Tuesday
November 25, 1980

Part III

Environmental Protection Agency

Receipt of Seventh Report of the Interagency Testing Committee to the Administrator; Request for Comments on Priority List of Chemicals

ENVIRONMENTAL PROTECTION AGENCY

[OPTS 41006; TSH-FRC 1680-1]

Seventh Report of the Interagency Testing Committee to the Administrator; Receipt of Report and Request for Comments Regarding Priority List of Chemicals

AGENCY: Environmental Protection Agency, (EPA).

ACTION: Notice.

SUMMARY: The Interagency Testing Committee (ITC), established under section 4(e) of TSCA, transmitted its Seventh Report to the Administrator of EPA on October 24, 1980. This report, which revises and updates the Committee's priority list of chemicals, adds two chemicals and two chemical categories to the list for priority consideration by EPA in the promulgation of test rules under section 4(a) of the Act and deletes one chemical that was icluded on the previous list. The Seventh Report is included in this Notice and the Agency invites interested persons to submit comments on the Report.

DATE: Comments should be submitted by December 26, 1980.

ADDRESS: Send comments to: Document Control Officer (TS-793), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm. E-447, 401 M St., SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Jr., Director, Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20406, Toll Free 800-424-9065; in Washington, D.C. 554-1404.

SUPPLEMENTARY INFORMATION:

Background

Sec. 4(a) of TSCA authorizes the Administrator of EPA to promulgate regulations requiring testing of chemical substances in order to develop data relevant to determining the risks that such chemical substances may present to health and the environment.

Sec. 4(e) of TSCA established an Interagency Testing Committee to make recommendations of chemical substances to the Administrator of EPA for priority consideration for proposing test rules under Sec. 4(a). The Committee may at any one time designate up to 50 of its recommendations for special priority consideration by EPA. Within 12 months of that designation, EPA must initiate rulemaking to require testing or publish in the Federal Register its reasons for not doing so.

The Committee's initial recommendations to the priority list, of four substances and six categories of substances, were published in the Federal Register of October 12, 1977 (42 FR 55028). EPA's response to the initial recommendations appeared in the Federal Register of October 26, 1978, (43 FR 50134). The ITC's revisions to the initial list appeared in the Committee's Second Report and were published in the Federal Register of April 19, 1978 (43 FR 16684). Those revisions were the addition of four substances and four categories of substances to the priority list. EPA responded to the Second ITC Report on May 14, 1979 (44 FR 28095). In its Third Report, published in the Federal Register of October 30, 1978 (43 FR 50631), the Committee recommended the addition of one chemical substance and two categories of chemical substances to the priority list. In its Fourth Report the Committee recommended the addition of 11 individual chemicals and one category to its priority list, each designated for priority consideration by EPA. The ITC's Fifth Report was received by the Administrator on November 7, 1979. In its Fifth Report, the Committee recommended the addition of two individual chemicals and three categories of chemicals to its priority list, each designated for priority consideration by EPA. The ITC's Sixth Report was received by the Administrator on April 15, 1980. In the Sixth Report the Committee recommended the addition of one category of chemicals to its priority list. The ITC's Seventh Report was received by the Administrator on October 24, 1980.

EPA proposed health effects testing for chloromethane and chlorinated benzenes and tentatively decided not to require health effects testing of acrylamide. Notice of these actions appeared in the Federal Register of July 18, 1980 (45 FR 48510). In the notice proposing testing of chloromethane, EPA addressed all of the concerns of the ITC; thus chloromethane has been removed from the ITC Priority List. Acrylamide and the higher and lower chlorinated benzenes remain on the list because the ITC recommended environmental effects testing for these chemicals and EPA has not yet addressed the ITC's environmental testing recommendations.

Public Comments

The ITC's Seventh Report follows. EPA invites interested persons to submit comments on the ITC's new recommendations. The Agency requests comments be submitted no later than December 26, 1980. All comments received by that date will be considered by the Agency in determining whether to propose test rules in response to the Committee's new recommendations.

EPA also intends to hold a public meeting concerning the ITC report shortly after the conclusion of the comment period. A notice of the date, time and place of the meeting providing more details concerning its intended scope, will be published in the Federal Register at a later date. The meeting is intended to be a scoping conference to provide an early opportunity for the academic community, labor, industry, environmental groups, and the general public to make additional information available to EPA and to raise issues that are significant for a determination as to whether to propose testing.

Comments should bear the identifying notation OPTS-41006 and should be submitted to the Document Control Officer, Room 447, East Tower, Office of Pesticides and Toxic Substances, (TS-793), EPA, 401 M St., SW., Washington, D.C., 20460. All written comments will be available for public inspection in Room 447, East Tower at the same address, between 8:00 a.m. and 4:00 p.m., weekdays, except legal holidays.

Dated: November 13, 1980.

Steven D. Jellinek,

Assistant Administrator for Pesticides and Toxic Substances.

Toxic Substances Control Act, Interagency Testing committee

Member agencies: Council on Environmental Quality, Department of Commerce, Environmental Protection Agency, National Cancer Institute, National Institute of Environmental Health Sciences, National Institute for Occupational Safety and Health, National Science Foundation, Occupational Safety and Health Administration.

Liaison agencies: Consumer Product Safety Commission, Department of Agriculture, Department of Defense, Department of the Interior, Food and Drug Administration, National Toxicology Program.

October 24, 1980.

The Honorable Douglas M. Costle,

Administator, U.S. Environmental Protection Agency, Washington, DC.

Dear Mr. Costle: I am pleased to present to you the seventh report of the TSCA Interagency Testing Committee. This report meets the statutory requirement under Section 4(e)(1)(B) of TSCA, which stipulates that the Committee shall make revisions in the Priority List, as it determines to be necessary, at least every six months.

In the Committee's seventh report, two chemicals (i.e., benzyl butyl phthalate and butyl glycolyl butyl phthalate) and two categories of chemicals (i.e., alkyltin compounds and fluoroalkenes) are added to the Priority List. Based on your response to

the Committee's earlier designation of chlormethane, this chemical is deleted from the Priority List. Although you have also responded to the Committee's designation of acrylamide and chlorinated benzenes, these chemicals remain on the Priority List for environmental effects testing. As a result of these actions, the Priority List now contains a total of 42 entries.

The Committee hopes that this seventh report is helpful to the EPA in its efforts to control toxic substances.

Sincerely yours,

James M. Sontag,

Chairman.

Seventh Report of the Toxic Substances Control Act Interagency Testing Committee to the Administrator, Environmental Protection Agency

October 1980.

Contents

Summary

Section 4 of the Toxic Substances Control Act of 1976 (TSCA, Pub. L. 94–469) provides for the testing of chemicals in commerce which may present an unreasonable risk of injury to health or the environment. It also provides for the establishment of a Committee, composed of representatives from eight designated Federal Agencies, to recommend chemical substances or mixtures to which the Administrator of the U.S. Environmental Protection Agency (EPA) should give priority consideration for the promulgation of testing rules. The Committee makes such revisions in the list (the Section 4(e) Priority List) as it determines to be necessary and transmits them to the EPA Administrator at least every six months.

