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ETHYLENE DIBROMIDE (EDB)
(Revised)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) Current Intelligence Bulletin is the primary product of the Current Intelligence System. The purpose of the Current Intelligence System is to promptly review, evaluate, and disseminate new information received by NIOSH that may indicate either the existence of an occupational hazard not previously recognized or a greater hazard than generally known. The Document Development Branch staff within the Division of Standards Development and Technology Transfer prepared this Bulletin.

Current Intelligence Bulletins are disseminated to NIOSH staff, other government agencies, and the occupational health community, including academia, industry, labor, and public interest groups. The Bulletins are intended to disseminate new data that may affect prevailing perceptions of occupational hazards. They convey important public health information and recommend voluntary protective measures. Current Intelligence Bulletins do not recommend occupational standards, nor do they have any regulatory status.

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NIOSH CURRENT INTELLIGENCE BULLETIN: #37

ETHYLENE DIBROMIDE (EDB)
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The National Institute for Occupational Safety and Health (NIOSH) reaffirms its 1977 recommendation that ethylene dibromide (EDB) be treated as a potential occupational carcinogen in the workplace. This includes a ceiling limit of 0.13 ppm (1.0 mg/m^3) as determined over any 15-minute sampling period and use of appropriate controls to reduce worker exposure. Recent animal studies involved exposure to ethylene dibromide by skin application, oral administration, and inhalation. Statistically significant increases in tumors of the respiratory tract, mammary gland, spleen, and nasal cavity were observed. Inhalation studies with rats and mice at ethylene dibromide concentrations below the current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 20 ppm demonstrated a carcinogenic risk. In addition, the new animal bioassay studies reaffirm the increased toxic effects reported in 1978 when EDB is administered with disulfiram, a widely-used drug in alcoholism control programs. This increased interaction may not necessarily be restricted to disulfiram, but may occur with similarly structured compounds such as Thiram®, a fungicide and seed disinfectant.

BACKGROUND

Purpose of Bulletin

This Bulletin is being released because of the anticipated increased use of EDB as a fruit fumigant, and to alert workers who may have a potential EDB exposure to recent information about its potential carcinogenic risk. This information reinforces NIOSH's 1977 assessment that EDB is highly toxic and may cause cancer in humans.[1] In the 1977 assessment, NIOSH concluded that persons chronically exposed to EDB may be at increased risk of adverse reproductive and other effects. Evidence from animal experiments indicates that these effects may include sterility, inheritable changes in offspring, teratogenesis, and adverse effects on the liver, kidneys, heart, and other internal organs. Skin contact with EDB was found to produce chemical burns as well as systemic effects from percutaneous absorption.

Production and Use

EDB was first produced on a commercial scale during the mid-1920's. Current U.S. production is estimated at approximately 300 million pounds annually. EDB is used primarily as a scavenger in leaded fuels in combination with ethylene dichloride. These scavengers are used to form volatile lead compounds during combustion, which are more completely removed from the

combustion chamber. This usage is decreasing as the consumption of leaded gasoline declines. EDB is also used as a soil, grain, and fruit fumigant, as an intermediate in the synthesis of dyes and pharmaceuticals, and as a solvent for resins, gums, and waxes. NIOSH estimates that approximately 108,000 U.S. workers are potentially exposed to EDB during its production and use. In addition, an estimated 875,000 workers are potentially exposed to very low levels of EDB while working with leaded gasoline.[2]

Exposure Standards and Guides

OSHA's current standard for occupational exposure to EDB is 20 ppm as a time-weighted average (TWA) concentration for an 8-hour work shift, with an acceptable ceiling concentration of 30 ppm. A maximum peak above the acceptable ceiling concentration for an 8-hour work shift of 50 ppm for not more than 5 minutes is also permitted (29 CFR 1910.1000). This standard was adopted from the American National Standards Institute recommendation (ANSI Z37.31-1970).

