JOINT

NIOSH / OSHA

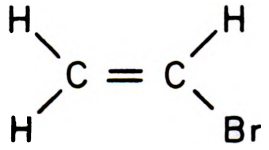
Current Intelligence Bulletin 28

September 21, 1978

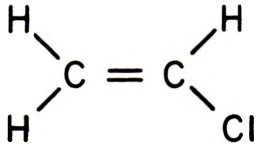
VINYL HALIDES

CARCINOGENICITY

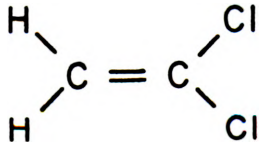
Vinyl Bromide



Vinyl Chloride



Vinylidene Chloride



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

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

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

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

FURTHER INFORMATION:

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

(301) 443-3680

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

(202) 523-8061

SYNONYMS

Identifiers and Synonyms are located on page 11.

DHEW (NIOSH) Publication No. 79-102

JOINT NIOSH/OSHA

CURRENT INTELLIGENCE BULLETIN: VINYL HALIDES - CARCINOGENICITY

Vinyl Bromide, Vinyl Chloride, and Vinylidene Chloride

September 21, 1978

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

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

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

LABORATORY STUDIES

Carcinogenicity

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

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

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

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

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

Mutagenicity

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

Other Adverse Effects

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

HUMAN STUDIES

Carcinogenicity

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

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

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

Mutagenicity and Reproductive Effects

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

Other Adverse Effects

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

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

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

OTHER VINYL HALIDES

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

USES, EXPOSURES, AND EXPOSURE STANDARDS

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

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

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

*No NOHS information available for vinyl fluoride

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

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

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

Table 4. Vinyl Halide Exposures (34).

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

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

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

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

Recommendations

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

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

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

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

REFERENCES

1. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health. Criteria for a Recommended Standard....Occupational Exposure to Vinyl Halides. (To be published late 1978 - Transmitted to OSHA September 12, 1978).

2. Maltoni, C: Predictive Value of Carcinogenesis Bioassays. N.Y. Acad. Sci. 271:431-447 (1976).

3. Huntingdon Research Center, HRC Project 7511-253. 18-Month Sacrifice Pathology Report, (Vinyl Bromide). New York. (June 26, 1978).

4. Maltoni, C: Recent Findings on the Carcinogenicity of Chlorinated Olefins. Env. Health Perspect. 21:1-5 (1977b).

5. Maltoni, C: Vinyl Chloride Carcinogenicity: An Experimental Model for Carcinogenesis Studies. In: Origins of Human Cancer, H.H. Hiatt, J.D. Watson, and J.A. Winston, eds., Cold Spring Harbor, 4:119-146 (1977a).

6. Bartsch, H., C. Malaveille, R. Montesano: Human, Rat and Mouse Liver-Mediated Mutagenicity of Vinyl Chloride in S. Typhimurium Strains. Int. J. Cancer 15:429-437 (1975).

7. Rannug, U., A. Johansson, C. Ramel, and C.A. Wachtmeister: The Mutagenicity of Vinyl Chloride After Metabolic Activation. Ambio. 3:194-197 (1974).

8. Garro, A.J., J.B. Guttenpaln, and P. Milvy: Vinyl Chloride Dependent Mutagenesis: Effects of Liver Extracts and Free Radicals. Mutat. Res. 38 (2):81-88 (1976).

9. Andrews, A.W., E.S. Zawistowski, and C.R. Valentine: A Comparison of the Mutagenic Properties of Vinyl Chloride and Methyl Chloride. Mutat. Res. 40:273 (1976).

10. McCann, J., E. Choi, E. Yamasake, and B.N. Ames: Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals. Proc. Nat. Acad. Sci. 72 (12):5135-5139 (1975).

11. Loprieno, N., R. Barale, and S. Baroncelli: Evaluation of the Genetic Effects Induced by Vinyl Chloride Monomer (VCM) Under Mammalian Metabolic Activation: Studies In Vitro and In Vivo, Mutat. Res. 40:85-95 (1976).

12. Greim H., G. Bonse, Z. Radwan, D. Reichert, and D. Henschler: Mutagenicity In Vitro and Potential Carcinogenicity of Chlorinated Ethylenes as a Function of Metabolic Oxirane Formation. Biochem. Pharmacol. 24:2013-2017 (1975).

13. Henschler D: Metabolism and Mutagenicity of Halogenated Olefins—A Comparison of Structure and Activity. Unpublished Report Submitted to National Institute for Occupational Safety and Health by Henschler, D., University of Wurzburg, Institute for Toxicology and Pharmacology, Wurzburg, West Germany, 19 pp. (April 1977).

14. Henschler D., G. Bonse, and H. Greim: Carcinogenic Potential of Chlorinated Ethylenes—Tentative Molecular Rules. INSERM 52:171-175 (1976).

