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 carcinogenicty 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.

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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 (± 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.