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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 1 thru 18

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

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

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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 20 Current Intelligence Bulletins have been issued as part of the information dissemination process. The first 18 Bulletins have been reprinted in this publication for the convenience of those who would like a complete series of Bulletins for reference purposes. 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 has since issued Criteria Documents with recommended occupational health standards.

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Current Intelligence Bulletin 1

January 20, 1975

CHLOROPRENE

CHLOROPRENE

Introduction

In a letter to Mr. Edward J. Baier, Acting Director, NIOSH, dated December 16, 1974, Dr. John A. Zapp, Director, Haskell Laboratory, E.I. du Pont de Nemours and Company (Du Pont), Wilmington, Delaware, expressed concern over the potential carcinogencity of chloroprene (2-chlorobutadiene). Du Pont had begun looking closely at this substance recently because of the similarity in chemical structure with vinyl chloride. Du Pont has utilized chloroprene in the production of neoprene (polychloroprene) since 1931.

In the course of a literature search on chloroprene toxicity, Du Pont uncovered two recent Russian articles that suggest an increased incidence of skin and lung cancer in workers exposed to chloroprene. Also, two other articles in the Russian literature were located that described animal experiments in which chloroprene adversely affected embryo development in rats and mice.

Du Pont has informed its employees of the Russian reports and has alerted its customers to the possibility of "escaping chloroprene" during the processing of neoprene. The Company is conducting epidemiological studies in humans and animals to ascertain the carcinogenic potential of chloroprene.

Background Information

Chloroprene is a colorless liquid that is slightly soluble in water. It is soluble in alcohol and diethyl ether, and has a vapor density of 3.0, three times that of air, with a boiling point of 59.4°C. Chloroprene is used as a chemical intermediate largely as a monomer for the manufacture of a synthetic rubber.[1] It is a chlorine-substituted derivative of 1,3-butadiene. Chloroprene can polymerize spontaneously at room temperature, the process being catalyzed by light, peroxides and other free radical initiators. It can also react with oxygen to form polymeric peroxides. Because of its instability, flammability, and toxicity, chloroprene has no end product uses. It is produced in large quantities mainly for polymerization and marketing under the trade name of Neoprene.[2]

Neoprene was developed in the U.S. by Carothers[3] and was originally introduced by Du Pont in 1931 under the brand name Duprene.[4] Although during recent years other suppliers have come on the market with their own brand name, neoprene is generally used as a generic name for polychloroprene rubbers.

Neoprene is obtained by emulsion polymerization of chloroprene (2-chlorobutadiene) and consists mainly of 1,4-transpolychloroprene. There are two main classes, the sulfur modified type and the nonsulfur modified type, indicating the differences in polymerization techniques. Several subtypes of both are available, differing in viscosity and crystalization rate.[4]

Neoprene's most valuable properties are its resistance to weathering and oil. It is also resistant to abrasion, heat, flame, oxygen, ozone, and solvents. The main applications of neoprene are in high performance articles such as cable sheaths, hoses, fabrics, adhesives, and a large number of technical rubber articles. The automotive industry is the largest consumer of neoprene.

Toxicity

Human:

The primary responses to chloroprene appear to be central nervous system depression and significant injury to lungs, liver, and kidneys.[1] Humans exposed to chloroprene have been reported to develop dermatitis, conjunctivitis, corneal necrosis, anemia, temporary loss of hair, nervousness, and irritability.[6]

Two Russian reports suggest that chloroprene exposure is associated with an increased incidence of skin and lung cancer.[7,8] These studies concern a large-scale epidemiological investigation of industrial workers in the Yerevan region of Russia. During the period 1956-1970, 137 cases of skin cancer were discovered through examination of 24,989 persons over age 25. The population was subdivided into five subgroups according to the character of their employment:

Group I: Persons who never worked in industrial plants

Group II: Persons working in nonchemical industries

Group III: Persons with extended work experience in chloroprene production

Group IV: Persons working in industries using chloroprene derivatives

Group V: Persons working with chemicals unrelated to chloroprene

The following table depicts the results of the study:

	Exposure Group				
	I	II	III	IV	V
Number examined	8520	8755	684	2250	4780
Number of cases	11	35	21	38	32
Percent	0.12	0.40	3.00	1.60	0.66
Average age of cases	72.1	68.9	59.6	59.1	64.4
Average duration of employment for cases (in years)	16.3	15.4	9.5	8.7	13.8

As can be seen from the table, the incidence of skin cancer was greatest in the chloroprene exposed group, and was substantially greater than that for the three unexposed groups. Persons exposed only to chloroprene derivatives also showed an increased incidence of skin cancer. A gradient in the skin cancer incidence is seen among the five groups reflecting the potential for exposure to toxic chemicals in the work environment The average age of the cases in both the chloroprene and chloroprene derivative groups was significantly less than that for the other groups. The average duration of employment was much shorter for the chloroprene and chloroprene derivative groups than for the other nonexposed groups. The investigators concluded that development of chloroprene-induced skin cancer is preceded by chronic dystrophic and inflammatory skin ailments which are caused by the binding of chloroprene to the free SH groups in the cells, with the formation of RS-CH compound types.

The incidence of lung cancer among 19,979 workers in the same region was also studied. During the period 1956-1970, 87 cases of lung cancer were identified from the records of the local oncology department. The population was subdivided into four subgroups according to type of employment:

Group I: Workers who had extended contact with chloroprene and/or its derivatives

Group II: The first "control group" consisting of truck drivers, polishers, cabinet makers, stokers, gasoline station attendants, typesetters, painters, and others

Group III: The second "control group" consisting mainly of electricians, carpenters, joiners, arc welders, tinsmiths, furnace workers, etc.

Group IV: The third "control group" consisting of persons who worked in professional occupations

The following table summarizes the results of the analysis:

	Exposure Group			
	I	II	III	IV
Number at risk	2934	4780	6045	6220
Number of cases	34	22	11	4
Percent	1.16	0.46	0.18	.064
Average age of cases	44.5	54.9	59.3	60.2
Average duration of employment for cases (in years)	8.7	10.3	19.9	18.5

As can be seen from the table, the group with exposure to chloroprene or its derivatives experienced the highest incidence of lung cancer. A gradient in the lung cancer incidence is seen according to exposure group which reflects (roughly) the potential for exposure to toxic chemicals in the work environment. As with the results for skin cancer, the average age and duration of employment for the cases in the chloroprene exposure group is substantially less than for the nonchloroprene control groups. It is interesting to note that the average age of the lung cancer cases in the chloroprene group (44.5) is significantly less than the average age of the skin cancer cases in the same group (about 59).

The authors note that the magnitude of the lung cancer risk in chloroprene-exposed workers is about the same as for chromate workers in the same district.

Of the 34 cases of lung cancer in workers exposed to chloroprene or its derivatives, 18 were among persons having direct and prolonged exposure to the chloroprene monomer. The remaining 16 cases were persons whose exposure was to chloroprene latexes. If this breakdown is applied to the two chloroprene subgroups shown in the skin cancer table (Groups III & IV), the lung cancer rates would be 2.6 (18÷684) for the group with exposure to chloroprene monomer and 0.7 (16÷2,250) for the group exposed to chloroprene latexes. This difference presumably reflects the gradient in total amount of exposure to chloroprene.

Animal:

Animal experiments have shown that a concentration of 250 ppm in air is toxic and a concentration of 75 ppm may be toxic with continued exposure. Exposure to vapor first causes irritation of the respiratory tract, followed by depression of respiration and, if exposure is continued, asphyxia. The vapor is a central nervous system depressant.

It causes severe degenerative changes in the vital organs, particularly the liver and kidneys. In addition, blood pressure is lowered and lung changes accompany exposure, especially at the higher concentrations.[6]

Chloroprene has caused hyperplasia of lymph nodes and a decrease in the number of lymphocytes in rats.[9] During acute and chronic chloroprene exposure, changes in adrenal gland function have also been noted.[10]

Even in low concentrations, chloroprene affects male reproductive organs causing degenerative changes resulting in reproduction interferences. Male reproductive organs appear to be more susceptible to the effect of chloroprene than female.[11]

Chloroprene has an effect on embryogenesis. In rats and mice, it causes an increase in the total embryonal mortality and reduction in the fetal weight of offspring of females exposed during pregnancy.[12,13]

Permissible Occupational Exposures

The American Conference of Governmental Industrial Hygienists established the threshold limit of chloroprene at 25 ppm (90 mg/m^3).[14] This level was based on the work of Cook[15] and Von Oettingen,[11] and is the current Occupational Safety and Health Administration, Department of Labor standard.

Priority List Status

Chloroprene is listed as number 412 on the NIOSH Priority List for Criteria Development for Toxic Substances and Physical Agents. An estimated 2,500 workers are exposed to chloroprene in the United States. The severity rating for chloroprene is 325 on a scale of 0 to 6,000.

Producers and Supplers

The following is a list of the major producers and suppliers of chloroprene and neoprene in the U.S.:

Chloroprene

	Location
Dupont	Victoria, Texas Laplace, Louisiana
Petro-tex Chemical Corp.	
Petro-tex Chemical Subsid.	Houston, Texas

Neoprene

	Location
Dupont	Laplace, Louisiana Louisville, Kentucky Montague, Michigan*
Petro-tex Chemical Corp. Petro-tex Chemical Subsid.	Houston, Texas

*Shut Down in 1972

Source: Adapted from 1974 Directory of Chemical Producers, USA, Stanford Research Institute, Menlo Park, California, 1974.

Annual production figures for chloroprene are not available. Following are the annual figures for neoprene:

Year	Neoprene Production (millions of pounds)
1968	340
1969	350
1970	325
1971	340
1972	370
1973	385

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Current Intelligence Bulletin 2

June 6, 1975

TRICHLOROETHYLENE (TCE)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

June 6, 1975

Dear Colleague:

The attached background material on trichloroethylene has been prepared by the Office of Occupational Health Surveillance and Biometrics, National Institute for Occupational Safety and Health, to alert members of the occupational health community to new information on a potential occupational hazard.

Your comments and suggestions for changes to future reports are solicited.

J. William Lloyd, Sc.D.
Director
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Surveillance and Biometrics

Attachment

TRICHLOROETHYLENE

Summary

Preliminary evaluation of the carcinogenic activity of trichloroethylene in laboratory rodents by the National Cancer Institute indicates that this material is a potent liver carcinogen. Trichloroethylene is a significant commerical product with a wide variety of industrial uses. In light of the potential risks of human exposure in the work environment, the National Institute for Occupational Safety and Health (NIOSH) is alerting the occupational health community to these findings. Additional animal studies as well as detailed epidemiologic investigations are anticipated.

Introduction

On March 21, 1975, the Associate Director for Carcinogenesis of the National Cancer Institute (NCI) informed the DHEW Committee to Coordinate Toxicology and Related Programs of the possible carcinogenicity of trichloroethylene. Subsequently, the National Institute for Occupational Safety and Health was informed by the NCI that an unusual incidence of hepatocellular carcinomas was observed in mice given trichloroethylene by gastric intubation. Requests for more detailed information on these findings should be directed to the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis, DCCP, National Cancer Institute, Bethesda, Maryland 20014. Because of the extensive use of trichloroethylene in the work environment and the potential for cancer induction in humans, NIOSH is alerting the occupational health community as an integral part of its current intelligence system.

Background Information

Trichloroethylene (TCE) is a colorless, volatile, nonflammable liquid that is immiscible in water with a vapor density of 4.45 and a boiling point of 87°C. It is miscible with alcohol, chloroform, and ether, and dissolves most fixed and volatile oils.

Trichloroethylene has a powerful solvent action for fats, greases, and waxes, and it is one of the most important chlorinated solvents for use in degreasing and drycleaning. Over 90 percent of TCE is consumed by the metal degreasing and drycleaning trades.(1) It is also used as an ingredient in printing inks, paints, lacquers, varnishes, and adhesives.(2) Trichloroethylene is used in minor quantities in a number of miscellaneous commercial products.(4)

A pharmaceutical grade of trichloroethylene is used as a general anesthetic in surgical and obstetrical procedures and as an analgesic in the treatment of trigeminal neuralgia.(3) TCE also has been used as an analgesic in dentistry for extractions, incisions of furuncles, and other short operative procedures.(4) In addition, TCE is used in the extraction caffeine for decaffeinated coffee.

Trichloroethylene was first produced in 1864 by Fischer, but did not not receive much attention as a potential chemical product until the early 1900's. It has been produced in the United States since 1925.(1) Trichloroethylene is produced from acetylene and ethylene; however, the amount produced from acetylene has been steadily declining. It is estimated that 85 percent of TCE was produced from acetylene in 1967 as compared with 51 percent in 1971.

Toxicity

Human:

The predominant physiological response is one of central nervous system depression. This is particularly true as a response from acute exposure. Visual disturbances, mental confusion, fatigue, and sometimes nausea and vomiting have been observed. The dangers of acute exposure to trichloroethylene may be accentuated by visual disturbances and incoordination, which may lead to poor manual manipulation and, therefore, unsafe mechanical operation.(6)

Prolonged skin contact may cause local irritation and blister formation and, under industrial conditions, intermittent, repeated immersion of the hands in TCE has caused paralysis of the fingers.(7) While TCE will penetrate the intact skin, it is considered unlikely that absorption of toxic quantities would occur by this route.(8)

Trichloroethylene is absorbed readily from the gastrointestinal tract, leading to respiratory failure or cardiac arrest causing death. Depending on the dose, signs and symptoms of toxicity may be delayed for several hours.(4)

Anesthetic doses frequently cause tachycardia or bradycardia and tachypnea. Cardiac arrhythmias are common but convulsions are rare.(4) Trichloroethylene, when inhaled by pregnant women, diffuses rapidly across the placenta.(9)

Deliberate inhalation of moderate concentrations of TCE induces a state of euphoria which has led to addiction.(1)(10) Sniffing commercial products containing TCE is a method for getting "high" among adolescents.(11)(12) The disappearance of disorientation, visual hallucinations, delusions, and other psychotic symptoms coincides with a fall in urinary levels of trichloroethylene metabolites.(10) It has been reported that the administration of glucose or insulin increases the amount and speed of excretion of metabolites of TCE.(13) Liver and kidney injuries attributed to overexposure to TCE are considered rare.(14) However, severe injuries to both the liver and kidneys have been reported.(1)

To date there have been no published reports of any association between TCE and cancer in humans.

(13)

Animal:

Clinical experience from acute exposure in animals has come mainly from the use of TCE as an anesthetic. TCE has been used as an inhalation anesthetic for a variety of animals. It has also been used as a disinfectant and detergent for the skin, minor wounds, and surgical instruments.(4)

Death in laboratory animals from an acute exposure to TCE vapor may result from respiratory failure or cardiac arrest.(6)(15) Trichloroethylene is reported to have direct action on the bone marrow of rabbits causing myelotoxic anemia.(16) It causes residual brain damage in rats(17), and produces liver and kidney changes and growth depression in a variety of laboratory animals.(6)

The National Cancer Institute (NCI) tested trichloroethylene by gastric intubation in both sexes of Osborne Mendel rats and B6C3F mice. Two dose levels were given in each animal group, five times weekly. Both sexes of rats were given either 1000 mg/kg or 500 mg/kg doses. Male mice were given 2400 mg/kg or 1200 mg/kg doses; female mice were given 1800 mg/kg or 900 mg/kg doses. No hepatocellular carcinomas were seen in the rats; 30 of 98 (30.6%) of the mice given the low dose, and 41 of 95 (43.2%) of the mice given the higher dose had hepatocellular carcinomas. Only one of 40 (2.5%) control mice developed these carcinomas.*

It should be noted that the National Cancer Institute information is the first report associating TCE with cancer in animals.

Permissible Occupational Exposures

The current Occupational Safety and Health Administration, Department of Labor standard for trichloroethylene is 100 ppm (525 mg/m^3) and is based on the threshold limit value established by the American Conference of Governmental Industrial Hygienists.(18)

On July 23, 1973, the National Institute for Occupational Safety and Health transmitted criteria for a recommended standard on trichloroethylene to the Department of Labor.

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*Unpublished preliminary report issued by the National Cancer Institute, 1975. Requests for further information should be directed to the National Cancer Institute, Bethesda, Maryland.

