NIOSH

Current Intelligence Bulletin

Reprints - Bulletins 19 thru 30 for 1978

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

NIOSH CURRENT INTELLIGENCE BULLETIN
REPRINTS - BULLETINS 19 thru 30 for 1978

Leonard J. Bahlman, Editor
Technical Evaluation and Review Branch

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Office of Extramural Coordination and Special Projects
Rockville, Maryland 20857

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DHEW (NIOSH) Publication No. 79-146

PREFACE

In January 1975, the National Institute for Occupational Safety and Health (NIOSH) developed a Current Intelligence System. Through this system, persons concerned with occupational health are informed of health and safety hazards that have gone unrecognized or are greater hazards than generally known. Since the inception of the NIOSH Current Intelligence System, over 30 Current Intelligence Bulletins have been issued as part of the information dissemination process. The 1978 Bulletins have been reprinted in this publication. It is important to note that the Bulletins have been reprinted essentially as originally published and do not contain information that may have become available since date of publication. Also, for some of the substances, NIOSH may have since issued Criteria Documents with recommended occupational health standards.

Bulletins #1 through #18 have been previously reprinted as a NIOSH publication #78-127. Copies of all Bulletins and reprints are available from NIOSH Publications Dissemination, Division of Technical Services, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

NIOSH

Current Intelligence Bulletin 19

January 13, 1978

2,4-DIAMINOANISOLE (4-METHOXY-m-PHENYLENEDIAMINE) IN HAIR AND FUR DYES

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

(2)

The Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

SYNONYMS

2,4-Diaminoanisole

Chemical Abstract Service Number 615-05-4
CI. 76050
CI. Oxidation Base 12
1,3-Diamino-4-methoxybenzene
Furro L
4-Methoxy-1,3-benzenediamine
4-Methoxy-*m*-phenylenediamine
Pelagol DA
Pelagol Grey L
Pelagol L

2,4-Diaminoanisole Sulfate

Chemical Abstract Service Number 39156-41-7
CI. 76051
1,3-Diamino-4-methoxybenzene Sulfate
4-Methoxy-1,3-benzenediamine Sulfate
4-Methoxy-*m*-phenylenediamine Sulfate

DHEW (NIOSH) Publication No. 78-111

CURRENT INTELLIGENCE BULLETIN:

2,4-Diaminoanisole in Hair and Fur Dyes

January 13, 1978

The National Institute for Occupational Safety and Health (NIOSH) recommends that 2,4-diaminoanisole (4-methoxy-m-phenylenediamine) and its salts* be handled in the workplace as if they were human carcinogens. This recommendation is based primarily upon a preliminary analysis of National Cancer Institute data indicating laboratory rats and mice fed 2,4-diaminoanisole sulfate experienced a statistically significant excess of site-specific malignant tumors as compared to controls. Caution is also indicated by NIOSH epidemiologic studies which suggest an elevated incidence of cancer among cosmetologists. As an interim measure, pending further evaluation of the carcinogenic potential of 2,4-diaminoanisole in the workplace, NIOSH believes it would be prudent to minimize occupational exposure to 2,4-diaminoanisole.

This Bulletin summarizes the results of the National Cancer Institute animal study, the NIOSH epidemiologic studies, other pertinent data, their implications for occupational health, and precautions for handling products containing 2,4-diaminoanisole in the workplace.

Background

The principal use of 2,4-diaminoanisole is as a component of oxidation ("permanent") hair and fur dye formulations. Approximately three-quarters of the current oxidation hair dye formulations contain 2,4-diaminoanisole in concentrations ranging from approximately 0.05% to approximately 2%. The concentration is determined by the shade of the dye. Oxidation hair dyes are very common among professional as well as over-the-counter products and account for approximately $200 million of the $280 million annual retail expenditure for hair dyes. NIOSH is unaware of any current domestic production of 2,4-diaminoanisole. Imports of 2,4-diaminoanisole are on the order of 25,000 pounds per year.

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* In this Bulletin, the phrase, "2,4-diaminoanisole," will be used to signity 2,4-diaminoanisole as well as its salts, such as 2,4-diaminoanisole sulfate (4-methoxy-m-phenylenediamine sulfate).

Potential Occupational Exposures

NIOSH estimates that approximately 400,000 workers have potential occupational exposure to 2,4-diaminoanisole. Hairdressers and cosmetologists comprise the largest portion of workers with potential exposure. (Gloves are usually worn by hairdressers when applying hair dyes). A relatively small number of fur dyers are probably exposed to higher levels of 2,4-diaminoanisole.

Epidemiologic Studies

NIOSH has conducted two epidemiologic studies which suggest excess cancer among cosmetologists.

A report[1] based on data from a case-control study of 25,416 hospital admissions between 1956 and 1965 at Roswell Park Memorial Institute suggests an excess of cancer of specific genital sites (corpus uteri, ovaries) among hairdressers and cosmetologists.

Another study currently being conducted by NIOSH is also suggestive of excess cancer among cosmetologists. This study involves a sample of 53,183 records which are representative of the 417,795 Social Security disability awards made to female workers between 1969 and 1972. Age and race adjusted proportional morbidity ratios* (PMbR's) have been constructed for 24 selected occupational groups. Among cosmetologists, elevated PMbR's were observed for cancer of the digestive organs, respiratory system, trachea, bronchus and lung, breast, and genital organs. Cosmetologists had a greater number of elevated PMbR's for specific primary malignant neoplasms than any other tabulated occupational group. Thus, the preliminary analysis of the Social Security Administration disability data is consistent with the hypothesis that persons employed in occupations classified within the broad category of cosmetology may be at elevated risks of developing a neoplasm due to exposures of occupational origin.

Other relevant epidemiologic studies with conflicting results have been reported.[2-6] These studies do not clearly demonstrate an association between hair dyes and cancer. NIOSH believes that its studies do suggest an association between cancer and employment as cosmetologists and hairdressers. However, it is recognized that cosmetologists and hairdressers are exposed to a large variety of substances, and it is difficult at this time to attribute any excess incidence of cancer to either hair dyes in general or 2,4-diaminoanisole in particular.

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* Each proportional morbidity ratio compares the observed number of women within an occupational category granted an award for a particular disability with the expected number of women (derived from all occupations in the entire sample) granted an award for the same disability.

Laboratory Studies

Preliminary analyses of National Cancer Institute data indicate that male and female laboratory rats and mice fed 2,4-diaminoanisole sulfate in their diets for seventy-eight weeks experienced a statistically significant excess of site-specific malignant tumors as compared to controls.

Groups of fifty male and fifty female Fisher 344 rats and B6C3F1 mice were used in the test. Feed containing 0.05% or 0.12% technical grade 2,4-diaminoanisole sulfate was administered to each group of treated rats; each group of treated mice received feed containing 0.12% or 0.24% technical grade 2,4-diaminoanisole sulfate. Fifty animals of each sex of each species served as controls. After the seventy-eight week treatment period, observation of the mice continued for an additional thirteen weeks and observation of the rats continued for an additional twenty-six weeks.

Significant excess cancer was observed in the thyroid gland and integumentary system (skin) of high dose exposed rats of both sexes, as well as in the thyroid gland of high dose exposed mice, and in the lymphatic system of low dose exposed mice.

In other studies, 2,4-diaminoanisole was tested by skin application to laboratory rodents. Testing by skin application has considerable merit since this route of administration approximates that resulting from the use of hair dyes. Laboratory mice and rats painted with 2,4-diaminoanisole have been reported to experience no statistically significant excess of cancer.[7,8] Kinkle and Holzman, for example, reported applying a mixture containing 0.4% 2,4-diaminoanisole to the shaved backs of Sprague-Dawley rats twice weekly for two years, and then continuing to observe the surviving animals for an additional six months.[8] However, the interpretation of the reported data is complicated by experimental design[9] and these experiments do not convincingly establish the safety of 2,4-diaminoanisole applied to skin.

NIOSH understands that recent and still unpublished data acquired by the Food and Drug Administration indicate that 2,4-diaminoanisole penetrates the skin and thereby enters the system of both man and rhesus monkey. This indicates that skin contact with 2,4-diaminoanisole must be avoided in the workplace.

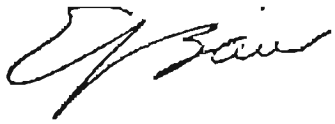
There are reports indicating that 2,4-diaminoanisole is mutagenic in bacterial systems[9] and in drosophila.[10] Mutagenic activity *per se* should be considered an important liability. In addition, empirical correlations have suggested a relationship between mutagenicity, especially in bacterial strains, and carcinogenicity in higher animals.

(6)

NIOSH Recommendation

Animal studies are valuable in helping identify human carcinogens. Substances that cause cancer in experimental animals must be considered to pose a potential cancer risk in man. Although safe levels of exposure to carcinogens have not yet been demonstrated, decreasing exposure to carcinogens does reduce their probability of initiating cancer development.

While the carcinogenicity of 2,4-diaminoanisole is being further evaluated, the National Institute for Occupational Safety and Health recommends, as an interim and prudent measure, that occupational exposure to 2,4-diaminoanisole and its salts be minimized. Exposures should be limited to as few employees as possible, while minimizing workplace exposure levels with engineering and work practice controls. In particular, skin exposures should be avoided. Although substitution is a possible control measure, NIOSH recommends that caution be exercised in selecting a substitute for hair and fur dye formulations containing 2,4-diaminoanisole. Alternatives should be fully evaluated with regard to possible human health effects. This is particularly important in view of the many questions which have been raised recently regarding the safety of numerous components of hair dye formulations.



Edward J. Baier
Deputy Director

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NIOSH

Current Intelligence Bulletin 20

JANUARY 20,1978

TETRACHLOROETHYLENE

(perchloroethylene)

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

(10)

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Synonyms

Ankilostin
Antisal 1
CAS 127-18-4
Didakene
Ethylene tetrachloride
Fedal-Un
Nema
Perclene
PerSec
NIOSH-RTECS KX38500
Tetracap
Tetrachlorethylene
Tetrachloroethene
Tetraguer
Tetraleno
Tetropil
Tetlen
1,1,2,2-Tetrachloroethylene

DHEW (NIOSH) Publication No. 78-112

TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

The National Institute for Occupational Safety and Health (NIOSH) recommends that it is prudent to handle tetrachloroethylene (perchloroethylene) in the workplace as if it were a human carcinogen. The recommendation is based on a recent study by the National Cancer Institute (NCI) indicating that tetrachloroethylene causes liver cancer in laboratory mice (1). This Bulletin is to advise you of the findings of the NCI study, other pertinent data, their implications for occupational health, and precautions for handling tetrachloroethylene.

Animal studies are valuable in helping identify human carcinogens. Substances that cause cancer in experimental animals must be considered to pose a potential cancer risk in man. Safe levels of exposure to carcinogens have not been demonstrated, but the probability of cancer development is lowered with decreasing exposure to carcinogens. Thus NIOSH recommends that occupational exposure to tetrachloroethylene be minimized, and is providing suggested industrial hygiene practices. This is an interim recommendation, while the carcinogenic potential of tetrachloroethylene in the workplace is being further evaluated.

The current Occupational Safety and Health Administration (OSHA) standard for occupational exposure to tetrachloroethylene is 100 ppm, (8-hour time-weighted average). In July 1976 NIOSH (3) recommended an exposure limit of 50 ppm (time-weighted average for up to a 10-hour workday, 40-hour workweek). Neither of these levels may provide adequate protection from potential carcinogenic effects because they were selected to prevent toxic effects other than cancer.

Potential Occupational Exposures

Tetrachloroethylene is a volatile liquid with an odor detectable at about 50 ppm. It is a solvent widely used in dry cleaning, fabric finishing, metal degreasing, and other applications. NIOSH estimates that approximately 500,000 workers are currently at risk of exposure to tetrachloroethylene in the United States. Over 20,000 dry cleaning establisbments and a large number of other industries manufacture or use this substance. About 700 million pounds of tetrachloroethylene are currently produced in the United States each year.

Two-thirds of the domestically consumed tetrachloroethylene is used for dry cleaning and for the processing and finishing of textiles. Tetrachloroethylene is used by three-quarters of the dry cleaners in the United States because it is an excellent cleaner of most fabrics, is easily recycled, and is not flammable.

Metal cleaning accounts for approximately fifteen percent of the domestic consumption of tetrachloroethylene, where exposures can occur during degreasing and cold cleaning. Tetrachloroethylene also serves as a chemical

intermediate in the synthesis of trichlorotrifluoroethane (fluorocarbon 113), dichlorotetrafluoroethane (fluorocarbon 114), chloropentafluoroethane (fluorocarbon 115), and hexafluoroethane (fluorocarbon 116). Tetrachloroethylene exposures may also occur in extraction processes, during its use as an industrial solvent, as a heat exchange fluid, and as a drug in treatment of internal parasite infestations.

Laboratory Animal Studies for Carcinogenicity

The long term animal study reported by NCI demonstrates tetrachloroethylene to be carcinogenic in laboratory mice. In the study, B6C3F1 mice were force fed tetrachloroethylene for 78 weeks. Male mice were treated at two dose levels (536 or 1072 mg/kg/day) and female mice were treated at two different dose levels (386 or 772 mg/kg/day). A significant increase of hepatocellular carcinoma (liver cancer) was observed in both sexes of treated mice when compared with control animals. At both dose levels more than 50% of the male mice and 40% of the female mice (each from groups of approximately 50 animals) developed liver cancer. By comparison, cancer developed in 12% or less of the groups of untreated or vehicle-matched controls. This NCI report is the first definitive association of tetrachloroethylene with cancer. To relate some of the above information to the work environment, a 70 kg man breathing a typical 10 cu m/day (over an 8-hour work shift) of air contaminated with 100 ppm of tetrachloroethylene would have an inhalation exposure of about 100 mg/kg/day.

In the same NCI report, Osborne-Mendel rats showed no significant increase of liver cancer under the same experimental procedure. Because many of the rats died early in the study, this bioassay was considered inadequate for the carcinogenicity testing of tetrachloroethylene. However there was a high incidence of kidney damage observed in both the rats and mice treated with tetrachloroethylene.

A study by The Dow Chemical Company (2) found many tumors in Sprague-Dawley rats exposed by inhalation to 300 or 600 ppm tetrachloroethylene, but for most tumors there was no statistically significant difference in tumor incidence between exposed and control rats. Some tumors were found in higher incidence in control animals. The only tumor seen at higher incidence in exposed animals was adrenal pheochromocytoma in female rats at the lower exposure level only. Pheochromocytoma is a tumor which gives rise to high blood pressure and hyperglycemia due to release of adrenalin and noradrenalin into the blood. Increased mortality occurred in male rats exposed to 600 ppm tetrachloroethylene.

Section references: 1,2

Other Laboratory Animal Studies

The liver is a principal target organ of tetrachloroethylene exposure in

animals. Typical toxic effects are fatty liver, liver enlargement, and abnormal liver function tests. Tetrachloroethylene has also been shown to cause kidney damage in mice following intraperitoneal injection and in rats and rabbits following inhalation.

Neurophysiological effects of tetrachloroethylene are reflected in the distinct alterations of the electroencephalogram (EEG) in rats. Central nervous system (CNS) depression, including abnormal weakness, handling intolerance, intoxication, restlessness, irregular respiration, muscle incoordination, and unconsciousness have been observed in exposed animals.

Tetrachloroethylene has been shown to be a primary eye and skin irritant in rabbits. Other effects of tetrachloroethylene exposure in laboratory animals include lung damage (excessive fluid accumulation, inflammation, congestion, or hemorrhage), cardiac depression, decreased blood pressure, depressed respiration, decreased oxygen consumption, and depression in growth rate.

One study suggests the teratogenic potential of tetrachloroethylene. Fetal and maternal toxicity was observed in mice and rats exposed to tetrachloroethylene on days 615 of gestation. In this study a decrease in the maternal weight gain in rats, an increase in the relative weight of the liver in pregnant mice, an increase of fetal reabsorption in rats, a decrease in fetal body weight and an increase of subcutaneous edema in fetal mice, were all associated with exposure to tetrachloroethylene. Delayed ossification of skull bones and split sternebrae were possible teratogenic effects observed in mice.

Section references: 3,5,6,7,8,13

Human Toxicity

Clinical evidence accumulated over the years clearly demonstrates that tetrachloroethylene is toxic to the liver and kidneys in humans. Liver impairment has been noted in cases of exposure to tetrachloroethylene as evidenced by abnormal liver function tests. Also, toxic chemical hepatitis, and enlargement of the liver and spleen have been associated with exposure to tetrachloroethylene. Tetrachloroethylene vapor is irritating to the eyes and upper respiratory tract, and may cause frontal sinus congestion and headache. Direct contact with skin can cause burns, blistering, and erythema due to the "degreasing" effect of tetrachloroethylene on the skin. Over a period of time this can result in extreme skin dryness with cracking and associated infection.

Altered physiological and behavioral responses observed in subjects exposed to tetrachloroethylene include vague nonspecific complaints generally attributed to CNS depression. These symptoms include vertigo, impaired memory, confusion, fatigue, drowsiness, irritability, loss of appetite, nausea

and vomiting. Motor coordination following tetrachloroethylene exposure requires additional mental effort, which along with memory impairment and fatigue have important implications for worker safety. Various disturbances of the peripheral nervous system such as tremors and numbness have also been associated with exposure to tetrachloroethylene. Excessive absorption of tetrachloroethylene can cause severe depression of the CNS leading to coma; ultimately death may occur from respiratory paralysis or circulatory failure.

Tetrachloroethylene is most commonly absorbed through the lungs and can be absorbed from the intestines if ingested. The skin is a less important absorption site. Physical exercise can significantly increase the amount of tetrachloroethylene absorbed through the lungs because of greater respiration and increased blood flow.

Metabolism and elimination of tetrachloroethylene is relatively slow. It is deposited in body fat and the biologic halflife of tetrachloroethylene in man is estimated at six days.

Section references: 3,4,8,9,10,11,12,14

NIOSH Action on Tetrachloroethylene

1. NIOSH has contracted for a retrospective mortality study of persons employed in dry cleaning establishments where there had been exposure to tetrachloroethylene. The contract will be monitored by the Biometry Section of the NIOSH Industry-wide Studies Branch.

2. The NIOSH Industrial Hygiene Section of the Industry-wide Studies Branch plans an industrial hygiene assessment of dry cleaning workers exposed to tetrachloroethylene.

3. The NIOSH Behavioral and Motivational Factors Branch is undertaking a tetrachloroethylene behavioral teratology study. The study results should be available in late 1978.

4. NIOSH has contracted for a control technology assessment of the dry cleaning industry. The contract will be monitored by the NIOSH Control Technology Research Branch.

5. NIOSH will coordinate research on tetrachloroethylene with the National Cancer Institute (NCI) which is also examining the mortality experience of persons employed in dry cleaning establishments.

6. NIOSH has contracted for a study to evaluate the potential teratogenicity and the mutagenicity of tetrachloroethylene. This contract will be monitored by the NIOSH Experimental Toxicology Branch.

7. Currently available NIOSH publications on tetrachloroethylene include:

   a) Criteria for a recommended standard....Occupational Exposure to Tetrachloroethylene (Perchloroethylene). HEW Publication No. (NIOSH) 76-185.

   b) Health and Safety Guide for Laundries and Dry Cleaners. HEW Publication No. (NIOSH) 75-151.

   c) Effects of Perchloroethylene/Drug Interaction on Behavior and Neurological Function HEW Publication No. (NIOSH) 77-191.

   d) A Behavioral and Neurological Evaluation of Dry Cleaners Exposed Perchloroethylene. HEW Publication No. (NIOSH) 77-214.

Edward J. Baier
Deputy Director

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SUGGESTED PROCEDURES FOR MINIMIZING EMPLOYEE EXPOSURE TO TETRACHLOROETHYLENE (PERCHLOROETHYLENE)

CONTROL OF OVEREXPOSURES

NIOSH recommends that it is prudent to handle tetrachloroethylene in the workplace as if it were a human carcinogen and that occupational exposure to tetrachloroethylene be minimized. Exposure to tetrachloroethylene should be limited to as few employees as possible, while minimizing workplace exposure levels. The area in which it is used should be restricted to those employees necessary to the process or operation. Furthermore, consideration should be given to isolating the tetrachloroethylene exposure area so that adjacent workers are not also exposed.

1. Exposure monitoring

The NIOSH Occupational Exposure Sampling Strategy Manual, NIOSH publication #77-173, may be helpful in developing efficient programs to monitor employee exposures to tetrachloroethylene. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for sampling, and selection of sampling times.

Employee exposure measurement samples can be obtained and analyzed using the guidelines in NIOSH method #P&CAM 127 in the second edition of the NIOSH Manual of Analytical Methods, NIOSH publication #77-157. Exposure measurements should consist of 8-hour TWA exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees).

2. Engineering controls

Engineering and work practice controls should be used to minimize employee exposure to tetrachloroethylene.

To ensure that ventilation equipment is working properly, it is advised that effectiveness be checked at least every three months (e.g., air velocity, static pressure or air volume). System effectiveness should also be checked within five days of any change in production, process, or control which might result in significant increases in airborne exposures to tetrachloroethylene.

3. Respiratory protection

Exposure to tetrachloroethylene should not be controlled with the use of respirators except:

During the time period necessary to install or implement engineering or work practice controls; or

In work situations in which engineering and work practice controls are technically not feasible; or

To supplement engineering and work practice controls when such controls fail to adequately control exposure to tetrachloroethylene; or

For operations which require entry into tanks or closed vessels; or

In emergencies.

Respirators should be approved by the National Institute for Occupational Safety and Health (NIOSH) or by the Mining Enforcement and Safety Administration (MESA). Refer to NIOSH Certified Equipment, December 15, 1975, NIOSH publication #76-145 and Cumulative Supplement June 1977, NIOSH Certified Equipment, NIOSH Publication #77-195. The use of face-seal coverlets or socks with any respirator voids NIOSH/MESA approvals.

Quantitative faceseal fit test equipment (such as sodium chloride or PDOP) should be used. Refer to A Guide to Industrial Respiratory Protection, NIOSH publication #76-189 for guidelines on appropriate respiratory protection programs.

Where respirators are used under the preceding guidelines, NIOSH recommends that for routine use the employer provide either a) Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode (30 CFR 11.70(a)) or b) A combination respirator which includes a Type-C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure or continuous flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or positive pressure mode (30 CFR 11.70(b)). For fire-fighting, the employer should provide a) Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode (30 CFR 11.70(a)). For escape the employer should provide a) Any gas mask providing protection against organic vapors (30 CFR 11.90) or b) Any escape self-contained breathing apparatus (30 CFR 11.70(a)).

PERSONAL PROTECTIVE EQUIPMENT

Employers should provide impervious, gloves, face shields (8-inch minimum) and other appropriate clothing necessary to prevent repeated or prolonged skin contact with liquid tetrachloroethylene.

Employers should see that employee clothing wet with liquid tetrachloroethylene is placed in closed containers for storage until it can be discarded or until the employer provides for the removal of tetrachloroethylene from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the tetrachloroethylene, the employer should inform the person

performing the operation of the hazardous properties of tetrachloroethylene including the fact that it is a possible human carcinogen.

Employers should see that permeable clothing which becomes contaminated with liquid tetrachloroethylene be removed promptly and not reworn until the tetrachloroethylene is removed from the clothing.

PERSONAL HYGIENE

Employers should see that employees who handle liquid tetrachloroethylene wash their hands thoroughly with soap or mild detergent before eating, smoking, or using toilet facilities.

Employers should see that employees whose skin becomes contaminated with liquid tetrachloroethylene promptly wash or shower with soap and mild detergent and water to remove any tetrachloroethylene from the skin.

NIOSH

Current Intelligence Bulletin 21

February 3, 1978

TRIMELLITIC ANHYDRIDE (TMA)

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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As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazards. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

Synonyms

ANHYDROTRIMELLITIC ACID

1,2,4-BENZENETRICARBOXYLIC ACID ANHYDRIDE

1,2,4-BENZENETRICARBOXYLIC ACID, CYCLIC 1,2-ANHYDRIDE

1,2,4-BENZENETRICARBOXYLIC ANHYDRIDE

4-CARBOXYPHTHALIC ANHYDRIDE

CHEMICAL ABSTRACTS SERVICE NUMBER: 552-30-7

CHEMICAL FORMULA: $C_9H_4O_5$

1,3-DIHYDRO-1,3-DIOXO-5-ISOBENZOFURANCARBOXYLIC ACID

1,3-DIOXO-5-PHTHALANCARBOXYLIC ACID

DIPHENYLMETHANE-4,4'-DIISOCYANATE-TRIMELLIC ANHYDRIDE-ETHOMID HT POLYMER

NIOSH - RTECS DC20500

TMA*

TMAN

TRIMELLITIC ACID ANHYDRIDE

TRIMELLITIC ACID 1,2-ANHYDRIDE

TRIMELLITIC ACID CYCLIC 1,2-ANHYDRIDE

*TMA is also an acronym for trimethylamine.