In 1977, NIOSH recommended that occupational exposure to EDB be limited to a ceiling concentration of 0.13 ppm (1.0 mg/m^3), as determined over any 15-minute sampling period.[1]

In 1978, the American Conference of Governmental Industrial Hygienists (ACGIH) voided their 20-ppm threshold limit value (TLV) recommendation and assigned EDB an A1b classification (Human Carcinogen) without a TLV. After further review of the data in 1980, the ACGIH changed the classification to A2 (Industrial Substances Suspect of Carcinogenic Potential for Man). No TLV for EDB is assigned.[3]

In addition, California's Division of Occupational Safety and Health (Cal/OSHA) has had an Emergency Temporary Standard of 0.13 ppm adopted that became effective September 23, 1981. If this level is not rejected by the California Office of Administrative Law, it will remain in effect for 120 days. This is the same level recommended by NIOSH in 1977.

Extent of Exposures

Most of the environmental data on EDB came from the monitoring of exposures at EDB manufacturing operations, gasoline production and distribution facilities, and fruit fumigation operations.

NIOSH performed an industrial hygiene survey of two manufacturing and two user facilities of EDB. Samples were taken for more than 69 potentially-exposed workers in 17 job classifications. Median EDB exposures by similar job types in the manufacturing processes ranged from 0.010 to 0.5 ppm (35 TWA personal samples), and 0.0002-0.054 ppm in antiknock blending operations (39 TWA personal samples). General area samples collected at breathing zone heights had median TWA levels of 0.2 ppm for 10 samples at process sites, and 0.5 ppm for 3 samples at laboratory sites.

For quality control samples, EDB ceiling levels ranged from 0.04 to 23.4 ppm; for loading and unloading of tank cars, they were 0.09-2.4 ppm.[4]

A NIOSH environmental survey of fruit fumigation operations reported worker exposure (personal samples) to EDB ranging from nondetectable (8 of 29 samples) to 2.92 ppm for a post fumigation fruit loader in the transport truck trailer. Forklift operator exposures ranged from 0.06 to 2.08 ppm. Area samples of airborne EDB concentrations ranged from nondetectable (13 of 33 samples) to 2.96 ppm at the EDB introduction point into the fumigation chamber.

In another survey, conducted at three fruit packing plants, personal and area air samples were collected for the determination of EDB exposures. Of the 14 personal samples collected, EDB was nondetectable in 13 samples, with the other indicating a concentration of 0.14 ppm for a fumigator. Area sample airborne EDB concentrations ranged from nondetectable (16 of 20 samples) up to 0.81 ppm for a sample collected at the door of the fumigation chamber.[6]

TOXICITY

Evidence of Carcinogenicity in Experimental Animals

In 1977, NIOSH reported the preliminary results of a National Cancer Institute (NCI) study that indicated potential carcinogenic effects in rats and mice when EDB was administered by gavage.[7] The completed bioassay was reported in 1978.[8] Under the conditions of this bioassay, EDB was carcinogenic to Osborne-Mendel rats and B6C3F1 mice. Additional animal carcinogenicity bioassays have been conducted since then to assess the carcinogenic potential of EDB by inhalation and skin absorption.

Van Duuren et al. reported in 1979 an increased incidence of skin papillomas, skin carcinomas, and lung tumors in treated male and female noninbred Ha:ICR Swiss mice. The animals received repeated skin applications of EDB 3 times weekly for 40-594 days at 25 or 50 mg/application/mouse. This was the first reported study demonstrating EDB to be carcinogenic by skin application.[9]

The National Toxicology Program (NTP) and NCI recently reported the results of a carcinogenesis bioassay of EDB by the inhalation route.[10] Groups of rats and mice of each sex were exposed to airborne EDB at concentrations of 10 and 40 ppm, levels below and above OSHA's PEL of 20 ppm. Animals were exposed 6 hours/day, 5 days/week for 78-103 weeks.

In this bioassay, EDB was found to be carcinogenic for rats at both the 10- and 40-ppm dosages, causing increased incidences of tumors of the nasal cavity and adenomas of the pituitary gland in males and females, hemangiosarcomas of the circulatory system and mesotheliomas in the tunica vaginalis in males, and fibroadenomas of the mammary gland in females. Likewise, EDB was carcinogenic for mice at both dosages, causing increased

incidences of alveolar/bronchiolar carcinomas in males and females, and fibrosarcomas in the subcutaneous tissue, hemangiosarcomas of the circulatory system, tumors of the nasal cavity, and adenocarcinomas of the mammary gland in females.