Producers and Suppliers

The following is a list of the major producers and suppliers of trichloroethylene in the United States:

Company	Location
Diamond Shamrock Corp. Electro Chems. Div.	Deer Park, Texas
Dow Chemical U.S.A.	Freeport, Texas
Ethyl Corp.	Baton Rouge, Louisiana
Occidental Petroleum Corp. Hooker Chem. Corp., subsid. Electrochemical & Specialities Div.	Taft, Louisiana
PPG Indust., Inc. Chem. Div. Indust. Chem. Div.	Lake Charles, Louisiana

Source: Adapted from the 1974 Directory of Chemical Producers, USA, Stanford Research Institute, Menlo Park, California, 1974

Occupational Exposure

Estimated Number of Workers Exposed to Trichloroethylene by Industry

Industry	Estimated Number Exposed*
Agricultural Services	124
Oil and Gas Extraction	267
Ordnance	57
Food Products	2,502
Textile Mill Products	1,014
Apparel/Textile Products	858
Lumber Products	72
Furniture Manufacturing	162
Paper Products Manufacturing	2,240
Printing Trades	2,876
Chemical Manufacturing	9,552
Petroleum Products	713
Rubber - Plastics Manufacturing	4,985
Leather Products	725
Stone/Clay Products	2,685
Primary Steel Manufacturing	11,672
Metal Fabrication	11,709
Machinery Manufacturing	7,481
Electrical Equipment	66,727
Transportation Equipment	54,174
Instrument Manufacturing	4,815
Miscellaneous Manufacturing	1,516
Trucking/Warehousing	642
Air Transportation	23
Communication	5,560
Wholesale Trade	3,327
Automotive Dealer	223
Furniture Stores	597
Banking	2,391
Personal Services	583
Miscellaneous Business Services	27,759
Auto Repair	5,246
Miscellaneous Repair	17,198
Amusement Services	7,987
Mechanical Services	20,053
Miscellaneous	4,138
Estimated Total	282,653

*Projections based on preliminary data obtained from the National Occupational Hazard Survey, Hazard Surveillance Branch, Office of Occupational Health Surveillance and Biometrics, NIOSH. (Does not include anesthetic use or use in tradename products).

Anesthesia Survey

It is estimated that approximately 5,000 medical, dental, and hospital personnel are routinely exposed to trichloroethylene as an anesthetic gas.*

Epidemiologic Studies

The Division of Field Studies and Clinical Investigations, NIOSH, is attempting to identify human populations at risk of trichloroethylene exposures for epidemiologic study.

*The 1974 Hospital Inhalation Producer Survey, conducted by the Division of Field Studies and Clinical Investigations, NIOSH, and a personal communication from a representative of the American Dental Association, 1975.

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Current Intelligence Bulletin 3

July 7, 1975

ETHYLENE DIBROMIDE (EDB)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

July 7, 1975

Dear Colleague:

The attached background material on ethylene dibromide has been prepared by the Office of Occupational Health Surveillance and Biometrics, National Institute for Occupational Safety and Health, to alert members of the occupational health community to new information on a potential occupational hazard.

Your comments and suggestions for changes to future reports are solicited.

Sincerely yours,

J. William Lloyd, Sc.D.
Director
Office of Occupational Health
Surveillance and Biometrics

Attachment

ETHYLENE DIBROMIDE

Summary

A preliminary report from the National Cancer Institute (NCI) indicates that ethylene dibromide (EDB) is carcinogenic in laboratory rodents. Ethylene dibromide is a synthetic organic chemical with several industrial uses. Because of the potential risk of exposure in the work environment, the National Institute for Occupational Safety and Health (NIOSH) is alerting the occupational health community to these findings.

Introduction

In a memorandum of alert dated October 16, 1974, the Associate Director for Carcinogenesis of the National Cancer Institute (NCI) informed the DHEW Committee to Coordinate Toxicology and Related Programs of the possible carcinogenicity of ethylene dibromide. Subsequently, NIOSH was informed by the NCI of the preliminary findings in bioassay which suggest a strong carcinogenic activity of ethylene dibromide in both rats and mice producing squamous cell carcinomas of the stomach.

Background

Ethylene dibromide* is a colorless, heavy, nonflammable liquid with a sweet odor. The odor is detectable at 10 ppm.(1) It is slightly soluble in water and miscible with most solvents. It has a vapor pressure of 17.4 mm and a boiling point of 131°C.(2)

In 1921, the antiknock properties of tetra-alkyl lead compounds were discovered. To prevent the deposition of lead, a substance capable of reacting with the lead to aid its removal from the engine cylinder was needed. Ethylene dibromide was found to be such a substance. Today, the primary uses of EDB are in antiknock compounds for gasoline and in fumigants for grains, fruits, and vegetables. It is also used as a soil fumigant for the control of nematodes. It is used less frequently in fire extinguishers, gauge fluids, and as a special solvent and catalyst in organic synthesis.(3,4) About 300 million pounds are produced annually in this country. Approximately 50 percent of this is used in fuel additives(6); much of the remainder is used in fumigants. When commercially fumigated grains were sampled from storage bins and analyzed for residues of organic fumigants, EDB was found in a range less than 0.01 to 6.10 ppm. The lower volatility of EDB resulted in disproportionally higher residues relative to other commonly used, more volatile compounds.(7)

Ethylene dibromide is strongly absorbed by wheat and wheat products. There is very little decomposition of the EDB or reaction with these materials at ordinary temperatures. On heating, a substantial proportion of the absorbed EDB undergoes decomposition to ethylene glycol and inorganic bromide.(8)

*Synonyms: 1,2 dibromoethane; glycol dibromide, ethane; 1-2 dibromo; ethylene bromide.

Toxicity

Human:

Direct contact with EDB causes irritation and injury to the skin and eyes. Exposure to the vapor has caused the development of respiratory tract inflammation along with anorexia and headache with recovery after discontinuance of exposure. Weakness and rapid pulse have been associated with EDB exposure as well as cardiac failure leading to death.(9)

Oral ingestion of EDB has led to liver necrosis and kidney tubular damage. Other symptoms which may be encountered following ingestion include excitement, tinnitus (ringing in the ears), and severe protracted vomiting.(10, 11)

To date, there have been no published reports of any association between EDB and cancer in humans.

Animal:

In laboratory rodents, the vapor of EDB has caused depression of the central nervous system, pulmonary irritation, and renal and hepatic damage.(12,13)

Oral administration of EDB to hens adversely influenced the production, size, and fertility of eggs.(14) The semen from bulls given oral doses of EDB had low density and the spermatozoa had poor motility. Obligospermia and degeneration of the spermatozoa were observed.(15) The spermicidal action of EDB is not direct but occurs during the process of spermatogenesis.(16) In addition, EDB has been shown to have mutagenic potential.(17,18)

The National Cancer Institute tested EDB by gastric intubation in both sexes of M6APS(OM) rats and C57BL-C3H mice. Among the animals treated with 40 mg/kg body weight of EDB administered in corn oil five times per week (for varying lengths of time 12 to 473 days); 70 of the 93 rats (76 percent) and 82 of the 94 mice (87 percent) developed squamous cell carcinomas of the stomach. No stomach tumors were observed among 22 untreated rats and 39 untreated mice.*

Stomach cancers were observed as early as ten weeks after initiation of EDB treatment. The tumor originated in the forestomach, invaded locally, and eventually metastisized throughout the abdominal cavity. No squamous cell carcinomas were observed in controls.(19,20)

Permissible Occupational Exposure

The current Occupational Safety and Health Administration, Department of Labor, Standard for EDB is 20 ppm as an 8 hour time weighted average; 30 ppm as an acceptable ceiling; and 50 ppm as a maximum peak with 5 minutes duration, based on the 1970 ANSI Z.37.31 Standard.(13)

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*Unpublished preliminary report issued by the NCI, 1974. Requests for further information should be directed to the NCI, Bethesda, Maryland.

Occupational Exposure

Estimated Numbers of Workers Exposed to Ethylene Dibromide by Industry*

Industry	No. Exposed
Fumigators and Exterminators	8,897
General Merchandising	110
Chemical Manufacturing	76
Petroleum Products Manufacturing	28
TOTAL	9,111**

Producers and Suppliers

The following is a list of the major producers and suppliers of ethylene dibromide in the United States.

Producer	Location
Bromet Co. (Ethyl Corp.)	Magnolia, Arkansas
Dow Chemical	Bayeity, Michigan
Dow Chemical	Magnolia, Arkansas
Great Lakes Chemical Co.	El Dorado, Arkansas
Houston Chemical Co.	Beaumont, Texas
Michigan Chemical Co.	El Dorado, Arkansas

TOTAL Consumption @ 330 million lbs./yr.

*Projections based on preliminary data from the National Occupational Hazard Survey, Hazard Surveillance Branch, Office of Occupational Health Surveillance and Biometrics, NIOSH. This does not include exposures to trade name products.

**Does not include approximately 650,000 persons employed in service stations with potential exposure to leaded gasoline.

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Current Intelligence Bulletin 4

June 24, 1975, October 7, 1975,
October 8, 1976

CHROME PIGMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

June 24, 1975

Dear Colleague:

A letter from the Lead Chromate Task Force of the Dry Color Manufacturers' Association (DCMA), dated June 18, 1975, to NIOSH regarding recently published information associating lung carcinoma with exposure to chromate pigments is attached for your review. The DCMA has already notified pigment manufacturers and their employees and customers of these findings. The result of epidemiologic investigation of chromate pigment production personnel and feeding studies in laboratory animals are expected from the DCMA later this year. Copies of the articles referred to in the letter from DCMA are available upon request from this office.

You will be kept apprised of future information as it becomes available.

Sincerely yours,

J. William Lloyd, Sc.D.
Director
Office of Occupational Health
Surveillance and Biometrics

Attachment

ES-3574 REV. 1-75

DUPONT
REG. U.S. PAT. OFF.
ESTABLISHED 1802

E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898
CENTRAL RESEARCH & DEVELOPMENT DEPARTMENT

HASKELL LABORATORY
FOR
TOXICOLOGY AND INDUSTRIAL MEDICINE

June 18, 1975

Mr. Edward J. Baier
Deputy Director
National Institute of Occupational Safety and Health
Public Health Service
Department of Health, Education, and Welfare
Danac Building
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Baier:

This letter is written on behalf of the Lead Chromate Task Force of the Dry Color Manufacturers' Association. Earlier this year I had occasion to inform you of a program of investigation sponsored by the Dry Color Manufacturers' Association which had as its intent an expansion of knowledge of the toxicity of lead chromate pigments and of any relationship that might exist between exposures to pigment dust and lung cancer. The program consists of a ninety-day feeding study with rats and dogs and an epidemiologic study in three manufacturing plants, two of which make lead chromate pigments and a third which makes lead chromate and zinc chromate pigments.

A final report on the feeding study will become available within a few weeks. The epidemiologic study is proceeding as scheduled and a final report will be available later this year.

It is the purpose of this letter to inform you that member companies of the Dry Color Manufacturers' Association have decided to notify employees in the manufacturing plants as follows:

(1) Recently published research results suggest that excessive exposures to the dust of lead chromate pigments, lead-molybdenum chromate pigments, and zinc chromate pigments could have a relationship with causation of lung cancer;

(2) the suggested relationship is under investigation by the means above described; and

(3) the effort to control dust within the limits of the existing OSHA regulation will be continued.

It has been decided to send similar notification to pigments customers of the manufacturing companies.

The recent publications which have prompted this decision at this time are:

(1) Langard, Sverre and Tor Norseth. A Cohort Study of Bronchial Carcinomas in Workers Producing Chromate Pigments. Brit. Jour. Indus. Med. 32 62-65 (1975).

(2) Maltoni, Cesare. Occupational Carcinogenesis International Congress Series No. 322 (ISBN 90 219 02281) Cancer Detection and Prevention, Proceedings of the Second International Symposium, Bologna, (April 1973).

Another development was transmission privately of results from a series of pellet implant studies in rats with chromate materials at the Chester Beatty Institute in England.

The results of these studies singly or collectively are not regarded by DCMA as conclusive with respect to either lead chromate or zinc chromate. The results from the epidemiologic study of lead chromate workers are awaited before forming further judgment. These results will be sent to you as soon as possible.

As you requested I am sending you herewith copies of the notifications that are being presented to employees (Item VI) and to customers (Item V).

Attached also for your convenience are copies of the two recent publications.

Very truly yours,

James F. Morgan

James F. Morgan
Consultant - Industrial Hygiene

JFM/egg
Attachments

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

October 7, 1975

Dear Colleague:

This is a further follow-up to information released by this office on June 24, 1975, concerning the potential carcinogenicity of chromate pigments.

On October 2, 1975, the Dry Color Manufacturers' Association (DCMA) informed NIOSH of the progress of an epidemiologic study sponsored by the DCMA and presented some preliminary results from an analysis of mortality data collected to date. These preliminary results are based on an examination of the relative frequency of deaths from cancer and other causes among the first 38 deaths identified by the researchers in a group of 580 workers exposed to lead chromate. Lung cancer was the cause of death for nearly 29 percent of the deceased workers. This figure was contrasted with estimates from other industrial populations in which lung cancer represented 7 to 9 percent of all deaths. Further review of the data revealed that lung cancer deaths accounted for 85 percent of all cancer deaths. These preliminary findings suggest an unusually high lung cancer risk among workers exposed to lead chromate pigments.

You will be kept apprised of future information as it becomes available.

Sincerely yours,

J. William Lloyd, Sc.D.
Director
Office of Occupational Health
Surveillance and Biometrics

October 8, 1976

LEAD CHROMATE - AN UPDATE

On July 7, 1976, the National Institute for Occupational Safety and Health (NIOSH) received the final report of a study of lead chromate workers sponsored by the Dry Color Manufacturers' Association (DCMA). This report included final results of an epidemiologic study (preliminary results were reported by NIOSH in October 1975) along with the findings of an industrial hygiene study.

Prior to this, there have been limited reports (since 1940) of lung cancer among chrome pigment workers in Germany, Norway, and the United States. Studies of laboratory animals have indicated the potential for chrome pigments to produce tumors at the site of implantation or injection.

The study of lead chromate workers recently conducted for DCMA by Equitable Environmental Health, Inc., included three lead chromate plants in operation since the mid-1920's, 1941, and 1949, respectively. Employees of two plants were found to have had only lead chromate exposures, while workers in the third plant (analyzed separately) also had zinc chromate exposure. The industrial hygiene study of the three plants showed that nearly one-half of the samples reached or exceeded OSHA standards for lead and chromium. (The standards in effect at the time of this study were: for lead, 0.2 mg/m^3; for chromium, soluble chromic, or chromous salts, .5 mg/m^3 as Cr; and for chromic acid or chromates, 0.1 mg/m^3 as CrO_3).

The levels of lead and chromium found in this study were assumed to be lower than levels in the past because of some process changes and modifications of engineering controls and work practices; however, this difference could not be quantitated because of changes in analytical methods.

The three-plant cohort analysis included a total of 548 men among whom 53 deaths had occurred prior to December 31, 1974. Standardized

mortality ratios (SMRs) were determined by comparing the observed deaths due to major causes with the number of expected deaths based on the 1960 male population of the state in which each plant was located. For all employees in two plants (with only lead chromate exposure), a 3-fold excess of respiratory cancer was observed (SMR 313.7 compared with an expected 100). Workers employed prior to 1960 (allowing for a 15-year "latency" period) were analyzed separately. For all persons in this group, regardless of length of employment, the SMR for respiratory cancer was 173.5; for persons who were hired prior to 1960 and who had worked there for at least 10 years, this SMR was 236.4.

Employees of the third plant (with both lead and zinc chromate exposure) were all hired before 1960 and had an SMR of 237.1 for respiratory cancer. In addition, 5 deaths due to stomach cancer were observed; this was 7 times the expected number.

Although the small number of observed deaths did not justify statistical tests, the Equitable Environmental Health researchers agree that this apparent excess of respiratory cancer in lead chromate workers is "consistent with the hypothesis that lead chromate is a respiratory carcinogen."

These findings are in accord with the NIOSH Criteria for a Recommended Standard on Hexavalent Chromium (December 1975) which states that lead chromate should be regarded as a human carcinogen.

John F. Finklea, M.D.
John F. Finklea, M.D.
Director

Current Intelligence Bulletin 5

August 8, 1975

ASBESTOS

ASBESTOS EXPOSURE DURING SERVICING OF MOTOR VEHICLE BRAKE AND CLUTCH ASSEMBLIES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

August 8, 1975

Dear Colleague:

This communication is intended to alert you to recently gathered information indicating a potential health hazard for persons exposed to asbestos during the servicing of motor vehicle brake and clutch assemblies.

On July 21, 1975, the National Institite for Occupational Safety and Health convened a meeting of government and university scientists, industry representatives, and labor union officials to discuss the present state of knowledge with respect to this problem. Data was presented by investigators from the Mount Siani School of Medicine in New York City indicating that workers engaged in the maintenance and repair of automobile and truck brake linings are exposed to potentially hazardous levels of airborne asbestos dust. Specific brake servicing operations studied included blow-out of automobile drum brake assemblies, grinding of used truck brake linings, and bevelling of new truck brake linings. Average peak asbestos air concentrations for these three activities based on personal samples taken within ten feet of the operator were, respectively, 10.5, 3.75, and 37.3 fibers (>5 microns in length) per ml. An analysis of samples of brake drum dust revealed that almost all of the asbestos fibers found were shorter than 0.4 microns in length.