TRIMELLITIC ANHYDRIDE (TMA)

The National Institute for Occupational Safety and Health (NIOSH) recommends that trimellitic anhydride (TMA) be handled as an extremely toxic agent in the workplace. Exposure to this compound may result in noncardiac pulmonary edema (apparently without benefit of a pulmonary irritation warning), immunological sensitization, and irritation of the pulmonary tract, eyes, nose, and skin, There is no current Occupational Safety and Health Administration (OSHA) exposure standard for trimellitic anhydride. The Amoco Chemicals Corporation, the sole domestic producer, suggests a limit of "0.05 mg/m^3 or less for susceptible individuals."(1)

NIOSH has prepared this Current Intelligence Bulletin to advise you of recent findings of toxic effects of trimellitic anhydride and to provide some precautions for handling trimellitic anhydride in the workplace. Attached are "Suggested Procedures for Minimizing Employees' Exposure to Trimellitic Anhydride."

Potential Occupational Exposures

NIOSH estimates approximately 20,000 American workers are currently at risk of exposure to trimellitic anhydride in its various applications. TMA is used as a curing agent for epoxy and other resins, in vinyl plasticizers, paints and coatings, polymers, polyesters, agricultural chemicals, dyes and pigments, pharmaceuticals, surface active agents, modifiers, intermediates, and specialty chemicals. The sole domestic producer of trimellitic anhydride is Amoco Chemicals Corporation which has a 50 million pound-per-year plant at Joliet, Illinois.

Human Toxicity

The ability for trimellitic anhydride to cause pulmonary edema (excessive fluid in the lungs) has been demonstrated by Rice et al.(2) Two workers had been employed by the same company for only a short period of time (3 and 6 weeks). They received multiple inhalation exposures to an epoxy resin containing trimellitic anhydride when it was

sprayed on heated pipes. The levels of trimellitic anhydride were not available to the authors. No mention was made of severe irritation of the upper respiratory tract while they were receiving their exposures, suggesting little or no warning of subsequent damage to the lungs. The possibility that the pulmonary edema was the result of a hypersensitivity reaction must therefore be considered. Resins can be sensitizers (e.g., toluene diisocyanate or TDI), though most of the reported effects have been those of direct irritation. (3)

Sensitization to trimellitic anhydride was reported by Zeiss et al.(4) Respiratory symptoms were observed in fourteen workers employed in the synthesis of trimellitic anhydride. The authors suggest three distinct syndromes induced by inhalation of TMA. The first, rhinitis and/or asthma, developed over an industrial exposure period of weeks to years. After this period, the sensitized worker exhibited symptoms immediately following exposure to trimellitic anhydride dust or fume, which abated after the work exposure had stopped. The second syndrome, termed "TMA-flu" by the workers, also required a sensitization period of exposure and was characterized by delayed onset cough, wheezing, and labored breathing starting 4 to 8 hours after a work shift and peaking at night. These respiratory symptoms were usually accompanied by malaise, chills, fever, muscle and joint aches, and appeared to be associated with relatively high exposures to trimellitic anhydride during particular work shifts. The third syndrome, which followed initial high exposure to TMA, was primarily an irritant effect. It was characterized by a "running" nose without itching or sneezing, occasional nosebleed, cough, labored breathing, and occasional wheezing. Symptoms usually abated after 8 hours and rarely lasted into the night.

The above studies suggest harmful respiratory effects of trimellitic anhydride at relatively high concentrations, but even at lower concentrations some workers may develop an immunological sensitization over a period of time.

Fawcett et al. (5) also observed sensitization in a worker exposed to trimellitic anhydride in the production of tubular steel shop fittings coated with an epoxy resin. The chemical agent responsible for asthma symptoms of six workers was identified by careful inhalation challenge testing, simulating work exposure. Typical attacks which began one year after onset of TMA exposure consisted of cough and breathlessness

lasting for 30 minutes, which subsided, only to be followed the same evening by sneezing which persisted for about 24 hours. Subsequent attacks were prevented by avoiding exposure.

Data on occupational exposures to trimellitic anhydride were also obtained during a NIOSH Health Hazard Evaluation of a paint and varnish company during the manufacture of an epoxy paint.(6) The Health Hazard Evaluation was conducted at the request of employees who were concerned about possible harmful effects of trimellitic anhydride exposure during processing and decontamination operations. The occupational airborne exposure levels averaged 1.5 mg/m^3 TMA (with a range from "none detected" to 4.0 mg/m^3) during processing operations and 2.8 mg/m^3 TMA (ranging from "none detected" to 7.5 mg/m^3) during decontamination operations. A total of 13 employees (5 present and 8 former employees) were interviewed and briefly examined. Employees' symptoms and complaints were: eye irritation, nasal irritation, shortness of breath, wheezing, cough, heartburn, nausea, headache, skin irritation, and throat irritation. Three of the former workers stated that they had left that department for health reasons. Complaints subsided when non-TMA-containing products were being formulated.

The Occupational Health and Safety Division, Department of Labour, Alberta, Canada, has reported to NIOSH that they are aware of employee reactions in two plants using TMA-epoxy powder pipe coatings. The one plant, started in 1971, had a number of employees with an immediate reaction. After instituting engineering and administrative controls, there has been no further incidence. In the second plant, began in 1974, the first adverse reaction occurred in 1975. There have been 9 cases of adverse reactions reported to date. Most of these employees were kept in intensive care while they recuperated and were advised by their physicians to seek new jobs. However, some returned to their previous jobs and became ill again. Due to the unavailability of a good analytical method for trimellitic anhydride occupational levels could not be documented until November of 1977. The TMA concentrations found ranged from 0.11 mg/m^3 to 0.27 mg/m^3.

In view of the employer's responsibility, "to furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees . . . ," occupational exposure to trimellitic anhydride should be minimized. It appears evident that trimellitic anhydride, a known irritant, can cause severe pulmonary edema, immunological sensitization, and asthma symptoms.

J. Donald Millar, M.D.
Assistant Surgeon General
Acting Director

References

1. Amoco-Industrial Hygiene Toxicology and Safety Data Sheet, Environmental Health Services, Medical and Health Services Department, July 8, 1976.

2. Rice, D. L., Jenkins, D. E., Gray, J. M., and Greenberg, S. D., "Chemical Pneumonitis Secondary to Inhalation of Epoxy Pipe Coating," Archives of Environmental Health 32(4):173-8, July-August 1977.

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6. National Institute for Occupational Safety and Health, Health Hazard Evaluation Determination Report No. 74-111-283.

SUGGESTED PROCEDURES FOR MINIMIZING EMPLOYEE EXPOSURE TO TRIMELLITIC ANHYDRIDE (TMA)

CONTROL OF OVEREXPOSURES

NIOSH recommends that trimellitic anhydride be handled in the workplace as an extremely toxic substance because it can cause noncardiac pulmonary edema, immunological sensitization, and severe respiratory irritation. Exposure to trimellitic anhydride should be limited to as few employees as possible, while minimizing workplace exposure levels. The area in which it is used should be restricted to those employees necessary to the process or operation. Furthermore, consideration should be given to isolating the trimellitic anhydride exposure area so that adjacent workers are not also exposed.

1. Exposure Monitoring

The NIOSH Occupational Exposure Sampling Strategy Manual, NIOSH Publication #77-173, may be helpful in developing efficient programs to monitor employee exposures to trimellitic anhydride. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for sampling, and selection of sampling times.

Exposure measurements should consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees).

2. Engineering Controls

Engineering and work practice controls should be used to minimize employee exposure to trimellitic anhydride.

To ensure that ventilation equipment is working properly, effectiveness (e.g., air velocity, static pressure or air volume) should be checked at least every three months.

System effectiveness should also be checked within five days of any change in production, process, or control which might result in significant increases in airborne exposures to trimellitic anhydride.

3. Respiratory Protection

Exposure to trimellitic anhydride should not be controlled with the use of respirators except:

- o During the time period necessary to install or implement engineering or work practice controls; or
- o In work situations in which engineering and work practice controls are technically not feasible; or
- o To supplement engineering and work practice controls when such controls fail to adequately control exposure to trimellitic anhydride; or
- o For operations which require entry into tanks or closed vessels; or
- o In emergencies.

Respirators should be approved by the National Institute for Occupational Safety and Health (NIOSH) or by the Mining Enforcement and Safety Administration (MESA). Refer to NIOSH Certified Equipment, December 15, 1975, NIOSH publication #76-145 and Cumulative Supplement June 1977, NIOSH Certified Equipment, NIOSH publication #77-195. The use of faceseal coverlets or socks with any respirator voids NIOSH/MESA approvals.

Quantitative faceseal fit test equipment (such as sodium chloride, dioctyl phthalate, or equivalent) should be used. Refer to A Guide to Industrial Respiratory Protection, NIOSH publication #76-189 for guidelines on appropriate respiratory protection programs.

Where respirators are needed and NIOSH recommendations allow their use to reduce employee exposure, the following types of respirators may be used. They are listed in order of increasing protection factors.

- Protection factor of 50: any chemical cartridge respirator with a full facepiece, organic vapor cartridge(s), and high efficiency filter(s) (30 CFR 11.150 and 11.130); any gas mask with a chin-style organic vapor canister and high efficiency filter (30 CFR 11.90(a) and 11.130); any supplied-air respirator with a full facepiece, helmet, or hood (30 CFR 11.110(a)); any self-contained breathing apparatus with a full facepiece (30 CFR 11.70(a)).

- Protection factor of 1000: any powered air purifying chemical cartridge respirator with full facepiece, organic vapor cartridge(s), and high efficiency particulate filter(s).

- Protection factor of 2000: any type C supplied-air respirator with a full facepiece operated in positive pressure-demand or other positive pressure mode or with a full facepiece, hood, or helmet operated in continuous flow mode (30 CFR 11.110(a)).

- Protection factor of 10,000+: self-contained breathing apparatus with a full facepiece operated in positive pressure-demand or other positive pressure mode (30 CFR 11.70(a)); any combination respirator which includes a type C supplied-air respirator with a full facepiece operated in positive pressure-demand or other positive pressure or continuous flow mode and an auxilary self-contained breathing apparatus operated in positive pressure-demand or positive pressure mode (30 CFR 11.70(b)).

PERSONAL PROTECTIVE EQUIPMENT

Employers should provide appropriate protective clothing and equipment necessary to prevent repeated or prolonged skin contact with trimellitic anhydride.

Employers should see that employees whose clothing may have become contaminated with trimellitic anhydride change into uncontaminated clothing before leaving the work premises.

Employers should see that non-impervious clothing which becomes contaminated with trimellitic anhydride be promptly removed and not reworn until the trimellitic anhydride is removed from the clothing.

Employers should see that clothing contaminated with trimellitic anhydride is placed in closed containers for storage until it can be discarded or removed from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the trimellitic anhydride, the employer should tell the person performing the cleaning operation of the hazardous properties of trimellitic anhydride.

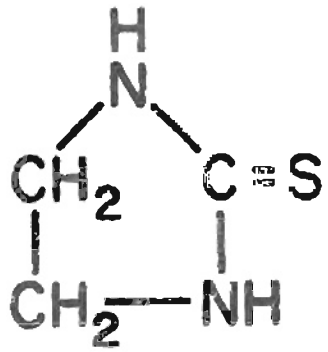
Employers should provide dust-resistant safety goggles where there is any possibility of trimellitic anhydride dust contacting the eyes.

NIOSH

Current Intelligence Bulletin 22

April 11, 1978

ETHYLENE THIOUREA



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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IDENTIFIERS AND SYNONYMS FOR ETHYLENE THIOUREA

Chemical Abstracts Service
Registry Number 96-45-7
NIOSH RTECS Number NI96250
Chemical Formula $C_3H_6N_2S$

4,5-Dihydroimidazole-2(3H)-thione
4,5-Dihydro-2-mercaptoimidazole
N,N'-(1,2-Ethanediyl)thiourea
Ethylene thiourea
Ethylenethiourea
1,3-Ethylene-2-thiourea
1,3-Ethylenethiourea
N,N'-Ethylenethiourea
ETU
Imidazolidinethione
Imidazoline-2-thiol
2-Imidazolidinethione
2-Imidazoline-2-thiol
Imidazoline-2(3H)-thione
Mercaptoimidazoline
2-Mercaptoimidazoline
2-Mercapto-2-imidazoline
NA 22
NA-22-D
Pennac CRA
Rhodanin S 62
Sodium-22 Neoprene accelerator
Tetrahydro-2H-imidazole-2-thione
2-Thiol-dihydroglyoxaline
Warecure C

DHEW (NIOSH) Publication No. 78-144

CURRENT INTELLIGENCE BULLETIN:

ETHYLENE THIOUREA (ETU)

April 11, 1978

The National Institute for Occupational Safety and Health (NIOSH) recommends that ethylene thiourea be handled in the workplace as if it were a human carcinogen and teratogen. During development of a NIOSH Special Occupational Hazard Review on ethylene thiourea (scheduled for issuance later in 1978) it became apparent that exposure to ethylene thiourea poses a risk of teratogenesis, particularly to the central nervous system, which is greater than has been generally recognized. The NIOSH literature review clearly shows ethylene thiourea to be a teratogen and a carcinogen in laboratory rats with supportive studies in other species. Pending completion of a NIOSH Special Occupational Hazard Review, this Current Intelligence Bulletin has been prepared to provide early dissemination of the information since NIOSH believes it would be prudent to minimize occupational exposure to ethylene thiourea. There is no current Occupational Safety and Health Administration (OSHA) exposure standard for ethylene thiourea.

Background

Ethylene thiourea is a white crystalline solid which is used extensively as an accelerator in the curing of polychloroprene (Neoprene®) and other elastomers. NIOSH estimates that approximately 3500 workers in the rubber industry have potential occupational exposure to ethylene thiourea. This estimate is based on the NIOSH National Occupational Hazard Survey which was conducted between 1972 and 1974, and included over 500,000 employees at 4775 facilities. In addition, exposure to ethylene thiourea also results from the very widely used ethylene bisdithiocarbamate fungicides. Ethylene thiourea may be present as a contaminant in the ethylene bisdithiocarbamate fungicides and can also be formed when food containing the fungicides is cooked.

Commercial ethylene thiourea is available as a solid powder, as a dispersion in oil (which retards the formation of fine dust dispersions in workplace air), and "encapsulated" in a matrix of compatible elastomers. In this latter form, ethylene thiourea may be least likely to escape into the workplace air.

Laboratory Animal Studies

Ethylene thiourea has been shown to be carcinogenic and teratogenic (causing malformations in offspring) in laboratory animals. In addition, ethylene thiourea can cause myxedema (the drying and thickening of skin, together with a slowing down of physical and mental activity), goiter, and other effects related to decreased output of thyroid hormone.

In a recent publication from E. I. du Pont de Nemours and Company's Haskell Laboratory, for example, Stula and Krauss report "marked teratogenic effects were demonstrated" when ethylene thiourea was applied to the skin of laboratory rats. (1) In this study, 50 milligrams ethylene thiourea per kilogram body weight was applied as a 20% solution in dimethylsulfoxide (DMSO) to the skin of pregnant, female Sprague-Dawley rats on the twelfth and also on the thirteenth day of gestation. Malformations were observed in all of seventy-three fetuses upon sacrifice of the pregnant females on the twentieth day of gestation. Appropriate control animals showed no fetal abnormality. A number of other reports in the literature further document the teratogenic potential of ethylene thiourea (e.g., 2 and references cited therein).

The Stula and Krauss study (1) further demonstrates that dose as well as day of gestation on which exposures occur are critical factors. When 50 mg/kg ethylene thiourea applications were made as above, but on the tenth and eleventh day of gestation, only five of eighty-three fetuses exhibited abnormalities; DMSO controls in this case exhibited one abnormality in forty fetuses. However, no fetal abnormalities were found among pregnant rats similarly exposed to 25 mg/kg ethylene thiourea on the tenth and also on the eleventh day of gestation.

Ethylene thiourea has been shown to cause cancer in laboratory animals. In one study, for example, Charles River CD rats were fed ethylene thiourea at 175 or 350 ppm in their diets for eighteen months and then observed while on a control diet for an additional six months. (3) Thyroid carcinomas were observed in seventeen of twenty-six males (2 with pulmonary metastases) and eight of twenty-six females at the high dose level, as well as three of twenty-six males and three of twenty-six females at the low dose level. In addition, solid-cell adenomas of the thyroid were observed in one female at the high dose level as well as two females at the low dose level. No thyroid carcinoma was found among the thirty-two male or thirty-two female controls. The International Agency for Research in Cancer (IARC) has concurred that oral administration of ethylene thiourea produces thyroid carcinoma in rats. (4) Other authors (5, 6) have also reported carcinogenic effects of ethylene thiourea in laboratory animals.

A more complete review of animal experiments on ethylene thiourea will be presented in the forthcoming NIOSH Special Occupational Hazard Review.

NIOSH Recommendation

Pending completion of the NIOSH Special Occupational Hazard Review and the development of specific recommended control measures for ethylene thiourea, the National Institute for Occupational Safety and Health recommends, as an interim and prudent measure, that occupational exposure to ethylene thiourea be minimized. Exposure should be limited to as few employees as possible, while minimizing workplace exposure levels with engineering and work practice controls. Although substitution is a possible control measure, alternatives to ethylene thiourea or ethylene bisdithiocarbamate fungicides should be fully evaluated with regard to possible human health effects.

J. Donald Millar, M.D.
Assistant Surgeon General
Acting Director

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1. Stula, E. F. and Krauss, W. C., "Embryotoxicity in Rats and Rabbits from Cutaneous Application of Amide-Type Solvents and Substituted Ureas," Toxicology and Applied Pharmacology, 41, 35-55, 1977.

2. Khera, K. S. and Tryphonas, L., "Ethylenethiourea-Induced Hydrocephalus: Pre-and Postnatal Pathogenesis in Offspring from Rats Given a Single Oral Dose during Pregnancy," Toxicology and Applied Pharmacology, 42, 85-97, 1977.

3. Ulland, B. M. et al., "Thyroid Cancer in Rats from Ethylene Thiourea Intake," J. Nat. Cancer Inst., 49, 583-584, 1972.

4. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, 7, 45-52, 1974.

5. Innes, J. R. M. et al., "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note," J. Nat. Cancer Inst., 42, 1101-1114, 1969.

6. Graham, S. L. et al., "Effects of Prolonged Ethylene Thiourea Ingestion on the Thyroid of the Rat, Food and Cosmetic Toxicology, 13, 493-499, 1975.

SUGGESTED GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO ETHYLENE THIOUREA (ETU)

NIOSH recommends that it would be prudent to handle ethylene thiourea in the workplace as if it were a human carcinogen and teratogen. Exposure to ethylene thiourea should be limited to as few employees as possible, while minimizing workplace exposure levels. The area in which it is used should be restricted to only those employees essential to the process or operation.

EXPOSURE MONITORING

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective.

The NIOSH Occupational Exposure Sampling Strategy Manual, NIOSH Publication #77-173, may be helpful in developing efficient programs to monitor employee exposures to ethylene thiourea. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for exposure evaluation, and selection of sampling times.

Employee exposure measurements should consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). Area and source measurements may be useful to determine problem areas, processes, and operations.

MINIMIZING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to ethylene thiourea. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation of any of these.

- Product Substitution

The substitution of an alternative material with a lower potential health and

safety risk is one method. However, extreme care must be used when selecting possible substitutes. Alternatives to ethylene thiourea should be fully evaluated with regard to possible human effects. Unless the toxic effects of the alternative have been thoroughly evaluated, a seemingly safe replacement, possibly only after years of use, may be found to induce serious health effects.

o Contaminant Controls

The most effective control of ethylene thiourea, where feasible, is at the source of contamination by enclosure of the operation and/or local exhaust ventilation.

If feasible, the process or operation should be enclosed with a slight vacuum so that any leakage will result in the flow of air into the enclosure.

The next most effective means of control would be a well designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

To ensure that ventilation equipment is working properly, effectiveness (e.g., air velocity, static pressure, or air volume) should be checked at least every three months. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposures to ethylene thiourea.

o Employee Isolation

A third alternative is the isolation of employees. It frequently involves the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those employees that must do process checks, adjustments, maintenance, and related operations.

o Personal Protective Equipment

The least preferred method is the use of personal protective equipment. This equipment, which may include respirators, goggles, gloves, and related items, should not be used as the only means to prevent or minimize exposure during routine operations.

Exposure to ethylene thiourea should not be controlled with the use of respirators except:

— During the time necessary to install or implement engineering or work practice controls; or

— In work situations in which engineering and work practice controls are technically not feasible; or

— For maintenance; or

— For operations which require entry into tanks or closed vessels; or

-- In emergencies.

Only respirators approved by the National Institute for Occupational Safety and Health (NIOSH) should be used. Refer to NIOSH Certified Equipment, December 15, 1975, NIOSH publication #76-145 and Cumulative Supplement June 1977, NIOSH Certified Equipment, NIOSH publication #77-195. The use of faceseal coverlets or socks with any respirator voids NIOSH approvals.

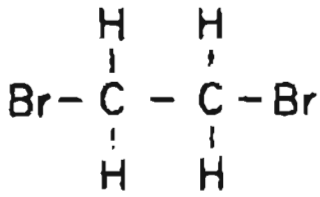
Quantitative faceseal fit test equipment (such as sodium chloride, dioctyl phthalate, or equivalent) should be used. Refer to A guide to Industrial Respiratory Protection, NIOSH publication #76-189 for guidelines on appropriate respiratory protection programs.

NIOSH

Current Intelligence Bulletin 23

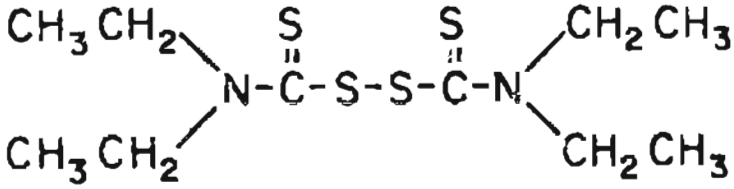
April 11, 1978

ETHYLENE DIBROMIDE



and

DISULFIRAM



TOXIC INTERACTION

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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DHEW (NIOSH) Publication No. 78-145

IDENTIFIERS AND SYNONYMS FOR DISULFIRAM

Chemical Abstracts Service Registry Number 97-77-8
NIOSH RTECS Number JO12250
Chemical Formula $C_{10}H_{20}N_2S_4$

Abstensil
Abstinil
Abstinyl
Alcophobin
Alk-aubs
Antabus
Antabuse
Antadix
Antaenyl
Antaethan
Antaethyl
Antaetil
Antalcol
Antetan
Antetil
Anteyl
Antiaethan
Antietanol
Anti-ethyl
Antietil
Antikol
Antivitium
Aversan
Averzan
Bis(diethylthiocarbamoyl) disulfide
Bis(N,N-diethylthiocarbamoyl) disulfide
Bonibal
Contralin
Contrapot
Cronetal
Dicupral
Disetil
Disulfan
Disulfiram
Disulfuram
1,1'-Dithiobis(N,N-diethylthioformamide)
Ekagom TEDS
Ekagom TETDS
Ephorran
Espenal
Esperal
Etabus
Ethyl Thiram
Ethyl Thiudad
Ethyl Thiurad
Ethyl Tuads
Ethyl Tuex
Ethyldithiourame
Ethyldithiurame
Exhorran
Hoca
Krotenal
Nocbin
Noxal
Refusal
Ro-Sulfiram
Stopaethyl
Stopethyl
Stopetyl
TATD
Tenurid
Tenutex
TETD
Tetidis
Tetradin
Tetradine
Tetraethylthioperoxydicarbonic diamide
Tetraethylthiram disulfide
Tetraethylthiuram
Tetraethylthiuram disulfide
N,N,N'N'-Tetraethylthiuram disulfide
Tetraetil
Teturam
Teturamin
Thiocid
Thiosan
Thioscabin
Thireranide
Thiuram E
Thiuranide
Tillram
Tiuram
TTD
TTS

(44)

IDENTIFIERS AND SYNONYMS FOR ETHYLENE DIBROMIDE

Chemical Abstracts Service Registry Number 106-93-4
NIOSH RTECS Number KH9275O
Chemical Formula $C_2H_4Br_2$

Aadibroom
Bromofume
Celmide
Dibromoethane
1,2-Dibromoethane
α,β-Dibromoethane
sym-Dibromoethane
Dowfume EDB
Dowfume MC-2
Dowfume W-8
Dowfume W-85
Dowfume 40
E-D-BEE
EDB
EDB-85
ENT 15,349
Ethylene Bromide
Ethylene Dibromide
Fumo-Gas
Glycol Dibromide
Iscobrome D
Kopfume
Nefis
Pestmaster
Pestmaster EDB-85
Sanhyuum
Soilbrom-40
Soilbrom-85
Soilfume
Unifume

CURRENT INTELLIGENCE BULLETIN:

ETHYLENE DIBROMIDE AND DISULFIRAM TOXIC INTERACTION

April 11, 1978

The National Institute for Occupational Safety and Health (NIOSH) recommends that no worker be exposed to both ethylene dibromide and disulfiram (Antabuse®, Ro-Sulfiram®, tetraethylthiuram disulfide; additional synonyms are tabulated in the appendix). This interim recommendation is based on preliminary results of NIOSH research currently in progress which suggests a serious toxic interaction between inhaled ethylene dibromide and ingested disulfiram resulting in exceedingly high mortality of laboratory rats.

