSE OF ITS HIGH TOXICITY.

For further precautions, see the NIOSH criteria document on occupational exposure to carbon disulfide [104].

Cap the sample vials as soon as the solvent is added to minimize volatilization. Agitate the vials occasionally during the desorption period. Desorption is complete in 30 minutes if the sample vial is shaken occasionally.

(d) Typical gas-liquid chromatographic conditions:

- (1) 50 ml/minute (60 psig) nitrogen carrier gas flow.
- (2) 50 ml/minute (24 psig) hydrogen gas flow to detector.
- (3) 500 ml/minute (50 psig) airflow to detector.
- (4) 200 C injector temperature.
- (5) 250 C manifold temperature (detector).
- (6) 125 C column temperature.

A retention time of approximately 10 minutes is to be expected for chloroprene under these conditions and using the column recommended. The carbon disulfide retention time will be shorter.

(e) Injection: The first step in the analysis is the injection of the sample into the gas-liquid chromatograph. To eliminate difficulties arising from blowback or evaporation within the syringe needle, use the solvent-flush injection technique. First, flush the 10- μ l syringe with carbon disulfide several times to wet the barrel and plunger. Draw 3 μ l of solvent into the syringe to increase the accuracy and reproducibility of the injected sample volume. Remove the needle from the solvent, and pull the plunger back about 0.2 μ l to separate the solvent flush from the sample with a pocket of air that will serve as a marker. Immerse the needle in the sample and withdraw a 5- μ l portion, taking into consideration the volume of the needle since the sample in the needle will be completely injected. After removing the needle from the sample and prior to injection

into the gas-liquid chromatograph, pull the plunger 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. Make duplicate injections of each sample and of the standard. No more than a 3% difference in peak areas is to be expected. An automatic sample injector can be used if it is shown to give reproducibility at least as good as the solvent-flush technique. In this case, 2- μl injections are satisfactory.

(f) Measurement of the area: Measure the area of the sample peak with an electronic integrator or some other suitable form of area measurement, and read preliminary results from a standard curve prepared as discussed below (see Calibration and Standards).

Determination of Desorption Efficiency

The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of chloroprene that is removed in the desorption process, provided that the same batch of charcoal is used.

Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 64-mm, 4-mm I.D. glass tube, flame sealed at one end. This charcoal must be from the same batch as that used in collecting the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm. A known amount of freshly prepared pentane solution of chloroprene containing 67.5 $\mu\text{g}/\mu\text{l}$ is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm. When using an automatic sample

injector, the sample vials, capped with Teflon-faced septa, may be used in place of the glass tubes. The amount injected is equivalent to that present in a 3-liter air sample at the selected level. It is not practical to inject the neat liquid directly because the amounts to be added would be too small to measure accurately.

Prepare at least six tubes at each of three levels (one-half, one, and two times the standard) in this manner and allow to stand overnight to assure complete adsorption of the chloroprene onto the charcoal. These six tubes are referred to as the samples. Treat a parallel blank tube in the same manner, but add no chloroprene to it. Two or three standards are prepared by injecting the same volume of chloroprene into 1 ml of carbon disulfide with the same syringe used in the preparation of the samples. Desorb and analyze the standards and sample and blank tubes in exactly the same manner as the sampling tube described in Analysis of Samples.

Determine the weight of chloroprene found in each tube from the standard curve (see Calibration and Standards). Desorption efficiency (DE) equals the difference between the average peak area of the samples and that of the blank divided by the average peak area of the standards, or:

$$DE = \frac{\text{average weight recovered (mg)}}{\text{weight added (mg)}}$$

The desorption efficiency is dependent on the amount of chloroprene collected on the charcoal. Plot the desorption efficiency versus the weight of chloroprene found. This curve is used (see Calculations) to correct for adsorption losses.

Calibration and Standards

A series of standards, varying in concentration over the range, is prepared and analyzed under the same gas-liquid chromatograph conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/ml versus peak area. Standard solutions must be analyzed at the same time that sample analysis is done to minimize the effect of known variations in the response of the flame ionization detector from day to day and from hour to hour within a single day.

Calculations are based on a molecular weight of 88.54 and a density of 0.958 for pure chloroprene. Since chloroprene polymerizes readily, special precautions must be taken in the preparation and storage of standards.

