

40-8134106

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July 1, 1981

Mrs. Anne Keller
9455 Cloverdale Court
Burke, Virginia 22015

Dear Mrs. Keller:

Per your request, we are enclosing a copy of the Organohalide Class Study Report. Please note that this study was conducted in 1977 and has not been brought up to date. However, we hope it will be of some use to you.

With kind regards.

Sincerely,

Victor A. Fung

Victor A. Fung, Ph.D.
Senior Organic and Environmental Chemist

VAF:mk

Enclosure

SRI International

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Not SRI

ORGANO BROMIDES, IODIDES, AND FLUORIDES

CLASS STUDY

Conducted by a
Class Working Group
of the
Chemical Selection Working Group

November 17, 1977

I. INTRODUCTION

This report completes the final phase of the class study of organo halides which was initiated in September 1976. A report on the first phase of the study, a review of all chlorinated organic compounds and gem polyhalogenated alkanes, was presented to the Chemical Selection Subgroup of the Clearinghouse for Environmental Carcinogens on April 18, 1977. The final phase of the study, described here, entailed a review of organo bromides, iodides, and fluorides to determine if any should be recommended as candidates for the NCI Bioassay Program.

The working group that studied the organo bromides, iodides, and fluorides consisted of the following individuals:

Dr. Lionel A. Poirier, NCI
Dr. Kirtland E. McCaleb, SRI
Dr. C. Tucker Helmes, SRI

II. METHOD OF APPROACH

A. Scope of Study

The study was limited to compounds that were not considered as part of the study of gem polyhalogenated alkanes and for which there is evidence of potential human exposure. An initial list of chemicals to be considered in each subclass (i.e., bromides, iodides, and fluorides) was developed from the following sources:

- SRI Exposure Ranked List
- U.S. International Trade Commission, Synthetic Organic Chemicals, U.S. Production and Sales, U.S. Government Printing Office, Washington, D.C.
- 1977 Directory of Chemical Producers - U.S.A., Chemical Information Services, Stanford Research Institute, Menlo Park, California, 1977.
- U.S. Environmental Protection Agency, Office of Toxic Substances, A Study of Industrial Data on Candidate Chemicals for Testing, EPA - 560/5-77-006, Washington, D.C., August 1977.
- EPA, Organic Compounds Identified in Drinking Water in the United States, Cincinnati, Ohio, 1976.
- Shackelford, W. M. and Keith, L. H., Frequency of Organic Compounds Identified in Water, EPA, Athens, Georgia, 1976.

B. Evaluation of Potential Exposure

Two types of quantitative data were used to assess potential human exposure to the chemicals in each subclass:

- production volume
- exposure estimates from the NCI/SRI Mark II data base.

Other factors, such as use information, the names of major producers, and the occurrence of the chemical in water, were used when necessary to supplement the available quantitative data in estimating potential exposure.

C. Evaluation of Potential Carcinogenicity

Available carcinogenicity data were evaluated in order to identify members of the class that have been tested adequately for carcinogenicity and to identify key structural features that are relevant in predicting the potential carcinogenic activity of untested members of the class. The following references were used as sources of information:

- PHS-149, Survey of Compounds That have been Tested for Carcinogenic Activity (the primary references cited in PHS-149 were consulted when necessary for an evaluation of the data).
- L. A. Poirier, G. D. Stoner, and M. B. Shimkin, Bioassay of Alkyl Halides and Nucleotide Base Analogs by Pulmonary Tumor Response in Strain A Mice. Cancer Res. 35, 1411-1415, 1975.

D. Nomination of Chemicals

The nomination of chemicals from each subclass involved two major steps. First, chemicals were eliminated from further consideration if they failed to meet certain qualifying criteria (e.g., produced in quantities greater than 10³ grams or 1000 lbs, not currently on test or previously considered by the CSWG, and not yet adequately tested for carcinogenicity). Second, a selected number of the remaining chemicals were nominated for consideration by the CSWG based on their level of exposure, potential carcinogenicity, and the representativeness of their structure.

III. RECOMMENDATIONS TO THE CSWG

A. Bromides

The organo bromides were divided into the following major categories: alkyl bromides, vicinal bromides, vinyl bromides, benzyl bromides, aryl bromides, and polybrominated aromatics. The chemicals in each of these groups initially considered as test candidates, and their exposure estimates and reported production volumes are listed in Table 1.