This Bulletin summarizes the current status of the NIOSH study, other pertinent data, occupational health implications, and NIOSH recommendations for reducing the risk from the toxic interaction.

Background — Ethylene Dibromide

Approximately 300 million pounds of ethylene dibromide are produced annually in the United States. Ethylene dibromide, a volatile liquid, is used primarily as a lead scavenger in leaded fuels (to retard lead deposition in the engine), but this use is decreasing as the consumption of leaded gasoline decreases. Ethylene dibromide is also used as a soil, grain, and fruit fumigant, as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums, and waxes. NIOSH estimates that approximately 9,000 employees are potentially exposed to ethylene dibromide during the course of these uses. (1) In addition, an estimated 650,000 gasoline station attendants are potentially exposed to very low levels of ethylene dibromide. (1) McDermott and Killiany have estimated maximum expected airborne concentrations of ethylene dibromide to be 0.08 parts per million parts of air (ppm) at 500 ppm leaded gasoline vapor in air. (2)

An employee exposure ceiling of 0.13 ppm (1.0 mg/m^3), as determined over any fifteen-minute sampling period, was recommended by NIOSH in August 1977 for ethylene dibromide. (1) However, toxic interaction effects with other chemicals were not considered in the development of this recommended standard. The current Occupational Safety and Health Administration, Department of Labor, standard for occupational exposure to ethylene dibromide is 20 ppm (8-hour time-weighted average).

Ethylene dibromide itself is a very toxic compound. Reported adverse health effects of employees chronically exposed to ethylene dibromide may

include the induction of cancer and sterility as well as malformations and heritable changes in offspring. Ethylene dibromide may also cause adverse effects to the liver, kidneys, heart, and other internal organs and systems. Skin contact with ethylene dibromide may cause chemical burns as well as systemic effects due to absorption of ethylene dibromide through the skin. A summary of the health effects of ethylene dibromide may be found in the NIOSH Criteria Document. (1)

Background — Disulfiram

Disulfiram is a prescription drug used as an alcohol deterrent and also is an accelerator used in the manufacture of rubber. Disulfiram may also be used as a fungicide and insecticide.

Disulfiram is widely used in alcoholism control programs under the tradenames Antabuse®and Ro-Sulfiram®. The intake of even small quantities of ethanol (ethyl alcohol) while on disulfiram results in flushing, breathing difficulty, nausea, vomiting, and low blood pressure. This violent and unpleasant reaction reinforces an individual's resolve to abstain from alcohol. The human therapeutic dose of disulfiram ranges from 125 to 500 mg/day; disulfiram therapy may continue for many months, even years.

Although the literature does contain reports of carcinogenic effects of disulfiram in laboratory animals, the International Agency for Research in Cancer (IARC) has concluded that, "the limited data available do not allow an evaluation of the carcinogenicity of disulfiram to be made." (3) Disulfiram is currently being tested for carcinogenicity by the National Cancer Institute.

NIOSH estimates that approximately 70,000 workers have occupational exposure to disulfiram. This estimate is based on the NIOSH National Occupational Hazard Survey which was conducted between 1972 and 1974, and included over 500,000 employees at 4,775 facilities. In addition, there may be as many as 100,000 people on disulfiram therapy for alcoholism.

Laboratory Animal Study of Toxic Interaction

In the NIOSH-sponsored research currently in progress, laboratory rats exposed to 20 ppm ethylene dibromide by inhalation (the current 8-hour TWA OSHA exposure standard) and also receiving a diet containing 0.05% disulfiram are experiencing exceedingly high mortality levels as well as a high incidence of tumors (including hemangiosarcomas of the liver, spleen, and kidney). Even in those sites where tumors often occur spontaneously in rats, such as the mammary gland in females, the incidence of tumors appears to be increased and the tumors are occurring at an earlier than expected age. These results are preliminary and control animals have not yet been completely studied. Although the clinical significance of the data has not yet been evaluated, great caution is indicated.

The NIOSH-sponsored research is being conducted by Midwest Research Institute, Kansas City, Missouri, under NIOSH contract #210-76-0131 (September 29, 1976 to January 31, 1979). Four groups of animals are in the study, each group comprised of 48 male and 48 female Sprague-Dawley rats. After approximately thirteen months of exposure, 45 of the 48 male and 47 of the 48 female rats exposed simultaneously to ethylene dibromide and disulfiram have died or have been terminated because they were dying (due to the formation of tumors.) A description of the four groups as well as a summary of their mortality experience at the end of approximately thirteen months of treatment is presented in Table 1.

TABLE 1 - Number of Deaths or Terminations/Total Number of Rats

Group	Treatment	Male	Female
Untreated	Filtered air; control diet	0/48	3/48
Disulfiram only	Filtered air; diet containing 0.05% disulfiram by weight	3/48	2/48
Ethylene dibromide only	Inhalation of 20 ppm ethylene dibromide 6 hours per day, 5 days per week; control diet	15/48	9/48
Ethylene dibromide/ disulfiram	Inhalation of 20 ppm ethylene dibromide 6 hours per day, 5 days per week; diet containing 0.05% disulfiram by weight	45/48	47/48

The extent to which this toxic interaction is specific for ethylene dibromide and disulfiram is not known. Similar toxic interactions may occur between disulfiram, as well as chemicals structurally related to disulfiram, and other halogenated hydrocarbons.

NIOSH Recommendations

While current NIOSH research continues and its significance is further evaluated, it is recommended, as an interim and prudent measure, that no worker be exposed to both ethylene dibromide and disulfiram.

Workers should not be exposed to ethylene dibromide during the course of disulfiram therapy. Disulfiram (Antabuse®, Ro-Sulfiram®) should not be administered to workers having potential occupational exposure to ethylene dibromide except in those cases where, in the best judgment of the responsible physician, the benefit of disulfiram therapy strongly outweighs the risk to the particular patient.

Whenever disulfiram [bis(diethylthiocarbamoyl) disulfide, tetraethylthiuram disulfide] is used in the workplace (e.g., as an accelerator in rubber production, as a fungicide or insecticide), precautions should be taken so that no worker is exposed to both ethylene dibromide and disulfiram.

Although NIOSH recognizes the complexity and many combinations possible in evaluating toxic interactions between various agents, NIOSH believes this is an area in need of further attention and study.

for J. Donald Millar, M.D.
Assistant Surgeon General
Acting Director

References

1. Criteria for a Recommended Standard . . . . Occupational Exposure to Ethylene Dibromide, U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio, August 1977.

2. McDermott, H. J., and Killiany, S. E., Jr., "Quest for a Gasoline TLV," Am. Ind. Hyg. Assoc. J., 39, 110-117, 1978.

3. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals in Man, 12, 85-95, 1976.

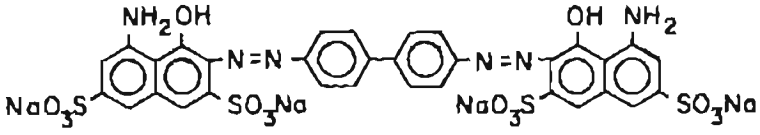
JOINT

NIOSH/NCI

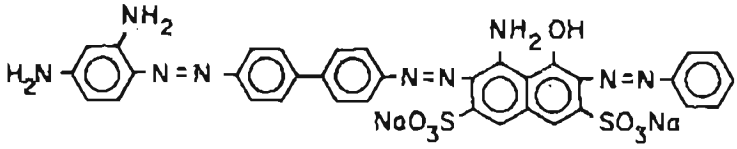
Current Intelligence Bulletin 24

April 17, 1978

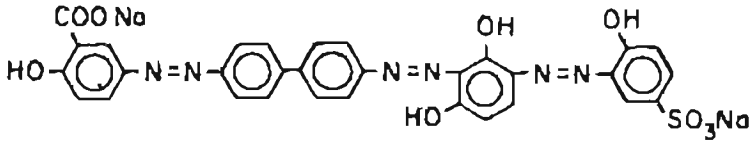
DIRECT BLUE 6



DIRECT BLACK 38



DIRECT BROWN 95 COPPER COMPLEX DERIVED FROM



Benzidine Derived Dyes

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

Center for Disease Control
National Institute for
Occupational Safety and Health

National Institutes of Health
National Cancer Institute

The Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

FURTHER INFORMATION:

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20014

Melva Weber
(301) 496-6641

Center for Disease Control
National Institute for
Occupational Safety and Health
Rockville, Maryland 20857

Jack Hardesty
(301) 443-2140

SYNONYMS

Identifiers and Synonyms on Attached Sheets

DHEW (NIOSH) Publication No. 78-148

IDENTIFIERS AND SYNONYMS FOR DIRECT BLACK 38

Chemical Abstracts Service Registry Number 1937-37-7
NIOSH/RTECS Number JM71700
Chemical Formula $C_{34}H_{25}N_9O_7S_2Na_2$

Ahco Direct Black GX
Airedale Black ED
Aizen Direct Deep Black EH
Aizen Direct Deep Black GH
Aizen Direct Deep Black RH
Amanil Black GL
Amanil Black WD
Apomine Black GX
Atlantic Black BD
Atlantic Black C
Atlantic Black E
Atlantic Black EA
Atlantic Black GAC
Atlantic Black GG
Atlantic Black GXCW
Atlantic Black GXOO
Atlantic Black SD
Atul Direct Black E
Azine Deep Black EW
Azocard Black EW
Azomine Black EWO
Belamine Black GX
Bencidal Black E
Benzanil Black E
Benzo Deep Black E
Benzo Leather Black E
Benzoform Black BCN-CF
Black 2EMBL
Black 4EMBL
Brasilamina Black GN
Brilliant Chrome Leather Black H
C.I. 30235
C.I. Direct Black 38
Calcomine Black
Calcomine Black EXL
Carbide Black E
Chloramine Black C
Chloramine Black EC
Chloramine Black ERT
Chloramine Black EX
Chloramine Black EXR
Chloramine Black XO
Chloramine Carbon Black S
Chloramine Carbon Black SJ
Chloramine Carbon Black SN
Chlorazol Black E
Chlorazol Black E (Biological Stain)
Chlorazol Black EA
Chlorazol Black EN
Chlorazol Burl Black E
Chlorazol Leather Black ENP
Chlorazol Silk Black G
Chrome Leather Black E
Chrome Leather Black EC
Chrome Leather Black EM
Chrome Leather Black G
Chrome Leather Brilliant Black ER
Coir Deep Black C
Columbia Black EP
Diacotton Deep Black
Diacotton Deep Black RX
Diamine Deep Black EC
Diamine Direct Black E
Diaphtamine Black V
Diazine Black E
Diazine Direct Black E
Diazine Direct Black G
Diazol Black 2V
Diphenyl Deep Black G
Direct Black Methyl
Direct Black A
Direct Black BRN
Direct Black CX
Direct Black CXR
Direct Black E
Direct Black EW
Direct Black EX
Direct Black FR
Direct Black GAC
Direct Black GW
Direct Black GX
Direct Black GXR

Direct Black JET
Direct Black Meta
Direct Black Methyl
Direct Black N
Direct Black RX
Direct Black SD
Direct Black WS
Direct Black Z
Direct Black 3
Direct Black 38
Direct Deep Black E
Direct Deep Black E Extra
Direct Deep Black EA-CF
Direct Deep Black EAC
Direct Deep Black EW
Direct Deep Black EX
Enianil Black CN
Erie Black B
Erie Black BF
Erie Black GAC
Erie Black GXOO
Erie Black JET
Erie Black NUG
Erie Black RXOO
Erie Brilliant Black S
Erie Fibre Black VP
Fenamin Black E
Fibre Black VF
Fixanol Black E
Formaline Black C
Formic Black C
Formic Black CW
Formic Black EA
Formic Black MTG
Formic Black TG
Hispamin Black EF
Interchem Direct Black Z
Kayaku Direct Deep Black EX
Kayaku Direct Deep Black GX
Kayaku Direct Deep Black S
Kayaku Direct Leather Black EX
Kayaku Direct Special Black AAX
Lurazol Black BA
Meta Black
Mitsui Direct Black EX
Mitsui Direct Black GX
Nippon Deep Black
Nippon Deep Black GX
Paper Black BA
Paper Black T
Paper Deep Black C
Paramine Black B
Paramine Black E
Peeramine Black E
Peeramine Black GXOO
Phenamine Black BCN-CF
Phenamine Black CL
Phenamine Black E
Phenamine Black E 200
Pheno Black EP
Pheno Black SGN
Pontamine Black E
Pontamine Black EBN
Sandopel Black EX
Seristan Black B
Telon Fast Black E
Tetrazo Deep Black G
Tertrodirect Black E
Tetrodirect Black EFD
Union Black EM
Vondacel Black N

IDENTIFIERS AND SYNONYMS FOR DIRECT BLUE 6

Chemical Abstracts Service Registry Number 2602-46-2
NIOSH/RTECS Number QJ64000
Chemical Formula $C_{32}H_{20}O_{14}N_6S_4Na_4$

Airedale Blue 2BD
Aizen Direct Blue 2BH
Amanil Blue 2BX
Atlantic Blue 2B
Atul Direct Blue 2B
Azocard Blue 2B
Azomine Blue 2B
Belamine Blue 2B
Bencidal Blue 2B
Benzanil Blue 2B
Benzo Blue BBA-CF
Benzo Blue BBN-CF
Benzo Blue GS
Blue 2B
Blue 2B Salt
Brasilamina Blue 2B
Calcomine Blue 2B
Chloramine Blue 2B
Chlorazol Blue B
Chlorazol Blue BP
Chrome Leather Blue 2B
CI 22610
C.I. 22610
C.I. Direct Blue 6
C.I. Direct Blue 6, Tetrasodium Salt
Cresotine Blue 2B
Diacotton Blue BB
Diamine Blue 2B
Diamine Blue BB
Diaphtamine Blue BB
Diazine Blue 2B
Diazol Blue 2B
Diphenyl Blue 2B
Diphenyl Blue KF
Diphenyl Blue M2B
Direct Blue A
Direct Blue 2B
Direct Blue 6
Direct Blue BB
Direct Blue GS
Direct Blue K
Direct Blue M2B
Enianil Blue 2BN
Fenamin Blue 2B
Fixanol Blue 2B
Hispamin Blue 2B
Indigo Blue 2B
Kayaku Direct
Kayaku Direct Blue BB
Mitsui Direct Blue 2BN
Naphtamine Blue 2B
Niagara Blue 2B
Nippon Blue BB
Paramine Blue 2B
Phenamine Blue BB
Pheno Blue 2B
Pontamine Blue BB
Sodium Diphenyl-4,4'-Bis-Azo-2"-8"-Amino -1"-Naphthol-3",6"-Disulphonate
Tertrodirect Blue 2B
Vondacel Blue 2B

IDENTIFIERS AND SYNONYMS FOR DIRECT BROWN 95

Chemical Abstracts Service Registry Number 16071-86-6
NIOSH/RTECS Number JM78780
Chemical Formula $C_{31}H_{20}N_6O_9SNa_2Cu$

Aizen Primula Brown BRLH
Aizen Primula Brown PLH
Amanil Fast Brown BRL
Amanil Supra Brown LBL
Atlantic Fast Brown BRL
Atlantic Resin Fast Brown BRL
Belamine Fast Brown BRLL
Benzanil Supra Brown BRLL
Benzanil Supra Brown BRLN
Brown 4EMBL
C.I. 30145
C.I. Direct Brown
Calcodur Brown BRL
Chloramine Fast Brown BRL
Chloramine Fast Cutch Brown PL
Chlorantine Fast Brown BRLL
Chrome Leather Brown BRLL
Chrome Leather Brown BRSL
Cuprofix Brown GL
Derma Fast Brown W-GL
Dermafix Brown PL
Dialuminous Brown BRS
Diaphtamine Light Brown BRLL
Diazine Fast Brown RSL
Diazol Light Brown BRN
Dicorel Brown LMR
Diphenyl Fast Brown BRL
Direct Brown 95
Direct Brown BRL
Direct Fast Brown BRL
Direct Fast Brown LMR
Direct Light Brown BRS
Direct Supra Light Brown ML
Durazol Brown BR
Durofast Brown BRL
Eliamina Light Brown BRL
Enianil Light Brown BRL
Fastolite Brown BRL
Fastusol Brown LBRSA
Fastusol Brown LBRSN
Fenaluz Brown BRL
Helion Brown BRSL
Hispaluz Brown BRL
KCA Light Fast Brown BR
Kayarus Supra Brown BRS
Paranol Fast Brown BRL
Peeramine Fast Brown BRL
Pontamine Fast Brown BRL
Pontamine Fast Brown NP
Pyrazol Fast Brown BRL
Pyrazoline Brown BRL
Saturn Brown LBR
Sirius Supra Brown BRL
Sirius Supra Brown BRS
Solantine Brown BRL
Solar Brown PL
Solex Brown R
Solius Light Brown BRLL
Solius Light Brown BRS
Sumilight Supra Brown BRS
Suprazo Brown BRL
Suprexcel Brown BRL
Tertrodirect Fast Brown BR
Tetramine Fast Brown BRDN Extra
Tetramine Fast Brown BRP
Tetramine Fast Brown BRS
Triantine Brown BRS
Triantine Fast Brown OG
Triantine Fast Brown OR
Triantine Light Brown BRS
Triantine Light Brown OG

NIOSH/NCI JOINT CURRENT INTELLIGENCE BULLETIN

DIRECT BLACK 38, DIRECT BLUE 6, AND DIRECT BROWN 95 BENZIDINE-DERIVED DYES

April 18, 1978

The National Institute for Occupational Safety and Health (NIOSH) recommends that three widely used benzidine-derived dyes, Direct Black 38, Direct Blue 6, and Direct Brown 95, be handled in the workplace as if they were human carcinogens. This recommendation is based primarily upon a preliminary analysis of National Cancer Institute (NCI) data from short-term feeding studies, and on early results from NIOSH field studies. Cancerous and precancerous liver conditions were found in rats, similar to the damage produced by known liver carcinogens. Degeneration of liver cells was found in mice. Although the dyes tested by NCI contained less than 4 ppm residual benzidine when fed to the test animals, greater quantities of benzidine were found in the urine of dosed rats and mice. Caution is also indicated by preliminary results from NIOSH field studies showing that humans working with these same dyes also excrete higher than expected levels of benzidine in their urine. Both laboratory and field studies indicate that these benzidine-derived dyes can be metabolized to benzidine which is present in the urine of animals and humans.

Based on the data from the short-term study, NCI scientists believe a cancer-causing potential exists upon exposure to the benzidine-derived dyes, most likely through the mechanism of metabolic conversion of the dyes to benzidine in the animal system. This NIOSH/NCI Joint Bulletin summarizes the results of the NCI animal study, the NIOSH field studies, other pertinent data, their implication for occupational health, and suggested guidelines for minimizing employee exposure to the three dyes.

Potential Occupational Exposures

The National Occupational Hazard Survey (NOHS), conducted between 1972 and 1974 by the National Institute for Occupational Safety and Health, indicates that workers are occupationally exposed to Direct Black 38, Direct Blue 6, and Direct Brown 95 in a variety of industries including: paper and allied products, petroleum and related industries, rubber and plastic products, leather and leather products, instrumentation and measuring devices, and banking. In addition, the

textile industry accounts for a substantial occupational exposure. It is estimated that 25 percent of the benzidine-derived azo dyes are applied to textiles, 40 percent to paper, 15 percent to leather, and the remainder to other diverse applications. (1)

The Colour Index, (2) a reference by Great Britain's Society of Dyers and Colourists, reports the following uses for the three dyes:

- Direct Black 38: Dyeing or staining of wool, silk, fibers for rope and matting, hogs hair, cellulose, acetate, nylon, and biological stains.
- Direct Brown 95: Dyeing or staining silk, cotton, acetate, cellulose, wool, nylon, leather, paper, and certain plastics.
- Direct Blue 6: Dyeing or staining silk, wool, cotton, nylon, leather, paper, biological stains and writing inks.

Historically, benzidine has been an important intermediate in dye production since its introduction to the dyestuff industry around 1890. (3,4) In 1948, production of benzidine-derived dyes was 35 million pounds which accounted for 25% of all domestic dyes manufactured and almost all of the direct class dyes. (5) Domestic production of direct benzidine-derived dyes has dropped to 11.4 million pounds in 1971. (6) Domestic production in 1978 should be limited to 12 benzidine dyes. The latest domestic production figures for Direct Black 38 show 7.3 million pounds in 1971, (6) down to 2.2 million pounds in 1975,(7) which rose to 3.76 million pounds in 1976. (8) Direct Brown 95 has shown an increased production to 600,000 pounds in 1976 which is up from 406,000 pounds in 1975 and 343,000 pounds in 1974. (8) Domestic production for Direct Blue 6 indicates that 327,000 pounds were produced in 1973, which is the last available figure for that dye. (9)

In the general population, unspecified exposure levels to the three dyes are thought to occur through the use of retail packaged dyes for home dyeing and for home and school use in art and craft projects such as tie-dyeing or batik. The Art Hazards Project of the Center for Occupational Hazards, New York City, has reported that package dyes sold in supermarkets, variety stores and hardware stores are combinations of direct, acid and basic dyes, and thus may contain benzidine-derived dye components. (10) Two of these dyes, Direct Black 38 and Direct Blue 6, have been used in hair dyes. (11)

NCI Dose-Ranging Feeding Study (11)

Ninety-day animal feeding tests have been completed by the National Cancer Institute for three widely-used dyes, Direct Black 38, Direct Blue 6, and Direct Brown 95. The first-phase tests are conducted routinely to establish dosage levels

in mice and rats for chemicals being screened for cancer-causing activity. The dose-ranging studies commonly precede standard bioassays--animal lifetime tests at dosages that do not shorten lifespans or impair growth.

All three of the dyes are benzidine-derived, having a unit of benzidine in their chemical structure. Benzidine is a known animal and human cancer-causing agent. (12) Residual free benzidine in the feed was below 4 parts per million (ppm).

A total of 120 rats and 120 mice were divided into groups of 10. One group of each sex and each species was reserved as undosed controls, while five groups of each sex and species received differing dosages of the dyes in feed. At the 4th and 12th week of the study, urine was collected from dosed rats and mice for benzidine analysis. After 91 days of feeding and one day of observation, the surviving animals were killed and their tissues examined.

After the 90-day trial, significant incidences of cancerous and precancerous changes in the liver were found in both male and female rats dosed with any of the three dyes, whereas, untreated control rats had no liver damage. The liver changes in dosed animals were similar to changes caused by benzidine.

In mice, all three dyes were found harmful to the liver, but no cancerous changes were found. This finding is compatible with the interpretation that the toxic effects may be related to benzidine, because benzidine is more likely to produce cancer in rats than in mice. No liver abnormalities or damage to any internal organs were found in the control animals of either species.

In addition, although the dyes were essentially benzidine-free when fed to the animals, substantial benzidine was found in the urine of dosed rats and mice, an indication that animal systems metabolize the dyes to benzidine.