Previous studies of the extent of asbestos emissions from automobile brake lining wear showed that only a very small fraction of the original asbestos content of the brake lining is found in brake drum dust (Ref. 1-3). It was presumed that this is due to thermal degradation of the fibers during braking. The present findings indicate that enough asbestos is preserved to produce significant exposures during certain brake servicing procedures.

The full extent of asbestos-related disease in brake servicing personnel is not known at present because this particular occupational group has not been studied systematically up to now. However, a review of the scientific literature on the association between asbestos exposure and mesothelial tumors of the pleura and peritoneum has revealed at least four cases of these rare tumors in persons who were employed in jobs involving automobile brake servicing (Ref. 4-6).

For your information and guidance, we are enclosing pertinent references, estimates of the population at risk, a NIOSH interim recommendation for brake and clutch servicing procedures, and a copy of the Department of Labor standard covering exposure to asbestos in the work place.

The environmental studies of brake lining servicing operations outlined above together with observations of mesothelial tumors in persons so employed affirms the necessity for instituting and maintaining recommended control measures in this industry so that the health hazards of asbestos are minimized.

Sincerely yours,

J. William Lloyd, Sc.D.
Director
Office of Occupational Health
Surveillance and Biometrics

Enclosures

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ESTIMATES OF THE WORKFORCE POTENTIALLY EXPOSED TO ASBESTOS IN THE MANUFACTURING AND SERVICING OF BRAKE LININGS AND CLUTCHES

Auto Mechanics	833,535
Garage Workers	67,679
Manufacture (original and rebuilding)	6,657
TOTAL	907,871

SOURCE: Adapted from 1972 Census of Manufacturers, 1972 County Business Patterns, and Census of Population: 1970 Occupation by Industry (all are Department of Commerce, Census Bureau publications)

RECOMMENDED (INTERIM) PROCEDURES FOR ASBESTOS BRAKE AND CLUTCH SERVICING

The National Institute for Occupational Safety and Health (NIOSH) has research underway concerning dust exposures during brake and clutch servicing. Due to preliminary data demonstrating significant asbestos exposures during presently used cleaning techniques, NIOSH has reviewed alternate techniques whereby asbestos exposures are reduced. The following are interim procedures recommended by NIOSH to minimize dust exposures.

1. If possible, an area shall be designated for all brake and clutch repairs. Entrances into this area shall be posted with an asbestos exposure warning sign as follows:

   Asbestos
   Dust Hazard
   Avoid Breathing Dust
   Wear Assigned Protective Equipment
   Do Not Remain in Area Unless Your Work Requires It
   Breathing Asbestos Dust May Cause Asbestosis and Cancer

2. During brake servicing, an air purifying respirator, either single use or with replaceable particulate filter(s), as approved by the Mining Enforcement and Safety Administration (formerly Bureau of Mines) or NIOSH, shall be worn during all procedures following removal of the wheels including reassembly. During manual clutch servicing, such a respirator shall be worn during removal and cleaning of the clutch, pressure plate and housing assembly and during installation of the new clutch assembly.

3. Dust shall first be cleaned from brake drums, brake backing plates, brake assemblies and clutch assemblies using an industrial type vacuum cleaner equipped with a high efficiency filter system (>99% efficiency for 0.3 μm diameter aerosols). After vacuum cleaning, any remaining dust shall be removed using a rag soaked in water and wrung until nearly dry. Under no circumstances shall compressed air or dry brushing be used for cleaning.

4. During arcing and riveting operations, an approved respirator, as described in (2) above, shall be worn. Grinding (arcing) machines shall be provided with local exhaust ventilation such that worker exposures are maintained at least below the 1976 OSHA asbestos standard (29 CFR 1910.1001).* At a minimum, the dust bag of the arcing machine shall be removed and replaced with the hose of the high efficiency industrial vacuum described in (3) above.

5. Industrial vacuum cleaner bags containing asbestos dust and cloths used for wiping brake and clutch assemblies shall be sealed in plastic bags and labeled with the following warning label printed in letters of sufficient size and contrast to be readily visible and legible:

Caution
Contains Asbestos Fibers
Avoid Breathing Dust
Breathing Asbestos Dust May Cause Asbestosis and Cancer

All asbestos waste shall be disposed of in accordance with the OSHA asbestos regulation, 29 CFR 1910.1001(h). During removal of vacuum bags, an approved respirator, as described in (2) above, shall be worn.

6. All floor cleaning in areas where brakes and clutches are repaired shall be done with the high efficiency industrial vacuum cleaner as described in (3) above. Grinding (arcing) machines shall also be cleaned with such a vacuum cleaner and any remaining dust wiped with a damp cloth. An approved respirator, as described in (2) above, shall be used during this cleaning.

7. Although adherence to the above procedures should minimize any contamination of work clothing, it is required that the appropriate portions of the OSHA regulations on asbestos (29 CFR 1910.1001(d) (3 and 4)) concerning special clothing, change rooms, etc. be followed.

NOTE: Strict adherence to the above procedures should minimize exposures to mechanics during brake and clutch servicing. These are interim recommendations and are subject to revision pending results of ongoing NIOSH research.

* Section 1910.1001 of the Code of Federal Regulations was formerly Section 1910.93a. This change was noted in the Federal Register, May 28, 1975.

Prepared By
Division of Field Studies and Clinical Investigations
National Institute for Occupational Safety and Health
Cincinnati, Ohio

Current Intelligence Bulletin 6

October 24, 1975

HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

October 24, 1975

Dear Colleague:

The enclosed background material on Hexamethylphosphoric Triamide has been prepared by the Office of Occupational Health Surveillance and Biometrics, National Institute for Occupational Safety and Health to alert members of the occupational health community to new information on a potential occupational hazard.

Your comments and suggestions for changes to future reports are solicited.

Sincerely yours,

J. William Lloyd, Sc.D.
Director
Office of Occupational Health
Surveillance and Biometrics

Enclosure

HEXAMETHYLPHOSPHORIC TRIAMIDE (HMPA)

Summary

The National Institute for Occupational Safety and Health (NIOSH) has received a report from an American producer of hexamethylphosphoric triamide (HMPA), a synthetic organic chemical, indicating that malignant tumors have been produced in laboratory animals by exposure to HMPA.

In light of the potential risk of human exposure to this chemical in the work environment, the National Institute for Occupational Safety and Health is advising the occupational health community of these findings.

Introduction

The E.I. du Pont de Nemours and Company (Du Pont) reported to the National Institute for Occupational Safety and Health in a letter dated September 24, 1975, that nasal tumors (squamous cell carcinoma) have been observed in rats exposed to hexamethylphosphoric triamide. NIOSH has also been advised that Du Pont has notified its customers and employees of these findings.

Background

HMPA is a colorless liquid with a density of 1.03 g/ml and a boiling point of 232°C. Synonyms for hexamethylphosphoric triamide include ENT 50882, hempa, hexametapol, hexamethylphosphamide, hexamethylphosphoramide, hexamethylphosphoric acid triamide, hexamethylphosphorotriamide, hexamethylphosphotriamide, HMPA, HMPT, HPT, phosphoric tris (dimethyamide), phosphoryl hexamethyltriamide, tris (dimethylamino) phosphine oxide, and tris (dimethylamino) phosphorous oxide.(1)

Hexamethylphosphoric triamide is a material possessing unique solvent properties and is widely used as a solvent, in small quantities, in organic and organo-metallic reactions in laboratories. (2,3) This is the major source of occupational exposure to HMPA in the United States.

Du Pont, the major manufacturer of hexamethylphosphoric triamide in the United States, periodically produces HMPA at its Chambers Works, Deepwater, New Jersey. Other producers of HMPA in the United States include Chemical Samples Company and Fike Chemical Company. None of Du Pont's HMPA is marketed; all is used internally at its Spruance Plant in Richmond, Virginia, as a processing solvent in the production of Kevlar* aramid fiber. Du Pont reports that Kevlar contains less than 1 ppm (w/w) of the HMPA which is so firmly held by the fiber that Du Pont believes there is no hazard to customers or employees handling the final fiber product.

Hexamethylphosphoric triamide had been manufactured and distributed in the past by Dow Chemical Company (as DORCOL) and Eastman Chemical Products, Inc. (as Inhibitor HPT). Both firms have advised NIOSH that they discontinued these products several years ago.(4) HMPA has been evaluated for use as an ultraviolet light inhibitor in polyvinyl chloride formulations, as an additive for antistatic effects, as a flame retardant, and as a de-icing additive for jet fuels.(4,5,6)

Hexamethylphosphoric triamide has also been extensively investigated as an insect chemosterilant.(7,8)

Toxicity

Human:

There are no data available on the toxic effects of hexamethylphosphoric triamide in humans.

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*Kevlar is a registered trademark of the Du Pont Company.

Animal:

HMPA is known to have a variety of toxic effects on laboratory animals. Acute toxic effects seen in rats fed HMPA include kidney disease, severe bronchiectasis and bronchopneumonia with squamous metaplasia and fibrosis in lungs.(9,10) In rabbits, repeated application of HMPA to the skin caused dose related weight loss, altered gastro-intestinal function and apparent nervous-system dysfunction.(11) Testicular atrophy and aspermia have been observed in rats following oral treatment with HMPA.(9,12) Oral treatment with HMPA has also been highly inhibitory to testicular development in cockerels.(13)

HMPA is known to produce mutagenic effects in fruit flies (Drosophila melanogaster).(14) However, studies of the effects of HMPA on human(15) and mice chromosomes(16) showed no greater frequency of HMPA induced chromosomal aberrations when compared with controls.

Preliminary results of an inhalation toxicity study of HMPA, recently released by Du Pont, show nasal tumors in rats exposed daily to 400 and 4,000 parts per billion (ppb) HMPA after 8 months of exposure. In some cases, the tumors originating from the epithelial lining of the nasal turbinate bones filled the nasal cavity and penetrated into the brain. No nasal tumors were reported among rats exposed to 50 ppb HMPA and controls.

Prior to the Du Pont observations, the only other known report of tumors associated with exposure to HMPA was a long-term feeding study by Kimbrough. While lung tumors were observed, the results of this study were inconclusive because the tumor incidence among HMPA exposed rats was not greater than among the control rats.(17)

Occupational Exposure

It is estimated that 5,000 people are occupationally exposed to hexamethylphosphoric triamide. More than 90 percent of these exposures are in research laboratories.

Permissible Occupational Exposure

There is no current Occupational Safety and Health Administration, Department of Labor standard for hexamethylphosphoric triamide exposure.

Producers and Distributors

The following is a list of the major producers and distributors of hexamethylphosphoric triamide:

Producers	Location
E.I. du Pont de Nemours & Co., Inc.	Deepwater, NJ
Chemical Samples Company	Columbus, OH
Fike Chemical Company	Nitro, WV

Distributors*	Location
Aldrich Chemical Company	Milwaukee, WS
J.T. Baker Chemical Company	Phillipsburg, NJ
Bodman Chemicals	Aston Township, PA
Chemical Samples Company	Columbus, OH
Eastman Organic Chemicals	Rochester, NY
E.M. Laboratories, Inc.	Elmsford, NY
Fike Chemical Company	Nitro, WV
Fisher Scientific Company	Pittsburgh, PA
Guardian Chemical Corporation	Hauppauge, NY
MCB Manufacturing Chemists	Cincinnati, OH
Orgmet	E. Hampstead, NH
Peninsular Chemical Research, Inc.	Gainesville, FL
Polyscience, Inc.	Warrington, PA

*Includes domestic and imported HMPA

SOURCE: Personal communications with representatives of chemical manufacturers, October, 1975

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Current Intelligence Bulletin 7

November 3, 1975

POLYCHLORINATED BIPHENYLS (PCBs)

Current Intelligence

Polychlorinated Biphenyls*

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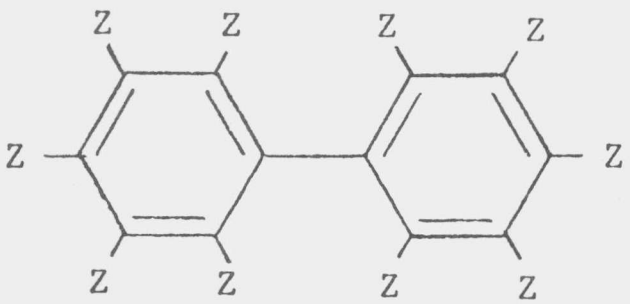
Reports of adverse health effects in humans and the demonstration of carcinogenic effects in certain animal species have led to the reexamination of the distribution of polychlorinated biphenyls (PCBs) in the environment and the potential health effects of human exposure.

Because the industrial environment represents the major source of potentially high exposures to PCBs, the National Institute for Occupational Safety and Health (NIOSH) has gathered pertinent information on the manufacture, uses, and reported deleterious effects of polychlorinated biphenyls and is advising the occupational health community of these hazards.

Background

Polychlorinated biphenyls (PCBs) describe a group of synthetic chlorinated organic compounds having the following structure:



where each of the ten Z's can represent either a hydrogen or a chlorine atom. There are 209 different chlorinated biphenyls and they are collectively referred to as PCBs although many are not actually *poly*chlorinated. Approximately half of these compounds have been synthesized and characterized.

Mixtures of polychlorinated biphenyls are important industrial products. The most common tradenames for these mixtures are Aroclor,* Inerteen,† Kanechlo‡† and Pyranol.¶ Other known tradenames for PCB-containing products are listed in Table 1. PCB-containing dielectrics (electrical insulators) are generally referred to as "askarels" in the electrical industry.

Mixtures of polychlorinated biphenyls are very resistant to degradation, are thermally stable, and resistant to oxidation, acids, bases, and other chemical agents. They are soluble in most of the common organic solvents and lipids, but only slightly soluble in water, glycerol, and glycols. PCBs are good electrical insulators. Although most individual polychlorinated biphenyls are solids at room temperatures, the mixtures vary in consistency from mobile oils to viscous liquids or sticky resins.

PCBs are generally prepared industrially by the chlorination of biphenyl with anhydrous chlorine in the presence of iron filings or a ferric chloride catalyst. Trace quantities of chlorinated naphthalenes and chlorinated dibenzofurans have been reported in some commercial samples of PCBs and it has been suggested that the presence of these impurities may be of toxicological significance.[1 2 3]

Commercial PCBs are generally mixtures of many different chlorinated biphenyls, as shown in Table 2, manufactured to meet operational specifications (such as dielectric constant, flash point, fire point, density, percent chlorine, and color); these commercial mixtures may vary chemically from batch to batch.

Table 1. — Tradenames for Known PCB Containing Products.

Tradename	Tradename Owner
Aroclor	Monsanto Company St. Louis, MO
Chlorextol	Allis-Chalmers Milwaukee, WI
Clophen	Farbenfabricken Bayer GmbH Germany
Dykanol	Federal Pacific Electric Co. Newark, NJ
Fenclor	Caffaro S.P.A. Italy
Inerteen	Westinghouse Electric Corp. Pittsburgh, PA
Kanechlor	Kanegafuchi Chemical Industry Co., Ltd. Japan
Noflamol	Wagner Electric Corporation Newark, NJ
Phenoclor	Prodelec France
Pyralene	Prodelec France
Pyranol	General Electric Co. Schenectady, NY
Santotherm	Mitsubishi-Monsanto Japan
Therminol*	Monsanto Co. St. Louis, MO

*Therminol products now formulated in the U.S. do not contain PCBs.

* From the Office of Occupational Health Surveillance and Biometrics, National Institute for Occupational Safety and Health, 5600 Fishers Lane, Rockville, M.D. 20852.
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PCBs have found wide use in industry and have been manufactured in the United States since 1929. The major domestic manufacturer, Monsanto Company, produces PCBs at Sauget, Illinois and reports manufacturing 40 million pounds of PCBs in the United States during 1974 (down from 85 million pounds in 1970).[4] Monsanto's domestic production and sales of PCBs by grade and category from 1957 through the first quarter of 1975 are shown in Table 3.

Uses

PCBs are employed in capacitors and transformers because they combine attractive dielectric properties with chemical stability and fire resistance. Approximately twice as many pounds of PCBs are used in the manufacture of capacitors as in the manufacture of transformers.

Prior to the environmental concern surrounding the persistence and ubiquitousness of PCBs,[5] they were more widely used in industry as fluids for heat transfer systems, hydraulic systems, gas turbines, and vacuum pumps, as fire retardants, and as plasticizers in adhesives, textiles, surface coatings, sealants, printing, and carbonless copy paper.