Concurrent with the NTP and NCI study, NIOSH sponsored a study on EDB's chronic inhalation toxicity in rats.[11] The study was designed to determine the effects of EDB inhalation at OSHA's current PEL of 20 ppm, with and without disulfiram in the diet. Rats were exposed 7 hours/day, 5 days/week, for 18 months to simulate occupational exposure to EDB.

The results showed a high mortality rate and a statistically significant increase in the incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity for rats exposed by inhalation to EDB at 20 ppm and fed the standard rat diet. Rats exposed by inhalation at 20 ppm and fed the diet containing 0.05% disulfiram by weight exhibited a higher mortality rate, as well as an earlier development and a statistically significant increased incidence of tumors of the liver and mesentery compared with those animals exposed to EDB alone.

These data[10,11] demonstrate EDB to be carcinogenic in rats and mice when exposed by inhalation. The data also show that the addition of disulfiram to the diet results in approximately a ten-fold increase in the incidence of hepatocellular carcinomas over exposure to EDB alone. EDB has also been shown to be carcinogenic in mice as a result of percutaneous absorption.[9]

Epidemiologic Evidence of Cancer in Humans

The epidemiologic studies of EDB reported in the literature are inconclusive because they suffer from small cohort size, incomplete or missing exposure data, and insufficient latencies to observe carcinogenic effects.

In 1980, a retrospective mortality study of 161 workers (99 in Plant A and 63 in Plant B) exposed to EDB at two EDB manufacturing plants, was reported. The results indicated an observed increase in deaths due to malignant neoplasms and nonmalignant respiratory disease among the workers from Plant B. However, when the data from both plants were combined, no significant increase in mortality was observed.[12] In another study only one death was observed in a group of 53 workers potentially exposed to EDB in a chemical manufacturing plant. The cause was listed as cancer of the kidney.[13]

In studies of the effect of EDB exposure on sperm production conducted in 1977 and 1978, sperm counts were performed on 59 workers potentially exposed to EDB in a chemical manufacturing plant. The author concluded that exposures to EDB at the levels found for this population (less than 5.0 ppm) had no adverse effect on sperm counts. Neither possible confounding exposures nor the health of the individuals was discussed. No tests were performed to determine sperm motility, penetrance, morphology, or density or to evaluate other sperm function parameters.[13]

In 1979, a retrospective evaluation of the reproductive histories of exposed workers at four EDB manufacturing plants was published. The authors assessed the reproductive histories in terms of the number of live births in 297 wives of workers. The observed number of live births (only 50% of the expected value) was significantly lower than expected at one of the four plants.

However, the employees at this plant had 22 known surgical and nonsurgical sterilizations, the highest rate of the four plants. No significant difference was observed in expected births at the other three plants. No information was given on total conceptions, including spontaneous or induced abortions, among workers' wives.[14]

Evidence of Mutagenicity

A 1979 study reported that gaseous EDB at concentrations ranging from 0.2 to 2 ppm induced significant numbers of sex-linked recessive lethal mutations in Drosophila melanogaster males. Mutation induction was directly proportional to both exposure time and exposure concentration up to 60 ppm-hours, for all cell stages tested. This genetic evidence is in concordance with the irreversible, cumulative nature of EDB toxicity.[15]

RECOMMENDATIONS

The recent experimental data reinforce NIOSH's 1977 conclusion that ethylene dibromide is carcinogenic in animals. Ethylene dibromide has been shown to cause significant increases in tumors of the respiratory tract, mammary gland, spleen, and nasal cavity when administered to animals by skin application, gavage, or inhalation. Furthermore, the data confirm that when disulfiram is administered concurrently with EDB both its toxicity and carcinogenicity are enhanced. As was reported in 1978 by NIOSH, the interaction of EDB and disulfiram warrants a special precaution, and measures should be taken to prevent any individual from being exposed to both substances at the same time.[16] This increased interaction may not necessarily be restricted to disulfiram, but may occur with similarly structured compounds such as Thiram®.

Although humans and animals may differ in their susceptibilities to specific chemical compounds, any substance that produces cancer in experimental animals should be considered a potential human carcinogen.

NIOSH urges employers to voluntarily assess the conditions under which their workers may be exposed to EDB, especially with concurrent exposures to disulfiram or other similarly structured chemicals, such as Thiram®. NIOSH reaffirms its 1977 recommended workplace environmental limit of 0.13 ppm. Employers should regard this level as the upper boundary of exposure and make every effort to maintain the exposure as low as is technically feasible.