The technical report "13-Week Subchronic Toxicity Studies — Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes" is available from the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20014.

Other Laboratory Animal Studies

As an historical point, an early realization of the metabolism of azo compounds in mammals came as a result of feeding Orange I, an azo dye, to dogs in 1911. (13) An intermediate of the dye, sulfanilic acid, was identified in the urine demonstrating for the first time that azo compounds may be metabolized by reductive cleavage of the azo group. Since then it has been repeatedly demonstrated that the intestinal flora within animals and many animal hepatic enzyme systems are capable of splitting the azo bond. (14,15) The majority of this work was performed with azo dyes intended for food coloring.

Yoshida and Miyakawa found that when sulfonated benzidine azo dyes were injected into surgically removed mice intestines and then incubated, free benzidine was

later found. They also showed that Escherichia coli as well as soil bacteria were quite capable of reducing benzidine dyes when incubated at 37 C. (16)

Another study showed that rhesus monkeys, fed benzidine-derived dyes with no residual benzidine, excreted benzidine in their urine. The levels excreted were estimated as being almost as high as if an equal amount of pure benzidine, as found in the dye moiety, were fed instead to the monkeys. (17) These studies lead NIOSH to believe that when dyes of these types are ingested by man, they result in benzidine in the urine thus posing a potential carcinogenic hazard.

NIOSH Field Studies

Preliminary results from NIOSH studies indicate the presence of benzidine, or monacetylbenzidine (MAB), a metabolite of benzidine, in the urine of workers in four out of five industrial facilities in which urine samples were collected. The facilities surveyed to date include two benzidine dye manufacturers, two textile finishing companies and a leather tannery.

In one dye manufacturing plant, benzidine and MAB were found in all dye workers who worked solely with the finished dyes. Bulk benzidine-based dyes were quantitatively analyzed for residual free benzidine content which ranged from less than 1 to 19 ppm. It was conservatively estimated that about 20 times more benzidine and up to 200 times more MAB were present in the urine of these dye workers, than if they had been exposed only to the residual benzidine content in the dyes. The concentrations of benzidine found in the urine of these workers were significant fractions of those concentrations associated with a high incidence of bladder cancer as reported in the scientific literature. Among textile dyers included in the NIOSH study, four of ten had benzidine or MAB present in their urine and all had elevated aromatic amine levels. No benzidine or MAB was detected in urine samples collected at a leather tannery where good work practices were observed. While there was biological variability in body burden tolerance and differences in metabolism among those studied, it appears likely that work practices and personal hygiene played a major role in minimizing exposure. Analyses of data from these NIOSH studies are ongoing.

The relatively large particle size of the dry dye powders causes inhaled dyes to be deposited largely in the upper respiratory tract and then ingested. Prevention of worker inhalation or ingestion of these dyes would greatly reduce absorption into the body and subsequent benzidine exposure.

Epidemiological and Medical Studies — Benzidine-Based Dyes

A strong association relating human exposure to benzidine-based dyes with the subsequent development of bladder tumors was presented after a case-control mortality study of 200 bladder cancer patients in Japan. (16) The patients were found to have been predominantly kimono painters and dyers. The kimono painters

had the habit of forming a point on their brushes by drawing the brush between their lips, which allowed for ingestion of the dyes.

Several other case-control mortality studies indicate an increased risk of developing bladder cancer in the textile and leather industries, both large users of direct dyes. However, only a few references have been made concerning benzidine-derived dyestuffs.

In Russia, a medical study concerning the early detection of bladder tumors among textile dyers using benzidine-derived dyes found an unusual incidence of bladder lesions, some of which were suggested as being of a precancerous nature. The greatest number of such lesions were found in those workers with the highest potential exposure to these dyes.(18)

The National Institute for Occupational Safety and Health and the National Cancer Institute have jointly prepared this Bulletin to facilitate the rapid dissemination of our preliminary findings on three benzidine-derived dyes: Direct Black 38, Direct Blue 6, and Direct Brown 95. NIOSH recommends that these dyes be handled in the workplace as if they were human carcinogens and requests that producers, distributors, professional associations, and unions transmit the information in this Bulletin to their customers, employees, associates, and members.

Arthur C. Upton, M.D.
Director
National Cancer Institute

J. Donald Millar, M.D.
Assistant Surgeon General
Acting Director,
National Institute for Occupational Safety and Health

NIOSH Action on Benzidine-Derived Dyes

1. The NIOSH Industrial Hygiene Section will shortly conduct a study in which workers who have had a one-day exposure to benzidine-based dyes are monitored over several days. This will hopefully confirm some assumptions on the excretion kinetics of such exposure and better establish the best time to monitor a worker's urine for benzidine.

2. The NIOSH Clinical and Biochemical Support Section has an interagency agreement with the National Center for Toxicological Research to conduct animal metabolism studies. Test animals will be fed Direct Black 38, Direct Blue 6 and Direct Brown 95. Metabolites will be identified in the urine and evaluated for mutagenic activity. Additional dyes made from 3,3-dimethylbenzidine, 3,3-dimethoxybenzidine, and 3,3-dichlorobenzidine will also be tested.

SUGGESTED GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO DIRECT BLACK 38, DIRECT BLUE 6, DIRECT BROWN 95 -- BENZIDINE-DERIVED DYES

NIOSH recommends that it would be prudent to handle Direct Black 38, Direct Blue 6, and Direct Brown 95 in the workplace as if they were human carcinogens. Exposure to Direct Black 38, Direct Blue 6, and Direct Brown 95 should be limited to as few employees as possible, while minimizing workplace exposure levels. The area in which they are used should be restricted to only those employees essential to the process or operation.

EXPOSURE MONITORING

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective.

The NIOSH Occupational Exposure Sampling Strategy Manual, NIOSH Publication #77-173, may be helpful in developing efficient programs to monitor employee exposures to Direct Black 38, Direct Blue 6, and Direct Brown 95. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for exposure evaluation, and selection of sampling times.

Employee exposure measurements should consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). Area and source measurements may be useful to determine problem areas, processes, and operations.

MINIMIZING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to Direct Black 38, Direct Blue 6, and Direct Brown 95. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation of any of these.

- Product Substitution

The substitution of an alternative material with a lower potential health and safety

risk is one method. However, extreme care must be used when selecting possible substitutes. Alternatives to Direct Black 38, Direct Blue 6, and Direct Brown 95 should be fully evaluated with regard to possible human effects. Unless the toxic effects of the alternative have been thoroughly evaluated, a seemingly safe replacement, possibly only after years of use, may be found to induce serious health effects.

o Contaminant Controls

The most effective control of Direct Black 38, Direct Blue 6, and Direct Brown 95, where feasible, is at the source of contamination by enclosure of the operation and/or local exhaust ventilation.

If feasible, the process or operation should be enclosed with a slight vacuum so that any leakage will result in the flow of air into the enclosure.

The next most effective means of control would be a well designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

To ensure that ventilation equipment is working properly, effectiveness (e.g., air velocity, static pressure, or air volume) should be checked at least every three months. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposures to Direct Black 38, Direct Blue 6, and Direct Brown 95.

o Employee Isolation

A third alternative is the isolation of employees. It frequently involves the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those employees that must do process checks, adjustments, maintenance, and related operations.

o Personal Protective Equipment

The least preferred method is the use of personal protective equipment. This equipment, which may include respirators, goggles, gloves, and other devices should not be used as the only means to prevent or minimize exposure during routine operations.

Exposure to Direct Black 38, Direct Blue 6, and Direct Brown 95 should not be controlled with the use of respirators except:

— During the time period necessary to install or implement engineering or work practice controls; or

— In work situations in which engineering and work practice controls are technically not feasible; or

— For maintenance; or

-- For operations which require entry into tanks or closed vessels; or

-- In emergencies.

Only respirators approved by the National Institute for Occupational Safety and Health (NIOSH) should be used. Refer to NIOSH Certified Equipment, December 15, 1975, NIOSH publication #76-145 and Cumulative Supplement June 1977, NIOSH Certified Equipment, NIOSH publication #77-195. The use of faceseal coverlets or socks with any respirator voids NIOSH approvals.

Quantitative faceseal fit test equipment (such as sodium chloride, dioctyl phthalate, or equivalent) should be used. Refer to A guide to Industrial Respiratory Protection, NIOSH publication #76-189 for guidelines on appropriate respiratory protection programs.

In addition, proper maintenance procedures, good housekeeping in the work area and education of employees concerning the nature of the hazard, its control and personal hygiene are all aspects of a good control program.

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NIOSH

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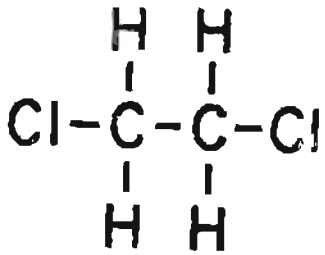
April 19, 1978

ETHYLENE DICHLORIDE



(1,2 - Dichloroethane)

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

The Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

Synonyms & Identifiers

NIOSH-RTECS: KI05250
CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER: 107-06-2
CHEMICAL FORMULA: $C_2H_4Cl_2$

α, β-DICHLOROETHANE
1,2-BICHLOROETHANE
BROCIDE
DESTRUXOL BORER-SOL
DI-CHLOR-MULSION
1,2-DICHLORETHANE
1,2-DICHLOROETHANE
DICHLOROETHYLENE
DUTCH LIQUID
EDC
ENT 1,656
ETHYLENE CHLORIDE
ETHYLENE DICHLORIDE
GLYCOL DICHLORIDE
sym-DICHLOROETHANE

DHEW (NIOSH) Publication No. 78-149

CURRENT INTELLIGENCE BULLETIN:

ETHYLENE DICHLORIDE (1,2-DICHLOROETHANE)

April 19, 1978

The National Institute for Occupational Safety and Health (NIOSH) recommends that as a prudent measure, ethylene dichloride (1,2-dichloroethane) be handled in the workplace as if it were a human carcinogen. This recommendation is based primarily upon an analysis of National Cancer Insitute (NCI) data indicating that laboratory rats and mice fed ethylene dichloride experienced a statistically significant excess of malignant and benign tumors, as compared to controls (1).

NIOSH has prepared this Bulletin to advise you of the findings of the NCI study, other pertinent data, including findings on the mutagenic and teratogenic qualities of ethylene dichloride, and their implications for occupational health. Also included are "Suggested Guidelines for Minimizing Employee Exposure to Ethylene Dichloride." We are requesting that producers, distributors, professional associations, and unions transmit the information in this Bulletin to their customers, employees, associates, and members.

Background

The current Department of Labor, Occupational Safety and Health Administration (OSHA) standard for occupational exposure to ethylene dichloride is 50 ppm (8-hour time-weighted average). In March 1976, NIOSH recommended an exposure limit of 5 ppm (time-weighted average for up to a 10-hour workday, 40-hour workweek) (2). Neither of these levels may provide adequate protection from potential carcinogenic effects because they were selected to prevent toxic effects other than cancer. The NIOSH recommendation was based on reports of adverse effects on the nervous system and liver of workers exposed to 10-15 ppm ethylene dichloride. Exposure to higher levels was also reported to affect the cardiac and respiratory systems. We further advised nursing mothers not to work with ethylene dichloride since the chemical has been found in the milk of exposed human mothers. At the time of the recommendation, there were no reports that ethylene dichloride caused cancer in animals or man. However, we did note that information on this subject was inadequate and that the National Cancer Institute (NCI) was conducting bioassay tests on ethylene dichloride.

Production and Use

Ethylene dichloride is one of the highest volume chemicals used in the United States. It is a colorless oily liquid with a chloroform-like odor, detectable over the range of 6 to 40 ppm, with a sweet taste (3). Patty (4) concluded that a person can become adapted to the odor of ethylene dichloride at low concentrations and that its odor is probably not sufficiently striking to be considered a significant warning of hazardous chronic exposure. Ethylene dichloride (1,2-dichloroethane), which has a carbon-carbon single bond, should be distinguished from 1,2-dichloroethene which has a carbon-carbon double bond.

Between 1973 and 1976, the United States annual average production of ethylene

dichloride was approximately 10 billion pounds. During these years, most of it was used as an intermediate in the production of vinyl chloride, but it was also used in the production of other chemicals, such as 1,1,1-trichloroethane, trichloroethylene, perchloroethylene, vinylidene chloride, and ethyleneamines (5). Ethylene dichloride is a lead scavenger, and therefore appears as a component of most leaded fuels. Ethylene dichloride was also used as an extraction solvent, as a solvent for textile cleaning and metal degreasing, in certain adhesives, and as a component in fumigants for upholstery, carpets, and grain. Other miscellaneous applications include paint, varnish, and finish removers, soaps and scouring compounds, wetting and penetrating agents, organic synthesis, ore flotation, and as a dispersant for nylon, rayon, styrene-butadiene rubber and other plastics.

Potential Occupational Exposures

The National Institute for Occupational Safety and Health estimates that as many as 2 million workers may have occupational exposure to ethylene dichloride. Of these workers, an estimated 34,000 are exposed to ethylene dichloride 4 hours or more per day. These projections are based on the NIOSH National Occupational Hazards Survey (NOHS) conducted between 1972 and 1974, which encompassed some 500,000 employees at approximately 4,775 facilities. According to the survey, numerous exposures occurred in the following industries: chemical and allied products, printing and publishing, electrical equipment and supplies, wholesale and retail trade, food and kindred products, leather and leather products, and machinery.

Laboratory Animal Studies for Carcinogenicity

On March 6, 1978, the Clearinghouse on Environmental Carcinogens (NCI) reviewed and accepted the results of the bioassay of ethylene dichloride, which was performed under contract for the National Cancer Institute.

In the bioassay, technical grade 1,2-dichloroethane was tested for possible carcinogenicity in Osborne-Mendel rats and B6C3F1 mice. 1,2-Dichloroethane in corn oil was force-fed at either of two dosages, to groups of 50 male and 50 female animals of each species. Untreated and vehicle control animals were also used. The time-weighted average high and low doses of 1,2-dichloroethane in the chronic study were 95 and 47 mg/kg/day, respectively for rats of both sexes. The high and low time-weighted average doses for the male mice were 195 and 97 mg/kg/day, respectively, and 299 and 149 mg/kg/day, respectively for the female mice.

To relate some of the above information to the work environment, a 70 kg man breathing a typical 10 cu m/day (over an 8-hour work shift) of air contaminated with 50 ppm of ethylene dichloride (the current OSHA standard for exposure to ethylene dichloride) would have an inhalation exposure of about 30 mg/kg/day. Because respiration rate increases with exertion, jobs with higher exertion are likely to be associated with increased respiratory intake.

The National Cancer Institute has concluded that under the conditions of the study, 1,2-dichloroethane was carcinogenic to Osborne-Mendel rats and B6C3F1 mice. Table 1 summarizes the statistically significant tumors found in the NCI Bioassay of 1,2-dichloroethane.

TABLE 1

Statistically Significant Tumors Found in NCI Bioassay of 1,2-Dichloroethane

Species/Sex	Adverse Effect	Site
Rats/Male	Squamous-Cell Carcinomas	Forestomach
	Hemangiosarcomas	Circulatory System
	Fibromas	Subcutaneous Tissue
Rats/Female	Adenocarcinomas	Mammary Gland
Mice/Female	Adenocarcinomas	Mammary Gland
Mice/Female	Stromal Polyps	Endometrium
	Stromal Sarcomas	Endometrium
Mice/Male & Female	Adenomas	Alveoli and Bronchioli

Two additional studies to assess the carcinogenic potential of ethylene dichloride are currently underway. In an ethylene dichloride inhalation study being conducted in Italy by Dr. C. Maltoni, animals will be exposed to ethylene dichloride for 2 years and observed until the end of their natural lives. No evidence of any exceptional tumor in rats or mice has been found following 100 weeks of exposure (6). Also, Dr. B. M. Goldschmidt has informed NIOSH of bioassays of 1,2-dichloroethane being conducted at the New York University Institute of Environmental Medicine. Groups of 30 female mice received skin applications of 1,2-dichloroethane for more than one year. None of the animals developed skin tumors, and autopsies did not reveal any unexpected internal lesions or tumors (7).

Other Laboratory Animal Studies

The toxic effects of ethylene dichloride exposure have been studied in a large number of animal species (2). Acute exposure to ethylene dichloride seemed to most frequently affect the cardiovascular system as evidenced by extreme lowering of blood pressure, and cardiac impairment. Other toxic effects include pulmonary edema, fatty degeneration of the liver and kidney (renal tubules) and degeneration of the adrenal cortex. Also, ethylene dichloride is reported to be a weak mutagen in bacteria and

mutagenic in fruit flies (8). In the rat, ethylene dichloride has been reported to cross the placental barrier, accumulate in the placenta and fetal tissues, and cause abnormal development of the fetus (9,10,11).

Human Toxicity

The acute effects of ethylene dichloride are similar for all routes of entry: ingestion, inhalation, and skin absorption. Acute exposures result in nausea, vomiting, dizziness, internal bleeding, bluish-purple discoloration of the mucous membranes and skin (cyanosis), rapid but weak pulse, and unconsciousness. Acute exposures can lead to death from respiratory and circulatory failure. Autopsies in such situations have revealed widespread bleeding and damage in most internal organs. Repeated long-term exposures to ethylene dichloride have resulted in neurologic changes, loss of appetite and other gastrointestinal problems, irritation of the mucous membranes, liver and kidney impairment, and death (2).

NIOSH Recommendation

The National Institute for Occupational Safety and Health is currently preparing an update to the March 1976 recommendations regarding exposure to ethylene dichloride, which will address the carcinogenic potential of this substance in the workplace. The NCI laboratory study showing ethylene dichloride to be a carcinogen in two animal species utilized forced-feeding (directly into the stomach) for the route of exposure. However, it is important to keep in mind that ethylene dichloride can and does enter the body via inhalation and through the skin, as well as orally. When evaluating the test results or potential exposure to the substance in the workplace, in addition to the route of entry into the body, the amount of ethylene dichloride which is absorbed and actually reaches the target tissue or organ is a significant issue in determining the extent or possibility of the health hazard.

Animal studies are valuable in helping identify human carcinogens. Although humans may be more sensitive or less sensitive than experimental animals to specific chemical compounds, substances that cause cancer in experimental animals must be considered to pose a potential cancer risk in man. Safe levels of exposure to carcinogens have not been demonstrated, but the probability of cancer development is lowered with decreasing exposure to carcinogens.

As an interim and prudent measure while the carcinogenicity of ethylene dichloride is being further evaluated, NIOSH recommends that occupational exposure be minimized. Exposures should be limited to as few employees as possible, while minimizing workplace exposure levels with engineering and work practice controls.

J. Donald Millar, M.D.
Assistant Surgeon General
Acting Director

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SUGGESTED GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO ETHYLENE DICHLORIDE (1,2-DICHLOROETHANE)

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JOINT

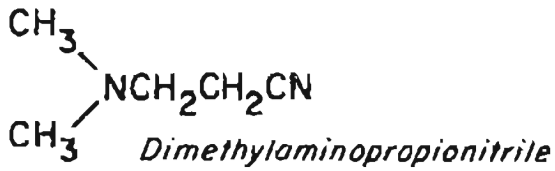
NIOSH / OSHA

Current Intelligence Bulletin 26

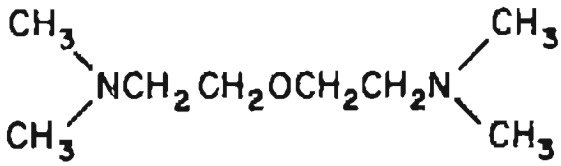
May 22, 1978

NIAX® Catalyst ESN . . . .

a mixture of



Dimethylaminopropionitrile



Bis[2-(dimethylamino)ethyl] ether

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

U. S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration

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IDENTIFIERS AND SYNONYMS FOR DIMETHYLAMINOPROPIONITRILE

Chemical Abstracts Service Registry Number 1738-25-6
NIOSH RTECS Number UG15750
Chemical Formula $C_5H_{10}N_2$

3-(Dimethylamino)propanenitrile
3-(Dimethylamino)propionitrile
β-(Dimethylamino)propionitrile
N,N-Dimethylamino-3-propionitrile
3-(N,N-Dimethylamino)propionitrile
β-N-Dimethylaminopropionitrile

IDENTIFIERS AND SYNONYMS FOR BIS(2-(DIMETHYLAMINO)ETHYL) ETHER

Chemical Abstracts Service Registry Number 3033-62-3
NIOSH RTECS Number KR94600
Chemical Formula $C_8H_{20}N_2O$

A99
A99 amine
Bis 2-(dimethylamino)ethyl)ether
Kalpur PC
NIAX A99
2,2'-Oxybis(N,N-dimethylethanamine)
2,2'Oxybis(N,N-dimethylethylamine)

DHEW (NIOSH) Publication No. 78-157

JOINT NIOSH/OSHA

CURRENT INTELLIGENCE BULLETIN: NIAX® CATALYST ESN

A Mixture of Dimethylaminopropionitrile and Bis(2-(dimethylamino)ethyl) ether

May 18, 1978

The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) jointly recommend that NIAX® Catalyst ESN and its components, dimethylaminopropionitrile and bis(2-(dimethylamino)ethyl) ether, as well as formulations containing either component, be handled in the workplace as exceedingly hazardous materials. Investigations of outbreaks of urinary dysfunction among workers at a number of facilities that manufacture flexible polyurethane foam strongly suggest an association between NIAX® Catalyst ESN and the urological disorders. There is no current Federal standard for occupational exposure to NIAX® Catalyst ESN or either of its components. However, on April 7, 1978, OSHA issued a Health Hazard Alert and indicated "it is imperative that worker exposure to ESN and its components be completely avoided."

Background

NIAX® Catalyst ESN, a proprietary product of Union Carbide Corporation, is composed of dimethylaminopropionitrile (95%) and bis(2-(dimethylamino)ethyl) ether (5%). Similar mixtures were also marketed as NIAX® Catalysts 125 and 126. These catalysts were used in the manufacture of flexible polyurethane foams and may comprise from 0.5% to 2% of the wet urethane liquid prior to foaming. Union Carbide has voluntarily discontinued the sale of these three catalysts as well as dimethylaminopropionitrile.

Dimethylaminopropionitrile is also used as a component of acrylamide based gels (for soil grouting and other purposes), and as an intermediate in the synthesis of dimethylaminopropylamine and some pharmaceuticals. Manufacturers of dimethylaminopropionitrile include Abbott Laboratories, American Cyanamid Company, Jefferson Chemical Company, and Union Carbide Corporation.

Bis(2-(dimethylamino)ethyl) ether is manufactured in the United States exclusively by Union Carbide and used extensively in their line of catalysts for flexible polyurethane foams. Bis (2-(dimethylamino)ethyl) ether may

comprise from 0.02% to 0.1% of the wet urethane liquid prior to foaming. NIOSH and OSHA are unaware of any other application of bis(2-(dimethylamino)ethyl)ether.

Human Toxicity

Preliminary results of NIOSH Health Hazard Evaluations suggest NIAX® Catalyst ESN is neurotoxic, producing urinary bladder dysfunction as the prevailing clinical feature.

Of the ten industrial facilities reported to have used commercial quantities of NIAX® Catalyst ESN, five are known to have had excessive numbers of their workers seek medical attention for urological and/or neurological problems. Common urinary tract symptoms after exposure include difficulty beginning urination, inadequate bladder emptying, strain on urination, increased duration of voiding time, and post void fullness. Other symptoms include frequent urination, pain and burning on urination, as well as impotence. Neurological manifestations include dysesthesias in the form of pins and needles sensation in the hands and feet. Muscular weakness, lassitude, nausea, and vomiting were also reported. Exposure may occur by inhalation, skin absorption, and ingestion.

NIOSH epidemiological and medical studies are presently underway in two of the industrial facilities involved. Clinical manifestations in exposed workers coincide with the introduction or increased use of the catalyst in manufacturing processes. After exposure is discontinued, improvement occurs in some individuals over a variable period of time. NIOSH is investigating whether symptoms persist after exposure to the catalyst is eliminated.

Approximately a third of the hundred workers exposed at one plant and half of the two hundred exposed workers at the other plant studied reported urinary problems. Detailed clinical and laboratory studies of eight workers severely affected with urinary problems revealed that five of the eight did not have a bladder reflex and were therefore unaware of the need to void as their bladders became full. Though not conclusive, the evidence suggests that the absent bladder reflex may be the cause of urinary retention and abnormal change in bladder habits. Long term urinary retention can lead to urinary tract infection and kidney damage, and thus can pose a threat to life. In addition to bladder dysfunction, some of the workers were found to have decreased nerve conduction times of the lower legs.