Beginning in 1971, Monsanto voluntarily restricted its domestic sales of PCBs to closed system dielectric applications in capacitors and transformers.[6] Other current domestic applications of PCBs include use in investment casting processes, as heat exchange fluids, and as hydraulic fluids. Imports of PCBs have been estimated to exceed 375,000 pounds for 1974. Reclaimed PCBs also are reported to be available.[7]

More than 95% of all power capacitors contain PCBs. Among their applications are use on electric utility lines, in air conditioners, and in the ballast of fluorescent lamp fixtures. PCBs are employed for safety, reliability, and long life, as well as to achieve size compatibility with equipment and installation requirements. However, non-PCB power capacitors are being manufactured (e.g., General Electric's Econol line and Sprague's Eccol line) which may serve as alternatives.[8§]

PCBs are employed in transformers at locations where their proximity to people and/or property demand a fire resistant dielectric. Approximately 5% of transformers are PCB filled and each of the transformers so filled contains between 40 and 500 gallons of PCBs (about 235 gallons is average). Possible alternatives to PCB filled transformers may include dry transformers (which are larger) as well as transformers filled with silicone fluids or other materials under evaluation.[8 9]

Chlorinated terphenyls, as well as PCBs, are used in some formulations of wax for investment casting processes.[8] The chemical structure of chlorinated terphenyls resembles that of PCBs. Chlorinated terphenyls have been reported to have toxicological effects similar to those of PCBs.[10]

Approximately 330,000 pounds of chlorinated terphenyls were imported into the United States during 1974[11] and 125,532 pounds during 1973.[12]

Toxicity

PCBs are poorly metabolized and tend to accumulate in animal tissues, including humans.[13-17] The accumulation, particularly in tissues and organs rich in lipids, appears to be higher in the case of *penta* and more highly chlorinated biphenyls.[18]

Studies have revealed PCBs in human fat tissue and blood plasma. PCBs, in amounts greater than 2 parts per million, were reported in 198 of 637 (31%) samples of human fat tissue taken from the general population of 18 states and the District of Columbia.[14] PCB residues ranging up to 29 parts per billion have also been found in 43% of 616 plasma samples collected from volunteers in a southeastern U.S. county.[15]

Human

The known toxic effects of PCBs in humans include an acnelike skin eruption (chloracne), pigmentation of the skin and nails, excessive eye discharge, swelling of eyelids, and distinctive hair follicles.[19]

For a number of years, chloracne of the face and neck has been reported among workers exposed to chlorinated hydrocarbons. Workers exposed to PCBs in the process of insulating cables,[20] in the production of condensers[21] and in the manufacture of chlorobiphenyls[22] have reported these skin lesions along with systemic effects such as digestive distur-

Table 2. — Description of PCB Mixtures.

	Aroclor® 1221*	Aroclor 1016*	Aroclor 1242*	Aroclor 1254*	Aroclor 1260†	Kanechlor® 300‡	Kanechlor 400‡	Kanechlor 500‡
Approximate Chlorine Content	21%	42%	42%	54%	60%	42%	48%	53%
Components								
Biphenyl	11	< 0.1	< 0.1	< 0.1				
Monochlorobiphenyls	51	1	1	< 0.1				
Dichlorobiphenyls	32	20	16	0.5		17	3	
Trichlorobiphenyls	4	57	49	1		60	33	5
Tetrachlorobiphenyls	2	21	25	21		23	44	27
Pentachlorobiphenyls	< 0.5	1	8	48	12	0.6	16	55
Hexachlorobiphenyls	none detected	< 0.1	1	23	38		5	13
Heptachlorobiphenyls	none detected	none detected	< 0.1	6	41			
Octachlorobiphenyls	none detected	none detected	none detected	none detected	8			
Nonachlorobiphenyls					1			

It must be emphasized that these are approximate compositions of the PCB mixtures and that a particular product may vary in chemical composition from batch to batch.

*Weight-weight percent. None detected = less than 0.01%. Source of component compositions: Monsanto Company, quoted in Hutzinger, O., et al., op. cit., p. 23

‡Percent. Source of component compositions: Thruston, A., PCB Newsletter, No. 3, July 1971, quoted in Hutzinger, O., et al., op. cit., p. 23

†Percent. Source of component compositions: Ito, N., et al., op. cit., p. 1637

bances, edema of the face and hands, burning of the eyes, impotence, and hematuria.[16 22]

The toxic effects of PCBs in humans are further illustrated by a 1968 outbreak of poisoning in Japan that involved over 1,000 people who ingested PCB contaminated rice bran oil for a period of several months. The contamination of the oil (estimated 1,500 to 2,000 ppm) occurred when heat transfer pipes immersed in the oil during processing developed pin-sized holes. The clinical aspects of the poisoning included chloracne, brown pigmentation of the skin and nails, distinctive hair follicles, increased eye discharge, swelling of eyelids, transient visual disturbance, and systemic gastrointestinal symptoms with jaundice.[19] In some patients, symptoms persisted three years after PCB exposure was discontinued. Infants

Table 3. — PCB Manufacture and Sales Monsanto Industrial Chemicals Company. 1965 Through 1975 (Thousands of Pounds)

	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	(1st quarter) 1975
U.S. Production	60480	65849	75309	82854	76389	85054	34994	38600	42178	40466	8532
Domestic Sales	51796	59078	62466	65116	67194	73061	34301	26408	37742	34406	7986
U.S. Export Sales	4234	6852	8124	11231	10624	13651		6388	8346	5395	1538
Domestic Sales by Category											
Heat Transfer	1237	1766	2262	2529	3050	3958	3060	752			
Hydraulics/ Lubricants	4616	4258	4643	5765	8039	7403	1552	0			
Misc. Industrial	1841	1779	1426	1283	1079	1627	1155	0			
Transformer	8657	8910	11071	11585	12105	13828	11134	25656	37742	34406	7986
Capacitor	23749	28884	29703	29550	25022	26708	14141				
Plasticizer Applications	11696	13481	13361	14404	16460	19537	3259	0			
Petroleum Additives	—	—	—	—	1439	—	—	0			
Domestic Sales by PCB Grade											
Aroclor 1221	369	528	442	136	507	1476	2215	171	35	57	10*
Aroclor 1232	7	16	25	90	273	260	171	0	0	0	0
Aroclor 1242	31533	39557	43055	44853	45491	48588	21981	728	6200	6207	2201†
Aroclor 1248	5565	5015	4704	4894	5650	4073	213	807	0	0	0
Aroclor 1254	7737	7035	6696	8891	9822	12421	4661	3495	7976	6185	2115†
Aroclor 1260	5831	5875	6417	5252	4439	4890	1725	305	0	0	0
Aroclor 1262	558	768	840	720	712	1023	1	0	0	0	0
Aroclor 1268	196	284	287	280	300	330	0	0	0	0	0
Aroclor 1016	0	0	0	0	0	0	3334	20902	23531	21955	3660*

*Used primarily in capacitors
†Used primarily in transformers

1957 Through 1964

	1957	1958	1959	1960	1961	1962	1963	1964
U.S. Production	(1)	(1)	(1)	37919	36515	38353	44734	50833
Domestic Sales	32299	26061	31310	35214	37538	38043	38132	44869
U.S. Export Sales	(2)	(2)	(2)	(2)	(2)	(2)	3647	4096
Domestic Sales by Category								
Heat Transfer	—	—	—	—	—	157	582	929
Hydraulics/Lubricants	1612	1549	2685	2523	4110	3915	3945	4374
Miscellaneous Industrial	704	755	1569	1559	2114	1681	1528	1692
Transformer	12955	5719	5984	7921	6281	7984	7290	7997
Capacitor	17028	14099	16499	16967	15935	15382	15606	19540
Plasticizer Applications	(1)	3939	4573	6244	9098	8924	9181	10337
Petroleum Additives	—	—	—	—	—	—	—	—
Domestic Sales by PCB Grade								
Aroclor 1221	23	16	254	103	94	140	361	596
Aroclor 1232	196	113	240	155	241	224	13	13
Aroclor 1242	18222	10444	13598	18196	19827	20654	18510	23571
Aroclor 1248	1779	2559	3384	2827	4023	3463	5013	5238
Aroclor 1254	4461	6691	6754	6088	6294	6325	5911	6280
Aroclor 1260	7587	5982	6619	7330	6540	6595	7626	8535
Aroclor 1262	31	184	359	326	361	432	414	446
Aroclor 1268	—	72	102	189	158	210	284	190
Aroclor 1016	—	—	—	—	—	—	—	—

(1) Production figures and Plasticizer Applications figures unavailable during year indicated.
(2) U.S. Export Sales figures unavailable during year indicated.
Source: Monsanto Industrial Chemicals Company, St. Louis, Missouri, September, 1975.

born to poisoned mothers had decreased birth weights, and showed skin discoloration due to PCB placental passage. Two stillbirths to PCB exposed women were also reported.[23]

Animal

The toxic effects of PCBs in animals have been studied extensively. Reports of malignant, nonmalignant, and reproductive effects are shown in Tables 4, 5, 6.

Occupational Exposure

It is estimated that 12,000 people are occupationally exposed to polychlorinated biphenyls. The majority of these exposures are in capacitor production and in investment casting processes.

Permissible Occupational Exposure

The current Occupational Safety and Health Administration, Department of Labor standards for chlorinated biphenyls are 1 mg/cubic meter for 42% chlorine mixtures and .5 mg/cubic meter for 54% chlorine mixtures. These are based on the Threshold Limit Values (TLV) established by the American Conference of Governmental Industrial Hygienists.[35]

Table 4. — Malignant Pathologic Effects Induced by PCBs in Animals.

PCB Mixture	Treatment	Animal	Effects
Kanechlor 500[24] Kanechlor 400 Kanechlor 300	500 ppm, 250 ppm and 100 ppm in diet for 32 weeks	Mice	Liver weight increased with percent chlorine and dosage. Kanechlor 400 and 500 produced liver cell hypertrophy. 500 ppm of Kanechlor 500 produced hyperplastic nodules in 7 of 12 mice and hepatocellular carcinomas in 5 of 12 mice No nodules or carcinomas in controls
Aroclor 1254[25]	300 ppm in diet for 6 & 11 months	Mice	Increased liver weight. Adenofibrosis in all mice fed for 11 months. Nine of 22 mice fed for 11 months had hepatomas. One of 24 mice fed for 6 months had a hepatoma. No hepatomas in control mice.
Aroclor 1260[26]	100 ppm in diet for 21 months	Rats	Hepatocellular alteration in 182 of 184 rats fed PCBs and in 28 of 173 control rats. Neoplastic nodules in 144 of 184 PCB fed rats and none in control rats. Hepatocellular carcinomas in 26 of 184 rats fed PCBs and in 1 of 173 control rats.

Table 5. — Nonmalignant Pathologic Effects Induced by PCBs in Animals.

PCB Mixture	Animal	Route of Administration	Effects
Acute Effects			
Unspecified Product Containing 42% Chlorine[27]	Guinea pigs Rats Rabbits	Subcutaneous injection Skin application Feeding	Fatty degeneration and central atrophy of the liver.
Aroclor 1242[28] Aroclor 1254	Guinea pigs Rats Mice Rabbits Cat	Inhalation	Aroclor 1242 produced no ill effects on basis of mortality, growth, pathology, organ enlargement, liver function, or hematological changes. Aroclor 1254 produced no harmful effects regarding growth or mortality, but did produce enlarged livers with microscopic evidence of hepatic cellular injury.
Aroclor 1248[29]	Monkeys	Feeding	Weight loss, hair loss, mouth and eyelid edema, acneform lesions, decreased hemoglobin and hematocrit, severe gastric mucosal ulceration and extreme hypertrophy of the liver.
Chronic Effects			
Aroclor 1254[30] Aroclor 1260	Rats	Feeding	Hypertrophy of the liver cells, a brown pigment in the Kupffer cells, lipid accumulation in the cytoplasm of hepatocytes and adenofibrosis.

Table 6. — Reproductive Effects of PCBs in Animals.

PCB Mixture	Animal	Route of Administration	Effects
Aroclor 1242[31] Aroclor 1254 Aroclor 1260	Chickens	Feeding	Aroclor 1242 and 1254 reduced egg production and hatchability and caused thin eggshells. Aroclor 1260 produced no harmful effects.
Aroclor 1254[32]	Mallards Bobwhites	Feeding	No adverse effects.
Aroclor 1254[33]	Pheasant	Feeding	Reduced egg production and hatchability.
Aroclor 1254[34]	Mink	Feeding	Severely affected reproduction.
Aroclor 1248[29]	Female monkeys	Feeding	Reduced ability to become pregnant. Pregnancies produced small infants with PCBs in tissues.

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*Aroclor is a registered trademark of the Monsanto Company.

†Inerteen is a registered trademark of the Westinghouse Electric Corporation for its brand of PCB containing dielectric fluids.

‡Kanechlor is a registered trademark of the Kanegafuchi Chemical Industry Company, Ltd.

¶Pyranol is a registered trademark of the General Electric Company for its brand of PCB containing dielectric fluids.

§In December, 1975, The Dow Chemical Company and McGraw Edison Company announced the development of a substitute for PCBs in high voltage capacitors, butylated monochlorodiphenyl oxide.

August 20, 1976

Dear Colleague:

In a June 24, 1976 letter, Mobil Oil Corporation advised the National Institute for Occupational Safety and Health (NIOSH) of a possible association between occupational exposure to polychlorinated biphenyls (PCBs) and cancer in humans. Mobil Oil reported preliminary results of an epidemiologic analysis based on medical records of employees exposed to PCBs at their Paulsboro, New Jersey plant. This study was conducted by Professor Anita K. Bahn (School of Medicine, University of Pennsylvania) and is being reported by Dr. Bahn in a letter to the editor of the New England Journal of Medicine, August 19, 1976.

The study included two cohorts of Mobil employees who were reported to have had varying exposure to Aroclor 1254 (a mixture of PCBs). The cohort of research and development employees was exposed to PCBs between 1949 and 1957 and the cohort of refinery plant employees between 1953 and 1958. The extent of exposure of these workers to other chemicals is not known. The cancer incidence among these workers for the period 1957 through 1975 was determined using Mobil medical records. Because medical records for 37 employees were incomplete, these workers were excluded from this analysis.

Among the 92 workers in these two cohorts for whom adequate medical records were available, eight cancers (in seven workers) were observed between 1957 and 1975. Of these eight cancers, three were malignant melanoma and two were cancer of the pancreas. This is significantly more skin cancer (melanoma) and pancreatic cancer than would be expected in a population of this size (based on the Third National Cancer Survey). The remaining cancers were found at three other sites in two employees; sarcoma of the right thigh and multiple myeloma in one employee, and recto-sigmoid cancer in the other.

Page 2 - Dear Colleague

NIOSH is unaware of any other published animal or human data which suggest a correlation between exposure to PCBs and skin (melanoma) or pancreatic cancer. However, hepatomas (mice, Aroclor 1254) and hepatocellular carcinomas (mice, Kanechlor 500; rats, Aroclor 1260) have been reported in PCB feeding studies of laboratory animals.

Background information on PCBs has been summarized in the NIOSH Current Intelligence Bulletin on Polychlorinated Biphenyls issued to the occupational health community on November 3, 1975, and subsequently published in the Journal of Occupational Medicine, Volume 18, pages 109-113, February 1976. Since the NIOSH Bulletin was first issued, a number of large firms have introduced products (e.g., butylated monochlorodiphenyl oxide and dimethyl siloxane polymer) claimed to be fire resistant dielectrics which can serve as alternatives to PCBs. In addition, one of the large domestic transformer manufacturers announced that it will cease using PCBs as fire resistant transformer fluids at the end of this year. NIOSH would like to stress that alternatives for PCBs should be thoroughly studied to assess the consequences they may pose to human health.

To aid in evaluating PCBs as a potential occupational health problem, NIOSH would welcome receiving reports of studies regarding the possible association between exposure to PCBs and human cancer.

Your cooperation in this matter is appreciated.

Sincerely yours,

John F. Finklea MD

John F. Finklea, M.D.
Director

Current Intelligence Bulletin 8

January 30, 1976

4,4-DIAMINODIPHENYLMETHANE (DDM)

(60)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
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January 30, 1976

The enclosed background material on 4,4'-diaminodiphenylmethane (DDM) has been prepared by the Office of Extramural Coordination and Special Projects, National Institute for Occupational Safety and Health to alert members of the occupational health community to new information on a potential occupational hazard.

Your comments and suggestions for changes to future reports are solicited.

Sincerely yours,

John F. Finklea, M.D.

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

This office has prepared the following summary of information on the production, uses, exposure and health effects of 4,4'-diaminodiphenylmethane (DDM).