As a result of its deliberations, the Committee is revising the TSCA Section 4(e) Priority List by the removal of one chemical and the addition of two chemicals and two categories of chemicals. Cholromethane is being removed from the list. The chemicals and categories of chemicals being added to the list are presented alphabetically, together with the types of testing recommended, as follows:

Chemical or category	Recommended studies
Alkylin Compounds	Carcinogenicity, mutagenicity reproductive effects, teratogenicity, developmental effects, chronic health effects, epidemiology, and environmental effects.
Benzyl butyl phthalate	Carcinogenicity, reproductive effects, and environmental effects
Butyl glycolyl butyl phthalate	Reproductive effects, mutagenicity and other short term tests for genotoxic effects, and environmental effects.
Fluoroalkenes	Carcinogenicity, mutagenicity, teratogenicity reproductive effects, and other toxic effects.

Each of the new recommendations is being designated by the Committee for action by the EPA within twelve months of the date of this Seventh Report, as stipulated by TSCA.

TSCA Interagency Testing Committee

Statutory Member Agencies and Representatives

Council on Environmental Quality
No Representative
Department of Commerce
Orville E. Paynter, Member
Bernard Greifer, Alternate member
Environmental Protection Agency
Joseph Seifter, Member
Carl R. Morris, Alternate member [1]
National Cancer Institute
James M. Sontag, Member and Chairperson
National Institute of Environmental Health Sciences
Warren T. Piver, Member [2]
Dorothy Canter, Alternate member [3]
National Institute for Occupational Safety and Health
Vera W. Hudson, Member and Vice Chairperson
Alfred M. Mibert, Alternate member [4]
National Science Foundation
Sidney Draggan, Member
Occupational Safety and Health Administration
Patricia Marlow, Member [5]
Lucille Adamson, Alternate member [6]

Liaison Agencies and Representatives

Consumer Product Safety Commission
Joseph McLaughlin
Department of Agriculture
Homer E. Fairchild and Fred W. Clayton
Department of Defense
Bernard P. McNamara
Department of the Interior
Charles R. Walker
Food and Drug Administration
Allen H. Heim and Winston deMonsabert
National Toxicology Program
Dorthy Canter [3]

Committee Staff

Martin Greif, Executive Secretary [7]
Vacant, Administrative Technician

Support Staff

Ellen Siegler—Office of the General Counsel, EPA
Edward Zillioux—Office of Toxic Substances, EPA

The Committee acknowledges and is grateful for the assistance and support given to it by Bruce Means, EPA Office of Toxic Substances, and the staff of Enviro Control, Inc. (technical support contractor).

[1] Dr. Morris replaced Dr. Amy Rispin as the Alternate member on August 21, 1980.

[2] Dr. Piver changed from the Alternate member to the Member on May 15, 1980.

[3] Dr. Canter joined the Committee as the Alternate member of the National Institute of Environmental Health Sciences and as the Liaison representative of the National Toxicology Program on May 15, 1980.

[4] Dr. Mibert replaced Dr. Michael Blackwell as the Alternate member on April 24, 1980.

[5] Dr. Marlow replaced Dr. David Logan as the Alternate member on May 15, 1980, and was appointed the Member, replacing Dr. Victor Alexander, on July 17, 1980.

[6] Dr. Adamson replaced Dr. Patricia Marlow as the Alternate member on July 17, 1980

[7] Mr. Greif joined the Committee Staff as Executive Secretary on July 28, 1980.

Chapter 1. Introduction.

1.1 *Background.* The TSCA Interagency Testing Committee (Committee) was established under section 4(e) of the Toxic Substances Control Act of 1976 (TSCA, Pub. L. 94–469). The specific mandate of the Committee is to identify and recommend to the Administrator of the U.S. Environmental Protection Agency (EPA) chemcial substances or mixtures in commerce which should be tested to determine their potential hazard to human health and/or the environment. The Act specifies that the Committee's recommendations shall be in the form of a Priority List, which is to be published in the Federal Register. The Committee is directed to make revisions to the List, as it determines to be necessary, and to transmit such revisions to the EPA Administrator at least every six months after submission of the Initial List.

The Committee is comprised of representatives from eight statutory member agencies, five liaison agencies, and one national program. The specific representatives and their affiliations are named in the front of this report. The Committee's chemical review procedures and prior recommendations are described in previous reports (Ref. 1 through 7).

1.2 *Committee's activities during this reporting period.* The Committee

has continued to review chemicals from its second round of scoring (see Ref. 2 for methodology). A third round was completed in July 1980. In this latest scoring effort the Committee utilized, for the first time, the public (non-confidential) portion of the TSCA Chemical Substance Inventory for 1977. Essentially the same method for scoring chemicals was used in the third round as in earlier ones. Only high production chemicals reported in the public portion of the Inventory (i.e., those with annual production known to be in excess of 2 million pounds) were considered. Chemicals scored previously were excluded.

1.3 *Committee's previous reports.* Six previous Reports to the EPA Administrator have been issued by the Committee and published in the Federal Register (Ref. 2 through 7). A total of 39 entries (i.e., chemicals and categories of chemicals) has been designated for priority consideration by the EPA Administrator in those reports.

1.4 *The TSCA Section 4(e) Priority List.* The Committee is removing chloromethane from the Priority List because the EPA Administrator has responded to the Committee's recommendations (Ref. 8).

The EPA Administrator has responded to the Committee's recommendations for health effects testing of acrylamide (Ref. 9, 10). However, acrylamide remains on the List because the EPA has not yet responded, as required by section 4(e)(1)(B) of TSCA, to the environmental effects testing recommendation of the Committee.

The EPA Administrator has responded to the health effects testing recommendations of the Committee on the chlorinated benzenes (mono-, di-, tri-, tetra-, and penta-) (Ref. 8). However, the chlorinated benzenes remain on the List because the EPA has not yet responded, as required by section 4(e)(1)(B) of TSCA, to the environmental effects testing recommendation of the Committee.

With the removal of one chemical from the Priority List and the designation of two new chemicals and two new categories of chemicals, the Section 4(e) Priority List now contains 42 entries. The entries and the dates of their designation by the Committee are presented in Table 1. The deletion from the Priority List and the date of its deletion by the Committee are presented in Table 2.

Table 1.—*The TSCA Section 4(e) Priority List*

Entry	Date of designation
1. Acetonitrile	April 1979.
2. Acrylamide	April 1978.[b,d]
3. Alkyl epoxides	October 1977.[a]
4. Alkyl phthalates	October 1977.[a]
5. Alkyltin compounds	October 1980.
6. Aniline and bromo, cloro and/or nitro anilines.	April 1979.
7. Antimony (metal)	April 1979.
8. Antimony sulfide	April 1979.
9. Antimony trioxide	April 1979.
10. Aryl phosphates	April 1978.[b]
11. Benzidine-based dyes	November 1979.
12. Benzyl butyl phthalate	October 1980.
13. Butyl glycolyl butyl phthalate	October 1980.
14. Chlorinated benzenes, mono- and di-	October 1977.[a,c]
15. Chlorinated benzenes, tri-, tetra- and penta-	October 1978.[c]
16. Chlorinated naphthalenes	April 1978.[b]
17. Chlorinated paraffins	October 1977.[a]
18. Cresols	October 1977.[a]
19. Cyclohexanone	April 1979.
20. o-Dianisidine-based dyes	November 1979.
21. Dicholoromethane	April 1978.[b]
22. 1,2-Dichloropropane	October 1978.
23. Fluoroalkenes	October 1980.
24. Glycidol and its derivatives	October 1978.
25. Halogenated alkyl epoxides	April 1978.[b]
26. Hexachloro-1,3-butadiene	October 1977.[a]
27. Hexachlorocyclopentadiene	April 1977.
28. Hydroquinone	November 1979.
29. Isophorone	April 1979.
30. Mesityl oxide	April 1979.
31. 4,4'-Methylenedianiline	April 1979.
32. Methyl ethyl ketone	April 1979.
33. Methyl isobutyl ketone	April 1979.
34. Nitrobenzene	October 1977.[a]
35. Phenylenediamines	April 1980.
36. Polychlorinated terphenyls	April 1978.[b]
37. Pyridine	April 1978.[b]
38. Quinone	November 1979.
39. o-Tolidine-based dyes	November 1979.
40. Toluene	October 1977.[a]
41. 1,1,1-Trichloroethane	April 1978.[b]
42. Xylene	October 1977.[a]