Sufficient evidence does exist to suggest that occupational exposure to NIAX® Catalyst ESN is associated with the urinary and neurologic abnormalities. The extent of toxicity of the catalyst to other systems and organs including kidney, liver, eye and skin are unknown. Definitive information regarding safe levels of exposure to NIAX® Catalyst ESN or its components is not available at this time.

Animal Studies

Dr. Alan Pestronk (The Johns Hopkins University) is currently investigating the effect of NIAX® Catalyst ESN, as well as its components, on the nervous system of laboratory rats. Results of this study are not yet available. Several propionitriles have been previously reported to be neurotoxins, however, specific data regarding the neurotoxicity of dimethylaminopropionitrile could not be located. Union Carbide is also sponsoring toxicity studies of NIAX® Catalyst ESN, dimethylaminopropionitrile and bis(2-(dimethylamino)ethyl)ether; these studies have been in progress for approximately two weeks but have not proceeded far enough to be adequately evaluated.

Conclusions

Although there does appear to be an association between NIAX® Catalyst ESN and the outbreaks of urinary dysfunction, it is not now known whether either component of the mixture could cause the disorder itself. Additional research in this area is clearly appropriate. Union Carbide has suggested that the nitrile component (dimethylaminopropionitrile) may be the causative agent. They stated that bis(2-(dimethylamino)ethyl) ether has been used in urethane catalyst systems for fifteen years and proper use of the material has not been known to cause any adverse health effects. (Acute overexposure may result in symptoms characteristic of amine toxicity).

Recommendation

The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) jointly recommend that occupational exposure to NIAX® Catalyst ESN its components, dimethylaminopropionitrile and bis(2-(dimethylamino)ethyl) ether, as well as formulations containing either component, be minimized. Exposures should be limited to as few employees as possible, while minimizing workplace exposure levels with engineering and work practice controls. Exposed employees should be carefully monitored for potential disorders of the nervous and genitourinary system. Although substitution is a possible control measure, alternatives to NIAX® Catalyst ESN or its components should be fully evaluated with regard to possible adverse health effects.

Eula Bingham, Ph.D.
Assistant Secretary of Labor
Occupational Safety and Health Administration

J. Donald Millar, M.D.
Assistant Surgeon General
Acting Director
National Institute for Occupational Safety and Health

SUGGESTED GUIDELINES FOR MINIMIZING EMPLOYEE EXPOSURE TO NIAX®CATALYST ESN and its Components, Dimethylaminopropionitrile and Bis(2-(dimethylamino)ethyl) ether

NIOSH and OSHA recommend that it would be prudent to handle NIAX® Catalyst ESN and its components in the workplace as exceedingly hazardous materials. Workplace exposure levels and employee exposure should be minimized. The area in which NIAX® Catalyst ESN, or either of its components, is used should be restricted to only those employees essential to the process or operation.

EXPOSURE MONITORING

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective. The sampling and analytical method recommended by the Union Carbide Corporation for the bis-ether component of NIAX® Catalyst ESN is currently being used and evaluated by NIOSH as a procedure for the analysis of dimethylaminopropionitrile as well as bis(2-(dimethylamino)ethyl)ether.

The NIOSH Occupational Exposure Sampling Strategy Manual, NIOSH Publication #77-173, may be helpful in developing efficient programs to monitor employee exposures to NIAX® Catalyst ESN and its components. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for exposure evaluation, and selection of sampling times.

Employee exposure measurements should consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). Area and source measurements may be useful to determine problem areas, processes, and operations.

MINIMIZING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to NIAX® Catalyst ESN and its components. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation of any of these.

o Product Substitution

One method is the substitution of an alternative material with a lower potential health risk. However, extreme care must be used when selecting possible substitutes. Alternatives to NIAX® Catalyst ESN and its components should be fully evaluated with regard to possible human effects. Unless the toxic effects of the alternative have been thoroughly evaluated, a seemingly safe replacement may be found to induce serious health effects, possibly only after years of use.

o Contaminant Controls

The most effective control of NIAX® Catalyst ESN and its components is by local exhaust ventilation and/or enclosure of the operation at the source of contamination.

If feasible, the process or operation should be enclosed with a slight vacuum so that any leakage will result in the flow of air into the enclosure.

The next most effective means of control is a well designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

To ensure that ventilation equipment is working effectively, air velocity, static pressure, or air volume should be checked every three months. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposures to NIAX® Catalyst ESN or its components.

In cases where the contaminant release is not excessive and is not in the workers' breathing area, good general dilution ventilation may assist in keeping the contaminant levels from reaching hazardous levels.

Care should be exercised in controlling exposure resulting from residual material in off-gassing from the uncured or curing products.

o Employee Isolation

A third alternative is the isolation of employees. It frequently involves the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those employees who must do process checks, adjustments, maintenance, and related operations.

o Personal Protective Equipment

The least desirable way to control employee exposures is with the use of personal protective equipment, which may include respirators, gloves, goggles, etc. This equipment should not be used as the only means to prevent or minimize exposure during routine operations.

Exposure to NIAX® Catalyst ESN or its components should not be controlled with the use of respirators except:

— During the time period necessary to install or implement engineering or work practice controls; or

— In work situations in which engineering and work practice controls are technically not feasible; or

— For maintenance; or

— For operations which require entry into tanks or closed vessels; or

— In emergencies.

Neither NIOSH or OSHA has definitive information concerning the warning properties of NIAX® Catalyst ESN or its components or the service lives of typical industrial respirator for these substances. Therefore, as an interim recommendation, NIOSH and OSHA feel that only the following type respirators may be used for personal respiratory protection against NIAX® Catalyst ESN or its components as allowed under the previous guidelines.

> A type C supplied-air respirator with a full facepiece operated in pressure-demand or other positive pressure mode or with a full facepiece, hood, or helmet operated in continuous-flow mode.
>
> Self-contained breathing apparatus with a full facepiece operated in pressure-demand or other positive pressure mode.
>
> A combination respirator which includes a type C supplied-air respirator with a full facepiece operated in pressure-demand mode or other positive pressure or continuous-flow mode and an auxiliary self-contained breathing apparatus operated in pressure-demand or positive pressure mode.

Only respirators approved by the National Institute for Occupational Safety and Health (NIOSH) should be used. Refer to NIOSH Certified Equipment,

December 15, 1975, NIOSH publication #76-145 and Cumulative Supplement June 1977, NIOSH Certified Equipment, NIOSH publication #77-195. The use of faceseal coverlets or socks with any respirator voids NIOSH approvals.

Refer to A Guide to Industrial Respiratory Protection, NIOSH publication #76-189 for guidelines on appropriate respiratory protection programs.

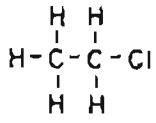
Proper maintenance procedures and good housekeeping in the work area are very important aspects of a good control program. In addition, it is vital that employees be educated as to the nature and control of the hazard, and proper personal hygiene.

NIOSH

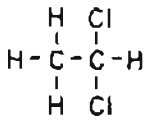
Current Intelligence Bulletin 21

August 21, 1978

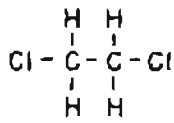
CHLOROETHANES:
REVIEW OF TOXICITY



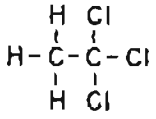
Chloroethane
(Ethyl Chloride)



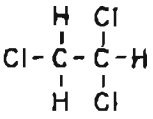
1,1,-Dichloroethane



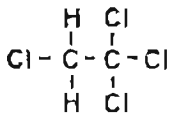
1,2-Dichloroethane
(Ethylene Dichloride)



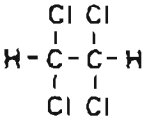
1,1,1-Trichloroethane
(Methyl Chloroform)



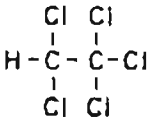
1,1,2-Trichloroethane



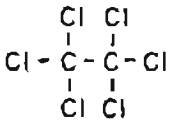
1,1,1,2-Tetrachloroethane



1,1,2,2-Tetrachloroethane



Pentachloroethane



Hexachloroethane

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

The NIOSH Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropraate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

IDENTIFIERS AND SYNONYMS FOR THE NINE CHLOROETHANES ARE LISTED

IN THE REAR PORTION OF THIS BULLETIN

ERRATA

In Bulletins #22 through #25 it was stated that the NIOSH National Occupational Hazard Survey (NOHS) had included "over 500,000 employees at 4,775 facilities." Actually the Survey included nearly 900,000 employees at 4,636 facilities.

In Bulletin #23 NIOSH erroneously listed Dowfume® MC-2 as a synonym for ethylene dibromide. Dow Chemical USA has advised NIOSH that Dowfume®MC-2 actually is 98% methyl bromide and 2% chloropicrin.

DHEW (NIOSH) Publication No. 78-181

NIOSH CURRENT INTELLIGENCE BULLETIN

CHLOROETHANES: REVIEW OF TOXICITY

The National Institute for Occupational Safety and Health (NIOSH) recommends that it would be prudent to handle 1,2-dichloroethane (ethylene dichloride); 1,1,2-trichloroethane; 1,1,2,2-tetrachloroethane; and hexachloroethane in the workplace as if they were human carcinogens. This recommendation is based primarily on consideration of National Cancer Institute (NCI) data indicating that laboratory animals administered these compounds experienced a statistically significant excess of cancer as compared to control animals (1-4). Additionally, NIOSH recommends that five other chloroethane compounds: chloroethane* (ethyl chloride); 1,1-dichloroethane; 1,1,1-trichloroethane (methyl chloroform); 1,1,1,2-tetrachloroethane; and pentachloroethane be closely monitored for carcinogenic effects in humans and/or laboratory animals. These five should also be treated in the workplace with caution because of their relation to the four chloroethanes shown to be carcinogenic in laboratory animals.

This Current Intelligence Bulletin summarizes information on some of the similarities and dissimilarities within the chloroethane group. NIOSH is concerned about the carcinogenic potential of chloroethanes based on emerging data from the NCI bioassay program. Concern for the carcinogenic potential of all members of the chloroethane series is based upon structural similarities within the group as well as the structural similarities to other carcinogenic organochlorine compounds. Extreme care must be used when selecting possible substitutes, and the alternatives should be fully evaluated with regard to human effects.

At present, NIOSH is not aware of any evidence associating chloroethane compounds with an increased risk of cancer in man. However, animal studies are valuable in helping identify human carcinogens. Substances that cause cancer in experimental animals must be considered a potential cancer risk in man. Safe levels of exposure to carcinogens have not been demonstrated, but lowered exposure to carcinogens decreases the probability of cancer development.

NIOSH issued Current Intelligence Bulletin #25 (April 1978), recommending that ethylene dichloride (1,2-dichloroethane) be handled in the workplace as if it were a human carcinogen (5). NIOSH is now distributing Bulletin #27 to advise of additional findings of the NCI chloroethane bioassays, other pertinent data, and possible implications for occupational health. Also included are "Suggested Guidelines for Controlling Employee Exposure to Chloroethanes." NIOSH requests that producers, distributors, professional associations, and unions transmit the information in this Bulletin to their customers, employees, associates and members.

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*to be referred to as monochloroethane in this Bulletin

Table 1. Summary of Some of the Industries and Occupations Which Use Chloroethanes.[a]

Chemical	Industries[b]	Occupations[c]
monochloroethane	medical and other health services; automotive dealers and service stations; wholesale trade; electric, gas and sanitary services; machinery, except electrical; special trade contractors; fabricated metal products; printing and publishing; rubber and plastics products not elsewhere classified; food and kindred products	registered nurses; automobile mechanics; physicians, medical and osteopathic; office machine mechanics and repairmen; garage workers and gas station attendants; not specified mechanics and repairmen; household appliance and accessory installers; assemblers; heavy equipment mechanics, including diesel; plumbers and pipe fitters
1,1-dichloroethane	chemicals and allied products; miscellaneous business services; stone, clay and glass products not elsewhere classified; petroleum and coal products	janitors and sextons; not specified clerical workers; electricians; assemblers; agricultural and biological technicians
1,2-dichloroethane	medical and other health services; automotive dealers and service stations; machinery, except electrical; wholesale trade; printing and publishing; eating and drinking places; primary metal industries; chemicals and allied products; miscellaneous business services; transportation equipment; electrical equipment and supplies; special trade contractors; fabricated metal products; stone, clay and glass products; food and kindred products; paper and allied products; rubber and plastics products not elsewhere covered; communication; water transportation; instruments and related products	automobile mechanics; janitors and sextons; heavy equipment mechanics, including diesel; registered nurses; miscellaneous specified machine operatives; miscellaneous operatives; assemblers; machinists; pressmen and plate printers, printing; cooks, except private household; garage workers and gas station attendants; cleaners and charwomen; electricians; telephone installers and repairmen; vehicle washers and equipment cleaners; secretaries not elsewhere classified; nursing aides, orderlies and attendants; checkers, examiners and inspectors, manufacturing; not specified mechanics and repairmen; painters, manufactured articles
1,1,1-trichloroethane	medical and other health services; automotive dealers and service stations; machinery, except electrical; wholesale trade; transportation equipment; printing and publishing; primary metal industries; electrical equipment and supplies; fabricated metal products; communication; special trade contractors; chemicals and allied products; eating and drinking places; miscellaneous services; transportation by air; stone, clay and glass products; retail general merchandise; instruments and related products; apparel and accessory stores; electric, gas and sanitary services; food and kindred products; rubber and plastics products not elsewhere classified; personal services; paper and allied products	auto mechanics; janitors and sextons; heavy equipment mechanics, including diesel; registered nurses; secretaries not elsewhere classified; machinists; machine operatives; miscellaneous specified; assemblers; not specified clerical workers; cleaners and charwomen; miscellaneous operatives; electricians; pressmen and plate printers, printing; garage workers and gas station attendants; telephone installers and repairmen; manufacturing checkers, examiners and inspectors; cooks, except private household; tool and die makers; administrators and managers, not elsewhere classified; nursing aides, orderlies and attendants; dishwashers; vehical washers and equipment cleaners; millwrights; miscellaneous mechanics and repairmen; office machine
1,1,2-trichloroethane	primary metal industries; wholesale trade; auto repair, services and garages; transportation equipment; communication; electrical equipment and supplies; special trade contractors; miscellaneous retail stores; machinery, except electrical; stone, clay and glass products; chemicals and allied products; medical and other health services; instruments and other related products	electricians; heavy equipment mechanics, including diesel; miscellaneous mechanics and repairmen; upholsterers; janitors and sextons; electrical and electronic engineering technicians; office machine mechanics and repairmen; radio and television; not specified mechanics and repairmen; air conditioning, heating and refrigeration; telephone installers and repairmen; miscellaneous operatives; assemblers; manufacturing checkers, examiners and inspectors; printing pressmen and plate printers
1,1,2,2-tetrachloroethane	electrical equipment and supplies; chemicals and allied products; electric, gas and sanitary services; miscellaneous business services; stone, clay and glass products	assemblers; janitors and sextons; not specified clerical workers; electricians; manufacturing checkers, examiners and inspectors
hexachloroethane	real estate; paper and allied products; lumber and wood products; amusement and recreation services not elsewhere classified	cleaners and charwomen; millwrights; machine operatives, miscellaneous specified; plumbers and pipefitters; electricians

(a) 1,1,1,2-tetrachloroethane and pentachloroethane were not mentioned in the NOHS survey (6)
(b) These are standard industrial titles from the Standard Industrial Classification Manual (7)
(c) These are standard occupational titles from the Bureau of the Census (8)

BACKGROUND

Chloroethanes are chlorinated organic compounds structurally related to ethane in which one or more of the hydrogen atoms have been replaced by a chlorine atom or atoms. Monochloroethane, for example, is shown to result from the replacement of one hydrogen atom in ethane by a chlorine atom.

ethane monochloroethane

At room temperature monochloroethane is a gas, hexachloroethane is a solid, and the seven other chloroethanes are liquids. Some of the chloroethanes are manufactured on a large scale and used extensively because of their low cost and excellent solvent properties. They are used as solvents and in degreasing agents, cutting fluids, fumigants, and in the manufacture of plastics, textiles, and other chemicals. Table 1 (opposite page) summarizes the major industries and occupations in which workers are potentially exposed to chloroethanes.

From 1972-1974, NIOSH conducted the NIOSH National Occupational Hazards Survey (NOHS), on a sample of about 900,000 employees at 4,636 facilities, in order to determine the potential for worker exposure to chemicals and physical agents. NOHS algorithms used Bureau of the Census 1970 population counts to permit extrapolation from the sample to the United States worker population of 1970. A total of over 3 million workers were estimated to be potentially exposed to one or more chloroethanes. Table 2 presents a summary of NOHS estimates of worker exposure to chloroethanes and some production figures (6,9, 40).

Table 2. Chloroethane Exposures and Production (6,9, 40).

Chemical	Estimated number of workers exposed	Annual Production quantities (pounds)
monochloroethane	113,000	670 million (1976)
1,1-dichloroethane	4,600	b
1,2dichloroethane	1,900,000	8 billion (1976)
1,1,1-trichloroethane	2,900,000	630 million (1976)
1,1,2-trichloroethane	112,000	c
1,1,1,2-tetrachloroethane	a	b
1,1,2,2-tetrachloroethane	11,100	c
pentachloroethane	a	b
hexachloroethane	1,500	b,d

[a] NOHS estimates not available
[b] does not appear to be commercially produced in the United States
[c] direct production information not available
[d] 730,000 kg were imported in 1976

Summaries of the current Department of Labor - Occupational Safety and Health Administration (OSHA) exposure standards (10) and NIOSH recommended exposure standards for the chloroethane compounds are given in Table 3.

Table 3. Chloroethane Exposure Standards.

Chemical	OSHA Exposure Standard (ppm)	NIOSH Recommended Exposure Standard (ppm)
monochloroethane	1000	none
1,1-dichloroethane	100	none
1,2-dichloroethane	50	5
1,1,1-trichloroethane	350	350
1,1,2-trichloroethane	10	none
1,1,1,2-tetrachloroethane	none	none
1,1,2,2-tetrachloroethane	5	1
pentachloroethane	none	*
hexachloroethane	1	*

* NIOSH has tentative plans for a Criteria Document for a Recommended Standard for this substance

The OSHA exposure standards and the NIOSH recommended standards and control measures for the chloroethanes were developed before the carcinogenic potential of these compounds was recognized. Therefore, an assessment of the carcinogenicity of these compounds was not included. The levels currently recommended or adopted may not provide adequate protection from potential carcinogenic effects.

LABORATORY ANIMAL STUDIES

Carcinogenicity

As of July 1978, four of the eight chloroethanes selected by NCI for testing have been shown to be carcinogenic in laboratory animals. The results of the bioassays (1-4,14) are summarized in Table 4. Each compound was studied separately in male and female Osborne-Mendel rats and male and female $B_6C_3F_1$ mice. Each experiment consisted of a high dose and a low dose group of 50 animals each. Twenty animals of each species/sex combination served as untreated controls and 20 animals of each species/sex combination served as vehicle controls. The chloroethane compounds were administered to the test animals in a corn oil vehicle by gastric intubation (stomach tube) five days a week for 78 weeks. The vehicle controls were intubated with pure corn oil at the same rate as the high dose animals.

Table 4. Summary of NCI Chlorothane Bioassay Results as of July 1978 (1-4,14).

Compound	Species/sex	Tumor site	Statistically significant tumors
monochloroethane	no testing planned		
1,1-dichloroethane	retesting recommended because initial results inconclusive		
1,2-dichloroethane	rats/female	mammary gland	adenocarcinomas
	rats/male	forestomach	squamous cell carcinomas
		circulatory system	hemangiocarcinomas
		subcutaneous tissue	fibromas
	mice/female	mammary gland	adenocarcinomas
		endometrium	stomal sarcomas
		lungs	adenomas
	mice/male	lungs	adenomas
1,1,1-trichloroethane	retesting in progress		
1,1,2-trichloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
	mice	adrenal glands	pheochromocytomas
1,1,1,2-tetrachloroethane	testing in progress, no report available		
1,1,2,2-tetrachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas
pentachloroethane	testing in progress, no report available		
hexachloroethane	mice/female	liver	hepatocellular carcinomas
	mice/male	liver	hepatocellular carcinomas

The National Cancer Institute has concluded that under the conditions of the bioassay 1,2-dichloroethane; 1,1,2-trichloroethane; 1,1,2,2-tetrachloroethane; and hexachloroethane are carcinogenic in mice, inducing liver cancer in both sexes (1-4). Additionally, results of the NCI bioassay of 1,2-dichloroethane indicate that this compound also causes cancer in male and female rats. In mice 1,1,2-trichloroethane was also associated with increased adrenal pheochromocytoma, a tumor which gives rise to high blood pressure and hyperglycemia. Toxic kidney damage was observed in all groups of both mice and rats treated with hexachloroethane (4).

Although the occurence of cancer in mice is highly significant, the results do not provide conclusive evidence that 1,1,2-trichloroethane; 1,1,2,2-tetrachloroethane; or hexachloroethane cause cancer in rats. A statistically significant association between increased dosage and accelerated mortality was observed in rats treated with hexachloroethane. NCI has concluded that early mortality may have obscured a carcinogenic effect in these animals.

The National Cancer Institute is currently conducting bioassays of pentachloroethane and 1,1,1,2-tetrachloroethane (14). They are also retesting 1,1-dichloroethane and 1,1,1-trichloroethane because the previous tests were inconclusive; low survival rates complicated the interpretation of the bioassay results. Monochloroethane has not yet been tested.

Other Adverse Effects

All of the chloroethane compounds are known to cause central nervous system (CNS) depression in laboratory animals. This is usually expressed as abnormal weakness, intoxication, restlessness, irregular respiration, muscle incoordination, and unconsiousness. Chloroethanes are generally irritating to the eyes and skin. Damage to the liver and/or kidney has been demonstrated in various animal species following exposure to these compounds (15).

It has been reported that some of the chloroethanes and their metabolites are mutagenic in bacterial systems (3,16). Mutagenic activity, per se, should be considered a substantial liability. In addition, research suggests a correlation between mutagenicity in some bacterial strains and carcinogenicity in higher animals. Other adverse effects of the chloroethanes may vary from one compound to another. Table 5 summarizes some of the toxicological studies in animal systems.

Table 5. Some Adverse Effects of Chloroethanes Reported in Animal Studies (5,11-13,17-37).

Chemicals	Species	Adverse Effect
monochloroethane	unspecified	kidney damage; fatty changes in liver, kidney, and heart
1,1-dichloroethane	cat	kidney damage
	dog	liver injury
	rat	liver injury; retarded fetal development
1,2-dichloroethane	bacterium	mutagen
	cat	retarded growth rate, fatty changes in liver; heart dilation; lung hyperemia
	dog	corneal clouding; fatty changes in liver; liver enlargement; weight loss
	fruit fly	mutagen
	guinea pig	fatty changes in liver; liver enlargement; weight loss
	monkey	fatty changes in liver
	rabbit	fatty changes in liver; hypotension; respiratory paralysis; EKG changes; anemia; bone marrow changes; liver dysfunction, hemorrhage and degeneration; kidney degeneration and dysfunction
	rat	embryotoxin; pulmonary congestion; fatty changes in liver
1,1,1-trichloroethane	cat	neuromuscular reflex changes
	dog	sudden death; respiratory failure
	guinea pig	fatty changes in liver; lung irritation
	mouse	cardiac arrythmias; liver dysfunction; pulmonary congestion
	monkey	cardiac arrythmias; myocardial depression; respiratory failure; staggering gait; tachycardia; tremors
	rat	cardiac failure; pulmonary congestion; pneumonitis; staggering gait; weakness; respiration; semiconsciousness; respiratory failure
1,1,2-trichloroethane	dog	liver and kidney injury
	guinea pig	liver and kidney injury
1,1,1,2-tetrachloroethane	rabbit	embryotoxin
	rat	embryotoxin; liver dysfunction; mutagen
1,1,2,2-tetrachloroethane	bacterium	mutagen
	dog	ascites; diarrhea; jaundice; liver enlargement; intestinal hemorrhage
	guinea pig	convulsions; weight loss; death
	monkey	anorexia; diarrhea; blood cell fluctuation; weight loss
	mouse	staggering gait; breathing difficulty; fatty degeneration of liver and kidney; death
	rabbit	altered immune system; altered blood chemistry; liver and kidney degeneration; fatty degeneration of liver and kidney; corneal reflex changes; liver enlargement; paralysis; death
	rat	blood cell changes; fatty degeneration of liver; liver dysfunction; death
pentachloroethane	cat	liver, kidney, and lung changes
	dog	fatty degeneration of liver; kidney and lung injury
	sheep	liver dysfunction
hexachloroethane	cattle	liver and kidney damage
	mouse	liver and kidney damage
	rat	liver and kidney damage
	sheep	liver and kidney damage

HUMAN TOXICITY

Although chloroethanes have been associated with cancer in laboratory animals, NIOSH is unaware of any definitive evidence indicating that chloroethanes are carcinogenic in humans. However, the chloroethanes have long been known to be capable of producing harmful local and systemic effects. As summarized in Tables 6 and 7, the chloroethanes may affect a variety of human organs or systems. The effects of chloroethane exposure vary from one compound to another, but, most are known to effect the central nervous system (CNS). In many instances, the clinical manifestations and laboratory findings associated with chloroethane toxicity are similar for the major routes of entry: inhalation, skin absorption, and ingestion. Liver and/or kidney injury, pulmonary irritation, and damage to the blood-forming system have been associated with inhalation of chloroethanes. Repeated or prolonged skin exposure can defat the skin and cause dermatitis.