DDM, 4,4'-diaminodiphenylmethane, also known as p,p'-methylenedianiline (MDA), is an important chemical intermediate. Over 200,000,000 pounds per year of DDM are manufactured in the United States. A list of the manufacturers and producers of DDM is attached. DDM is produced by the condensation of aniline with formaldehyde in the presence of an acid catalyst.

Approximately ninety-nine percent of the DDM produced is consumed in its crude form (occasionally containing not more than 50% DDM and polyDDM) at its production site by reaction with phosgene in the preparation of isocyanates and polyisocyanates. These isocyanates and polyisocyanates are employed in the manufacture of rigid polyurethane foams which find application as thermal insulation. Polyisocyanates are also used in the preparation of the semiflexible polyurethane foams used for automotive safety cushioning.

DDM is also used as:

- an epoxy hardening agent
- a raw material in the production of polyurethane elastomers
- in the rubber industry
  - a curative for neoprene (1)
  - an anti-frosting agent (anti-oxidant) in footwear
- a raw material in the production of Qiana Nylon
- a raw material in the preparation of poly(amide-imide) resins (used in magnet wire enamels)

It is estimated that 2,500 workers are exposed to DDM. Many of these exposures to DDM are in the preparation of isocyanates and polyisocyanates and, on construction sites, in the application of epoxy coatings.

In 1965, the hepatotoxic effects of DDM in humans were first seen in the so-called "Epping Jaundice" outbreak in Great Britain. In this incident 84 people who had eaten DDM contaminated bread, experienced hepatocellular damage evidenced by elevated SGOT and SGPT levels (2,3). DDM has also been shown to produce liver lesions in a group of intragastrically fed rats (4) and has caused liver degeneration and spleen lesions in another group of DDM fed rats (5.)

DDM in the occupational environment has been implicated in a number of cases of toxic hepatitis. During an 18 month period beginning April 1972, six cases of hepatitis developed among about 300 men who used epoxy resins in the construction of a nuclear power plant in Alabama. Two chemicals, DDM and 2-nitropropane, were held suspect in this study (6,7). In another study, 13 cases of hepatitis developed between 1966 and 1972 among workers who added DDM to a mixture to produce a hard plastic insulating material. All of these men became ill within a few days of working intensively with DDM (8). One other case of hepatitis, possibly associated with DDM, was reported by a person who wrote to the Environmental Protection Agency describing an episode of acute hepatitis as well as CNS and pulmonary symptoms he experienced following exposure to a surfacing agent containing DDM.

The carcinogenic effects of DDM have also been studied. In one study, 16 rats were given 4 or 5-20 mg DDM doses by stomach tube over 8 months. A hepatoma and a haemangioma like tumor of the kidney were found in one rat after 18 months and an adenocarcinoma of the uterus was found in another after 24 months (9). In another report, of 48 rats given DDM intragastrically 5 times weekly, all developed liver cirrhosis, four developed hepatomas (2 benign) and others, miscellaneous tumors (10). In a third report, 50% of 50 DDM injected rats developed tumors (4 hepatomas) compared with 26% of a control group (11). There have been no reported human cancers associated with DDM.

If, as hypothesized in the Center for Disease Control study of nuclear power plant construction workers, not all workers are susceptible to liver injury after exposure to DDM, and if the 1-2% incidence of liver disease seen in this study were applied to all workers with possible exposure to DDM, we would expect to see 25 to 50 cases of DDM associated toxic hepatitis a year.

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LISTED MANUFACTURERS AND PRODUCERS OF
4,4'-Diaminodiphenylmethane

COMPANY	PLANT LOCATION
Allied Chemical Corporation Specialty Chemicals Division	Moundsville, West Virginia
Dow Chemical, U.S.A.	Midland, Michigan
Jefferson Chemical Company, Inc.	Port Neches, Texas
Mobay Chemical Corporation	New Martinsville, West Virginia Cedar Bayou, Texas
Rubicon Chemicals, Inc.	Geismar, Louisiana
Uniroyal, Inc. Uniroyal Chemical Division	Naugatuck, Connecticut
The Upjohn Company Polymer Chemicals Division	La Porte, Texas

Adapted from the following sources:

1975 Directory of Chemical Producers, Stanford Research Institute, Menlo Park, California, page 818, 1975.

Synthetic Organic Chemicals, U.S. Production and Sales, 1973, U.S. International Trade Commission, ITC Publication 728, U.S. Government Printing Office, Washington, D.C., pages 23, 41 and 139, 1975.

Current Intelligence Bulletin 9

March 15, 1976

CHLOROFORM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

March 15, 1976

The enclosed background material on chloroform has been prepared by the Office of Extramural Coordination and Special Projects, National Institute for Occupational Safety and Health, to alert members of the occupational health community to new information on a potential occupational hazard.

Your comments and suggestions for changes to future reports are solicited.

Sincerely yours,

John F. Finklea, M.D.

John F. Finklea, M.D.
Director

Enclosure

CHLOROFORM

Summary

Chloroform has been shown to be carcinogenic by ingestion in laboratory mice and rats, according to a report recently released by the National Cancer Institute. Because of the uses of chloroform in the work environment and the potential for cancer induction in humans, the National Institute for Occupational Safety and Health (NIOSH) is alerting the occupational health community as part of its Current Intelligence System. In addition, NIOSH is attempting to identify a worker population at risk of chloroform exposures for epidemiologic study.

Introduction

On March 1, 1976, the National Cancer Institute released its report on the carcinogenic bioassay of chloroform.[1] According to this report, chloroform ingestion produced malignant kidney tumors in rats and hepatocellular carcinoma in mice.

Background

Chloroform is a colorless volatile liquid, has a normal boiling point of 61°C, and is miscible with the principal organic solvents. Chloroform is manufactured by the chlorination of methane in a process which can be made to yield varying proportions of methyl chloride, methylene chloride, chloroform, and carbon tetrachloride. A list of domestic manufacturers and producers of chloroform is presented in Table 1 and the domestic distributors of chloroform are listed in Table 2.

During 1974, 302 million pounds of chloroform were produced in the United States. Domestic sales for the same year were 252 million pounds.[3]

Most of the chloroform produced is consumed as a raw material in the preparation of fluorocarbons. [Fluorocarbons are used as aerosol propellants, refrigerants, and blowing agents as well as in the manufacture of fluorocarbon resins such as polytetrafluoroethylene].

Other applications[5] of chloroform have included use in the extraction and purification of penicillin and other antibiotics, in the purification of alkaloids, in the solvent extraction of vitamins and flavors, as a general solvent, as an intermediate in the preparation of dyes, drugs, and pesticides, and as an anesthetic. Chloroform is currently found in cough and cold preparations, dental preparations (tooth-ache drops, toothpastes, mouthwashes), and topical liniments. Chloroform would be found in most chemistry laboratories.

Toxicity

Human:

Chloroform was first used as an anesthetic in 1847. Its narcotic effects on the central nervous system have been well-documented.[6,7,8] Toxic hepatitis has been reported among chemical workers exposed to chloroform[9] and, in addition, cardiac irregularities during anesthesia, and local irritation when applied to skin, have also been reported.[10]

Two epidemiologic studies of occupational exposure to chloroform found episodes of lassitude, dry mouth, depression, irritability and painful urination.[9,11]

To date, there have been no published reports of any association between chloroform and cancer in humans.

Animal:

Depression of the central nervous system has been seen in a number of animal studies of effects of chloroform inhalation.[12] Inhalation of chloroform also produces dilation of pupils of the eyes, reduced reaction to light, and reduced intraocular pressure. Fatty degeneration and necrosis of the liver as well as kidney impairment have been seen in experimental animals after ingestion, inhalation, and intravenous administration.[13]

Carcinogenic effects of chloroform in laboratory animals have been reported in two published studies. Eschenbrenner, in 1945, produced hepatomas in 7 of 10 female mice fed 30 doses at 4-day intervals of approximately 600 to 1200 mg/kg/dose over a four-month period. The other three female mice died within the first week of the experiment. Male mice receiving similar doses also died within the first week.[14]

In the recent National Cancer Institute study[1], Osborne-Mendel rats were fed chloroform in corn oil (at 90 and 180 mg/kg body weight for males and at 100 and 200 mg/kg for females) for 111 weeks. A significant increase in epithelial tumors of the kidney in treated male rats was observed. Of the 13 tumors of renal tubular cell epithelium observed in 12 of the 50 high dose male rats, ten were carcinomas and three adenomas; two of the carcinomas were found to have metastasized. Two carcinomas and two adenomas of renal tubular epithelium were observed among the 50 low dose male rats. The tubular cell adenocarcinoma widely metastasized. An increase in thyroid tumors in chloroform-treated female rats was also seen; however, NCI does not consider these to be significant findings.

Mice (B6C3F) were fed chloroform for 92-93 weeks at 138 and 277 mg/kg doses for males and at 238 and 477 mg/kg doses for females. A highly significant increase in hepatocellular carcinomas was observed in both sexes of treated mice when compared with control animals. The incidence of hepatocellular carcinoma was 98% for males and 95% for females at the high dose, and 36% for males and 80% for females at the low dose compared with 6% in both matched and colony control males, none in matched control females, and 1% in colony control females. Nodular hyperplasia of the liver was observed in many low dose male mice that had not developed hepatocellular carcinoma.

Occupational Exposure

The National Institute for Occupational Safety and Health estimates that 40,000 persons are exposed occupationally to chloroform. The majority of these are workers in industries where chloroform is used in small amounts. These industries include those producing biological products, pharmaceutical preparations, paint and allied products, and surgical supplies, as well as hospitals, paper milling, petroleum refining and metal industries.

The current Occupational Safety and Health Administration ceiling value standard for workplace air is 50 ppm.[15]

On September 11, 1974, the National Institute for Occupational Safety and Health transmitted criteria for a recommended standard on chloroform to the Department of Labor. NIOSH's recommendations included that no worker be exposed to chloroform in excess of 10 ppm determined as a time-weighted average exposure for up to a 10-hour workday, 40-hour work week, or for any 10-minute period to more than 50 ppm.[10]

Epidemiologic Studies

The Division of Surveillance, Hazard Evaluations, and Field Studies, NIOSH, is planning to conduct environmental and mortality studies in industries in which people are exposed to chloroform. Efforts are now in progress to identify worker populations at risk of chloroform exposures for epidemiologic study.

TABLE 1

DOMESTIC MANUFACTURERS AND PRODUCERS OF CHLOROFORM

Allied Chemical Corporation Specialty Chemicals Division	Moundsville, West Virginia
Diamond Shamrock Corporation Diamond Shamrock Chemical Company Electro Chemicals Division	Belle, West Virginia
Dow Chemical U.S.A.	Freeport, Texas Plaquemine, Louisiana
E.I. DuPont de Nemours & Company, Inc. Industrial Chemicals Department	Niagara Falls, New York
Stauffer Chemical Company Industrial Chemical Division	Louisville, Kentucky
Vulcan Materials Company Chemicals Division	Newark, New Jersey Wichita, Kansas Geismar, Louisiana

Adapted From:

1975 Directory of Chemical Producers, United States of America, Stanford Research Institute, Menlo Park, California, 1975, p. 478.

Synthetic Organic Chemicals, U.S. Production and Sales, 1973, U.S. International Trade Commission, ITC Publication 728, Washington, D.C., 1975, p. 231.

TABLE 2

DOMESTIC DISTRIBUTORS OF CHLOROFORM

Distributors	Headquarters Address
Aldrich Chemical Co., Inc.	940 W. St. Paul Avenue Milwaukee, WI 53233
Allied Chemical	Morristown, NJ 07960
American Drug & Chemical Co.	3555 Hayden Avenue Culver City, CA 90230
Analabs, Inc. Sub. New England Nuclear	80 Republic Drive North Haven, CT 06473
Apache Chemicals, Inc.	P.O. Box 126 Seward, IL 61077
Ashland Chemical Company Industrial Chemicals & Solvents Division	Box 2219 Columbus, OH 43216
J.T. Baker Chemical Co.	Phillipsburg, NJ 08865
Bayside Research Corp.	P.O. Box 630146 Miami, FL 33163
Bodman Chemicals	P.O. Box 500 Media, PA 19063
Burdick & Jackson Laboratories, Inc.	1953 South Harvey Street Muskegon, MI 49442
Chemical Industries, Inc.	Box 991 Borger, TX 79007
Chemical Samples Co.	P.O. Box 20305 Columbus, OH 43220
Chem Service, Inc.	851 Lincoln Ave. P.O. Box 194 West Chester, PA 19380
Columbia Organic Chemical Co., Inc.	P.O. Box 9096 Columbia, SC 29290
Diamond Shamrock Corp.	1100 Superior Ave. Cleveland, OH 44114

DOMESTIC DISTRIBUTORS OF CHLOROFORM
(Continued)

Distributors	Headquarters Address
Dow Chemical Corp.	Barstow Bldg., 2020 Dow Center Midland, MI 48640
EM Laboratories, Inc.	500 Executive Blvd. Elmsford, NY 10523
Eastern Chemical Div. of Guardian Chemical Corp.	230 Marcus Blvd. Hauppauge, NY 11787
Eastman Organic Chemicals Eastman Kodak Company	Rochester, NY 14650
Fisher Scientific Co.	711 Forbes Avenue Pittsburgh, PA 15219
Gallard Schlesinger Chemical Manufacturing Corporation	584 Mineola Avenue Carle Place, NY 11514
Great Lakes Terminal & Transport	1750 North Kingsbury St. Chicago, IL 60614
J.F. Henry Chemical Co. Industrial and Fine Chemicals	245 Park Avenue East Rutherford, NJ 07073
I.C.N.-K & K Life Sciences Group	121 Express Street Plainview, NY 11803
I.C.N. Pharmaceuticals, Inc. Life Sciences Group	2727 Campus Drive Irvine, Cal 92664
Intsel Corp.	825 Third Avenue New York, NY 10022
Isotope Labeling Corp.	P.O. Box 838 Teaneck, NJ 07666
MC & B Manufacturing Chemists	2909 Highland Avenue Cincinnati, OH 45212
Mallinckrodt, Inc.	2nd & Mallinckrodt Street St. Louis, MO 63160
Merck & Company, Inc. Merck Chemical Division	Rahway, NJ 07065

DOMESTIC DISTRIBUTORS OF CHLOROFORM
(Continued)

Distributors	Headquarters Address
Miles Laboratories, Inc. Research Products	R 700, 1127 Myrtle Street Elkhart, IN 46514
New England Nuclear	549 Albany Street Boston, MA 02118
Norell Chemical Co., Inc.	Arbor Avenue and Clara Street Landisville, NJ 08326
Ruger Chemical Company	P.O. Box 806 Hillside, NJ 07295
Simmler and Son, Inc.	3755 Forest Park Avenue St. Louis, MO 63108
G. Frederick Smith Chemical Co.	867 McKinley Avenue Columbus, OH 43223
Stauffer Chemical Company Industrial Chemical Division	Westport, CT 06880
Tridom Chemical, Inc.	255 Oser Avenue Hauppauge, NY 11787
Joseph Turner & Company	Ridgefield, NJ 07657
Union Oil Company of California Amsco Division	3100 S. Meacham Road Palatine, IL 60067
VWR Scientific	Box 3200 San Francisco, CA 94119
Vulcan Materials Company Chemical Division	P.O. Box 545 Wichita, KS 67201

Adapted from Chem. Sources U.S.A., 1976 Edition, Directories Publishing Company, Flemington, New Jersey.

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Current Intelligence Bulletin 10

May 11, 1976

RADON DAUGHTERS

May 11, 1976

It has recently come to the attention of the National Institute for Occupational Safety and Health (NIOSH) that measurements of the radioactive decay product "daughter" concentrations of radon gas in a number of National Park Service caves are near the occupational limits as set forth in Occupational Safety and Health Administration's (OSHA) standards for uranium miners. National Park Service caves in which one or more samples greater than 0.30 working levels (WL) were found include Carlsbad Caverns National Park, New Mexico; Lehman Caves National Monument, Nevada; Mammoth Cave National Park, Kentucky; Oregon Caves National Monument, Oregon; and Round Spring Cave in Ozark National Scenic Riverways, Missouri. In addition to the radiation levels inside the caves, buildings above the ground at Mammoth Cave, cooled with cave air, had 0.6 WL alpha radiation. Studies of uranium miners have shown that the alpha radiation emitted by the radon "daughters" caused an increase in pulmonary malignancies which became evident ten or more years after individuals first started mining.