Stock Standard Solution: Pure chloroprene is obtained by fractionally distilling commercially available 50% chloroprene in xylene solution under vacuum (Note 1). A stock standard solution is prepared from freshly distilled chloroprene. Exactly 1.0 ml (0.958 g at 20 C) of pure chloroprene is delivered from a delivery type pipet under the surface of pentane in a partially filled 10-ml volumetric flask, and then the solution is made up to exactly 10 ml with pentane. This solution may be stable for 1 day or even longer if stored at -15 C (Note 2).

Note 1. The chloroprene used in the laboratory validation study was distilled at 31 C at a pressure of 354 mmHg.

Note 2. Since chloroprene tends to polymerize, even in solutions, it may be necessary to monitor its concentrations in the standard solutions.

Working Standard Solutions: Aliquots of the stock standard solution are delivered below the surface of carbon disulfide in partially filled 10-ml volumetric flasks. Each solution is diluted to exactly 10 ml with carbon disulfide and carefully mixed. A calibration curve should be prepared for the concentration range representing 0.1-3 times the recommended environmental limit.

Solutions for Desorption Efficiency Tests: An appropriate aliquot of the stock standard solution is delivered from appropriate pipets below the surface of pentane in a 10-ml volumetric flask partially filled with pentane. Appropriate aliquots are used for desorption efficiency tests after dilution to volume with pentane.

Standards should be prepared immediately from freshly distilled chloroprene and stored at -15 C when not in use. A reference standard of hexane in carbon disulfide in a sealed vial with septum cap can be used to monitor the stability of the chloroprene standards. The concentration of the hexane reference standard should be chosen so that its flame ionization detector response is close to that of the chloroprene standards. When the ratio of the concentration of chloroprene standards to reference standard appears to decrease, new standards should be prepared.

Calculations

Read the weight in milligrams corresponding to each peak area from the standard curve. No volume corrections are needed because the standard curve is also based on mg/ml of carbon disulfide and the volume of sample injected is identical to the volume of the standards injected.

Make corrections for the blank for each sample by subtracting the

amounts of chloroprene found on the front section of the blank from the amounts found in the front section of the sample tube, or:

$$\text{mg} = \text{mg sample} - \text{mg blank}$$

where:

$$\text{mg sample} = \text{mg found in front section of sample tube}$$

$$\text{mg blank} = \text{mg found in front section of blank tube}$$

A similar procedure is followed for the backup sections.

Add the weights present in the front and backup sections of the same sample tube to determine the total weight of chloroprene in the sample. Read the desorption efficiency (DE) from the curve for the amount of chloroprene found in the front section, and divide the total weight by this desorption efficiency to obtain the corrected mg/sample:

$$\text{corrected mg/sample} = \frac{\text{total weight}}{\text{DE}}$$

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

$$\text{corrected volume} = f \times t \sqrt{\frac{P_1 \times T_2}{P_2 \times T_1}}$$

where:

f = flowrate sampled

t = sampling time

P1 = pressure during calibration of sampling pump (mmHg)

P2 = pressure of air sampled (mmHg)

T1 = temperature during calibration of sampling pump (degrees K)

T2 = temperature of air sampled (degrees K)

The concentration of chloroprene in the air sampled can be expressed in mg/cu m, which is numerically equal to $\mu\text{g/liter}$ of air:

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

Another method of expressing concentration is ppm:

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

where:

P = pressure (mmHg) of air sampled

T = temperature (degrees C) of air sampled

24.45 = molar volume (liter/mole) at 25 C and 760 mmHg

MW = molecular weight (g/mole) of chloroprene

760 = standard pressure (mmHg)

298 = standard temperature (degrees K)

XI. APPENDIX III
MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.

Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines 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.

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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 ₂ O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H ₂ O, % 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: _____

XII. TABLES AND FIGURE

TABLE XII-1

PHYSICAL AND CHEMICAL PROPERTIES OF CHLOROPRENE

Appearance	Colorless
Odor	Pungent, ethereal
Molecular formula	$\text{CH}_2\text{C}(\text{Cl})\text{CHCH}_2$
Formula weight	88.5
Boiling point	59.4 C at 760 mmHg
Freezing point	-130 C
Specific gravity	0.9583 at 20 C
Solubility	Soluble in ethanol, diethyl ether, acetone, benzene, and organic solvents; very slightly soluble in water
UV maximum absorption	223 nm (log extinction = 4.15)
Viscosity	0.394 centipoise at 25 C
Critical temperature	261.7 C
Flashpoint	-20 C (open cup)
Explosive limits	4-20%
Relative vapor density	3.0 (air = 1.0)
Vapor pressure	188 mmHg at 20 C
Saturation concentration (20 C)	25,000 ppm (90,000 mg/cu m)
Conversion factors (760 mmHg and 25 C)	1 ppm = 3.6 mg/cu m 1 mg/liter = 278 ppm 1 mg/cu m = 0.278 ppm