In addition to the toxic effects of chloroethanes and their metabolites, the oxidative decomposition of products produced in the presence of open flames, hot metals, or lighted cigarettes should be taken into account. The chloroethane compounds may degrade to phosgene, hydrogen chloride and dichloroacetylene. Phosgene is considered to be dangerous to life in 30 to 60 minutes at 12.5 ppm (37).

Table 6. Adverse Effects of Chloroethanes on Human Organs and Systems (5,11-13,39-41).*

CHEMICAL	IMMUNOLOGICAL: ALLERGIC	HEMATOLOGICAL	CARDIOVASCULAR	PULMONARY	RENAL: UROLOGIC	GASTROINTESTINAL	HEPATIC: BILIARY	MUSCULOSKELETAL	NEUROLOGIC	DERMATOLOGIC	OPTHALMOLOGIC	OTHER
monochloroethane	●		●	●		●			●	●	●	●
1,1-dichloroethane				●					●	●		
1,2-dichloroethane		●	●	●	●	●	●	●	●	●		●
1,1,1-trichloroethane		●	●			●	●		●	●	●	●
1,1,2,2-tetrachloroethane		●	●	●	●	●	●		●	●		●
hexachloroethane									●		●	

*adverse human health effects have not been reported to NIOSH for 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, and pentachloroethane

Table 7. Specific Adverse Effects of Chloroethanes on Humans, by System (5,11-13,37-39).

Chemical	System	Adverse Effect
monochloroethane	neurologic	central nervous system depression, headache, dizziness, incoordination, feeling inebriated, unconsciousness
	gastrointestinal	abdominal cramps
	respiratory	respiratory tract irritation, respiratory failure
	cardiovascular	cardiac arrhythmias, cardiac arrest
	dermatological	skin irritation, frostbite, allergic eczema
	other	eye irritation, death
1,1-dichloroethane	neurologic	central nervous system depression
	respiratory	respiratory tract irritation
	dermatologic	skin burn
1,2-dichloroethane	neurologic	headache, dizziness, unconsciousness, vertigo, hand tremors, generalized weakness, sleepiness, nervousness, mental confusion
	hepatic	liver function abnormalities, cellular damage, toxic chemical hepatitis, jaundice, liver enlargement
1,1,1-trichloroethane	neurologic	central nervous system depression, headache, dizziness, incoordination, feeling inebriated, unconsciousness; impaired perceptual speed, manual dexterity and equilibrium; increased reaction time, lightheadedness, drowsiness, sleepiness, generalized weakness, ringing sound in ears, unsteady gait, burning and/or prickling sensation in hands and/or feet
	hepatic	cellular damage, liver function abnormalities
	gastrointestinal	nausea, vomiting, diarrhea
	cardiovascular	drop in blood pressure (hypotension), decrease in heart rate (bradycardia), cardiac arrhythmias
	hematologic	blood clotting changes
	dermatologic	dryness, cracking, scaliness, inflammation
	other	eye irritation, fatigue, death
1,1,2-trichloroethane		NIOSH is unaware of reports of adverse occupational exposure (see Table 5)
1,1,1,2-tetrachloroethane		NIOSH is unaware of reports of adverse occupational exposure (see Table 5)
1,1,2,2-tetrachloroethane	neurologic	central nervous system depression, headache, feeling inebriated, unconsciousness, drowsiness, unsteady gait, vertigo, hand tremors, numbness in limbs, prickling sensation of fingers and toes, pain in sole of feet, loss of knee jerk, paralysis of some muscles of the hands and feet, inflammation of the peripheral nerves slight paralysis of the soft palate, loss of the gag reflex, irritability, mental confusion, delirium, convulsions, stupor, coma
	hepatic	liver function abnormalities, massive cell damage toxic chemical hepatitis, jaundice, liver enlargement, sensation of pressure in the liver area
	gastrointestinal	abdominal pain, nausea, vomiting, unpleasant taste in the mouth, loss of appetite (anorexia), vomiting of blood (hematemesis), increased flatulence, diarrhea, constipation, pale stools
	urologic	kidney damage, presence of bile pigments, albumen, and casts in the urine
	respiratory	excessive fluid in the lungs (pulmonary edema), respiratory paralysis
	cardiovascular	fatty degeneration of the heart muscle (in lab animals)
	hematologic	anemia, increase in white blood cells, (and blood platelets)
	dermatologic	dryness, cracking, scaliness, inflamation, purpuric rash
	other	insomnia, general malaise, fatigue, excessive sweating, weight loss
pentachloroethane		NIOSH is unaware of reports of adverse occupational exposure (see Table 5)
hexachloroethane	neurologic	inability to close eyelid
		eye irritation, tearing of eyes, inflamation of delicate membrane lining the eye, visual intolerance to light, (photophobia)

NIOSH Recommendation

Animal studies are valuable in helping identify human carcinogens. Substances that cause cancer in experimental animals must be considered a potential cancer risk in man. Although safe levels of exposure to carcinogens have not yet been demonstrated, decreasing exposure to carcinogens does reduce their probability of initiating cancer development.

As an interim and prudent measure while the carcinogenicity of chloroethanes is being further evaluated, NIOSH recommends that occupational exposure to 1,2-dichloroethane; 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, and hexachloroethane be minimized. Exposures should be limited to as few employees as possible, while minimizing workplace exposure levels with engineering and work practice controls. Additionally, monochloroethane; 1,1-dichloroethane; 1,1,1-trichloroethane; 1,1,1,2-tetrachloroethane; and pentachloroethane should be treated in the workplace with caution.

J. Michael Lane, M.D.
Acting Director

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SUGGESTED GUIDELINES FOR CONTROLLING EMPLOYEE EXPOSURE TO CHLOROETHANES

NIOSH recommends that it would be prudent to handle 1,2-dichloroethane (ethylene dichloride); 1,1,2-trichloroethane; 1,1,2,2-tetrachloroethane; and hexachloroethane in the workplace as if they were human carcinogens. Exposure to these chloroethanes should be limited to as few employees as possible, and workplace exposure levels should be minimized. The areas in which they are used should be restricted to only those employees essential to the process or operation and these employees should be adequately protected.

Additionally, NIOSH recommends that the other five chloroethane compounds: monochloroethane (ethyl chloride); 1,1-dichloroethane; 1,1,1-trichloroethane (methyl chloroform); 1,1,1,2-trichloroethane; and pentachloroethane should be treated in the workplace with caution because of their relation to the four chloroethanes shown to be carcinogenic in laboratory animals. These five chloroethanes should be closely monitored for carcinogenic effects in humans.

EXPOSURE MONITORING

Detailed sampling and analytic methods for most of the chloroethane exposure measurements are described in the NIOSH Manual of Analytical Methods, Second Edition (1). These are:

Chemical	NIOSH Method
monochloroethane	not available
1,1-dichloroethane	S123
1,2-dichloroethane	P&CAM 127 and S122
1,1,1-trichloroethane	P&CAM 127 and S328
1,1,2-trichloroethane	P&CAM 127 and S134
1,1,1,2-tetrachloroethane	not available
1,1,2,2-tetrachloroethane	S124
pentachloroethane	not available
hexachloroethane	S101

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective.

The NIOSH Occupational Exposure Sampling Strategy Manual (2) may be helpful in developing efficient programs to monitor employee exposures to chloroethanes. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for exposure evaluation and selection of sampling times.

Employee exposure measurements should primarily consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). In addition, short term samples should be taken during periods of maximum expected exposure by using all available knowledge regarding the area, employee work procedures, and process. Area and source measurements may be useful to determine problem areas, processes, and operations.

CONTROLLING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to chloroethanes. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation.

o Product Substitution

The substitution of an alternative material with a lower potential health risk is one method. However, extreme care must be used when selecting possible substitutes. Alternatives to chloroethanes should be fully evaluated with regard to possible human effects. Unless the toxic effects of the alternative have been thoroughly evaluated a seemingly safe replacement, possibly only after years of use, may be found to induce serious health effects.

o Contaminant Controls

The most effective control of chloroethanes, where feasible, is at the source of contamination by enclosure of the operation and/or local exhaust ventilation. Guidelines for selected processes and operations can be found in the NIOSH Recommended Industrial Ventilation Guidelines (3).

If feasible, the process or operation should be enclosed with a slight vacuum so that any leakage will result in the flow of external air into the enclosure.

The next most effective means of control would be a well designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

To ensure that ventilation equipment is working properly, effectiveness (e.g., air velocity, static pressure, or air volume) should be checked at least every three months. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposure to chloroethanes.

o Employee Isolation

A third alternative is the isolation of employees. It frequently involves the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect employees who must do process checks, adjustments, maintenance, and related operations.

o Personal Protective Equipment

The least preferred method is the use of personal protective equipment. This equipment, which may include respirators, goggles, gloves, etc., should not be used as the only means to prevent or minimize exposure during routine operations.

Exposure to chloroethanes should not be controlled with the use of respirators except:

— During the time period necessary to install or implement engineering or work practice controls; or

— In work situations in which engineering and work practice controls are technically not feasible; or

— For maintence; or

— For operations which require entry into tanks or closed vessels; or

— In emergencies.

Only respirators approved by the National Institute for Occupational Safety and Health (NIOSH) under the provisions of Federal regulations 30 CFR 11 should be used. Refer to Cumulative Supplement June 1977, NIOSH Certified Equipment (4) for a listing of NIOSH-approved respirators. Note that the use of faceseal coverlets or socks with respirators voids NIOSH approvals.

Quantitative faceseal fit test equipment (such as sodium chloride, dioctyl phthalate, or equivalent) should be used. Refer to NIOSH's A Guide to Industrial Respiratory Protection (5) for guidelines on appropriate respiratory protection programs.

In addition, proper maintenance procedures, good housekeeping in the work area, and employee education are all vital aspects of a good control program. Employees should be informed as to the nature of the hazard, its control, and appropriate personal hygiene procedures.

REFERENCES FOR SUGGESTED GUIDELINES

1) NIOSH Manual of Analytical Methods, 2nd Edition, Vol. 1: GPO #017-033-00267-3, $8.75: Vol. 2: GPO #017-033-00260-6, $9.75; Vol. 3: GPO #017-033-0247-9, $9.00.

2) NIOSH Occupational Exposure Sampling StrategyManual, GPO #017-033-00247-9, $2.75.

3) NIOSH Recommended Industrial Ventilation Guidelines, GPO #017-033-00136-7, $3.90.

4) NIOSH Cummulative Supplement June 1977, NIOSH Certified Equipment, NIOSH #77-195, no charge.

5) A Guide to Industrial Respiratory Protection, GPO #017-033-00153-7, $2.30.

GPO publications must be ordered from:
Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

Reference #4 can be ordered from:
Publications Dissemination, DTS
NIOSH
4676 Columbia Parkway
Cincinnati, Ohio 45226

IDENTIFIERS AND SYNONYMS FOR CHLOROETHANE

Chemical Abstracts Service Registry Number 75-00-3
NIOSH RTECS Number KH75250
Chemical Formula C_2H_5Cl

Aethylis
Aethylis Chloridum
Anodynon
Chelen
Chlorene
Chlorethyl
Chloridum
Chloroethane
Chloryl
Chloryl Anesthetic
Cloretilo
Dublofix
Ethane, Chloro-
Ether Chloratus
Ether Hydrochloric
Ether Muriatic
Ethyl Chloride
Hydrochloric Ether
Kelene
Monochloroethane
Muriatic Ether
Narcotile

IDENTIFIERS AND SYNONYMS FOR 1,1-DICHLOROETHANE

Chemical Abstracts Service Registry Number 75-34-3
NIOSH RTECS Number KI01750
Chemical Formula $C_2H_4Cl_2$

Chlorinated Hydrochloric Ether
1,1-Dichlorethane
1,1-Dichloroethane
Ethane, 1,1-Dichloro-
Ethylidene Chloride
Ethylidene Dichloride
NCI-C04535

IDENTIFIERS AND SYNONYMS FOR 1,2-DICHLOROETHANE

Chemical Abstracts Service Registry Number 107-06-2
NIOSH RTECS Number KI05250
Chemical Formula $C_2H_4Cl_2$

1,2-Bichloroethane
Brocide
Borer Sol
Destruxol Borer-Sol
Di-Chlor-Mulsion
Dichloremulsion
1,2-Dichlorethane
1,2-Dichloroethane
α,β-Dichloroethane
sym-Dichloroethane
Dutch Liquid
EDC
ENT 1,656
Ethane, 1,2-Dichloro-
Ethane Dichloride
Ethylene Chloride
Ethylene Dichloride
Glycol Dichloride

IDENTIFIERS AND SYNONYMS FOR 1,1,1-TRICHLOROETHANE

Chemical Abstracts Service Registry Number 71-55-6
NIOSH RTECS Number KJ29750
Chemical Formula $C_2H_3Cl_3$

Aerothene TT
Chloroethene NU
Chlorotene
Chlorothane NU
Chlorothene
Chlorothene NU
Chlorothene VG
Chlorten
Ethane, 1,1,1-Trichloro-
Inhibisol
Methyl Chloroform
Methyltrichloromethane
NCI-C04626
Alpha-T
Trichloroethane
1,1,1-Trichloroethane
α-Trichloroethane

IDENTIFIERS AND SYNONYMS FOR 1,1,2-TRICHLOROETHANE

Chemical Abstracts Service Registry Number 79-00-5
NIOSH RTECS Number KJ31500
Chemical Formula $C_2H_3Cl_3$

Ethan Trichloride
Ethane, 1,1,2-Trichloro-
NCI-C04579
Beta-T
1,1,2-Trichlorethane
1,1,2-Trichloroethane
β-Trichloroethane
Vinyl Trichloride
Vinyltrichloride

IDENTIFIERS AND SYNONYMS FOR 1,1,1,2-TETRACHLOROETHANE

Chemical Abstracts Service Registry Number 630-20-6
NIOSH RTECS Number KI8450000
Chemical Formula $C_2H_2Cl_4$

Ethane, 1,1,1,2-tetrachloro-
NCI-C52459
1,1,1,2-Tetrachloroethane

IDENTIFIERS AND SYNONYMS FOR 1,1,2,2-TETRACHLOROETHANE

Chemical Abstracts Service Registry Number 79-34-5
NIOSH RTECS Number KI85750
Chemical Formula $C_2H_2Cl_4$

Acetylene Tetrachloride
Bonoform
Cellon
1,1-Dichloro-2,2-Dichloroethane
Ethane, 1,1,2,2-tetrachloro-
NCI-C03554
Tetrachloroethane
1,1,2,2-Tetrachloroethane
sym-Tetrachloroethane
TCE

IDENTIFIERS AND SYNONYMS FOR PENTACHLOROETHANE

Chemical Abstracts Service Registry Number 76-01-7
NIOSH RTECS Number KI63000
Chemical Formula C_2HCl_5

Ethane Pentachloride
Ethane, Pentachloro-
NCI-C53894
Pentachloroethane
Pentalin

IDENTIFIERS AND SYNONYMS FOR HEXACHLOROETHANE

Chemical Abstracts Service Registry Number 67-72-1
NIOSH RTECS Number KI40250
Chemical Formula C_2Cl_6

Avlothane
Carbon Hexachloride
Distokal
Distopan
Distopin
Egitol
Ethane Hexachloride
Ethane, Hexachloro-
Falkitol
Fasciolin
Hexachlorethane
1,1,1,2,2,2-Hexachloroethane
Hexachloroethylene
Mottenhexe
NCI-C04604
Perchloroethane
Phenohep

JOINT

NIOSH / OSHA

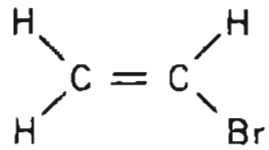
Current Intelligence Bulletin 28

September 21, 1978

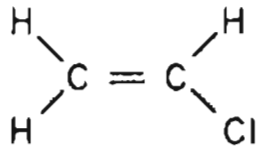
VINYL HALIDES

CARCINOGENICITY

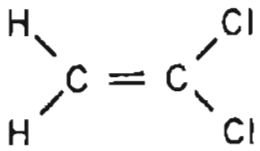
Vinyl Bromide



Vinyl Chloride



Vinylidene Chloride



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

U. S. DEPARTMENT OF LABOR
Occupational Safety and Health Administration

This Current Intelligence Bulletin is a joint effort of the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) and is part of the NIOSH Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

FURTHER INFORMATION:

Director
Division of Criteria Documentation
and Standards Development
National Institute for Occupational
Safety and Health
5600 Fishers Lane
Rockville, Maryland 20857

(301) 443-3680

Director
Technical Support
Occupational Safety and
Health Administration
200 Constitution Avenue, N.W.
Washington, D.C. 20210

(202) 523-8061

SYNONYMS

Identifiers and Synonyms are located on page 11.

DHEW (NIOSH) Publication No. 79-102

JOINT NIOSH/OSHA

CURRENT INTELLIGENCE BULLETIN: VINYL HALIDES - CARCINOGENICITY

Vinyl Bromide, Vinyl Chloride, and Vinylidene Chloride

September 21, 1978

The National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA) jointly recommend that vinyl bromide and vinylidene chloride be considered in the workplace as potential carcinogens to humans and controlled with the same degree of prudence as vinyl chloride, another vinyl halide currently regulated as a carcinogen by OSHA. This recommendation is based on the results of recent studies indicating that exposure to vinyl bromide and to vinylidene chloride causes angiosarcoma of the liver and other cancers in laboratory animals. Safe levels of exposure to carcinogens have not been demonstrated, but lowered exposure to carcinogens may in general decrease the probability of cancer development.

Vinyl chloride is known to cause angiosarcoma of the liver and cancers of other sites in laboratory animals and in humans. At this time, adequate carcinogenicity studies of vinyl bromide and vinylidene chloride have been conducted only in laboratory animals. In view of the present state of knowledge in carcinogenesis, substances that cause cancer in laboratory animals are considered a potential cancer risk to humans.

Vinyl chloride is the only vinyl halide for which an OSHA exposure standard currently exists. In light of the recent laboratory animal studies demonstrating carcinogenicity of vinyl bromide and vinylidene chloride, NIOSH and OSHA have jointly prepared this Current Intelligence Bulletin. Its purpose is to advise the occupational health community of the pertinent data and implications for exposed workers. NIOSH and OSHA request that producers, distributors, professional associations, and unions transmit the information in this Bulletin to their customers, employees, associates, and members.

LABORATORY STUDIES

Carcinogenicity

Laboratory studies have demonstrated that exposure by inhalation to vinyl chloride (1,2), vinyl bromide (3), and vinylidene chloride (1,4) all caused angiosarcoma of

the liver and other cancers in animals. Angiosarcoma of the liver was induced in rats exposed to 25 ppm vinyl chloride, in rats exposed to 50 ppm vinyl bromide, and in mice exposed to 55 ppm vinylidene chloride.

At lower levels, exposure to vinyl chloride (1 ppm) has induced mammary carcinomas (5), exposure to vinyl bromide (10 ppm) has induced lymph node angiosarcoma (3), and exposure to vinylidene chloride (25 ppm) has induced adenocarcinomas of the kidney (4). Table 1 presents a summary of tumors in animals exposed to these vinyl halides.

Table 1. Some Tumors Reported in Vinyl Halide Animal Studies. (1,3,4).

Chemical	Species	Site	Tumor
vinyl bromide	rat	liver	angiosarcoma
		zymbal gland	squamous cell carcinoma
		lung	metastatic angiosarcoma, bronchioalveolar carcinoma, bronchioalveolar adenoma
		breast	adenocarcinoma
		mesenteric lymph node	angiosarcoma
		lymphatic	lymphosarcoma
vinyl chloride	rat	mammary gland	carcinoma
		skin	squamous cell carcinoma
		liver	angiosarcoma
		lung	adenocarcinoma, angiosarcoma
		zymbal gland	carcinoma
		kidney	nephroblastoma
	mouse	liver	angiosarcoma
		mammary gland	anaplastic and squamous metaplasia
		lung	bronchioalveolar adenoma
		liver	hepatic cell carcinoma
		kidney	renal adenoma
		skin	keratoacanthoma
	rabbit	skin	acanthoma
		lung	adenocarcinoma
	hamster	liver	angiosarcoma
		skin	trichoepithelioma, basalioma
		lymphatic	lymphoma
vinylidene chloride	mouse	liver	angiosarcoma
		lung	bronchioalveolar adenoma
		kidney	adenocarcinoma
	rat	mesenteric lymph node	angiosarcoma
		breast	mammary tumor
		zymbal gland	carcinoma

Mutagenicity

Several investigators have reported that vinyl chloride is mutagenic in Salmonella typhimurium and pombe (6-11) and in Escherichia coli (12-14). Vinyl chloride also has been shown to be mutagenic in the yeast mutation assay (11), in the Drosophila recessive lethal test (15,16), and in the host-mediated assay (11). Studies also have shown vinyl chloride to be mutagenic in Tradescantia (17). Three reports bearing on the mutagenicity of vinyl bromide have been noted to date. Bartsch et al., (18) and Simmons (19) have independently reported that vinyl bromide induced mutations in the bacterium, Salmonella typhimurium. In addition, Sparrow (17) has demonstrated a significant increase in mutants in Tradescantia exposed to vinyl bromide vapors. Vinylidene chloride has been shown to induce mutations in Salmonella typhimurium (10, 20-22), in Escherichia coli (12), and in Tradescantia (17).

Other Adverse Effects

Other adverse health effects in animals attributed to exposure to vinyl halides include central nervous system (CNS) effects, cardiovascular effects, respiratory effects, skin effects, skeletal effects, and liver or spleen abnormalities (1).

HUMAN STUDIES

Carcinogenicity

Studies of workers exposed to vinyl chloride have demonstrated an excessive risk of death from cancer of the lung, brain, lymphatic system, and angiosarcoma of the liver (1, 23). Cancers of the same sites were previously induced in animals following exposure to vinyl chloride (2).

Liver angiosarcoma in humans is a very rare malignant tumor of the blood vessels. Though no clinical signs or symptoms, or laboratory examinations have been found to be specific for the early diagnosis of this cancer, affected individuals may complain of fatigue, abdominal pain, weight loss, anorexia, nausea, vomiting, melena, indigestion, jaundice, hematemesis, or diarrhea. Other manifestations may include liver enlargement and liver function abnormalities. In adults, untreated angiosarcoma of the liver usually is fatal within 8 months. Even with treatment, death usually occurs within 16 months.

To date there have been no reported cases of cancer in humans associated with exposure to vinyl bromide or vinylidene chloride. However, vinyl bromide has been in commercial production in the U.S. only since 1971. Due to the long latent period characteristic of occupationally-induced cancers, typically 15-40 years, no unusual risk of cancer among exposed workers would be expected to be be detected at this time. Vinylidene chloride has been in commercial production and use since the early 1940's. The only study (24) reported to date showed no excessive cancer risk among workers occupationally exposed to vinylidene chloride, but methodologic limitations of this study do not permit an adequate evaluation of the carcinogenic risk of vinylidene chloride to humans.

