

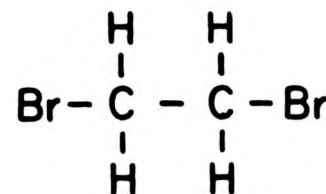
NIOSH

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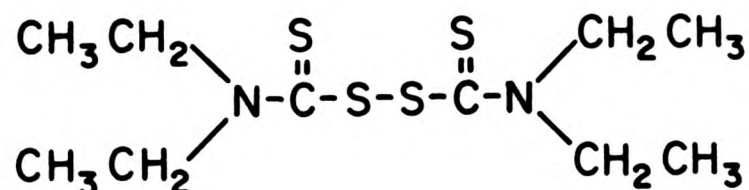
April 11, 1978

ETHYLENE DIBROMIDE

and



DISULFIRAM



TOXIC INTERACTION



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

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

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

DHEW (NIOSH) Publication No. 78-145

IDENTIFIERS AND SYNONYMS FOR DISULFIRAM

Chemical Abstracts Service Registry Number 97-77-8

NIOSH RTECS Number J012250

Chemical Formula $C_{10}H_{20}N_2S_4$

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

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

α, β -Dibromoethane

sym-Dibromoethane

Dowfume EDB

Dowfume MC-2

Dowfume W-8

Dowfume W-85

Dowfume 40

E-D-BEE

EDB

EDB-85

ENT 15,349

Ethylene Bromide

Ethylene Dibromide

Fumo-Gas

Glycol Dibromide

Isobrome D

Kopfume

Nefis

Pestmaster

Pestmaster EDB-85

Sanhyuum

Soilbrom-40

Soilbrom-85

Soilfume

Unifume

CURRENT INTELLIGENCE BULLETIN:
ETHYLENE DIBROMIDE AND DISULFIRAM TOXIC INTERACTION

April 11, 1978

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

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

Background --- Ethylene Dibromide

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

An employee exposure ceiling of 0.13 ppm (1.0 mg/m³), as determined over any fifteen-minute sampling period, was recommended by NIOSH in August 1977 for ethylene dibromide. (1) However, toxic interaction effects with other chemicals were not considered in the development of this recommended standard. The current Occupational Safety and Health Administration, Department of Labor, standard for occupational exposure to ethylene dibromide is 20 ppm (8-hour time-weighted average).

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

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

Background --- Disulfiram

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

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

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

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

Laboratory Animal Study of Toxic Interaction

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

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

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

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

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


NIOSH Recommendations

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

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

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

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


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

References

1. Criteria for a Recommended Standard Occupational Exposure to Ethylene Dibromide, U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio, August 1977.
2. McDermott, H. J., and Killiany, S. E., Jr., "Quest for a Gasoline TLV," Am. Ind. Hyg. Assoc. J., 39, 110-117, 1978.
3. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals in Man, 12, 85-95, 1976.