The OSHA requirements for uranium mines and deemed by Environmental Protection Agency (EPA) applicable to natural caves are as follows:

- Above 0.1 WL alpha radiation -- all underground smoking stopped

- 0.1 to 0.2 WL -- monitor workspace at least once yearly

- 0.2 to 0.3 WL -- monitor workspace quarterly

- Above 0.3 WL -- monitor workspace weekly and maintain exposure records on all exposed employees

- 1.0 to 2.0 WL -- immediate corrective action to lower the concentration below 1.0 WL

- Above 2.0 WL -- withdraw all workers not necessary to lower the concentrations below 1.0 WL

- Cumulative individual exposure shall not exceed 4 working level months in any calendar year

EPA states that the individual exposure limit of 4 WL months per year recommended by OSHA cannot be characterized as safe since the risk of lung cancer would be expected to double after 10 to 20 years employment. Therefore, it might be advisable to rotate long-term employees working in high radiation areas.

NIOSH supports the above recommendations, and is taking this opportunity to advise State Radiological Health officials of the potential hazards for privately owned caves and "cave air" conditioned buildings. Because there are a number of state and privately owned caves throughout the United States, NIOSH would also recommend the radiation levels in these caves be assessed.

Sincerely yours,

Edward J. Baier
Deputy Director

Current Intelligence Bulletin 11

July 7, 1976

DIMETHYLCARBAMOYL CHLORIDE (DMCC) REVISED

July 7, 1976 (Revised)

Dear Colleague:

On February 11, 1976, Dr. Norton Nelson, Professor and Chairman of the Institute of Environmental Medicine at New York University Medical Center, informed the National Institute for Occupational Safety and Health (NIOSH) of the carcinogenic potential of dimethylcarbamoyl chloride (DMCC) by inhalation in laboratory rats.

Presently, the only known uses of dimethylcarbamoyl chloride in the United States are in the synthesis by Hoffmann-LaRoche, Inc. (Nutley, NJ) of pharmaceuticals used in the treatment of myasthenia gravis (neostigmine bromide, neostigmine methylsulfate, and pyridostigmine bromide) and as a reagent for the synthesis of carbamates in chemical research laboratories.

Dimethylcarbamoyl chloride may be employed in the synthesis of carbamates (which are used as drugs and pesticides), in the synthesis of dyes, and in the synthesis of unsymmetrical dimethylhydrazine (a rocket fuel). It should also be noted that DMCC may be formed in side reactions during the manufacture of other products. For example, by letter of June 23, 1976, E.I. du Pont de Nemours & Company advised NIOSH that they have taken measures to protect their employees and customers due to the formation of up to 6 ppm (w/w) DMCC during Du Pont's production of phthaloyl chlorides.

Dimethylcarbamoyl chloride is prepared by the reaction of phosgene with trimethylamine. Domestic producers of DMCC have included Ashland Chemical Company (Great Meadows, NJ), Chemetron Corporation (La Porte, TX), Fabtex Corporation (Englewood Cliffs, NJ) and the Ott Division of Story Chemical Corporation (Muskegon, MI). The last known domestic commercial production of DMCC, approximately 3000 lbs., was manufactured about a year ago for use in pharmaceuticals. DMCC is manufactured in Germany by BASF, Aktiengesellschaft. DMCC is available from many suppliers of laboratory chemicals.

The very limited production and commercial use of DMCC in the United States suggests that only a small number of workers are exposed to this substance. It is estimated that fewer than 200 persons are at risk of occupational exposure to DMCC. Most of these would be intermittent exposures occurring in chemical laboratories; not included here are potential exposures to DMCC formed in side reactions during the synthesis of other products.

The acute toxic effects of DMCC that have been observed in laboratory animals include irritation to eye membranes, respiratory organs, and, after repeated contact, inflammation of the skin. The carcinogenic potential of DMCC was first reported by Van Duuren (Institute of Environmental Medicine, NYU Medical Center) in a 1972 preliminary report (J Nat Cancer Inst 48:1539-1541, 1972) and in 1974 (J Nat Cancer Inst 53:695-700, 1974). In this study, Van Duuren observed a high incidence of skin tumors and subcutaneous sarcomas, along with some papillary tumors of the lung in ICR/Ha Swiss mice following applications of DMCC to skin by both subcutaneous injection and intraperitoneal injection.

In the current study by Drs. Sidney Laskin and Marvin Kuschner (Institute of Environmental Medicine, New York University), reported to NIOSH by Dr. Nelson, rats exposed by inhalation to 1 ppm DMCC developed squamous cell carcinomas of the nose within 200 days. These tumors were seen in 89 of the 93 rats exposed. This very high incidence of nasal cancer and the short latency period in rats suggests a potentially serious hazard for workers exposed to DMCC. Therefore, NIOSH is distributing this Current Intelligence Bulletin to inform the occupational health community of these findings.

Sincerely yours,

John F. Finklea M.D.

John F. Finklea, M.D.
Director

Current Intelligence Bulletin 12

July 7, 1976

DIETHYLCARBAMOYL CHLORIDE (DECC)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

July 7, 1976

DIETHYLCARBAMOYL CHLORIDE (DECC)

In a May 5, 1976 letter, Dr. Norton Nelson, Professor and Chairman of the Institute of Environmental Medicine, New York University Medical Center, informed the Director of the National Institute for Occupational Safety and Health (NIOSH) of the mutagenic potential of diethylcarbamoyl chloride (DECC).

A study conducted by Dr. Frank Mukai (Institute of Environmental Medicine, New York University Medical Center), has shown DECC to be mutagenic in two E. coli strains (WP2 and WP2S from Witkin). However, DECC was not as mutagenic as its close analog, dimethylcarbamoyl chloride (DMCC). (DMCC has carcinogenic potential in laboratory rodents by subcutaneous and intraperitoneal injection and by inhalation, as reported in the NIOSH Current Intelligence Bulletin on dimethylcarbamoyl chloride).

Annual production of diethylcarbamoyl chloride (DECC) in recent years has been less than 15,000 pounds. The only known commercial domestic use of DECC is in the synthesis of the pharmaceutical diethylcarbamazine citrate, an anthelmintic (worming agent), produced and marketed under the trade names Hetrazan and Caricide by Lederle Laboratories, a division of American Cyanamid.

Current Intelligence Bulletin 13

August 16, 1976

EXPLOSIVE AZIDE HAZARD

CURRENT INTELLIGENCE BULLETIN: EXPLOSIVE AZIDE HAZARD

August 16, 1976

The National Institute for Occupational Safety and Health (NIOSH) is alerting you to an explosive hazard which may exist in hospital and clinical laboratory plumbing systems due to sodium azide formulated into diluents used in conjunction with automatic blood cell counters. These counters are found in over 15,000 hospitals and clinical laboratories throughout the United States.

NIOSH has recently learned of violent sodium azide-related explosions associated with automatic blood cell counters at a number of hospitals in the United States and Canada. In addition, we are aware of a violent azide explosion occurring while a constant temperature water bath in which sodium azide had been used as a preservative was being repaired. These explosions have the propensity to propel metallic fragments over a wide area and the potential for causing serious injury to exposed workers and others in the vicinity.

Sodium azide is a common preservative in many in vitro diagnostic products and is found in concentrations up to 0.1% in diluents used with automatic blood cell counters. After completion of the blood count procedure, the waste (containing azide) is commonly discharged into a drain used solely for this purpose, thus bathing the drain pipeline with solutions of sodium azide. Over a period of time, the azide reacts with copper, lead, brass, or solder in the plumbing system to form an accumulation of lead and/or copper azide. Lead azide is a more sensitive primary explosive than nitroglycerine and a more effective detonating agent than mercury fulminate; in comparison with lead azide, copper azide is even more explosive and too sensitive to be used commercially.

Future accumulation of lead and copper azides in plumbing systems can be retarded by thoroughly flushing any drain known to receive azides with copious amounts of water several times a day. The use of copper-and lead-free lines between the point of discharge of azide and the nearest pipe in which there is a good stream of water, or the use of azide-free reagents, may prevent future accumulation of explosive azides in plumbing. HOWEVER, THESE MEASURES WILL NOT DECONTAMINATE PLUMBING ALREADY CONTAINING EXPLOSIVE AZIDES. Procedures for the decontamination of plumbing systems containing copper and/or lead azide are enclosed.

Laboratory maintenance workers, especially plumbers, should be alerted to the azide hazard so that proper precautions can be taken. Violent explosions have resulted when plumbers have attempted to penetrate blocked azide-contaminated drainage systems with a flexible metal probe (snake) or to cut or saw azide-contaminated drain lines.

NIOSH would appreciate being advised of the details of any azide-related explosions and welcome your comments regarding the effectiveness of the enclosed decontamination procedures.

John F. Finklea, M.D.

John F. Finklea, M.D.
Director

Enclosure

DECONTAMINATION PROCEDURES FOR AZIDE CONTAMINATED PLUMBING

The following procedure[1] has been suggested by the Center for Disease Control, U.S. Public Health Service, for use in its laboratories:

1. Prepare 1 to 2 liters of 10% sodium hydroxide solution (100 g NaOH per liter of water).

2. Syphon all liquid from the trap and drain using a soft rubber or plastic hose. Use proper precautions against any hazardous chemicals which may be present.

3. Slowly pour the sodium hydroxide solution into the trap.

4. Tape to the sink a warning sign reading "Do Not Use Sink...Contains Caustic Material."

5. Allow the solution to remain in the trap for a minimum of 16 hours.

6. Flush the drain with water for a minimum of 15 minutes.

   If the drain will not flow, the sodium hydroxide should be removed by syphoning, if possible, then diluted with water. Maintenance personnel should be advised that the drain is potentially contaminated with explosive agents and caustic material.

The above procedure is designed to decontaminate a drain trap. Longer lengths of drain lines can be decontaminated with a similar procedure after plugging the drain below the point at which any azide contamination is likely to have occurred and then filling the entire length of pipe with 10% sodium hydroxide solution.

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[1]Manual Guide--Safety Management No. CDC-22, Decontamination of Laboratory Sink Drains to Remove Azide Salts, Center for Disease Control, Atlanta, Georgia, April 30, 1976.

Where it is not possible for a drain line to remain filled with sodium hydroxide solution for at least 16 hours, Coulter Electronics, Inc. has suggested the following:[2]

1. Pour five gallons of sodium hydroxide solution into the piping rapidly enough to simulate the flushing action of a water closet. CAUTION: The solution is caustic!

2. Allow the pipe to remain undisturbed by water or other effluents for at least 16 hours.

3. Flush with copious amounts of water.

4. Repeat steps 1, 2, and 3 two more times at intervals of a week or so.

Descriptions of several other procedures which have been suggested for the decontamination of azides are listed in the Journal of Chemical Education.[3]

PRECAUTIONS

Because the possibility of residual sodium hydroxide will always exist, personnel should wear gloves and face shields when breaking the drain line or trap for maintenance. (This equipment should be worn when breaking any laboratory drain, as the presence of hazardous chemicals should always be suspected.)

Extreme caution should be exercised when plugging a drain line potentially contaminated with heavy metal azides.

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[2] Personal Communication from Coulter Diagnostics, Inc., June 3, 1976.

[3] James O. Wear, "Azide Hazards with Automatic Blood Cell Counters," Journal of Chemical Education, 52, A23-A25, January 1975.

The decontamination of plumbing systems containing copper or its alloys (e.g., brass) should include a supplemental treatment with nitrous acid, since the sodium hydroxide procedure may not adequately remove accumulations of copper azides. The following nitrous acid decontamination procedure[4] has been employed with success:

1. Close the exit of the drain beyond the point of potential azide accumulation.

2. Fill the drain line with nitrous acid, prepared immediately before use by mixing equal volumes of a 20% solution of acetic acid with a 20% solution of sodium nitrite.

   CAUTION! The area should be well ventilated, as toxic vapors (oxides of nitrogen) may be released when azide reacts with nitrous acid.

3. Allow the nitrous acid solution to remain in the drain for twenty-four hours.

4. Open the exit of the drain.

5. Immediately repeat procedure once.

NOTE

The decontamination of plumbing systems is complicated by a number of factors, including the possible coating of heavy metal azides by impervious materials as well as the possible accumulation of heavy metal azides in cracks and threads of plumbing. Although the decontamination procedures do reduce the risk of explosion, even a "decontaminated" system should be treated with respect in recognition of the possibility of its being explosive. Maintenance people should be alerted so that proper precautions can be taken before working on plumbing potentially contaminated with heavy metal azides. Good work practices include shielding the person working on the plumbing, maximizing the distance between the person and the plumbing, and keeping all unnecessary personnel out of the area.

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[4]This procedure has been recommended and used by the Department of Health and Social Security, Government of the United Kingdom.

Current Intelligence Bulletin 14

September 27, 1976

INORGANIC ARSENIC
RESPIRATORY PROTECTION

September 27, 1976

Dear Colleague:

Because some inorganic arsenic compounds have a significant vapor pressure, the National Institute for Occupational Safety and Health (NIOSH) has recently eliminated certain types of respirators from its list of recommended protective equipment for workers exposed to inorganic arsenic.

The NIOSH recommendations for an inorganic arsenic standard suggest particular types of personal respiratory protective devices as suitable for employee protection under defined conditions. The current NIOSH recommendations are:

> Full face coverage---necessary to prevent eye and facial irritation. Half-mask respirators are eliminated from the list of approved devices.
>
> High efficiency particulate filters for inorganic arsenic compounds that have no significant vapor pressure---to enable meeting the recommended standard of 2.0 µg arsenic per cubic meter of air as specified in the criteria document transmitted to the Occupational Safety and Health Administration on June 23, 1975.
>
> Air-purifying respiratory protection with an acid gas canister, as a minimum, for inorganic arsenic compounds with significant vapor pressure (such as arsenic trichloride)---to prevent exposure to greater than the recommended maximum concentration of arsenic due to the passage of volatile arsenicals through a high efficiency filter.

Engineering controls are recommended to maintain arsenic concentrations below the occupational environment limit. Compliance should not be achieved by the use of respirators except during the time period necessary to install or test the required engineering controls, for nonroutine operations (such as a brief exposure to concentrations in excess of the limit as a result of maintenance or repair activities), or during emergencies when air concentrations of arsenic exceed the limit.

We hope you find this information helpful.

Sincerely yours,

Edward J. Baier
Deputy Director

Current Intelligence Bulletin 15

October 6, 1976

NITROSAMINES IN CUTTING FLUIDS

CURRENT INTELLIGENCE BULLETIN: NITROSAMINES IN CUTTING FLUIDS

October 6, 1976

On September 17, 1976, the National Institute for Occupational Safety and Health (NIOSH) was informed by the National Science Foundation (NSF) that Dr. David H. Fine (Thermo Electron Corporation, Waltham, Massachusetts), one of its grantees, confirmed the presence of a nitrosamine, diethanolnitrosamine, in commercial cutting fluids produced by four randomly selected companies.

Historically, nitrosamines have been regarded as one of the most potent families of animal carcinogens. Although nitrosamines are suspected to be human carcinogens, their carcinogenic potential in man has not been proven.

In the past year, two developments have drawn attention to the issue of nitrosamines as an occupational health hazard. The first is the introduction of a new analytical method, thermal energy analysis (TEA), with a sensitivity for nitrosamines in the part per billion (ppb) range. The other development is the recognition of the potential for formation of nitrosamines in air and other non-acidic media by reaction of secondary and tertiary amines with nitrites or other oxides of nitrogen.

The formation of diethanolnitrosamine in cutting fluids was first postulated and reported by Zingmark and Rappe in Sweden (AMBIO, Vol. 5 No. 2, 80-81, 1976). They measured diethanolnitrosamine in a specifically formulated "grinding fluid" containing nitrite and triethanolamine. They concluded that the potential hazard of working with these types of products should not be underestimated. Dr. Fine's results of September 17, 1976 underscore the concern raised by Zingmark and Rappe. Dr. Fine initially reported finding from 400 to over 1,000 ppm diethanolnitrosamine in eight commercial cutting fluids produced by four different manufacturers. He has also provided NIOSH with results which indicate up to 3% diethanolnitrosamine in certain cutting fluids. In addition, Dr. Fine has reported a study conducted during an actual machining operation showing the presence of 1000 ppm diethanolnitrosamine in the diluted cutting fluid prior to use, and 384 ppm after use. This

finding strongly suggests that machine operators may be continuously exposed to nitrosamines.

Occupational exposure to cutting fluids, primarily among machine operators, has been studied for possible health effects. A recent published account by Decoufle (Ann. N.Y. Acad. Sci., 271:94-101, 1976) relates that a slight excess mortality (not statistically significant) from respiratory and digestive cancers was observed among male workers exposed to cutting fluids in metal machining jobs.

Nomenclature for cutting fluid is not standardized. The term generally applies to substances used in drilling, gear cutting, grinding, lathing, milling, and other machining operations, for the purpose of cooling, lubricating, and removing metal or plastic chips, filings, and cuttings from the contact area. These substances are variously referred to as cutting, cooling, grinding, industrial, lubricating, and synthetic oils or fluids.