[a] Responded to by the EPA Administrator in 43 FR 50134–50138.
[b] Responded to by the EPA Administrator in 44 FR 28095–28097.
[c] Responded to by the EPA Administrator in 45 FR 48524–48564.
[d] Responded to by the EPA Administrator in 45 FR 48510–48512.

Table 2.—*Removal from the TSCA Section 4(e) Priority List*

Removal	Date of removal
1. Chloromethane[a]	Oct. 1980.

[a] Responded to by the EPA Administrator in 45 FR 48524–48564.

References

1. Preliminary List of Chemical Substances for Further Evaluation. Toxic Substances Control Act Interagency Testing Committee, July 1977.

2. Initial Report to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, October 1, 1977. Published in the Federal Register, Vol. 42, No. 197. Wednesday, October 12, 1977. pp. 55026–55080. Corrections published in Federal Register, Vol. 42, November 11, 1977. pp. 58777–58778. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560–10–78/001. January 1978.

3. Second Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1978. Published in the Federal Register, Vol. 43, No. 76, Wednesday, April 19, 1978. pp. 16684–16688. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560–10–78/002, July 1978.

4. Third Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, October 1978. Published in the Federal Register, Vol. 43, No. 210, Monday, October 30, 1978. pp. 50630–50635. The report and supporting dossiers also were published by the Environmental Protection Agency, EPA 560–10–79/001, January 1979.

5. Fourth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1979. Published in the Federal Register, Vol. 44, No. 107, Friday, June 1, 1979. pp. 31866–31869.

6. Fifth Report of the TSCA Interagency Committee to the Administrator, Environmental Protection Agency, TSCA Interagency Testing Committee, November 1979. Published in the Federal Register, Vol. 44, No. 237, Friday, December 7, 1979. pp. 70664–70674.

7. Sixth Report of the TSCA Interagency Testing Committee to the Administrator, Environmental Protection Agency. TSCA Interagency Testing Committee, April 1980. Published in the Federal Register, Vol. 45, No. 104, Wednesday, May 28, 1980. pp. 35897–35910.

8. Chloromethane and Chlorinated Benzenes Proposed Test Rule: Amendment to Proposed Health Effects Standards. Published in the Federal Register, Vol. 45, No. 140, Friday, July 18, 1980. pp. 48524–48564.

9. Acryulamide: Response to the Interagency Testing Committee. Published in the Federal Register, Vol. 45, No. 140, Friday, July 18, 1980. pp. 48510–48512.

10. Assessment of Testing Needs: Acrylamide, Support Document for Decision Not to Require Testing for Health Effects, U.S. Environmental Protection Agency, Washington, D.C. 20460, EPA–560/11–8016, July 1980.

Chapter 2. Recommendations of the Committee

2.1 *Chemical substances and categories designated for action by the EPA.* As directed by section 4(e)(1)(B) of TSCA, the Committee is adding two chemical substances and two categories to the Section 4(e) Priority List. The designation of these entries was determined after considering the factors identified in section 4(e)(1)(A) and other available relevant information, as well as the professional judgment of Committee members. The recommended studies for these entries and the

rationales to support the recommendations are given in section 2.2 of this report. In accordance with section 4(e) of TSCA, the Committee designates these entries for action by the EPA within twelve months of the date of this seventh Committee report.

2.2 *Recommendations and rationales.*

2.2.a *Alkyltin Compounds.*

Recommended Studies

Health.

Carcinogenicity
Mutagenicity
Teratogenicity
Reproductive effects
Developmental effects
Other chronic effects
Epidemiology

Environmental:

Environmental effects.

The recommended studies are conditional, based upon the considerations discussed below.

Studies for carcinogenic and mutagenic effects. One dialkyltin compound (i.e., dibutyltin diacetate) has been studied for carcinogenicity. The results of the study were inconclusive and the compound should be retested. Before long-term bioassay studies are recommended for other members of this category, short-term screening tests should be performed to determine and assess other genotoxic effects and to identify those compounds having a potential for causing mutations or otherwise altering genetic material.

Studies for reproductive, teratogenic, and developmental effects. Certain members of this category have produced reproductive effects in laboratory animals. Studies of these category members indicate that they reach and are transported across the blood-placental and blood-testicular organ barriers. Transport to and across these blood-organ barriers can affect reproduction and cause teratogenic and post-natal developmental effects. Studies of other members of this category are needed to assess their capacity to be transported across the relevant blood-organ barriers to determine their effect on reproduction, teratogenicity, and postnatal development.

Chronic health effects studies. Chronic health effects studies with laboratory animals have been performed on a limited number of the alkyltin compounds in this category. These studies indicate that exposure to certain members of this category caused adverse effects on the liver, lungs, kidney, and central nervous system. For those compounds tested, the observed response appeared to be related to the number of alkyl groups covalently bonded to the tin atom and the chemical composition of the alkyl group. Additional studies, however, are needed on the untested members of this category to determine their toxic effects on target organ systems. For those compounds that have been tested, observed systemic effects are a strong function of absorption, distribution, and retention at target organs. Therefore, attention should be given to different routes of exposure. In addition to these studies on target organ toxicity, biochemical studies are required to determine metabolic pathways, binding affinities to proteins and other macromolecules, and the ability of these chemicals to inhibit enzymatic processes necessary to cellular and organ function.

Epidemiological studies. No epidemiological studies on people engaged in the production of category members have been found in the open literature. Because of the known toxicity of several members of this category, retrospective and prospective studies are needed to determine the effects of occupational exposure to category members through inhalation and eye and skin contact.

Environmental studies. The discharge of members of this category to aquatic environments and the impact of this release on exposed plants and animals, either directly or indirectly, have not been adequately studied. Because these compounds are insoluble in water and have a very low vapor pressure, studies are needed to determine mechanisms for their transport, partitioning, and accumulation in food-chain organisms, and the transformation of category members by chemically and biologically mediated processes. In addition, studies with both the parent compounds and their transformed products are needed to determine the ranges of sensitivities for a wide variety of aquatic plants and animals, including representative invertebrates.

Category Identification

The general formula for compounds that comprise this category is:

R_nSnY_{4-n}

Where:

R represents an alkyl group containing one to eight carbon atoms covalently bonded to the tin atom.

n represents the number of alkyl groups covalently bonded to the tin atom; n can have a value between 1 and 4.

Y represents a singly charged anion or anionic organic group bonded to the tin atom.

Sn is the chemical symbol for the element tin.