Mutagenicity and Reproductive Effects

Cytogenetic studies have demonstrated a significant increase in the frequency of chromosomal aberrations in the lymphocytes of workers exposed to vinyl chloride (25–31). Further evidence for the mutagenicity of vinyl chloride has been provided by investigations showing an increase in fetal wastage among wives of male workers following occupational exposure to vinyl chloride (32,33). No studies addressing mutagenic or reproductive hazards among vinyl bromide or vinylidene chloride exposed populations have been reported.

Other Adverse Effects

Numerous other adverse health effects have been observed in humans exposed to vinyl chloride, as detailed in Table 2. Reports of effects on workers exposed to vinylidene chloride in combination with other vinyl compounds include liver function abnormalities, headache, vision problems, dizziness, fatigue, weakness, and neurological sensory disturbances. No similar reports for vinyl bromide exposure were found (1).

Table 2. Other Adverse Effects of Vinyl Chloride on Humans (1).

System	Adverse Effect
neurologic	dizziness, lightheadedness, dulling vision and hearing, drowsiness, headache, loss of memory, euphoria, nervousness, numbness or tingling in fingers or toes
gastrointestinal	nausea, loss of appetite, abdominal distress, varices of esophagus or stomach, black stools, bloody vomitus
cardiovascular	increased blood pressure, Raynaud's Syndrome
hepatic	liver enlargement, liver function abnormalities, increased sulphbromophthalein retention, liver damage, serum enzyme abnormalities
respiratory	coughing and sneezing, bronchial rales, emphyzema, pulmonary fibrosis, decreased respiratory function, lung function disturbances
hematologic	anemia, reticulocytosis, leukopenia, thrombocytopenia, splenomegaly
dermatologic	contact dermatitis, scleroderma-like skin changes
musculoskeletal	calf and joint pain, acroosteolysis
other	increased perspiration, cold sensation in fingers and hands, fatigue, weight loss, weakness, impotency

OTHER VINYL HALIDES

There is a lack of information regarding the carcinogenicity of vinyl fluoride and vinylidene fluoride. However, both have been shown to be mutagenic in bacterial systems (1). This evidence of mutagenicity is cause for concern.

USES, EXPOSURES, AND EXPOSURE STANDARDS

The vinyl halides are of widespread industrial use, especially in the plastics industry. They are easily polymerized and copolymerized with various materials such as acrylonitrile, vinyl acetate, and styrene, to form pliable, lightweight plastics or thermoplastic resins. Table 3 summarizes the major industries in which workers are potentially exposed to vinyl halides, according to the NIOSH National Occupational Hazards Survey (NOHS).

Table 3. Some Industries Which Use Vinyl Halides Based on NIOSH NOHS Data (34).

Chemical*	Industries
vinyl chloride	chemicals and allied products electrical equipment and supplies furniture and fixtures
vinyl bromide	chemicals and allied products rubber and plastics products leather and leather products fabricated metal products wholesale trade
vinylidene chloride	chemicals and allied products special trade contractors fabricated metal products general building contractors wholesale trade leather and leather products
vinylidene fluoride	chemicals and allied products machinery, except electrical electrical equipment and supplies food and kindred products medical and other health services

*No NOHS information available for vinyl fluoride

From 1972-1974, NIOSH conducted the NIOSH National Occupational Hazards Survey (NOHS), on a sample of about 900,000 employees at 4,636 facilities, in order to determine the potential for worker exposure to chemicals and physical agents.

NOHS algorithms used Bureau of the Census 1970 population counts to permit extrapolation from the sample to the United States worker population of 1970. Table 4 presents a summary of NOHS estimates of worker exposure to vinyl halides (34).

The exposure estimates include two categories. Definite estimates are extrapolated from actual observations of the use of the specific chemical or the use of a trade name product known to contain the chemical. Probable estimates include additional extrapolations from observations of trade name products suspected of containing the chemical because of generic formulations.

Table 4. Vinyl Halide Exposures (34).

Chemical	Estimated Number of Workers Potentially Exposed	
	Definite	Probable
vinyl chloride	27,000	2,200,000
vinyl bromide	360	26,000
vinylidene chloride	6,500	58,000
vinylidene fluoride	1,900	32,000
vinyl fluoride	NOT AVAILABLE	NOT AVAILABLE

Summaries of the current Department of Labor - Occupational Safety and Health Administration (OSHA) exposure standards and NIOSH recommended exposure standards for the vinyl halide compounds are given in Table 5.

Table 5. Vinyl Halide Exposure Standards (1,35).

Chemical	OSHA Exposure Standard (ppm)	1978 NIOSH Recommended Exposure Standard (ppm)
vinyl chloride	1	1
vinyl bromide	none	1
vinylidene chloride	none	1
vinylidene fluoride	none	1
vinyl fluoride	none	1

Recommendations

Vinyl chloride is regulated by OSHA as a demonstrated carcinogen in humans with an occupational exposure limit of 1 ppm. Recent evidence for vinyl bromide and vinylidene chloride demonstrates a pattern of tumor induction in animals similar to that of vinyl chloride, including angiosarcomas at low exposure levels. Safe levels of exposure to carcinogens have not been demonstrated, but decreasing exposure may in general reduce the probability of cancer development. Therefore, as a prudent measure NIOSH and OSHA recommend that occupational exposure to vinyl bromide and vinylidene chloride be reduced to the lowest possible levels. Exposures should be limited to as few employees as possible, and workplace exposure levels should be reduced with engineering and work practice controls.

Detailed NIOSH recommendations for the control of exposure to these substances in the workplace are contained in the Vinyl Halides Criteria Document (1).

Eula Bingham, Ph.D.
Assistant Secretary of Labor
Occupational Safety and Health
Administration

J. Michael Lane, M.D.
Acting Director
National Institute for Occupational
Safety and Health

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IDENTIFIERS AND SYNONYMS FOR VINYL CHLORIDE

Chemical Abstracts Service Registry Number 75-01-4
NIOSH RTECS Number KU96250
Chemical Formula C_2H_3Cl

Chlorethene
Chlorethylene
Chloroethene
Chloroethylene
Ethene, Chloro-
Ethylene, Chloro-
Ethylene Monochloride
Monochloroethene
Monochloroethylene
Trovidur
VC
VCM
Vinyl Chloride
Vinyl Chloride Monomer
Vinyl C Monomer

IDENTIFIERS AND SYNONYMS FOR VINYL BROMIDE

Chemical Abstracts Service Registry Number 593-60-2
NIOSH RTECS Number KU84000
Chemical Formula C_2H_3Br

Bromoethene
Bromoethylene
Ethene, Bromo-
Ethylene, Bromo-
NCI-C50373
Vinyl Bromide

IDENTIFIERS AND SYNONYMS FOR VINYLIDENE CHLORIDE

Chemical Abstracts Service Registry Number 75-35-4
NIOSH RTECS Number KV92750
Chemical Formula $C_2H_2Cl_2$

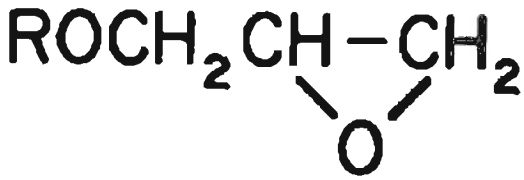
1,1,-DCE
1,1,-Dichloroethene
1,1,-Dichloroethylene
Ethene, 1,1,-Dichloro-
Ethylene, 1,1,-Dichloro
NCI-C54262
Sconatex
Vinylidene Chloride
Vinylidene Chloride (II)

NIOSH

Current Intelligence Bulletin 29

OCTOBER 12, 1978

GLYCIDYL ETHERS



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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IDENTIFIERS, SYNONYMS, AND CHEMICAL STRUCTURES FOR SEVERAL GLYCIDYL ETHERS ARE TABULATED IN THE REAR PORTION OF THIS BULLETIN

DHEW (NIOSH) Publication No. 79-104

CURRENT INTELLIGENCE BULLETIN

GLYCIDYL ETHERS

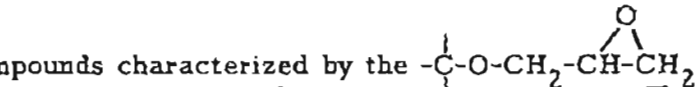
October 12, 1978

The National Institute for Occupational Safety and Health (NIOSH) would like to inform the occupational health community of the possibility of adverse effects to the testes and the hemopoietic (blood forming) system in workers exposed to glycidyl ethers.

During development of a NIOSH criteria document on glycidyl ethers, a pattern of research findings emerged which indicates that some of the glycidyl ethers may be capable of producing testicular atrophy and hemopoietic abnormalities in various species of laboratory animals. Additionally, after the issuance of the June 1978 NIOSH criteria document, a 1957 study was released to NIOSH reporting testicular atrophy in laboratory rats exposed to n-butyl glycidyl ether. While none of the individual research reports are conclusive with respect to the ability of glycidyl ethers to produce permanent changes to the testes or hemopoietic system in laboratory animals, some of the changes observed may act as predisposing factors to systemic problems. NIOSH is not aware of any studies investigating the possiblity of occurrence of testicular atrophy or hemopoietic abnormalities occurring in humans exposed to glycidyl ethers. The possibility of these effects occurring in humans is reason for concern. Therefore, NIOSH requests that any information regarding testicular atrophy or hemopoietic abnormalities observed in workers exposed to glycidyl ethers be reported to the NIOSH Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-Wide Studies Branch, Medical Section, Telephone: (513) 684-3593 .

NIOSH advises strict adherence to the detailed recommended occupational standard described in the glycidyl ethers criteria document. Particular attention should be given to appropriate medical surveillance in order to detect testicular atrophy or hemopoietic abnormalities in exposed workers. NIOSH requests that producers, distributors, users, professional associations, and unions transmit this information to their customers, employees, associates and members.

BACKGROUND

Glycidyl ethers are synthetic compounds characterized by the  group and find their major use as components of epoxy resin systems. The "diglycidyl ether of bisphenol A" has been a traditional basic active ingredient of

epoxy resins; other glycidyl ethers are frequently incorporated into epoxy resin systems as reactive diluents. The epoxy group of the glycidyl ethers reacts during the curing process and glycidyl ethers are therefore generally no longer present in completely cured products. Epoxy resins containing glycidyl ethers are used in a variety of applications including protective coatings, reinforced plastics, as well as bonding materials and adhesives.

Much occupational exposure to glycidyl ethers results from the use of proprietary or trade name products which do not disclose the presence of toxic agents in their formulations. This complicates efforts to take appropriate precautionary measures for the prevention of occupational disease. For example, unrecognized hazardous situations can occur where protective coatings containing epoxy resins are sprayed, thereby facilitating the inhalation of even non-volatile materials, and where there is skin contact with epoxy resins containing glycidyl ethers.

Data collected by the NIOSH National Occupational Hazards Survey (NOHS) have been used to estimate the number of people having potential occupational exposure to glycidyl ethers, as well as in identifying the industries in which the exposures occur. Pertinent data from NOHS are presented in Tables 1 and 2. NIOSH has previously estimated that approximately 1,000,000 workers are exposed to epoxy resins (1).

Table 1. NIOSH National Occupational Hazard Survey Estimates of Occupational Exposure to Glycidyl Ethers

Glycidyl Ether	Estimated Number of Workers Potentially Exposed*
Glycidyl Ethers**	71,000
Diglycidyl Ether of Bisphenol A	36,000
n-Butyl Glycidyl Ether	13,000
Phenyl Glycidyl Ether	8,000
Resorcinol Diglycidyl Ether	3,000
Allyl Glycidyl Ether	2,000
Octyl-Decyl Glycidyl Ether	200
Diglycidyl Ether	150
Isopropyl Glycidyl Ether	100
Triglycidyl Glycerol Ether	70

*A worker may be exposed to more than one glycidyl ether, thus the exposure estimates are not additive. Due to the difficulty of obtaining data regarding the composition of trade name products, these estimates may be low.

**Exposures were entered into the NOHS data base either under the specific glycidyl ether (when the information was available) or under the general term "glycidyl ethers" (when more specific information was not available). To the extent that an exposure to a specific glycidyl ether was reported as exposure to "glycidyl ethers," the data may underestimate occupational exposure to individual glycidyl ethers.

Table 2. Industries Where the Majority of Occupational Exposures to Glycidyl Ethers Occur*

Transportation Equipment	Stone, Clay, and Glass Products
Instruments and Related Products	Medical and Other Health Services
Chemicals and Allied Products	Fabricated Metal Products
Electrical Equipment and Supplies	Building Materials and Farm Equipment
Special Trade Contractors	Food and Kindred Products
Automotive Dealers and Service Stations	Rubber and Plastic Products
Transportation by Air	Furniture and Fixtures
Miscellaneous Repair Services	Amusement and Recreation Services
Machinery, except electrical	Leather and Leather Products
Communication	

*These are standard industrial titles from the Standard Industrial Classification Manual (2).

The National Occupational Hazard Survey, conducted between 1972 and 1974, was based on a sample of businesses selected by the Bureau of Labor Statistics and consisted of approximately 5,000 establishments employing nearly 900,000 workers in 67 standard metropolitan areas throughout the United States. This sample was representative of non-agricultural businesses covered under the Occupational Safety and Health Act of 1970.

NIOSH is not aware of any studies investigating the possible occurrence of testicular atrophy or hemopoietic abnormalities in humans exposed to glycidyl ethers. However, other effects observed in humans include dermatitis, irritation, and allergic reactions. The NIOSH glycidyl ethers criteria document (1) provides a detailed evaluative review of reported adverse effects resulting from exposure to glycidyl ethers.

LABORATORY ANIMALS — Testicular Atrophy and Hemopoietic Abnormalities

Studies in several different research laboratories indicate that some of the glycidyl ethers are capable of producing adverse effects to the testes and hemopoietic system in various species of laboratory animals. Reported testicular abnormalities (including testicular atrophy with decreased spermatogenic activity) following exposure to glycidyl ethers are presented in Table 3. Table 4 summarizes reported hemopoietic abnormalities following exposure to glycidyl ethers, including alteration of the leukocyte count, atrophy of lymphoid tissue, and bone marrow cytotoxicity. These abnormalities were usually observed along with pneumonia and/or toxemia, and therefore may be secondary effects. However, especially in light of the generalized reduction in leukocytes and the atrophy of lymphoid tissues, the observed hemopoietic abnormalities may have been predisposing factors to pneumonia. While none of the individual research reports are conclusive with respect to the ability of glycidyl ethers to produce permanent changes to the testes or hemopoietic system in laboratory animals, the pattern of effects displayed in Tables 3 and 4 is reason for concern.

The NIOSH glycidyl ethers criteria document (1) contains an evaluative review of the literature on effects of exposure to glycidyl ethers. Reported adverse effects in laboratory animals include sensitization, and skin and eye irritation, as well as mutagenic and tumorigenic activity.

Table 3. Reported Testicular Disorders Following Exposure to Glycidyl Ethers

Agent (reference)	Animal	Exposure	Reported Testicular Disorder
Allyl Glycidyl Ether (3)	Rat	400 mg/kg intramuscular injections on days 1,2,8, and 9 animals sacrificed on day 12	focal necrosis of the testis in 1 of 2 of the 3 surviving rats
n-Butyl Glycidyl Ether (4)	Rat	38 ppm, 75 ppm, 150 ppm, 300 ppm by inhalation, seven hours/day, five days/week for a total of 50 exposures	atrophic testes in 5 of 10 at 300 ppm; very small testes in 1 of 10 at 300 ppm; slight patchy atrophy of the testes in 1 of 10 animals at 75 ppm
Diglycidyl Ether (5)	Rat	125 mg/kg, 250 mg/kg cutaneous daily application, 5 days/week, total of six applications	focal necrosis of the testes
		3 ppm by inhalation 4 hours/day, 5 days/week total of 19 exposures	necrosis of the tubules of the testes in 1 of 15 animals
		0.3 ppm by inhalation, 4 hours/day, 5 days/week total of 60 exposures	poorly defined focal degeneration of the germinal epithelium in 5 of 10 animals
	Rabbit	single 24 hour inhalation exposure of 24 ppm	greatly atrophied testes in two animals which died on the evening of the fifth day
Phenyl Glycidyl Ether (6)	Rat	1.75 ppm, 5.84 ppm, 11.20 ppm by inhalation 6 hours/day for 19 consecutive days	Initial Report: focal degenerative changes involving the seminiferous tubules in both gonads in 1 of 8 at 1.75 ppm, 1 of 8 at 5.84 ppm, and 3 of 8 11.20 ppm Supplemental Examination: 1 of 8 in each of 1.75, 5.84, and 11.20 ppm groups had a marked degree of gonad change
Triethylene Glycol Diglycidyl Ether (7)	Mouse	7208 mg/kg total dose administered in 12 intraperitoneal injection, 3 per week for four weeks, animals sacrificed 39 weeks after the first injection	testular atrophy with decreased spermatogenic activity

Table 4. Reported Hemopoietic Abnormalities in Animals Following Exposure to Glycidyl Ethers

Agent (reference)	Animal	Exposure	Reported Abnormality
Allyl Glycidyl Ether (3)	Rat	400 mg/kg intramuscular injections on days 1,2,8, and 9 animals sacrificed on day 12	atrophy or loss of lymphoid tissue in 2 of 3 rats decreased leukocyte count
n-Butyl Glycidyl Ether (3)	Rat	400 mg/kg intramuscular injections for 3 consecutive days	increased leukocyte count
Butanediol Diglycidyl Ether (8)	Rat	100 mg/kg, 200 mg/kg single intraperitoneal injection	bone marrow cytotoxicity
Diethylene Glycol Diglycidyl Ether (8)	Rat	100 mg/kg, 200 mg/kg, 400 mg/kg single intraperitoneal injection	bone marrow cytotoxicity
Diglycidyl Ether (5)	Rat	single application of 0.5 g/kg, 1 g/kg to shaved backs	decreased leukocyte count
		daily skin application of 125 mg/kg, 5 days/week for 4 weeks; skin application on days 1,2,3,4,5, and 8 of 250 mg/kg, 500 mg/kg	decreased leukocyte count increase in percentage of polymorphonuclear cells
			fewer nucleated cells of the bone marrow
			enlarged myeloid cells in 250 and 500 mg/kg groups.
			lymphoid atrophy of the thymus at 500 mg/kg.
		3 ppm by inhalation, 4 hours/day, 5 days/week, total of 19 exposures	decreased leukocyte count
	Rabbit	Single application of 1.13 g/kg to shaved back	decreased leukocyte count
		Single intravenous injection of 50 mg/kg, 100 mg/kg, 200 mg/kg	decreased leukocyte count
			23 nucleated erythrocytes per 100 leukocytes in 100 mg/kg group
	Dog	25 mg/kg intravenous injection, 2 injections, six days apart, in two dogs 3 weekly injections in one dog	decreased leukocyte count
Phenyl Glycidyl Ether (3)	Rat	400 mg/kg intramuscular injections for 3 consecutive days	increased leukocyte count

NIOSH RECOMMENDATION

Reports from different laboratories present a pattern of findings indicating that some of the glycidyl ethers may be capable of producing testicular atrophy and hemopoietic abnormalities in various species of laboratory animals. While none of the individual research reports are conclusive with respect to the ability of glycidyl ethers to produce permanent changes to the testes or hemopoietic system in laboratory animals, some of the changes observed may act as predisposing factors to systemic problems. NIOSH is not aware of any studies investigating the possible occurrence of testicular atrophy or hemopoietic abnormalities in humans exposed to glycidyl ethers. The possibility of these effects occurring in humans is reason for concern. Therefore, the occupational health community is advised of the possibility of these effects appearing in workers exposed to glycidyl ethers.

The "NIOSH Criteria for a Recommended Standard . . . . Occupational Exposure to Glycidyl Ethers" was transmitted to the Occupational Safety and Health Administration (OSHA), Department of Labor, on June 30, 1978 (1). This criteria document contains detailed recommendations regarding maximum exposure levels, medical surveillance, labeling and posting, personal protective clothing and equipment, informing employees of hazards, work practices, sanitation, monitoring, and recordkeeping requirements as well as sampling and analytical procedures. Existing occupational exposure limits for specific glycidyl ethers are listed in Table 5.

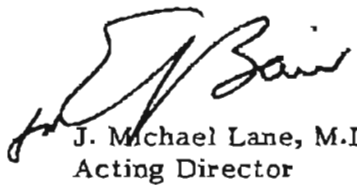
Table 5. Existing Occupational Exposure Limits for Specific Glycidyl Ethers

	Present OSHA Exposure Standard (9)				NIOSH Recommended Exposure Standard (1) (Ceiling)			
Allyl Glycidyl Ether	10	ppm	(45	mg/cu m)*	45	mg/cu m	(9.6	ppm)
n-Butyl Glycidyl Ether	50	ppm	(270	mg/cu m)**	30	mg/cu m	(5.6	ppm)
Diglycidyl Ether	0.5	ppm	(2.8	mg/cu m)*	1	mg/cu m	(0.2	ppm)
Isopropyl Glycidyl Ether	50	ppm	(240	mg/cu m)**	240	mg/cu m	(50	ppm)
Phenyl Glycidyl Ether	10	ppm	(60	mg/cu m)**	5	mg/cu m	(1	ppm)

*Ceiling
**8-hour time-weighted average

NIOSH advises strict adherence to this detailed recommended occupational standard for glycidyl ethers described in the NIOSH criteria document. Particular attention should be given to appropriate medical surveillance in order to detect testicular atrophy or hemopoietic abnormalities in exposed workers.

NIOSH requests that any information regarding testicular atrophy or hemopoietic abnormalities in workers exposed to glycidyl ethers be reported to the NIOSH Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-Wide Studies Branch, Medical Section, Telephone: (513) 684-3593.



