

Current Intelligence Bulletin 9

March 15, 1976

CHLOROFORM



(66)

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

NATIONAL INSTITUTE FOR OCCUPATIONAL
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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.
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 applications⁵ 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 chloroform⁹ 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 study¹, 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

<u>Distributors</u>	<u>Headquarters Address</u>
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)

<u>Distributors</u>	<u>Headquarters Address</u>
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)

<u>Distributors</u>	<u>Headquarters Address</u>
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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16. Number not used.

NIOSH

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Center for Disease Control
National Institute for Occupational Safety and Health