The alkyl groups of commercially important alkyltin compounds are methyl, ethyl, *n*-butyl, and *n*-octyl groups. Table 1 lists these important compounds along with their production histories. Table 2 lists selected physical and chemical data for these compounds and their major commercial uses. Additional members of this category that have commercial value, but on which only limited data on their uses and production could be found, are presented in Table 3. The chemicals listed in Table 3 were derived from a report prepared for NIOSH (NIOSH, 1978) and from the TSCA Chemcial Substance Inventory.

BILLING CODE 6560-01-M

Table 1 ESTIMATED ANNUAL U.S. PRODUCTION HISTORY OF SELECTED ALKYLTIN COMPOUNDS (MILLION POUNDS PER YEAR)(a)

Year	Bu IOMA	Me IOMA	Bu LM	Bu Maleate	Oct. IOMA	Oct. Maleate	DBTDL	DBTH	TBTO	TBTF	Total
1965	2.3	--	1.0	0.22	--	--	0.6	--	0.86	--	5.0
1966	4.6	--	1.0	0.22	--	--	0.9	--	0.93	--	7.6
1967	4.9	--	0.9	0.48	--	--	1.2	--	1.20	--	8.7
1968	6.2	--	0.9	0.52	0.16	0.02	1.6	--	1.32	--	10.7
1969	7.1	--	0.9	0.57	0.20	0.03	2.0	--	1.50	--	12.3
1970	8.3	0.7	1.1	0.59	0.32	0.05	2.4	--	1.67	0.01	15.2
1971	8.2	1.4	1.1	0.62	0.37	0.06	2.8	--	1.97	0.02	16.6
1972	10.5	2.9	1.3	0.26	0.56	0.08	2.5	0.8	1.61	0.05	20.6
1973	10.1	4.0	1.3	0.22	0.62	0.08	3.0	0.9	1.98	0.08	22.8
1974	9.3	4.5	1.3	0.21	0.37	0.07	3.5	1.1	2.07	0.12	22.5
1975	7.0	4.0	1.0	0.20	0.50	0.07	3.0	0.9	1.40	0.30	18.4
1976	9.0	4.5	1.1	0.22	0.60	0.07	4.3	1.0	2.30	0.50	23.0
Total	87.5	22.0	12.9	4.33	3.70	0.53	27.8	4.7	18.81	1.08	183.4

Key to Notation:

Symbol	Chemical Name	Formula	CAS No.
Bu IOMA	Butyltin-tris(isooctylmercaptoacetate)	$C_4H_9\ Sn(SCH_2COOC_8H_{17})_3$ plus blends	25852-70-4
Me IOMA	Methyltin-tris(isooctylmercaptoacetate	$CH_3\ Sn(SCH_2COOC_8H_{17})_3$ plus blends	54849-38-6
Bu LM	Dibutyltin-bis(laurylmercaptide)	$(C_4H_9)_2\ Sn(SC_{12}H_{25})_2$	1185-81-5
Bu Maleate	Dibutyltin-bis(isooctylmaleate)	$(C_4H_9)_2\ Sn(O_2CCH = CHCO_2C_8H_{17})_2$	29575-02-8
Oct. IOMA	Di(n-octyl)tin-S,S'-bis(isooctylmercaptoacetate)	$(C_8H_{17})_2\ Sn(SCH_2COOC_8H_{17})_2$	26401-97-8
Oct. Maleate	Di(n-octyl)tin maleate polymers	$[(C_8H_{17})_2\ Sn(O_2CCH = CHCOO)]_x$	16091-18-2
DBTDL	Dibutyltin dilaurate	$(C_4H_9)_2\ Sn(O_2CC_{11}H_{23})_2$	77-58-7
DBTH	Dibutyltin-bis(2-ethyl hexoate)	$(C_4H_9)_2\ Sn(O_2CCH(C_2H_5)C_4H_9)_2$	2781-10-4
TBTO	Bis(tributyltin) oxide	$[(C_4H_9)_3\ Sn]_2O$	56-35-9
TBTF	Tributyltin fluoride	$(C_4H_9)_3\ SnF$	1983-10-4

(a) Midwest Research Institute, 1977.

Table 2 SELECTED PHYSICAL PROPERTIES AND PRODUCT USES OF SELECTED ORGANOTIN COMPOUNDS(a)

Compound	Appearance	Solubility		Product Uses			
		H_2O	Organic Solvents	Catalyst	Stabilizer	Biocide	Other
Monomethyltin-tris(isooctylmercaptoacetate)	Liquid				X		
Monobutyltin-tris(isooctylmercaptoacetate)	Liquid				X		
Dibutyltin-bis(laurylmercaptide)	Clear pale liquid	Insol.	Sol.		X		
Dibutyltin dilaurate	Liquid or low m.p. solid	Insol.	Sol.	X			5
Dibutyltin-bis(isooctylmaleate)	White powder	Insol.	Insol. in almost all solvents	X	X		5
Di(n-octyl)tin-S,S'-bis-(isooctylmercaptoacetate)	Clear yellow liquid	Insol.	Sol.		X		
Di(n-octyl)tin maleate polymers	Powder	Insol.	Sol.		X		
Bis(tributyltin) oxide	Yellow liquid	Insol.	Sol.	X		X	1,2,3,4,5,6
Tributyltin fluoride	White powder	Insol.	Sol.			X	
Dibutyltin-bis(2-ethyl hexoate)	Waxy white solid	Insol.	Sol.	X		X	

Other Use Code: 1. Flame resistant polymer 2. Wood preservative 3. Spreading coefficient of solder
4. Water repellent coating 5. Antioxidant or corrosion inhibitor 6. Adhesives preservative

(a) Source: Taken from Midwest Research Institute, 1977, which used the following references:
NIOSH, Occupational Exposure to Organotin Compounds, U. S. Department of HEW, No. 77-115, November 1976.
Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed., Vol. 20, John Wiley and Sons, New York, 1969.
M & T Chemicals, Inc., Rahway, New Jersey.
Tin Research Institute, Greenford, Middlesex, ENGLAND.

Table 3 ADDITIONAL SELECTED COMMERCIALLY IMPORTANT ALKYLTIN COMPOUNDS FOR WHICH PRODUCTION AND USE DATA WERE NOT COMPLETE[a]