J. Michael Lane, M.D.
Acting Director

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IDENTIFIERS AND SYNONYMS FOR ALLYL GLYCIDYL ETHER

Chemical Abstracts Service Registry Number 106-92-3
NIOSH RTECS Number RR0875000
Chemical Formula $C_6H_{10}O_2$

AGE
Allyl 2,3-Epoxypropyl Ether
Allyl Glycidyl Ether
1-Allyloxy-2,3-epoxypropane
1,2-Epoxy-3-allyoxypropane
Ether, Allyl 2,3-epoxypropyl
Glycidyl Allyl Ether
Oxirane, [(2-Propenyloxy)methyl]-
Propane, 1-(Allyloxy)-2,3-epoxy-

IDENTIFIERS AND SYNONYMS FOR n-BUTYL GLYCIDYL ETHER

Chemical Abstracts Service Registry Number 2426-08-6
NIOSH RTECS Number TX4200000
Chemical Formula $C_7H_{14}O_2$

BGE
1-Butoxy-2,3-epoxypropane
3-Butoxy-1,2-epoxypropane
Butyl Glycidyl Ether
n-Butyl Glycidyl Ether
2,3-Epoxypropyl Butyl Ether
ERL 0810
Ether, Butyl 2,3-Epoxypropyl
Ether, Butyl Glycidyl
Glycidyl Butyl Ether
Oxirane, (Butoxymethyl)-
Propane, 1-Butoxy-2,3-epoxy-

IDENTIFIERS AND SYNONYMS FOR DIGLYCIDYL ETHER

Chemical Abstracts Service Registry Number 2238-07-5
NIOSH RTECS Number KN2350000
Chemical Formula $C_6H_{10}O_3$

Bis(2,3-Epoxypropyl) Ether
DGE
Di(2,3-epoxy)propyl Ether
Diglycidyl Ether
Ether, Bis(2,3-epoxypropyl)
Ether, Diglycidyl
Glycidyl Ether
NSC 54739
Oxirane, 2,2'-[Oxybis(methylene)]bis-

IDENTIFIERS AND SYNONYMS FOR DIGLYCIDYL ETHER OF BISPHENOL A

Chemical Abstracts Service Registry Number 1675-54-3
NIOSH RTECS Number TX3800000
Chemical Formula $C_{21}H_{24}O_4$

4,4'-Bis(2,3-epoxypropoxy)diphenyldimethylmethane
2,2-Bis [p-(2,3-epoxypropoxy)phenyl]propane
2,2-Bis [4-(2,3-epoxypropoxy)phenyl]propane
Bis(4-glycidyloxyphenyl)dimethylmethane
2,2-Bis(p-glycidyloxyphenyl)propane
2,2-Bis(4-glycidyloxyphenyl)propane
Bis(4-hydroxyphenyl)dimethylmethane Diglycidyl Ether
2,2-Bis(p-hydroxyphenyl)propane Diglycidyl Ether
2,2-Bis(4-hydroxyphenyl)propane Diglycidyl Ether
Bisphenol A Diglycidyl Ether
D.E.R. 332
Dian Diglycidyl Ether
Diglycidyl Bisphenol A
Diglycidyl Bisphenol A Ether
Diglycidyl Diphenylolpropane Ether
Diglycidyl Ether of 2,2-Bis(p-hydroxyphenyl)propane
Diglycidyl Ether of 2,2-Bis(4-hydroxyphenyl)propane
Diglycidyl Ether of Bisphenol A
Diglycidyl Ether of 4,4'-Isopropylidenediphenol
4,4'-Dihydroxydiphenyldimethylmethane Diglycidyl Ether
p,p'-Dihydroxydiphenyldimethylmethane Diglycidyl Ether
Diomethane Diglycidyl Ether
EPI-REZ 510
Epoxide A
ERL-2774
4,4'-Isopropylidenebis[1-(2,3-epoxypropoxy)benzene]
4,4'-Isopropylidenediphenol Diglycidyl Ether
2,2'[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)] bisoxirane
Oxirane, 2,2'[(1-Methylethylidene)bis(4,1-phenyleneoxymethylene)] bis-
Propane, 2,2-Bis [(p-(2,3-epoxypropoxy)phenyl] -

IDENTIFIERS AND SYNONYMS FOR ISOPROPYL GLYCIDYL ETHER

Chemical Abstracts Service Registry Number 4016-14-2
NIOSH RTECS Number TZ3500000
Chemical Formula $C_6H_{12}O_2$

1,2-Epoxy-3-isopropoxypropane
Glycidyl Isopropyl Ether
IGE
3-Isopropoxy-1,2-epoxypropane
(Isopropoxymethyl)oxirane
Isopropyl Glycidyl Ether
[(1-Methylethoxy)methyl] oxirane
Oxirane, [(1-Methylethoxy)methyl]-
Propane, 1,2-Epoxy-3-isopropoxy-

IDENTIFIERS AND SYNONYMS FOR PHENYL GLYCIDYL ETHER

Chemical Abstracts Service Registry Number 122-60-1
NIOSH RTECS Number TZ3675000
Chemical Formula $C_9H_{10}O_2$

Benzene, (2,3-Epoxypropoxy)-
1,2-Epoxy-3-phenoxypropane
2,3-Epoxypropyl Phenyl Ether
2,3-Epoxypropylphenyl Ether
Ether, 2,3-Epoxypropyl Phenyl
Glycidol Phenyl Ether
Glycidyl Phenyl Ether
Oxirane, (Phenoxymethyl)-
PGE
Phenol Glycidyl Ether
1-Phenoxy-2,3-epoxypropane
3-Phenoxy-1,2-epoxypropane
3-Phenoxy-1,2-propylene Oxide
(Phenoxymethyl)oxirane
Phenoxypropene Oxide
Phenoxypropylene Oxide
γ-Phenoxypropylene Oxide
Phenyl 2,3-Epoxypropyl Ether
Phenyl Glycidyl Ether
Phenylglycidyl Ether
3-Phenyloxy-1,2-epoxypropane
Propane, 1,2-Epoxy-3-phenoxy-

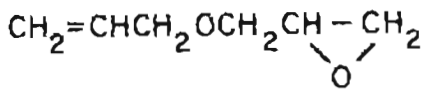
IDENTIFIERS AND SYNONYMS FOR RESORCINOL DIGLYCIDYL ETHER

Chemical Abstracts Service Registry Number 101-90-6
NIOSH RTECS Number VH1050000
Chemical Formula $C_{12}H_{14}O_4$

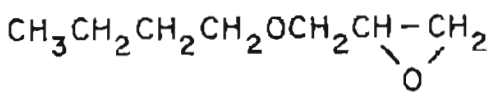
Araldite ERE 1359
Benzene, m-Bis(2,3-epoxypropoxy)-
Diglycidyl Resorcinol Ether
m-Bis(2,3-epoxypropoxy)benzene
1,3-Bis(2,3-epoxypropoxy)benzene
NCI - C54966
Oxirane, 2,2'-[1,3-Phenylenebis(oxymethylene)] bis-
2,2-[1,3-Phenylenebis(oxymethylene)]bisoxirane
RDGE
Resorcinol Bis(2,3-epoxypropyl) Ether
Resorcinol Diglycidyl Ether
Resorcinol Glycidyl Ether
Resorcinyl Diglycidyl Ether

CHEMICAL STRUCTURES OF SOME GLYCIDYL ETHERS

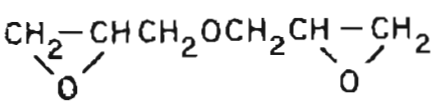
allyl glycidyl ether



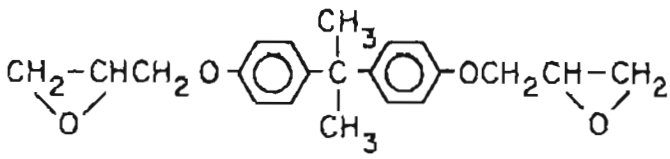
n-butyl glycidyl ether



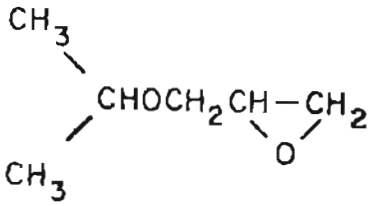
diglycidyl ether



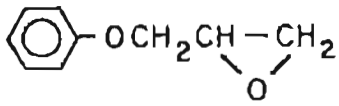
diglycidyl ether of bisphénol A



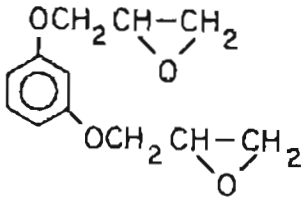
isopropyl glycidyl ether



phenyl glycidyl ether



resorcinol diglycidyl ether

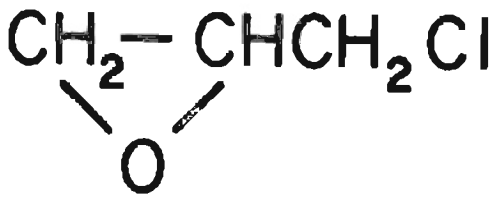


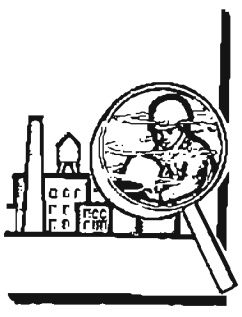
NIOSH

Current Intelligence Bulletin 30

OCTOBER 12, 1978

EPICHLOROHYDRIN





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

The NIOSH Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and supplement new information received by NIOSH on occupational hazards that are either unrecognized or are greater than generally known.

As warranted by this evaluation, the information is capsulized and disseminated to NIOSH staff, other government agencies, and the occupational health community, including labor, industry, academia, and public interest groups. With respect to currently known hazard information this system also serves to advise appropriate members of the above groups of recently acquired specific knowledge which may have an impact on their programs or perception of the hazard. Above all, the Current Intelligence System is designed to protect the health of American workers and to allow them to work in the safest possible environment.

IDENTIFIERS AND SYNONYMS FOR EPICHLOROHYDRIN ARE LISTED

IN THE REAR PORTION OF THIS BULLETIN

DHEW (NIOSH) Publication No. 79-105

CURRENT INTELLIGENCE BULLETIN

EPICHLOROHYDRIN

October 12, 1978

The National Institute for Occupational Safety and Health (NIOSH) recommends that as a prudent measure, epichlorohydrin be handled in the workplace as if it were a human carcinogen. This recommendation is based primarily on two recent studies: a long term epidemiologic study showing a significant increase in respiratory cancer deaths of exposed workers, and an inhalation study showing an increase in nasal carcinomas in rats. In addition, cytogenic studies of human peripheral lymphocytes have shown a highly significant increase in chromosome abnormalities in exposed workers. Pending further evaluation of its carcinogenic potential, NIOSH believes it would be prudent to minimize occupational exposure to epichlorohydrin.

NIOSH has prepared this Bulletin to advise you of these recent studies, their implications for occupational health, and precautions for handling products containing epichlorohydrin. We request that producers, distributors, and users transmit this information to their customers and employees, and that professional associations and unions inform their members.

EXPOSURE STANDARDS

The current Department of Labor, Occupational Safety and Health Administration (OSHA) standard for occupational exposure to epichlorohydrin is 5 ppm (19 mg/cu m) as an 8-hour time-weighted average (1). Studies of carcinogenicity were not available when this standard was developed.

In September 1976, NIOSH recommended an occupational exposure limit of 2 mg/cu m of air (approximately 0.5 ppm) determined as a time-weighted average (TWA) concentration for up to a 10 hour work day in a 40 hour work week, and a ceiling concentration standard of 19 mg/cu m (approximately 5 ppm) as determined by a sampling time of 15 minutes (2). After a comprehensive review of the literature, NIOSH concluded that risks from exposure to epichlorohydrin may include carcinogenesis, mutagenesis and sterility, as well as damage to the kidneys, liver, respiratory tract, and skin. Since most of the available evidence on adverse effects of epichlorohydrin was obtained from animal experiments which were inadequate to determine scientifically acceptable exposure limits, the 1976 NIOSH recommendation was based on professional judgement which quantitatively considered the cumulative toxic effects.

PRODUCTION, USES, AND OCCUPATIONAL EXPOSURES

Epichlorohydrin is a liquid at room temperatures. In 1978, domestic annual production capacity was 470 million pounds. An important constituent of epoxy resin is synthesized by alkylating bisphenol A with epichlorohydrin (2). Epichlorohydrin is used in the manufacture of epoxy resins, surface active agents, pharmaceuticals, insecticides, agricultural chemicals, textile chemicals, coatings, adhesives, ion-exchange resins, solvents, plasticizers, glycidyl esters, ethynylethylenic alcohol and fatty acid derivatives.

According to the NIOSH National Occupational Hazard Survey (NOHS) (3), an estimated 85,000 workers are potentially exposed to epichlorohydrin in the workplace. Table 1 lists occupations and industries in which a potential exists for exposure to epichlorohydrin. The NOHS survey data were collected during 1972 to 1974 from a sample of approximately 5,000 businesses employing nearly 900,000 workers. 1970 Census figures were used in extrapolating the sample data to the working population employed in industries covered by the Occupational Safety and Health Act of 1970. The potential exposure estimates include data on actual observations of the use of the specific chemical or the use of a trade name product known to contain the chemical as well as additional observations of generic formulations (trade name products suspected of containing the chemical).

Table 1. Some Occupations and Industries Which Use Epichlorohydrin

Occupations[a]	assemblers; miscellaneous specified machine operatives; aircraft machinists; construction and maintanance painters; miscellaneous operatives; chemists; mining operatives; painters of manufactured articles; sheetmetal workers and tinsmiths; pattern and model makers, except paper
Industries[b]	chemicals and allied products; transportation equipment; instruments and related products; transportation by air; electrical equipment and supplies; special trade contractors; miscellaneous repair services; rubber and plastics not elsewhere classified; machinery, except electrical; stone, clay, and glass products

(a) Standard occupational titles from the Bureau of the Census (4)
(b) Standard industrial titles from the Standard Industrial Classification Manual (5).

HUMAN CARCINOGENICITY

A statistically significant ($p < .05$) increase in deaths due to respiratory cancer has been observed in a long-term epidemiologic study conducted on workers exposed to epichlorohydrin at two facilities of the Shell Chemical Company (6). The data were analyzed by Dr. Philip Enterline of the University of Pittsburgh (7, 8). There were

864 workers identified as having been occupationally exposed to epichlorohydrin for 6 months or more, before January 1, 1966. Ninety-eight percent of the workers were traced as of December 31, 1976. For men estimated to have had moderate to heavy exposure who were followed for 15 years or more, observed deaths were also greater than those expected for the categories of all cancers, leukemia, and suicide, although those differences were not statistically significant. Information was not available for most workers on smoking history, or the extent of exposure to other chemicals (9). NIOSH feels that the study results are suggestive of a carcinogenic effect of epichlorohydrin on humans, and deserve attention.

The Dow Chemical Company has informed NIOSH that it is currently conducting a mortality study of workers engaged in the manufacture and conversion of epichlorohydrin (10). Dow estimates that the results will be made available November, 1978.

ANIMAL CARCINOGENICITY

In ongoing inhalation studies, rats exposed to epichlorohydrin have shown a statistically significant increase in nasal cancer ($p < .05$) (11). In experiments initiated under Dr. Sidney Laskin and continued under Dr. Norton Nelson at the New York University Institute of Environmental Medicine, 140 rats have been exposed to 100 ppm epichlorohydrin for 6 hours/day, 5 days/week, for 30 days, with subsequent lifetime observation. Fifteen of the animals have died with pathologically confirmed squamous cell nasal cancinoma (11). Another animal developed a nasal papilloma. No spontaneous nasal cancer was seen in a group of 50 controls. Of another group of 100 animals exposed to 30 ppm of epichlorohydrin for 6 hours/day, 5 days/week, in a chronic lifetime study one animal has developed a papilloma of the larynx, another has developed a nasal squamous cell carcinoma (12). In contrast, no spontaneous nasal carcinomas were seen in the 50 animal control group.

Further information on previous studies that investigated the other evidence relating to carcinogenicity of epichlorohydrin can be found in the NIOSH epichlorohydrin criteria document (2, 13).

HUMAN MUTAGENICITY

Epichlorohydrin has been shown to induce a significant increase in chromosomal aberrations found in the white blood cells of workers occupationally exposed to epichlorohydrin. In 1977, Kucerova et al. (14) conducted a prospective cytogenetic study of 35 workers occupationally exposed to epichlorohydrin. Each worker served as his own control. After exposure for one year, these workers showed a significant increase in chromosomal aberrations. After two years of exposure to epichlorohydrin, the increase in chromosomal aberrations was significant at the $p < .0001$ level.

In 1976, Sram et al. (15) found chromosome abnormalities in human peripheral lymphocytes exposed in vitro to epichlorohydrin. They concluded that a genetic risk for man exists following exposure to epichlorohydrin. A quantitative risk was not estimated.

OTHER TOXIC EFFECTS

Epichlorohydrin is a highly toxic substance which is easily absorbed through the skin. Skin contact with epichlorohydrin can cause severe chemical burns, although the effects may not appear until sometime after exposure. The latent period can range from several minutes to several days, depending on the duration and intensity of exposure. Allergic response has been noted (16). Exposure to epichlorohydrin vapor induces transient burning of the eyes and nasal passages at concentrations as low as 20 ppm. Exposure to high concentrations (100 ppm) leads to pulmonary edema (fluid accumulation in the lung) and kidney problems in laboratory animals. A comprehensive discussion of the toxic effects is found in the NIOSH epichlorohydrin criteria document (2). Table 2 summarizes the reported toxic effects in humans at varying exposure levels.

Table 2. Other Toxic Effects of Epichlorohydrin on Humans (2).

Route of Exposure	Effect
dermal	burning sensation, redness, swelling, red papules, itching, blisters, skin erosion, enlarged lymph nodes
inhalation	burning of the eyes, nose and throat; cough; chest congestion; running nose; eye tenderness; headache followed by nausea; vomiting; facial swelling; dyspnea

Exposure to epichlorohydrin has been shown to induce sterility in rats (2), and a fertility study has been conducted in male workers exposed to epichlorohydrin (17). While the study concluded that exposure to epichlorohydrin did not decrease sperm counts or affect hormonal activity in the workers, the data were not analyzed statistically.

NIOSH RECOMMENDATIONS

In light of the statistically significant increase in respiratory cancer seen in workers exposed to epichlorohydrin, and the statistically significant increase in nasal carcinomas seen in rat inhalation studies, as well as the chromosomal aberrations seen in the peripheral lymphocytes of exposed workers, NIOSH recommends that epichlorohydrin be treated in the workplace as if it were a human carcinogen. Pending further evaluation of its carcinogenic potential, NIOSH believes it would be prudent to minimize occupational exposure to epichlorohydrin. Exposures should be limited to as few employees as possible while workplace exposure should be minimized with engineering and work practice controls. In particular, skin exposure should be avoided.

J. Michael Lane, M.D.
Acting Director

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SUGGESTED GUIDELINES FOR MONITORING AND CONTROLLING EMPLOYEE EXPOSURE TO EPICHLOROHYDRIN

NIOSH recommends that it would be prudent to handle epichlorohydrin in the workplace as if it were a human carcinogen. Exposure to epichlorohydrin should be limited to as few employees as possible, and workplace exposure levels should be minimized. The area in which it is used should be restricted to only those employees essential to the process or operation and these employees should be adequately protected.

EXPOSURE MONITORING

A detailed sampling, and analytical method for epichlorohydrin exposure measurements is described in the NIOSH Manual of Analytical Methods, Second Edition (1) as NIOSH method #S118 in Volume 2.

Initial and routine employee exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to determine the extent of employee exposure and to ensure that controls are effective.

The NIOSH Occupational Exposure Sampling Strategy Manual (2), may be helpful in developing efficient programs to monitor employee exposures to epichlorohydrin. The manual discusses determination of the need for exposure measurements, selection of appropriate employees for exposure evaluation and selection of sampling times.

Employee exposure measurements should primarily consist of 8-hour TWA (time-weighted average) exposure estimates calculated from personal or breathing zone samples (air that would most nearly represent that inhaled by the employees). In addition, short term samples should be taken during periods of maximum expected exposure by using all available knowledge regarding the area, employee work procedures, and process. Area and source measurements may be useful to determine problem areas, processes, and operations.

CONTROLLING EMPLOYEE EXPOSURE

There are four basic methods of limiting employee exposure to epichlorohydrin. None of these is a simple industrial hygiene or management decision and careful planning and thought should be used prior to implementation.

o Product Substitution

The substitution of an alternative material with a lower potential health risk is one method. However, extreme care must be used when selecting possible substitutes. Alternatives to epichlorohydrin should be fully evaluated with regard to possible human effects. Unless the toxic effects of the alternative have been thoroughly evaluated a seemingly safe replacement, possibly only after years of use, may be found to induce serious health effects.

o Contaminant Controls

The most effective control of epichlorohydrin where feasible, is at the source of contamination by enclosure of the operation and/or local exhaust ventilation. Guidelines for selected processes and operations can be found in the NIOSH Recommended Industrial Ventilation Guidelines (3).

If feasible, the process or operation should be enclosed with a slight vacuum so that any leakage will result in the flow of external air into the enclosure.

The next most effective means of control would be a well designed local exhaust ventilation system that physically encloses the process as much as possible, with sufficient capture velocity to keep the contaminant from entering the work atmosphere.

To ensure that ventilation equipment is working properly, effectiveness (e.g., air velocity, static pressure, or air volume) should be checked at least every three months. System effectiveness should be checked soon after any change in production, process, or control which might result in significant increases in airborne exposure to epichlorohydrin.

o Employee Isolation

A third alternative is the isolation of employees. It frequently involves the use of automated equipment operated by personnel observing from a closed control booth or room. The control room is maintained at a greater air pressure than that surrounding the process equipment so that air flow is out of, rather than into, the room. This type of control will not protect those employees that must do process checks, adjustments, maintenance, and related operations.

o Personal Protective Equipment

The least preferred method is the use of personal protective equipment. This equipment, which may include respirators, goggles, gloves, etc., should not be used as the only means to prevent or minimize exposure during routine operations.

Exposure to epichlorohydrin should not be controlled with the use of respirators except:

— During the time period necessary to install or implement engineering or work practice controls; or

-- In work situations in which engineering and work practice controls are technically not feasible; or

— For maintenance; or

-- For operations which require entry into tanks or closed vessels; or

-- In emergencies.

Only respirators approved by the National Institute for Occupational Safety and Health (NIOSH) under the provisions of Federal regulations 30 CFR 11 should be used. Refer to Cumulative Supplement June 1977, NIOSH Certified Equipment (4) for a listing of NIOSH-approved respirators. Note that the use of faceseal coverlets or socks with respirators voids NIOSH approvals.

Quantitative faceseal fit test equipment (such as sodium chloride, dioctyl phthalate, or equivalent) should be used. Refer to NIOSH's A Guide to Industrial Respiratory Protection (5) for guidelines on appropriate respiratory protection programs.

In addition, proper maintenance procedures, good housekeeping in the work area, and employee education are all vital aspects of a good control program. Employees should be informed as to the nature of the hazard, its control, and appropriate personal hygiene procedures.

REFERENCES FOR SUGGESTED GUIDELINES

1) NIOSH Manual of Analytical Methods, 2nd Edition, Vol. 1: GPO #017-033-00267-3, $8.75: Vol. 2: GPO #017-033-00260-6, $9.75: Vol. 3: GPO #017-033-0247-9, $9.00.

2) NIOSH Occupational Exposure Sampling Strategy Manual, GPO #017-033-00247-9, $2.75.

3) NIOSH Recommended Industrial Ventilation Guidelines, GPO #017-033-00136-7, $3.90.

4) NIOSH Cumulative Supplement June 1977, NIOSH Certified Equipment, NIOSH # 77-195, no charge.

5) A Guide to Industrial Respiratory Protection, GPO #017-033-00153-7, $2.30.

GPO publications must be ordered from:

Superintendent of Documents
U.S. Government Printing Office
Washington, D.C. 20402

Reference #4 can be ordered from:

Publications Dissemination, DTS
NIOSH
4676 Columbia Parkway
Cincinnati, Ohio 45226

IDENTIFIERS AND SYNONYMS FOR EPICHLOROHYDRIN

Chemical Abstracts Service Registry Number: 106-89-8
NIOSH RTECS Number: TX4900000
Chemical Formula: C_3H_5OCl

1-Chloro-2,3-epoxypropane
3-Chloro-1,2-epoxypropane
3-Chloro-1,2-propylene oxide
(Chloromethyl)ethylene oxide
(Chloromethyl)oxirane
2-Chloromethyl oxyrane
3-Chloropropene-1,2-oxide
Chloropropylene oxide
γ-Chloropropylene oxide
ECH
ECHH
Epichlorohydrin
α-Epichlorohydrin
1,2-Epoxy-3-chloropropane
2,3-Epoxypropyl chloride
Glycerol epichlorohydrin
Glycidyl chloride
Oxirane, (chloromethyl)-
Oxirane, 2-(Chloromethyl)-
Propane, 1-chloro-2,3-epoxy-
SKEKhG

CUMMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

1.	Chloroprene	- January 20, 1975
2.	Trichloroethylene (TCE)	- June 6, 1975
3.	Ethylene Dibromide (EDB)	- July 7, 1975
4.	Chrome Pigment	- June 24, 1975 - October 7, 1975 - October 8, 1976
5.	Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies	- August 8, 1975
6.	Hexamethylphosphoric Triamide (HMPA)	- October 24, 1975
7.	Polychlorinated Biphenyls (PCBs)	- November 3, 1975 - August 20, 1976
8.	4,4'-Diaminodiphenylmethane (DDM)	- January 30, 1976
9.	Chloroform	- March 15, 1976
10.	Radon Daughters	- May 11, 1976
11.	Dimethylcarbamoyl Chloride (DECC) Revised	- July 7, 1976
12.	Diethylcarbamoyl Chloride (DECC)	- July 7, 1976
13.	Explosive Azide Hazard	- August 16, 1976
14.	Inorganic Arsenic - Respiratory Protection	- September 27,1976
15.	Nitrosamines in Cutting Fluids	- October 6, 1976
16.	Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine	- December 17,1979
17.	2-Nitropropane	- April 25, 1977
18.	Acrylonitrile	- July 1, 1977
19.	2,4-Diaminoanisole in Hair and Fur Dyes	- January 13, 1978
20.	Tetrachloroethylene (Perchloroethylene)	- January 20, 1978
21.	Trimellitic Anhydride (TMA)	- February 3, 1978
22.	Ethylene Thiourea (ETU)	- April 11, 1978
23.	Ethylene Dibromide and Disulfiram Toxic Interaction	- April 11, 1978
24.	Direct Black 38, Direct Blue 6, and Direct Brown 95 Benzidine Derived Dyes	- April 17, 1978
25.	Ethylene Dichloride (1,2-Dichloroethane)	- April 19, 1978
26.	NIAX® Catalyst ESN	- May 22, 1978
27.	Chloroethanes - Review of Toxicity	- August 21, 1978
28.	Vinyl Halides - Carcinogenicity	- September 21,1978
29.	Glycidyl Ethers	- October 12, 1978
30.	Epichlorohydrin	- October 12, 1978

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