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Assistant Surgeon General
Director

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APPENDIX I

IDENTIFIERS AND SYNONYMS FOR ETHYLENE DIBROMIDE

Chemical Abstracts Service Registry Number 106-93-4
NIOSH RTECS Number KH92750
Chemical Formula $C_2H_4Br_2$

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

APPENDIX II

MANUFACTURERS OF ETHYLENE DIBROMIDE

Dow Chemical U.S.A.
2030 Dow Center
Midland, Michigan

Ethyl Corporation
330 South Fourth Street
Richmond, Virginia

Great Lakes Chemical Corp.
P. O. Box 2200
West Lafayette, Indiana

PPG Industries, Inc.
One Gateway Center
Pittsburgh, Pennsylvania

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS

1.	Chloroprene	- January 20, 1975
2.	Trichloroethylene (TCE)	- June 6, 1975
3.	Ethylene Dibromide (EDB)	- July 7, 1975
4.	Chrome Pigment	- June 24, 1975 - October 7, 1975 - October 8, 1976
5.	Asbestos - Asbestos Exposure during Servicing of Motor Vehicle Brake and Clutch Assemblies	- August 8, 1975
6.	Hexamethylphosphoric Triamide (HMPA)	- October 24, 1975
7.	Polychlorinated Biphenyls (PCB's)	- November 3, 1975 - August 20, 1976
8.	4,4'-Diaminodiphenylmethane (DDM)	- January 30, 1976
9.	Chloroform	- March 15, 1976
10.	Radon Daughters	- May 11, 1976
11.	Dimethylcarbamoyl Chloride (DMCC) Revised	- July 7, 1976
12.	Diethylcarbamoyl Chloride (DECC)	- July 7, 1976
13.	Explosive Azide Hazard	- August 16, 1976
14.	Inorganic Arsenic - Respiratory Protection	- September 27, 1976
15.	Nitrosamines in Cutting Fluids	- October 6, 1976
16.	Metabolic Precursors of a Known Human Carcinogen, Beta-Naphthylamine	- December 17, 1976
17.	2-Nitropropane	- April 25, 1977
18.	Acrylonitrile	- July 1, 1977
19.	2,4-Diaminoanisole in Hair and Fur Dyes	- January 13, 1978
20.	Tetrachloroethylene (Perchloroethylene)	- January 20, 1978
21.	Trimellitic Anhydride (TMA)	- February 3, 1978
22.	Ethylene Thiourea (ETU)	- April 11, 1978
23.	Ethylene Dibromide and Disulfiram Toxic Interaction	- April 11, 1978
24.	Direct Black 38, Direct Blue 6, and Direct Brown 95 Benzidine Derived Dyes	- April 17, 1978
25.	Ethylene Dichloride (1,2-Dichloroethane)	- April 19, 1978
26.	NIAX® Catalyst ESN	- May 22, 1978
27.	Chloroethanes - Review of Toxicity	- August 21, 1978
28.	Vinyl Halides - Carcinogenicity	- September 21, 1978
29.	Glycidyl Ethers	- October 12, 1978
30.	Epichlorohydrin	- October 12, 1978
31.	Adverse Health Effects of Smoking and the Occupational Environment	- February 5, 1979
32.	Arsine (Arsenic Hydride) Poisoning in the Workplace	- August 3, 1979
33.	Radiofrequency (RF) Sealers and Heaters: Potential Health Hazards and Their Prevention	- December 4, 1979
34.	Formaldehyde: Evidence of Carcinogenicity	- April 15, 1981

CUMULATIVE LIST OF NIOSH CURRENT INTELLIGENCE BULLETINS (CONTINUED)

35. Ethylene Oxide (EtO): Evidence of Carcinogenicity - May 22, 1981
36. Silica Flour: Silicosis - June 30, 1981
37. Ethylene Dibromide (EDB) Revised - October 26, 1981

NOTE: Bulletins #1 through #18 and #19 through #30 have been reprinted as NIOSH publications, #78-127 and #79-146 respectively, for the convenience of those that desire a complete series of Current Intelligence Bulletins. Distribution of these publications and single copies of Bulletins #31 and later are available from NIOSH Publications Dissemination, Division of Standards Development and Technology Transfer, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

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