Chemical Name	CAS Number	Formula
Monobutyltin trichloride	1118-46-3	$C_4H_9SnCl_3$
Monomethyltin trichloride	993-16-8	CH_3SnCl_3
Dibutyltin dichloride	683-18-1	$(C_4H_9)_2SnCl_2$
Dibutyltin dibutoxide	3349-36-8	$(C_4H_9)_2Sn(OC_4H_9)_2$
Dibutyltin-bis(laurylmaleate)	7324-75-6	$(C_4H_9)_2Sn(O_2CCH{=}CHCO_2C_{12}H_{25})_2$
Dibutyltin dinonylate	4731-77-5	$(C_4H_9)_2Sn(O_2CC_8H_{17})_2$
Dibutyltin dimethoxide	1067-55-6	$(C_4H_9)_2Sn(OCH_3)_2$
Dibutyltin oxide	818-08-6	$(C_4H_9)_2SnO$
Dimethyltin dichloride	753-73-1	$(CH_3)_2SnCl_2$
Dimethyltin oxide	2273-45-2	$(CH_3)_2SnO$
Dioctyltin oxide	870-08-6	$(C_8H_{17})_2SnO$
Dioctyltin dichloride	3542-36-7	$(C_8H_{17})_2SnCl_2$
Dimethyltin-bis(isooctylmercapto-acetate)	26636-01-1	$(CH_3)_2Sn(SCH_2COOC_8H_{17})_2$
Dimethyltin-bis(dodecylmercaptide)	51287-84-4	$(CH_3)_2Sn(SC_{12}H_{25})_2$
Tributyltin (2-hydroxypropyl maleate)	4342-30-7	$(C_4H_9)_3Sn(O_2CCH{=}CHCO_2CH_2CH(OH)CH_3)$
Tributyltin chloride	1461-22-9	$(C_4H_9)_3SnCl$
Tributyltin hydroxide	1067-97-6	$(C_4H_9)_3SnOH$
Tributyltin (2-methyl-2-propenoate)	2155-70-6	$(C_4H_9)_3Sn(O_2CC(CH_3){=}CH_2)$
Triethyltin hydroxide	994-32-1	$(C_2H_5)_3SnOH$
Trimethyltin chloride	1066-45-1	$(CH_3)_3SnCl$
Tetrabutyltin	1461-25-2	$(C_4H_9)_4Sn$
Tetraethyltin	597-64-8	$(C_2H_5)_4Sn$
Tetraoctyltin	3590-84-9	$(C_8H_{17})_4Sn$

(a) Sources: NIOSH, The Development of a List of Organometallics Found in the Workplace, Contract No. 210-76-0146. 1978.
EPA, TSCA Chemical Substance Inventory for 1977.

BILLING CODE 6560-01-C

Reasons for recommendtions

The alkyl groups covalently bonded to the tin atom of category members enhance the solubility of these compounds in organic solvents, increase their volatility, and facilitate their penetration of biological tissues. The chain length and number of alkyl groups bonded to the tin influence the physical-chemcial properties of these compounds and their rates of absorption, distribution, metabolism, excretion, retention, and accumulation in target organs. The role of anionic groups in the toxicity of these compounds is unknown.

Routes of exposure. The manufacture and uses of the category members represent the major routes of direct exposure. Most of the compounds listed in Table 1 occur as liquids and waxy solids, so exposure would occur by dermal or eye contact and by inhalation of aerosols. Several of the lower molecular weight compounds listed in Table 3 are volatile and exposure to them would occur by inhalation. Depending on the method of synthesis, commercial alkyltin category members may contain mono-, di-, tri-, and tetra-alkyltin compounds as impurities (Midwest Research Institute, 1977). In the United States there are two synthetic routes for the manufacture of alkyltin compounds, the Grignard method and the direct method. It is estimated that a total of 30,000 workers are exposed to all of the compounds that make up this category (NIOSH, 1976).

During synthesis and purification of final product compounds, workers may be exposed to the final products, intermediates, by-products, and reaction aids required for synthesis.

Unintentional exposure to category members may occur as a result of commercial uses of these compounds. For example, exposure may occur by the migration of these compounds from medical devices that are in contact with biological fluids (Guess and Haberman, 1968; Guess, 1970; Duke and Vane, 1968) and the migration from containers and packaging materials that are in contact with foods (Carr, 1969; Woggan et al., 1969).

Toxic effects of alkyltin compounds. In this discussion of toxic effects, only data for alkyltin compounds are presented. Other commercially important organometallic compounds of tin contain covalently bonded aromatic groups. Because these aryltin compounds are used primarily as fungicides, bactericides, and herbicides, they are regulated under the Federal Insecticide, Fungicide, and Rodenticide Act. A large body of literature exists on the toxic effects of the aryltin compounds (Kimbrough, 1976; NCI, 1978; Innes et al., 1969; Klimmer, 1964; Pate and Hays, 1968; Newton and Hays, 1968).

Toxic effects in humans. The chlorides of dibutyltin and tributyltin were reported to be highly irritating to the skin and eyes of workers employed as product material handlers (Lyle, 1958). Workers engaged in spray painting with latex paints containing bis(tributyltin) oxide reported eye irritation and irritation of the respiratory tract (Landa et al., 1973).

Much of the research on alkyltin compounds resulted from a poisoning incident that occurred in France in 1954 and claimed the lives of over 100 people. Death was linked to the ingestion of the drug Stalinon (Barnes and Stoner, 1959), taken for the systemic treatment of staphylococcal infections of the skin. The active ingredient in the drug was diethyltin diiodide, but it was discovered that the probable cause of death was the presence of triethyltin iodide, an impurity. Autopsied victims showed marked interstitial edema of the brain white matter, but with no apparent Wallerian degeneration of the nervous system tissues.

Experimental animal studies. Depending on their chemical composition and route of exposure, alkyltin compounds differ in the severity of their acute effects and the organs they affect. The trialkyltin compounds appear to be the most toxic, followed by the dialkyltin compounds, and finally the monoalkyltins. The tetraalkyltins are metabolized to their trialkyltin counterparts (Cremer, 1958), so their toxicity is dependent on their rate of metabolism. The trialkyltin compounds appear to affect the central nervous system in all animals species studied (Magee et al., 19570. The dialkyltin compounds do not affect all animal species in the same way (Barnes and Stoner, 1958; Calley et al., 1967; Verschuuren et al., 1966; Klimmer, 1964), but liver damage appears to be the most common effect. Exposure to high oral doses of monoalkyltins (4000 mg/kg) caused fatty degeneration and hyperemia in the kidneys of rats (Pelikan and Cerny, 1968a, 1970a, 1970b; Pelikan et al., 1970).

Inhalation studies with triethyltin bromide, tripropyltin bromide, and tributyltin bromide caused death by pulmonary edema in mice (Glass et al., 1942). Inhalation by rats of tributyltin bromide caused bronchitis and bronchogenic pneumonia (Igarashi, 1959).

In rats, skin absorption of a tributyltin compound produced liver damage, as well as a slight edema of the skin at the site of application (Pelikan and Cerny, 1968, 1969). Possible liver and kidney damage occurred in rabbits after dermal applications of tributyltin chloride, bromide, and iodide (Kawai, 1962).

Biochemical studies. In vitro studies have been conducted with several trialkyltin compounds. Their purpose was to study the inhibition of enzyme function and alterations of metabolic processes in an attempt to understand the relationship of these biochemical changes to observed disease endpoints.

It was suggested that, after exposure to triethyltin iodide, the edematous lesion in the white matter of the brain was due to interference in ATP utilization and inhibition of oxidative phosphorylation (Magee et al., 1957; Barnes and Magee, 1958; Cremer, 1970; Aldridge and Street, 1970). Inhibition of oxidative phosphorylation was thought to be due to the uncoupling of this process. This supposition is supported by studies on the binding of triethyltin to histidine molecules that comprise the "proton conducting tube" necessary for oxidative phosphorylation to occur (Rose and Lock, 1970). The capacity for other alkyltin compounds to inhibit enzymatic functions has not been examined adequately.

In studies with rats (Joo et al., 1969), exposure to triethyltin produced collapse of the blood-brain barrier. Its collapse was a function of the triethyltin concentration. the triethyltin compound may have caused increased permeability of the barrier and/or resulted in metablic disturbances in the brain.