Adapted from references 3 and 4

TABLE XII-2

WORKERS WITH POTENTIAL EXPOSURE TO CHLOROPRENE

Chloroprene chemical workers
Chloroprene derivative workers
Neoprene latex sheet operators
Chloroprene maintenance workers
Neoprene latex handlers
Neoprene workers
Railroad tank car cleaners
Rubberized tapestry workers
Shoe gluers

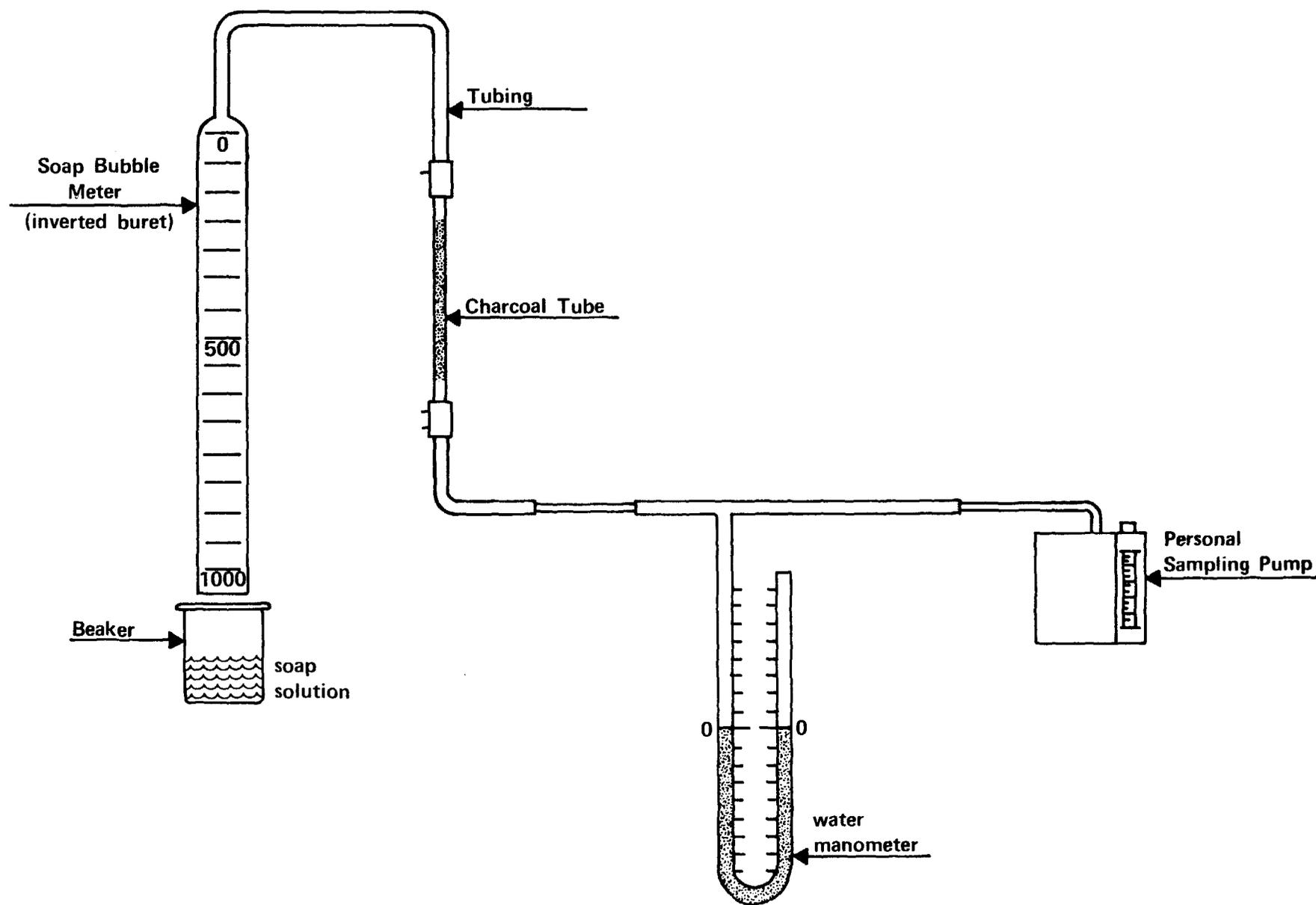


FIGURE XII-1

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH CHARCOAL TUBE

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
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