15. Bartsch H., and R. Montesano: Mutagenic and Carcinogenic Effects of Vinyl Chloride. Mutat. Res. 32:93-113 (1975).

16. Magnusson J., and C. Ramel: Mutagenic Effects of Vinyl Chloride in Drosophila Melanogaster. Mutat. Res. 38:115 (1976).

17. Personal Communication dated May 6, 1976 from Mr. Arnold H. Sparrow, Brookhaven National Laboratory, to Dr. Peter Infante National Institute for Occupational Safety and Health (NIOSH).

18. Bartsch, H., C. Malaveille, A. Barbin, G. Planche, and R. Montesano: Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissues. Proc. Amer. Assoc. Cancer Res. 17 March (1976).

19. Correspondence, May 21, 1976, Ethyl Corporation to National Institute for Occupational Safety and Health (NIOSH).

20. Bartsch, H., C. Malaveille, R. Montesano, and L. Tomatis: Tissue Mediated Mutagenicity of Vinylidene Chloride and 2-Chlorobutadiene in Salmonella Typhimurium. Nature 255:641-643 (1975).

21. Baden, J., R. Whurton, B. Hitt, M. Brinkenhoff, V. Simmons, and R. Mazze: Mutagenicity of Volatile Anesthetics. Fed. Proc. 35:410 (1976).

22. Barsch, H., C. Malaveille, and R. Montesano: The Predictive Value of Tissue-Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals In: Screening Tests in Chemical Carcinogenesis. IARC Scientific Publications No. 12., eds., Montesano, R., H. Barsch, and L. Tomatis, Lyon, France, World Health Organization, International Agency for Research on Cancer 467-491 (1976).

23. Reinl, W., H. Weber, E. Greiser: Epidemiologische Studies Uber Die Sterblichkeit Vinylchlorid(VC)-Exponierter Arbeiter in der Bundesrepublik. Deutschland Medichem. (September 1977).

24. Ott, M.G., W.A. Fishbeck, J.C. Townsend, E.J. Schneider: A Health Study of Employees Exposed to Vinylidene Chloride. J. Occup. Med. 18:735-738 (1976).

25. Leonard A., G. Decat, E.D. Leonard, M.J. Lefevre, L.J. Decuyper, C. Nicaise: Cytogenetic Investigations on Lymphocytes from Workers Exposed to Vinyl Chloride. J. Toxicol. Environ. Health. 2:1135-1141 (1977).

26. Heath, C.W. Jr., C.R. Dumont, J. Gamble, R.J. Waxweiler: Chromosomal Damage in Men Occupationally Exposed to Vinyl Chloride Monomer and Other Chemicals. Environ. Res. 14:68-72 (1977).

27. Ducatman, A., K. Hirschhorn, I.J. Selikoff: Vinyl Chloride Exposure and Human Chromosome Aberrations. Mutat. Res. 31:163-168 (1975).

28. Funes-Cravioto, F.B. Lambert, J. Lindsten, L. Ehrenberg, A.T. Natarajan, and S. Osterman-Golkar: Chromosome Aberrations in Workers Exposed to Vinyl Chloride. Lancet 1:459 (1975).

29. Purchase, I.F.H., C.R. Richardson, and D. Anderson: Chromosomal and Dominant Lethal Effects of Vinyl Chloride. Lancet 2:410-11 (1975).

30. Szentesi, I., E. Hornyaki, G. Ungvary, A Gzeizel, Z. Bognar, and M. Timar: High Rate of Chromosomal Aberration in PVC Workers. Mutat. Res. 37:313-316 (1976).

31. Purchase, I.F.H., C.R. Richardson, D. Anderson, G.M. Paddle, and W.G.F. Adams: Chromosomal Analyses in Vinyl Chloride-Exposed Workers. Mutat. Res. 57: 325-334 (1978).

32. Infante, P.F., J.K. Wagoner, A.J. McMichael, R.J. Waxweiler, and H. Falk: Genetic Risks of Vinyl Chloride. Lancet 1:734-735 (1976).

33. Infante, P.F., J.K. Wagoner, and R.J. Waxweiler: Carcinogenic, Mutagenic and Teratogenic Risks Associated with Vinyl Chloride. Mutat. Res. 41:131-142 (1976).

34. Personal Communications dated August 1978 from Mr. David P. Sundin, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health (NIOSH), to Leonard J. Bahlman, Office of Extramural Coordination and Special Projects (NIOSH).

35. United States Department of Labor, Occupational Safety and Health Administration: General Industry Standards, OSHA Publication 2206, 29 CFR 1910.1017 (January 1976).

IDENTIFIERS AND SYNONYMS FOR VINYL CHLORIDE

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

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

IDENTIFIERS AND SYNONYMS FOR VINYL BROMIDE

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

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

IDENTIFIERS AND SYNONYMS FOR VINYLIDENE CHLORIDE

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

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