Metabolism of alkyltin compounds occurs in the liver microsomes by the monooxygenase system (Kimmel et al., 1977). Metabolism involves the progressive dealkylation of these comounds, with the final liberation of Sn^{+4}. Inorganic tin appears to accumulate preferentially in the bone, with other sites being the lung, liver, and kidney (Hiles, 1974).

Carcinogenicity and mutagenicity. A carcinogenicity study of dibutyltin diacetate in rats and mice was inconclusive (NCI, 1979). No data on the mutagenicity of alkyltin compounds were found for bacterial assay systems. However, studies designed to use inhibition of bacterial growth as an indicator of mutagenicity gave negative results for the inorganic forms of tin that represent the +2 (stannous) and +4 (stannic) oxidation states (Nishioka, 1975; Kanematsu and Kada, 1978). The bacterial system was a recombination-deficient of *Bacillus subtilis* strains H17

(Rec+, arg−, and trp−) and M45 (Rec−, arg−, and trp−).

Reproductive, teratogenic, and developmental effects. Few studies were found on reproductive, teratogenic, and developmental effects resulting from exposure to alkyltin compounds. After inhalation exposure to tributyltin bromide, no effects were observed in the sex organs of male rats, but a marked atrophic destruction of the glandular epithelium and an increase in interstitial connective tissues of the uterus were observed in female rats (Iwamoto, 1960). No changes were observed in the ovaries. In a study with dioctyltin-S,S'-bis(isooctylmercaptoacetate), an increased number of resorptions and fetal deaths were observed as a result of oral administration of the compound to pregnant rats (Nikonorow et al., 1973).

Environmental Effects. No data were found in the open literature on the environmental degradation of alkyltin compounds.

Soil mobility tests have been conducted to determine the capacity of certain category members to be transported from land burial sites (Midwest Research Institute, 1977). Leaching tests indicated that the compounds are tightly bound by clay and organic matter in soil and are immobilized, but a complete analysis of all soil factors that influence transformation and transport of these compounds into ground water was not reported.

Many species of fresh-water fish are sensitive to low levels of tributyltin compounds. For example, the 24-hour LC_{50} for rainbow trout to tributyltin oxide is reported to be 0.027 ppm (EPA, 1973). Other aquatic organisms may be tolerant to low levels of these alkyltin compounds, but they have not been identified. Before the impact of exposure to low levels of these compounds can be understood, acute toxicity data are needed for a broader range of aquatic organisms. Such data will identify sensitive and tolerant species and narrow the number of important food-chain species that need additional bioaccumulation and chronic toxicity studies.

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2.2.b. *Benzyl Butyl Phthalate.*

Recommended Studies

Health:

Carcinogenicity.
Reproductive effects.

Environmental:

Environmental effects.

Substance Identification: CAS No. 85–68–7.

Reasons for Recommendations

The evidence from one study suggests that an increased incidence of leukemias in female rats may have been related to their exposure to benzyl butyl phthalate (BBP). The parallel study in male rats was inadequate due to excessive toxicity and mortality among the animals treated with BBP. These results indicate a need for a more thorough evaluation of the potential carcinogenicity of BBP.

Toxicity data suggest that BBP may influence mammalian reproductivity. Other phthalate esters have been reported to produce testicular effects in both male rats and mice and decreased fertility in male mice. These findings indicate the need to test BBP for its potential reproductive effects.

Little information is available on the environmental effects of BBP. Structurally similar phthalate esters, however, are toxic to aquatic organisms in the parts per billion range and accumulate in aquatic plant and animal tissues. This information indicates the need for further environmental monitoring and testing of BBP. Chronic toxicity to aquatic organisms and potential effects on reproduction should be emphasized.

Production, usage, and exposure. The BBP production for 1977 was reported in the public portion of the TSCA Chemical Substance Inventory to be in the range of 101 million to 510 million pounds. It is used primarily as a plasticizer in medical and dental devices, synthetic leather, and sealing and coating applications. The National Occupational Hazards Survey (NOHS) estimates that 68,500 workers are exposed to BBP (NIOSH, 1980).

Carcinogenicity. An elevated incidence of leukemias was reported in female rats treated with BBP (NCI, 1980a). The report stated that BBP "* * * was not clearly carcinogenic for female F344 rats; however, existing evidence suggests that the leukemias of the hematopoietic system may have been related to the administration of the test chemical." In the same study, the test in male rats was considered to be inadequate because of excessive toxicity and mortality among the treated animals. In the male rats, however, abnormal effects in the hematopoietic system was observed. No carcinogenic effect was found in the male or female mice treated with BBP. In another study, di(2-ethylhexyl)phthalate was reported to be carcinogenic in rats and mice (NCI, 1980b).

In the strain A mouse pulmonary adenoma induction system, BBP failed to produce a significant incidence of lung tumors among the treated animals (Theiss et al., 1977).

In view of the inconclusive findings in the long-term rat study, the Committee recommends that a more thorough evaluation of the potential carcinogenicity of BBP be undertaken.

Reproductive effects. A slight reduction in testicular weight was observed in male mice treated with BBP (Calley et al., 1966). Other phthalate esters have been reported to produce testicular atrophy in both male rats and mice (Carter et al., 1977; NCI, 1980b) and decreased fertility in male mice (Oishi and Hiraga, 1980). Based on these findings, the Committee recommends that BBP be tested for its potential reproductive effects.

Environmental effects. A study of the toxicity of BBP on aquatic organisms demonstrated that BBP affects the reproduction of *Daphnia magna* and the growth rates of algae, diatoms, and daphnids (Gledhill et al., 1980). The extent to which BBP affects these organisms is important since many fish and shellfish are dependent on their availability as a food source.

A bioconcentration factor of 663 was observed for BBP at equilibrium in bluegills exposed to the compound (Borrows et al., in press, as quoted in Gledhill et al., 1980).

The log of the octanol/water partition coefficient for BBP (4.8) approximates the log K_{ow} of di(2-ethylhexyl)phthalate (DEHP). DEHP has been shown to bioaccumulate rapidly in a number of aquatic plants and animals and to biodegrade slowly in algae, diphnids, mosquito larvae, snails, and clams (Metcalf et al., 1973). Low pH and anaerobic conditions prolong environmental degradation, which suggests that phthalic acid esters may persist in aquatic sediments (Bower et al., 1970; Habermann et al., 1968).

For the above reasons, and because of BBP's high production volume, environmental effects testing is recommended. Because of BBP's likely persistence in the environment, chronic toxicity to aquatic organisms and potential reproductive effects in terrestrial animals should be emphasized, although this recommendation is not limited only to these areas.

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2.2.c. *Butyl glycolyl lbutyl phthalate.*

Recommended Studies

Health:

Mutagenicity and other short-term tests for genotoxic effects.

Reproductive effects.

Environmental:

Environmental effects.

Substance Identification: CAS No. 85–70–1

Reasons for Recommendations

A significant number of chromatid gaps in Chinese hamster cells in vitro was reported in one study of butyl glycolyl butyl phthalate (BGBP). In another study, increased incidences of chromatid gaps, chromosomal breaks, and translocations in vitro were reported. The results of these studies indicate the need for further evaluation of BGBP in short-term studies for potential genotoxic effects.

Little information is available on the potential reproductive effects of BGBP. Data on other phthalate esters suggest toxicity that may influence mammalian reproductivity, including testicular effects in both male rats and mice and decreased fertility in male mice. These data indicate the need to determine the potential reproductive effects of BGBP.