Commercial cutting fluids can be divided into four categories:

- Cutting Oils or Straight Oils --- contain mineral oil, fat, and additives. These oils are water insoluble.

- Soluble Cutting Oils --- contain mineral oil, fat, emulsifiers (may include amines), additives (rarely nitrite*), and water.

- Semi-Synthetic Cutting Oils --- contain mineral oil, water, fat, a soluble base (usually including amines), emulsifiers (may include amines), and additives (usually including nitrite).

- Synthetic Cutting Fluids --- a soluble base (usually including amines), additives (usually including nitrite) and water.

Various proprietary cutting fluids are produced by over one thousand companies in the United States. NIOSH estimates that 780,000 persons are occupationally exposed in the manufacture and use of cutting fluids.

Synthetic cutting fluids, semi-synthetic cutting oils, and soluble cutting oils may contain nitrosamines, as found by Dr. Fine, either as contaminants in amines, or as products from the reaction of amines (e.g., triethanolamine) with nitrite. Straight oils do not contain

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*Some consumers may incorporate additives containing nitrite into the soluble cutting oil while preparing it for use.

nitrites or amines but may contain polynuclear aromatic compounds (recognized as having carcinogenic potential).

Since many of the proprietary ingredients of cutting fluids have not undergone complete toxicological evaluation, NIOSH would caution any user contemplating changing from one cutting fluid formulation to another to give full consideration to the potential hazards of the substitute.

Enclosed are some industrial hygiene practices which can help minimize dermal and respiratory exposures to cutting fluids.

The potential for nitrosamine exposure during the use of cutting fluids will be further assessed as part of a proposed NIOSH project to determine the levels of nitrosamines in a number of factory environments. Follow-up epidemiologic studies are also anticipated. Studies of cancer induction in laboratory animals exposed to cutting fluids or cutting fluid components are also planned. In addition, a Criteria for a Recommended Standard which will address the problem of cutting fluids is scheduled to be completed in 1977.

John F. Finklea, M.D.

John F. Finklea, M.D.
Director

INDUSTRIAL HYGIENE PRACTICES TO MINIMIZE DERMAL AND RESPIRATORY EXPOSURE TO CUTTING FLUIDS

The following are suggested good industrial hygiene practices that can help in minimizing exposure to cutting fluids. The recent detection of nitrosamines in certain cutting fluids has compounded the recognized problem of cutting oil control.

1. Engineering Control. The most effective control of any contaminant is control at the source of generation. Effective engineering measures include the use of local exhaust ventilation, with a suitable collector, or the use of electrostatic precipitator.

2. Substitution. The substitution of a cutting fluid that does not contain either nitrosamine contaminated amines, or the necessary ingredients (amines and nitrites) for nitrosamine formation, is another possible control measure. Since many of the proprietary ingredients of cutting fluids have not undergone complete toxicological evaluation, caution should be used when contemplating any change from one cutting fluid formulation to another, giving full consideration to the potential hazards of the substitute.

3. Respirators. Personal respiratory protective devices should only be used as an interim measure while engineering controls are being installed, for non-routine use and during emergencies. Considering the carcinogenic potential and the lack of a standard for nitrosamines as a group, the only available personal respiratory protective measure is the use of a positive pressure supplied air respirator or a positive pressure self-contained breathing apparatus.

4. Protective clothing. Impervious clothing should be provided and should be replaced or repaired as necessary. Non-impervious clothing is not suggested, but if used, it should be removed and laundered frequently to remove all traces of cutting fluids before being reworn. (Laundry personnel should be made aware of the potential hazard from handling contaminated clothing.)

5. Personal cleanliness. All exposed areas of the body and any area that becomes wet with cutting fluids should be washed with soap or mild detergent. Frequent showering is recommended.

6. Isolation. Where possible, any operations involved with cutting fluids should be placed in an isolated area to reduce exposure to employees not directly concerned with the operations.

7. Barrier creams. Barrier creams may provide protection against dermal irritation and skin absorption, however, the barrier cream should not contain secondary or tertiary amines (which may react to form nitrosamines in the presence of nitrites).

Current Intelligence Bulletin 16

December 17, 1976

METABOLIC PRECURSORS OF A KNOWN HUMAN CARCINOGEN, BETA-NAPHTHYLAMINE

CURRENT INTELLIGENCE BULLETIN:

METABOLIC PRECURSORS OF A KNOWN HUMAN CARCINOGEN, BETA-NAPHTHYLAMINE

December 17, 1976

The National Institute for Occupational Safety and Health (NIOSH) has recently learned that both N-phenyl-β-naphthylamine (a widely used rubber antioxidant) and 2-nitronaphthalene (a by-product of α-naphthylamine production) are metabolized to the known human carcinogen, β-naphthylamine. This Bulletin emphasizes the potential problem of the metabolic conversion of materials believed to be relatively innocuous into known human carcinogens.

PHENYL-BETA-NAPHTHYLAMINE

In an October 8, 1976 letter to NIOSH, The B. F. Goodrich Company reported findings indicating that phenyl-β-naphthylamine (PBNA) is metabolized to β-naphthylamine (BNA) by the human body. This confirms an earlier study by Shell Nederland (T.Soc.Geneesk., 53:415-19, 1975).

PBNA was developed as a replacement chemical for BNA when, in the late 1940's, an association was shown to exist between BNA and human bladder cancer. It should be noted, however, that commercial PBNA is contaminated with 20-30 parts per million BNA.

In recent years, there have been three major domestic manufacturers of PBNA. E. I. du Pont de Nemours and Company manufactured PBNA at Deepwater, New Jersey, until December 1975. The only known current domestic producers of PBNA are The B. F. Goodrich Company at Akron, Ohio and Uniroyal, Inc., at Naugatuck, Connecticut. Total domestic production

of PBNA was 4.9 million pounds in 1973, 3 million in 1974, and 1.5 million in 1975.

Most of the phenyl-β-naphthylamine manufactured today is used as an antioxidant in rubber where it can comprise as much as 1% of the finished product. It can also find use as an antioxidant for greases and oils, as a stabilizer during the manufacture of synthetic rubber, and as an intermediate in the synthesis of dyes as well as other antioxidants. NIOSH estimates that 15,000 workers are potentially exposed to PBNA during its manufacture and use. The majority of these exposures are found among rubber fabricators.

Due to the wide use of PBNA in the rubber industry and its structural similarity to BNA, Shell Nederland studied the metabolism of PBNA. This study included four process operators with occupational exposure (by inhalation) to PBNA, along with 19 volunteers who each ingested 10 mg PBNA. Subsequently, one of these volunteers ingested an additional 30 mg PBNA. BNA measured in 24-hour urine samples was in excess of the quantity that would be expected as an impurity of the ingested PBNA. For the volunteers who consumed 10 mg PBNA (contaminated with 0.008 µg BNA), 0.4 to 3 µg BNA was found in their urine. The process operators, estimated to have inhaled 40 mg PBNA (contaminated with 0.032 µg BNA), were found to have 3 to 8 µg BNA in their urine samples.

As a confirmation of Shell's findings, B. F. Goodrich found 3 to 4 µg BNA in 24-hour urine samples from two volunteers who ingested 50 mg PBNA (containing 0.7 µg BNA) and from workers (unspecified number) estimated to have inhaled 30 mg PBNA. These findings, like the Shell study, indicate that phenyl-β-naphthylamine is at least partially metabolized by the human body to β-naphthylamine.

The acute and chronic toxicity of PBNA has been demonstrated in laboratory animals, however, its toxic effects in man are virtually unknown. An epidemiologic study, involving deaths among workers who entered the rubber industry after 1949 (when BNA was replaced by PBNA), shows no significant excess risk of bladder tumors in the industry when compared to the general population. The authors point out, however, that their data is not conclusive (Brit.J.Ind.Med., 31:140-51, 1974).

In addition to the studies demonstrating that PBNA is metabolized to BNA in humans, evidence has been presented which indicates that PBNA is also metabolized to BNA in dogs. At the Imperial Chemical Industries Laboratory in Manchester, England, radioactive PBNA was fed to dogs and radioactive BNA was found in collected urine.

The carcinogenic potential of PBNA in laboratory animals has undergone limited evaluation. In a study involving three female dogs (fed 540 mg

PBNA per day over a period of years), no bladder tumors were seen after 4.5 years. The investigators point out that the relatively few years of exposure to PBNA limits interpretation of these data (Proc.9thInt. Cong.Ind.Med., Budapest, 1948).

In a limited number of laboratory mice fed PBNA for 18 months, the incidence of hepatomas, when compared with controls, was significantly greater than expected. Other laboratory mice, given a single subcutaneous injection of PBNA, showed an increase in the total number of tumors when compared with controls; however, in this group, the incidence of site-specific tumors was not significantly greater than expected (National Cancer Institute, Aug. 1968).

2-NITRONAPHTHALENE

On August 19, 1976, E. I. du Pont de Nemours and Company informed NIOSH of unpublished studies regarding the carcinogenic potential and the metabolism of 2-nitronaphthalene in dogs. This compound (an unmarketed by-product produced during the commercial preparation of α-naphthylamine), like PBNA, is metabolized in laboratory dogs to BNA.

In a study by DuPont, 2-nitronaphthalene was fed (100 mg/kg and 50 mg/kg) to a female Beagle dog and β-naphthylamine was found in the urine. In another study (conducted by Allied Chemical), four female dogs were fed 100 mg of 2-nitronaphthalene daily for 8 months. After 10.5 years, bladder papillomas were observed in various stages of malignancy in the 3 dogs for which autopsy results were available. Allied concluded from this study that 2-nitronaphthalene is an active carcinogen in the female dog. In addition, 2-nitronaphthalene has been shown to be metabolized in monkeys to BNA (JNCI, 50:989-95, 1973). However, there are no reports concerning the metabolic fate of 2-nitronaphthalene in man.

RECOMMENDATIONS

The fact that certain substances, as illustrated by PBNA and 2-nitronaphthalene, can be metabolized to known carcinogens, lends a new perspective to controlling workplace hazards. NIOSH therefore recommends that:

> Industrial hygiene practices should be followed to minimize exposure to phenyl-β-naphthylamine in the workplace (attached).

- Although there are a number of antioxidants which may be substituted for phenyl-β-naphthylamine, alternatives should be fully evaluated with regard to possible human effects.

- More consideration should be given to the assessment of metabolic pathways of chemical agents found in the workplace.

- Materials which can be metabolized by the human body to known carcinogens should be handled in the same manner as carcinogens.

The National Institute for Occupational Safety and Health is making recommendations to the Occupational Safety and Health Administration (OSHA) for regulatory action.

John F. Finklea, M.D.

John F. Finklea, M.D.
Director

Enclosure

INDUSTRIAL HYGIENE PRACTICES TO MINIMIZE EXPOSURE TO PHENYL-β-NAPHTHYLAMINE

The recent confirmation of β-naphthylamine as a metabolic by-product, as well as a contaminant of phenyl-β-naphthylamine (PBNA) has indicated the need for minimizing exposure to PBNA. The following are suggested good industrial hygiene practices.

A. Regulated Area. Regulated areas should be established where PBNA is manufactured, processed, used, repackaged, released, handled or stored.

1. Access. Access should be restricted to employees who have been properly informed of the potential hazard of PBNA exposure and proper control methods.

2. Engineering Controls. The most effective control of any potentially toxic substance is control at the source of generation. Effective engineering measures include the use of walk-in hoods or specific local exhaust ventilation with suitable collectors.

3. Respirators. Personal respiratory protective devices should only be used as an interim measure while engineering controls are being installed, for non-routine use and during emergencies. Considering the carcinogenic potential and the lack of a standard, the appropriate personal respiratory protective measure is the use of a positive pressure supplied air respirator or a positive pressure self-contained breathing apparatus.

4. Protective Clothing. Protective full body clothing should be provided and its use required for employees entering the regulated area. Upon exiting from the regulated area, the protective clothing should be left at the point of exit. With the last exit of the day, the protective clothing should be placed in a suitably marked and closed container for disposal or laundering. (Laundry personnel should be made aware of the potential hazard from handling contaminated clothing.)

5. Personal Cleanliness. Employees should be required to wash all exposed areas of the body upon exiting from the regulated area.

6. Empty Containers. Empty PBNA containers should be placed in impervious bags to reduce possible contamination. These containers should be disposed of in a safe manner.

B. Medical Monitoring. All employees with a potential exposure to PBNA should be placed under a medical monitoring program including history and medical examinations to detect the presence of bladder cancers and specific urine analysis for β-naphthylamine.

C. Substitution. The substitution of another antioxidant for PBNA is a possible control measure. However, alternatives to PBNA should be fully evaluated with regard to possible human effects.

Current Intelligence Bulletin 17

April 25, 1977

2-NITROPROPANE

CURRENT INTELLIGENCE BULLETIN:

2-NITROPROPANE

April 25, 1977

A recently completed inhalation study indicates that 2-nitropropane, a widely used solvent in industrial coatings and printing inks, causes liver cancer in rats. In this study sponsored by the National Institute for Occupational Safety and Health (NIOSH), all laboratory rats exposed to 207 ppm 2-nitropropane over a six month period developed hepatocellular carcinoma or hepatic adenoma. Although this study suggests that 2-nitropropane is carcinogenic, its carcinogenic potential in man has not yet been researched.

This Bulletin provides the results of this animal study along with other pertinent data, their implications for occupational health, and precautions for handling 2-nitropropane in the workplace.

Background

Solvent systems containing 2-nitropropane are used in coatings (e.g., vinyl, epoxy, nitrocellulose, and chlorinated rubber), printing inks, and adhesives. Occupational exposure to these products may occur in various industries including industrial construction and maintenance, printing (rotogravure and flexographic inks), highway maintenance (traffic markings), shipbuilding and maintenance (marine coatings), furniture, food packaging, and plastic products. NIOSH estimates that 100,000 workers are potentially exposed to 2-nitropropane in these and other industries.

Synonyms for 2-nitropropane include dimethylnitromethane, isonitropropane, nitroisopropane, and 2-NP. Trade names under which 2-nitropropane is marketed include NiPar S-20™ (commercial grade 2-nitropropane) and NiPar S-30™ (mixtures of 1- and 2-nitropropane). 2-Nitropropane (in concentrations ranging from approximately 5 to 25 percent) is used in a number of solvent systems to contribute desirable properties such as improved drying time, more complete solvent release, better flow and film integrity, retardation of blushing, greater wetting ability, improved electrostatic spraying, and increased pigment dispersion.

The sole known domestic producer of 2-nitropropane has been Commercial Solvents Corporation (recently acquired by International Minerals and Chemical Corporation, IMC). 2-Nitropropane has been manufactured at their Sterlington, Louisiana plant since 1955, and in a pilot plant in Peoria, Illinois from 1940 to 1955. Of the estimated thirty million pounds of 2-nitropropane produced annually, twelve million pounds per year are sold domestically; the remainder is either used internally at IMC or exported.

Toxicology

In an inhalation study conducted by Huntingdon Research Center under a NIOSH contract (HEW/NIOSH Project No. 210-75-0039), Sprague-Dawley male rats and New Zealand White male rabbits were exposed to commercial grade 2-nitropropane for seven hours per day, five days per week. One group of fifty rats and fifteen rabbits was exposed to 207 ppm 2-nitropropane; a second group of the same size was exposed to 27 ppm, while a third group was maintained as a control. Ten rats from each group were killed after exposure periods of two days, ten days, one month, three months, and six months. Liver neoplasms, described as hepatocellular carcinoma or hepatic adenoma, were observed in all ten rats killed after six months of exposure to 207 ppm 2-nitropropane. No tumors were observed in any other animals in this study, including controls. However, hepatocellular hypertrophy, hyperplasia, and necrosis were reported in rats exposed to 207 ppm 2-nitropropane for three months. In addition, elevated liver weights were found in rats exposed to 207 ppm 2-nitropropane for one, three, and six months. Liver histopathology, as well as the liver weights, of rats exposed to 27 ppm 2-nitropropane did not differ from controls.

Although certain shortcomings do exist in the conduct of this study,* the experiment is sufficient to merit the concern of the occupational health community. NIOSH has been advised that further investigation of the toxicity of 2-nitropropane has recently begun (April, 1977) under the sponsorship of the IMC Chemical Group, Inc.

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* The fifty rats exposed to 207 ppm 2-nitropropane were weanling rats (younger and smaller than the other exposed rats and the control group) which were introduced to replace rats experiencing excess mortality during the first few days of exposure to 400 ppm 2-nitropropane. In addition, throughout the entire study, exposure to 2-nitropropane was conducted while food and water were present, thus introducing the potential for exposure by the oral route.