No information was found on the environmental effects of BGBP. Structurally similar phthalate esters, however, are toxic to aquatic organisms in the parts per billion range and accumulate in aquatic plant and animal tissues. Such information indicates the need for further environmental monitoring and testing of BGBP. Chronic toxicity to aquatic organisms and potential effects on reproduction should be emphasized.

Production, usage, and exposure. BGBP production for 1977 was reported in the public portion of the TSCA Chemical Substance Inventory to be in the range of 1 million to 10 million pounds. It is used primarily as a plasticizer fopr polyvinyl resins. Plastics containing BGBP are used for building and construction materials, home furnishings, and medical and dental devices, including PVC tubing, plastic storage bags, and acrylic dentures. The National Occupational Hazards Survey (NOHS) estimates that 5,500 workers are exposed to BGBP (NIOSH, 1980).

Mutagenicity and other short-term tests for genotoxic effects. Chromatid gaps were observed in Chinese hamster cells exposed in vitro to BGBP (Odashima and Ishidate, 1975, as quoted by Omori, 1976; the original publication of the results could not be located for review). In another study (Ishidate and Idashima, 1977), an increased incidence of chromatid gaps, chromosomal breaks, and translocations was observed in Chinese hamster cells exposed in vitro to BGBP. The results were considered suspicious by the authors, but not conclusive of a treatment-related effect.

Neither DNA repair damage nor mutagenic effects were observed following exposure of *Bacillus subtilis* or *Escherichia coli* to BGBP (Kurata, 1975). These results are inconclusive because of inadequacies in the test design. Other phthalate esters have been reported not to be mutagenic in bacterial assay systems. Benzyl butyl phthalate was reported not to be mutagenic for *E. coli* (Kurata, 1975), while the carcinogenic di[2-ethylhexyl]phthalate was not mutagenic for *Salmonella typhimurium* (Simmon et al., 1977).

In view of the above findings, the Committee recommends that additional short-term studies be conducted to evaluate the genotoxicity of BGBP.

Reproductive effects. BGBP was reported to increase the percentage of resorptions of rate embryos following intraperitoneal injection on the 5th, 10th, and 15th days of gestation (Singh et al., 1972). Fetus weight decreased at all dose levels. In the same study, administration of BGBP to female rats did not interfere with fertility, as reflected by the ratio of corpora lutea to implantation sites.

Available data on other phthalate esters suggest toxicity that may influence mammalian reproductivity. These esters have been shown to produce testicular atrophy in both male rats and mice (Carter et al., 1977; NCI, 1980), decreased fertility in male mice (Oishi and Huiraga, 1979), reduced testicular weight in male mice (Calley et al., 1966), and increased relative testicular weight in male mice (Oishi and Hiraga, 1980).

The above findings indicate the need to test BGBP for its potential reproductive effects.

Environmental effects. The log of the octanol/water partition coefficient for BGBP (4.4) approximates the log k_{ow} of di(2-ethylhexyl) phthalate (DEHP). DEHP has been shown to bioaccumulate rapidly in a number of aquatic plants and animals and to biodegrade slowly in algae, daphnids, mosquito larvae, snails, and clams (Metcalf et al., 1973). Low pH and anaerobic conditions prolong environmental degradation, which suggests that phthalic acid esters may persist in aquatic sediments (Bower et al., 1970; Habermann et al., 1968).

The literature on other phthalate esters indicates that some of them can produce adverse effects in aquatic organisms at concentrations in the parts per billion range (Johnson et al., 1977; Mayer et al., 1977; Mayer and Sanders, 1973).

Because of the lack of environmental effects data on BGBP and because of its structural similarity to phthalate esters that persist and/or are toxic at low concentrations, environmental effects testing is recommended. Particular attention should be given to effects on reproduction in terrestrial animals and to chronic toxicity in aquatic organisms, although this recommendation is not limited only to these areas.

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2.2.d. *Fluoroalkenes.*

Recommended Studies

Health:

Carcinogenicity.
Mutagenicity.
Teratogenicity.
Reproductive Effects.
Other Toxic Effects.

Category Indentification

This category is defined as fluoroalkenes of the general formula:

$C_nH_{2n-x}F_x$

Where n equals 2 or 3 and x equals 1 to 6. Six fluoroalkenes, meeting the category definition, were identified in the public portion of the TSCA chemical Substance Inventory. This category includes those six fluoroalkenes (shown below) but is not limited to them:

Chemical	CAS No.
Tetrafluoroethene	116-14-3
Trifluoroethene	359-11-5
Vinylidine fluoride (VDF)	75-38-7
Vinyl fluoride (VF)	75-02-5
Hexafluoropropene	116-15-4
Trifluoromethylethene	677-21-4

Reasons for Recommendations

There is little information on the toxicity of compounds in this category. The testing of vinyl fluorides has generally been given low priority because of the lack of reactivity of compounds with the carbonfluorine bond. However, the substitution of additional fluorines onto the vinyl carbon leaves it susceptible to nucleophilic attack and thereby capable of direct alkylation, possibly of DNA and other cellular constituents.

Since several vinyl halides have been reported to be carcinogenic, vinyl halides are generally regarded as suspect. A recent report described VDF as a carcinogen in rats. Other studies are needed to clarify the carcinogenicity of category members.

Mutagenicity experiments were found on only two compounds. Additional short-term studies are necessary to clarify the genotoxic effect of members of this category.

Other studies have shown that certain category members act as weak anesthetics, release fluoride ion, and cause kidney damage. The toxic effects in experimental animals of acute inhalation of VF and VDF are enhanced after induction of liver enzymes. Given the demonstration of adverse health effects by certain category members, along with the strong suspicion engendered from analogy with other vinyl halides, appropriate members of this category should be tested in the recommended studies.

Production, usage, and exposure. A substructure search was made of the public portion of the TSCA Chemical Substance Inventory for chemicals within the category definition. A total of six chemcials was identified in the Inventory (Table 1). Data on production volume were not available on four chemicals and were incomplete for the other two.

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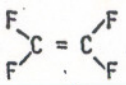
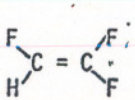
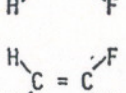
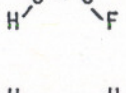
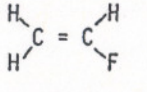
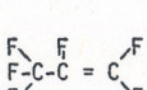
Table 1 SELECTED CHEMICAL AND ECONOMIC INFORMATION ON CATEGORY MEMBERS

Name CAS No.	Structure	Molecular Weight	Boiling Point(1)	Consumption lb/yr U.S. Production(2)	Occupational Exposure(3)	Major Uses (4)
Tetrafluoroethene 116-14-3		100.2	-76°C	10-50 million	5,000	Monomer for polytetrafluoroethylene.
Trifluoroethene 359-11-5		82.0	-51	2 manufacturers(5)	No information	No information
Vinylidine fluoride (1,1-difluoroethene) 75-38-7		64.0	-82	2 manufacturers(5)	19,000	Monomer for polyvinylidine fluoride. Also copolymerized with other monomers.
Vinyl fluoride (fluoroethene) 75-02-5		46.0	-72	1 manufacturer(5)	No information	Monomer for polyvinyl fluoride. Also copolymerized with other monomers.
Hexafluoropropene (1,1,2,3,3,3-hexafluoro-1-propene) 116-15-4		150.0	-29	1-10 million Some imported	224	Monomer for copolymerization, to impart nonflammability and nonoxidizing characteristics. Intermediate in organic synthesis
Trifluoromethylethene (3,3,3 -trifluoro-1-propene) 677-21-4		96.0	-16(-18)	1 manufacturer(5)	No information	No information

NOTES:
(1) Lovelace et al., 1958
(2) TSCA Chemical Substance Inventory (EPA, 1977)
(3) NIOSH, 1980
(4) Matheson Gas Data Book. 5th ed. 1971; West and Holcomb, 1979
(5) No production data provided in the public portion of the TSCA Chemical Substance Inventory (EPA, 1977)

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Chemicals in this category are used primarily in the synthesis of polymers and copolymers with high resistance to heat and corrosion. The usage patterns of the polymers (e.g., in the automotive industry and in pollution control) would indicate an increasing demand for these chemcials (West and Holcomb, 1979).

The United States has no occupational exposure limits for category members. A Russian study showed that the workplace concentration of fluorinated aliphatic hydrocarbons, including tetrafluoroethene and polymers based on these compounds, exceeded that country's acceptable limits by significant amounts (Filicheva, 1975).

The Committee concludes that the lack of exact production and usage information on some category members is insufficient cause to defer designation of the category. The fact that certain members are known to be produced in large volumes, the potential health effects of these chemicals, and the widespread use of products derived from these monomers necessitate an adequate assessment of the toxicity of members of this category.

Chemical and biochemical considerations related to toxicity. The tendency of halogenated alkenes to undergo chemical transformation to epoxides is a function of both the electron-withdrawing characteristic of the halogen constituents and their locations relative to the olefinic linkage. The enzymatic formation of epoxides is believed to be an important step in the activation of halogenated alkenes to a form that can alkylate active sites on nucleotides and peptides. It has been observed, however, that increasing the electron-withdrawing strength of a halogen substituent results in a decrease in the susceptibility of the olefinic linkage to epoxidation. Among the halogens, fluorine exerts the greatest electron-withdrawing strength. Thus, as the number of substituent fluorines is increased, the ease of epoxidation would be expected to decrease. However, as the number of fluorines is increased, it has been observed that the potential for nucleophilic attack at the olefinic carbon and the order of observed reactivity increase with intermediate carbanion stability (Cook and Pierce, 1973). For example, the following order of nucleophilic susceptibility would be expected:[1]

$(CF_3)_2C=CF_2 > CF_2CF=CF_2 > CF_2=CF_2 > HFC=CF_2 > H_2C=CF_2 > H_2C=CHF$

This rank order has been reported to follow that of the acute toxicities of these compounds (Cook and Pierce, 1973; Chambers and Mobbs, 1965; Clayton, 1977). One report on vinyl fluorides describes the ease with which the carbon-fluorine bond can be broken (Chambers and Mobbs, 1965). For example, fluoro-olefins react quite readily with amines, thiols, and, in the presence of a base, with alcohols to give saturated and unsaturated products. It has been suggested that the high susceptibility of perfluoroisobutene to nucleophilic attack might give rise to its extremely high toxicity (Clayton, 1977).

In summary, category members may be biologically reactive by alkylation through epoxide formation and through direct displacement of the fluorine ion.

Carcinogenicity. One report describes the experimental evidence for the carcinogenicity of VDF in rats (Maltoni and Tovoli, 1979). Although tumors of fat tissue were found in the treated animals, certain features of the study are questionable. In another study, VDF was reported to produce premalignant hepatocellular lesions in rats (Stockle et al., 1979).

Two reports presented evidence showing that, in rats pretreated with PCB, VF caused liver toxicity similar to that of vinyl chloride (Conolly and Jaeger, 1977; Conolly et al., 1978). Pretreatment with trichloropropane epoxide enhanced VF toxicity. These findings suggest that the toxicity of VF may be mediated through epoxide intermediates.

The Committee concludes that the above studies raise concern about the potential carcinogenic activity of category members. The Committee, therefore, recommends that members of this category be tested for carcinogenicity.

Mutagenicity. Both VF and VDF have been reported to be mutagenic, without metabolic activation in *Escherichia coli*, producing a response of up to 100 times the spontaneous mutation rate (Landry and Fuerst, 1968). In another study, VF was found to cause a marginal increase over the spontaneous mutation frequency of *Salmonella typhimurium* TA–100 (Bartsch et al., 1979). In a third study, VF was reported not to be mutagenic in *S. typhimurium* strains TA–1535, TA–1537, TA–1538, TA–98, and TA–100, with and without metabolic activation (Mortelmans and Riccio, 1979). VDF was found to exhibit mutagenicity in *S. typhimurium* TA–1535, both with and without metabolic activation (Jagannath and Brusick, 1977).

In a study of the ability of VDF to transform BALB/3T3 cells, one set of test plates showed a series of increased numbers of transformed colonies (Matheson and Brusick, 1978). However, the authors concluded that VDF was inactive in this study.

Based on these varying and inconclusive findings, the Committee recommends that appropriate short-term tests be undertaken to assess the genotoxic effects of members of this category.

Teratogenic and reproductive effects. No reports were found of studies investigating the teratogenic and reproductive effects of fluoroalkenes. Based on the biological activity of members of this category and the lack of information on these effects, the Committee recommends that appropriate tests for teratogenic and reproductive effects be undertaken.

Other toxic effects. The acute inhalation toxicity of fluoroalkenes varies widely (Clayton 1962, 1967, 1968, 1977). Tetrafluoroethene and hexafluoropropene were reported to impair renal function in rats.

Five fluoroalkenes [2] were reported to be metabolized when inhaled by male rats (Dilley et al., 1974). A cyclic excretion of fluoride ion 4–6 and 12–14 days post-exposure was observed. The fluoroalkene exposure produced an increase in urinary potassium ion and diuresis, which persisted for 2 weeks. Chronic exposure to fluoroalkenes may be of concern since the fluoride ion release affects the kidney, causing potassium depletion which may eventually affect the cardiovascular system. Based on these reports, the Committee recommends that members of this category be assessed for chronic health effects, with particular emphasis on the renal and cardiovascular systems.

Environmental Effects. No data on environmental effects were found in the literature. However, from data on structure-activity relationships, the 96-hour LC_{50} to fathead minnows of VDF has been estimated to be greater than 100 mg/l (Veith, 1980; EPA, 1980). This estimated low acute toxicity suggests that aquatic testing is not warranted. The high volatility and other chemical characteristics of the category members indicate that persistence and bioaccumulation are not of concern in aquatic environments.

When released into the atmosphere, fluoroalkene molecules degrade at a moderate rate. For example, the half-life

[1] The position of $CF_2CH=CH_2$ in this rank order is not readily apparent.

[2] Hexafluoropropene, tetrafluoroethene, trifluoroethene, vinylidene fluoride, and vinyl fluoride.

of VDF, calculated from rate constants, is slightly less than one week (Howard, 1976). The reactive atmospheric components (ozone, hydroxyl radicals, and atomic oxygen) attack the fluoroalkenes by adding to or cleaving the molecule at the double bond to produce products such as carbonyl fluoride (Huie et al., 1972). Based on the above considerations, the Committee does not recommend environmental effects studies for category members.

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