The effects of 2-nitropropane inhalation in laboratory animals have also been studied by Treon and Dutra (Arch. Ind. Hyg. and Occ. Med., 5:52, 1952). Five species of laboratory animals (2 animals of each species per exposure level) were exposed to various concentrations of 2-nitropropane. Acute exposures ranged up to 9000 ppm for short time periods (as low as one hour), while chronic exposure levels ranged down to 83 ppm 2-nitropropane for as long as 26 weeks. Treon and Dutra reported no histologic changes in the monkeys, rabbits, guinea pigs and rats exposed to 328 ppm or less regardless of exposure time.** However, both cats died within 17 days of exposure to 328 ppm and had severe liver damage and slight to moderate damage to the kidney and heart.

There are a number of published reports concerning acute health effects of occupational exposure to 2-nitropropane. One report of two workers attributes the death of one and liver damage in both workers to high level exposure to 2-nitropropane while painting the inside of a tank (Gaultier, M., et. al., Arch. d. Mal. Prof. 25:425, 1964). Another paper relates that continual exposure to concentrations of 20 to 45 ppm 2-nitropropane caused workers in one plant to experience nausea, vomiting, diarrhea, anorexia, and severe headaches (Skinner, J.B., Ind. Med. 16:441, 1947). A third report indicates that workers exposed to from 165 to 445 ppm mixed 1-and 2-nitropropane also experienced nausea, dizziness, headaches, and diarrhea (Documentation of Threshold Limit Values, American Conference of Governmental Industrial Hygienists, 1971). In addition, Williams, et. al., (New Eng. J. of Med., 291:1256, 1974) reported an excess of toxic hepatitis among construction workers applying epoxy resins to the walls of a nuclear power plant. Although the hepatitis in this case was attributed to exposure to a known hepatotoxin, p,p'-methylenedianiline (4,4'-diaminodiphenylmethane), these men were also observed to have used 2-nitropropane to remove the hardened resin from their skin.

**On subsequent examination by a NIOSH pathologist in March 1977, liver sections from two rats in this study which were exposed to about 300 ppm 2-nitropropane for seventeen exposures (7 hours each) showed clear cell foci. These and similar lesions are frequently seen prior to the development of hepatocellular carcinoma in rats exposed to known hepatic carcinogens. The lesions observed in the Treon and Dutra study are similar to those found in the liver sections of the rats in the Huntingdon study which were sacrificed after three months exposure to 207 ppm 2-nitropropane.

NIOSH Action and Recommendation

In order to characterize the potential for exposure to 2-nitropropane in the work environment, the National Institute for Occupational Safety and Health plans to conduct industrial hygiene surveys at facilities where 2-nitropropane is manufactured or consumed. In addition, an attempt will be made to identify a suitable worker population for epidemiologic studies.

The current Occupational Safety and Health Administration (OSHA) standard for occupational exposure to 2-nitropropane is 25 ppm. However, in light of the new information generated by the Huntingdon study, and while the carcinogenic potential of 2-nitropropane is being further evaluated, NIOSH believes that it would be prudent to handle 2-nitropropane in the workplace as if it were a human carcinogen. The attached interim recommended industrial hygiene practices were developed by NIOSH to help reduce occupational exposure to 2-nitropropane.

John F. Finklea M.D.

John F. Finklea, M.D.
Director

Attachment

INDUSTRIAL HYGIENE PRACTICES TO REDUCE EXPOSURE TO 2-NITROPROPANE

The following are suggested good industrial hygiene practices that can help to reduce exposure to 2-nitropropane. The recent finding of liver cancer in laboratory rats exposed by inhalation to 207 ppm 2-nitropropane for six months has indicated a need to reduce worker exposure.

A. Regulated Area. Regulated areas should be established during manufacture, filling operations, use, release, handling or storage.

1. Access. Access should be restricted to employees who have been properly informed of the potential hazard of 2-nitropropane exposure and proper control measures.

2. Engineering Controls. The most effective control of any contaminant is control at the source of generation wherever possible. Effective engineering measures may include the use of walk-in hoods, or specific local exhaust ventilation. Suitable collectors should be used to prevent community air pollution.

   a. Due to the explosive potential of 2-nitropropane spark proof ventilation systems should be selected.

   b. Wherever possible the operations utilizing 2-nitropropane should be enclosed (with appropriate ventilation) to reduce exposures to the operators and others in the area.

3. Respirators. Personal respiratory protective devices should only be used as an interim measure while engineering controls are being installed, for non-routine use and during emergencies. Considering the carcinogenic potential of 2-nitropropane and the current Occupational Safety and Health Administration (OSHA) standard based on other toxicity, the appropriate personal respiratory protective measure is the use of a positive pressure supplied air respirator, or a positive pressure self-contained breathing apparatus.

4. Protective Clothing. Protective full body clothing should be provided and its use required for employees entering the regulated area. Upon exiting from the regulated area, the protective clothing should be left at the point of exit. With the last exit of the day, the protective clothing should be placed in a suitably marked and closed container for disposal or laundering. (Laundry personnel should be made aware of the potential hazard from handling contaminated clothing.)

5. Cleanliness. Employees should be required to wash all exposed areas of the body upon exiting from the regulated area.

6. Isolation. Any operations involving 2-nitropropane should be placed in an isolated area, in combination with other engineering controls, to reduce exposure to employees not directly concerned with the operations.

B. Medical Monitoring. All employees with a potential exposure to 2-nitropropane should be placed under a medical monitoring program including history and medical examinations with specific emphasis on liver function tests.

C. Substitution. The substitution of a solvent that does not contain 2-nitropropane is another possible control measure. Caution should be exercised in selecting a substitute for 2-nitropropane, giving full consideration to the possible toxic effects of the substitute.

Current Intelligence Bulletin 18

July 1, 1977

ACRYLONITRILE

CURRENT INTELLIGENCE BULLETIN:

ACRYLONITRILE

July 1, 1977

The National Institute for Occupational Safety and Health (NIOSH) has recently been informed that occupational exposure to acrylonitrile may be associated with an excess of lung and colon cancer.

In May 1977, E. I. du Pont de Nemours & Company, Inc., informed NIOSH of results of a preliminary epidemiologic study demonstrating an excess of cancer among workers exposed to acrylonitrile at a Du Pont textile fibers plant in Camden, South Carolina. Additionally, in April, NIOSH received from the Manufacturing Chemists Association (MCA) a one-year interim report of on-going ingestion and inhalation studies of acrylonitrile in laboratory rats; the rats developed a variety of tumors, including carcinomas.

Background

Acrylonitrile is an explosive, flammable liquid having a normal boiling point of 77°C and a vapor pressure of 80 mm (20°C). The toxic effects of acrylonitrile are similar to cyanide poisoning. The chemical structure of acrylonitrile, CH_2=CHCN, resembles that of vinyl chloride, a material known to cause human cancer. Synonyms for acrylonitrile include acrylon, carbacryl, cyanoethylene, fumigrain, 2-propenenitrile, VCN, ventox and vinyl cyanide.

Approximately one and one-half billion pounds per year of acrylonitrile are manufactured in the United States by the reaction of propylene with ammonia and oxygen in the presence of a catalyst. A number of other processes have been used in the past. Current domestic producers of acrylonitrile are American Cyanamid Company (New Orleans, Louisiana), E. I. du Pont de Nemours & Company, Inc. (Beaumont, Texas and Memphis, Tennessee), Monsanto Company (Chocolate Bayou, Texas), and The Standard Oil Company (Ohio) (Lima, Ohio).

The major use of acrylonitrile is in the production of acrylic and modacrylic fibers by copolymerization with methyl acrylate, methyl methacrylate, vinyl acetate, vinyl chloride, or vinylidene chloride. Acrylic fibers, marketed under tradenames including Acrilan, Creslan, Orlon, and Zefran, are used in the manufacture of apparel, carpeting, blankets, draperies, and upholstery. Some applications of modacrylic fibers are synthetic furs and hair wigs; tradenames for modacrylic fibers include Acrylan, Elura, SEF, and Verel. Acrylic and/or modacrylic fibers are manufactured from acrylonitrile by American Cyanamid Company (Milton, Florida), Dow Badishe Company (Williamsburg, Virginia), E. I. du Pont de Nemours & Company, Inc. (Camden, South Carolina and Waynesboro, Virginia), Eastman Kodak Company (Kingsport, Tennessee), and Monsanto Company (Decatur, Alabama).

Other major uses of acrylonitrile include the manufacture of acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins (used to produce a variety of plastic products), nitrile elastomers and latexes, and other chemicals (e.g., adiponitrile, acrylamide). Acrylonitrile is also used as a fumigant. The U.S. Food and Drug Administration has recently banned the use of an acrylonitrile resin for soft drink bottles.

NIOSH estimates that 125,000 persons are potentially exposed to acrylonitrile in the workplace.

Human Epidemiologic Studies

A preliminary epidemiologic study conducted by the E. I. du Pont de Nemours & Company, Inc., indicated an excess risk of lung and colon cancer among workers with potential acrylonitrile exposure. This study examined the cancer experience of a cohort of 470 male workers who began working in the polymerization operation at Du Pont's Camden, South Carolina textile fibers plant between 1950 and 1955; only persons who are actively employed or who have retired from Du Pont were included in the study. A more complete analysis will include an approximately 400 additional workers also employed during this time, but who quit or were laid off.

In a study based on Du Pont's Mortality File, the cohort experienced a total of 8 deaths due to cancer between 1969 and 1975 (allowing for a 20-year latency period). Only 4 deaths would have been expected among this cohort based on Du Pont company mortality rates, 1969-75 (excluding the mortality experience of the cohort), and about 5 deaths would have been expected based on rates for U.S. white males, 1970. Of the eight cancer deaths, four were due to cancer of the lung while the expected number of lung cancer deaths was 1.5.

In another analysis, data from the Du Pont Cancer Registry (including only cancer diagnoses for active employees enrolled in Du Pont's insurance program) revealed 16 cancer cases occurring between 1969 and 1975 among

the cohort of workers (again allowing for a 20-year latency period). Only 5.8 cases would have been expected based on Du Pont company rates (excluding the cohort). Six of these cases were lung cancers (1.5 expected), three were cancers of the large intestine (0.5 expected), and the remaining seven cancers were from seven other primary sites. Because of incomplete reporting, skin cancer cases were excluded from this analysis.

A total of 18 cancers (appearing on Du Pont's Mortality File and/or Cancer Registry) occurred between 1969 and 1975 among the cohort of 470 workers first exposed between 1950 and 1955. All cancer cases occurred among the approximately 350 workers who were first exposed to acrylonitrile during the start-up of the plant between 1950 and 1952. Du Pont stresses the preliminary nature of these findings and does "not consider this study to provide definitive evidence of the carcinogenicity of acrylonitrile in man;" however, Du Pont did state that these findings, when considered in light of the recent animal tests, "raise a serious suspicion that it [acrylonitrile] may be a human carcinogen."

Laboratory Animal Studies

In April 1977, the Manufacturing Chemists Association reported interim results of two-year feeding and inhalation studies of acrylonitrile in laboratory rats. The following results were reported at the end of the first year of investigation by The Dow Chemical Company.

In the ingestion study, acrylonitrile is being incorporated into the drinking water of laboratory rats at concentrations of 0, 35, 100, or 300 ppm (corresponding to doses of approximately 0, 4, 10, or 30 mg/kg body weight/day). Rats ingesting 35 ppm acrylonitrile exhibited mild signs of toxicity (decreased water and food consumption, and decreased body weight gain), while those ingesting 100 or 300 ppm showed marked signs of toxicity. Male and female rats that ingested 100 or 300 ppm acrylonitrile for 12 months were reported to have developed stomach papillomas (1 of 20 rats at 100 ppm, and 12 of 20 at 300 ppm), central nervous system tumors (2 of 20 at 35 ppm, 6 of 20 at 100 ppm, and 3 of 20 at 300 ppm), and Zymbal gland carcinoma (2 of 20 at 100 ppm, and 2 of 20 at 300 ppm); no such tumors were seen in control animals.

In the inhalation study, male and female rats are being exposed to 0, 20, or 80 ppm acrylonitrile for six hours per day, five days per week. Following one year of exposure to 80 ppm acrylonitrile, 26 rats were killed; three of these were found to have developed central nervous system tumors comparable to those reported in the ingestion study. The investigators also reported that gross examination of other rats in this study exposed to 80 ppm acrylonitrile has revealed an increased incidence of ear canal tumors and mammary region masses. In animals exposed to 20 ppm, there was an apparent increase in subcutaneous masses of the mammary region although

no ear canal or central nervous system tumors were observed at this dose level.

Acute toxic effects of acrylonitrile have been extensively studied in a wide variety of laboratory animals. There is considerable variation in resistance to acrylonitrile exposure in different species. Guinea pigs seem to be the most resistant to the toxic effects of acrylonitrile inhalation while dogs are least resistant. Toxic effects of acrylonitrile inhalation which have been noted in animals include damage to the central nervous system, lung, liver, and kidneys (Krysiak, Medycyna Pracy, 22:601-10, 1971; Knobloch, Medycyna Pracy, 22:257-69, 1971). When administered to pregnant mice, acrylonitrile has also been found to be embryotoxic (Scheufler, Biol. Rundsch., 14:227-9, 1976).

NIOSH Action

In light of the Du Pont data, the National Institute for Occupational Safety and Health (NIOSH) has apprised major manufacturers and users of the possible health effects associated with acrylonitrile exposure. NIOSH has also suggested that these firms examine medical records of their employees in order to determine the existence of any such health effects. In addition, NIOSH is taking action to identify a suitable worker population for possible epidemiologic studies.

NIOSH is conducting an assessment of control technology in the plastics and resins industry (including acrylonitrile processes), which will identify and define technology for reducing occupational exposures. NIOSH is also developing a criteria document containing a recommended standard for occupational exposure to nitriles, including acrylonitrile.

Recommendation

The current Occupational Safety and Health Administration (OSHA) standard for occupational exposure to acrylonitrile is an 8-hour Time Weighted Average of 20 ppm. However, in light of the new human information generated by Du Pont, as well as the animal data provided by MCA, NIOSH believes it would be prudent to handle acrylonitrile in the workplace as if it were a human carcinogen. The attached interim recommended industrial hygiene practices were developed by NIOSH to help reduce occupational exposure to acrylonitrile.

John F. Finklea, M.D.
Director

Attachment

INDUSTRIAL HYGIENE PRACTICES TO REDUCE EXPOSURE TO ACRYLONITRILE

The recent finding of cancer associated with workers occupationally exposed to acrylonitrile has indicated a need to reduce worker exposure. The following are suggested good industrial hygiene practices that can help to reduce exposure to acrylonitrile.

A. Regulated Area. Regulated areas should be established during manufacture, polymerization, use, handling or storage.

1. Access. Access should be restricted to employees who have been properly informed of the potential hazard of acrylonitrile and proper control measures.

2. Engineering Controls. The most effective control of any contaminant is control at the source of generation wherever possible. Effective engineering measures may include enclosure and/or specific local exhaust ventilation with suitable collectors to prevent community air pollution.

a. Wherever possible the operations utilizing acrylonitrile should be enclosed (with appropriate ventilation) to reduce exposures to the operators and others in the area.

b. Due to the explosive potential of acrylonitrile, spark proof ventilation systems should be selected.

c. Regularly scheduled examinations for leakage of acrylonitrile from the system should be performed using appropriate instrumentation, or sampling and analytical techniques.

d. With specific respect to the polymerization operation, double mechanical pump seals have reduced leakage. Effective stripping of the acrylonitrile monomer before the polymer is dried and blended has decreased occupational exposure to the monomer.

3. Respirators. Personal respiratory protective devices should only be used as an interim measure while engineering controls are being installed, for non-routine use and during emergencies. Considering the carcinogenic potential of acrylonitrile, the appropriate personal respiratory protective measure is the use of a positive pressure supplied air respirator, or a positive pressure self-contained breathing apparatus.

4. Protective Clothing. Protective full body clothing should be provided and its use required for employees entering the regulated area. Upon exiting from the regulated area, the protective clothing should be left at the point of exit. With the last exit of the day, the protective clothing should be placed in a suitably marked and closed container for disposal or laundering. (Laundry personnel should be made aware of the potential hazard from handling contaminated clothing.)

5. Cleanliness. Employees should be required to wash all exposed areas of the body upon exiting from the regulated areas.

6. Isolation. Any operations involving acrylonitrile should be placed in an isolated area, in combination with other engineering controls, to reduce exposure to employees not directly concerned with the operations.

B. Medical Monitoring. All employees with a potential exposure to acrylonitrile should be placed under a medical monitoring program including history and periodic medical examinations.

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