Table 1

BROMIDES

CAS No.	Name	Exposure (g/yr)	Production (g/yr)
<u>Alkyl bromides</u>			
77667	Acetylcarbromal	2.15×10^5	n.d.
3296900	2,2-Bis(bromomethyl)-1,3-propanediol	n.d.	$>10^5$
78762	2-Bromobutane	n.d.	$>10^5$
109706	1-Bromo-3-chloropropane	n.d.	$>10^5$
2032351	2-Bromo-1,1-diethoxyethane	n.d.	$>10^5$
7252837	2-Bromo-1,1-dimethoxyethane	n.d.	$<10^5$
540512	2-Bromoethanol	n.d.	$>10^5$
107824	1-Bromo-3-methylbutane	n.d.	$>10^5$
110532	1-Bromopentane	n.d.	$>10^5$
107813	2-Bromopentane	n.d.	$>10^5$
106945	1-Bromopropane	n.d.	$>10^5$
75263	2-Bromopropane	n.d.	$>10^5$
106956	3-Bromopropene	n.d.	$>10^5$
109659	n-Butylbromide	n.d.	$>10^5$
77656	Carbromal	1.81×10^7	$>10^5$
4333566	Cyclopropyl bromide	n.d.	$>10^5$
110521	1,4-Dibromobutane ^a	n.d.	$>10^5$
626879	1,4-Dibromopentane	n.d.	$>10^5$
111240	1,5-Dibromopentane	n.d.	$>10^5$
109648	1,3-Dibromopropane	n.d.	$>10^5$
74964	Ethyl bromide	n.d.	$>10^5$
74839	Methyl bromide	n.d.	1.6×10^{10}
<u>Vicinal bromides</u>			
96128	1,2-Dibromo-3-chloropropane	n.d.	1.1×10^{10}
106934	1,2-Dibromoethane	n.d.	1.2×10^{11}
96139	2,3-Dibromo-1-propanol	n.d.	$>10^9$
	Hexabromocyclododecane	n.d.	$>10^5$
	Pentabromo-6-chlorocyclohexane	n.d.	$>10^5$
<u>Vinyl bromides</u>			
103640	2-Bromoethenylbenzene	4.82×10^5	n.d.
513315	2,3-Dibromopropylene	n.d.	n.d.
593602	Vinyl bromide	n.d.	$>10^5$
<u>Aryl bromides</u>			
	1-Amino-4-bromo-9,10-dihydro-9,10-dioxo-2-anthracene sulfonic acid	n.d.	$>10^5$
	5(and 8)-Amino-8(and 5)-bromo-9,10-dihydroxy-9,10-dioxo-1,6(and 1,7)-anthracene disulfonic acid	n.d.	$>10^5$
	1-Amino-2-bromo-4-hydroxyanthraquinone	n.d.	2.9×10^8
	1-Amino-2-bromo-4-p-toluidinoanthraquinone	n.d.	$>10^5$

Table 1 (Concluded)

<u>CAS No.</u>	<u>Name</u>	<u>Exposure (g/yr)</u>	<u>Production (g/yr)</u>
<u>Aryl bromides (concluded)</u>			
81492	1-Amino-2,4-dibromoanthraquinone	n.d.	>10 ⁵
	1-Benzamido-4-bromoanthraquinone	n.d.	>10 ⁵
81969	3-Bromobenzanthrone	n.d.	2.5 x 10 ⁷
108861	Bromobenzene	n.d.	>10 ⁵
106398	Bromochlorobenzene	n.d.	>10 ⁵
	1-Bromo-4-(methylamino)anthraquinone	n.d.	>10 ⁵
	1-Eromonaphthalene	n.d.	>10 ⁵
980712	<u>gamma</u> -(4-Bromophenyl)-N,N-dimethyl- 2-pyridinepropanamine, (2)-butene- dioate (1:1)	2.3 x 10 ⁶	>10 ⁵
36563470	Bromophenyl phenyl ether	n.d.	n.d.
18088124	2-[(4-Bromophenyl)phenylmethoxy]-N,N- dimethylethanamine hydrochloride	4.6 x 10 ⁵	>10 ⁵
95465	<u>o</u> -Bromotoluene	n.d.	>10 ⁵
106387	<u>p</u> -Bromotoluene	n.d.	>10 ⁵
	1-Bromo-2,4,6-triethylbenzene	n.d.	>10 ⁵
1336457	Chlorbromuron	n.d.	4.5 x 10 ⁸
81981	3,9-Dibromo-7H-benz(d,e)anthracen-7- one	n.d.	>10 ⁵
106376	<u>p</u> -Dibromobenzene	n.d.	>10 ⁵
1689845	3,5-Dibromo-4-hydroxybenzoxitrile	n.d.	2.3 x 10 ⁶
827941	2,6-Dibromo-4-nitroaniline	n.d.	1.8 x 10 ⁷
81345	5,13-Dibromo-8,16-pyranthreonedione	n.d.	<10 ⁵
4776061	Fluorosalan	4.02 x 10 ³	>10 ⁵
129168	Mercurichrome	3.98 x 10 ⁵	>10 ⁵
<u>Polybrominated aromatics</u>			
548265	Bromo acid (Eosine yellowish)	1.16 x 10 ⁶	>10 ⁵
	Decabromobiphenyl	n.d.	>10 ⁵
152750	Eosine acid (D+C Red No. 21)	3.64 x 10 ⁷	2.1 x 10 ⁷
87821	Hexabromobenzene	n.d.	>10 ⁵
36355018	Hexabromobiphenyl	n.d.	<10 ⁵
	Octabromobiphenyl	n.d.	>10 ⁵
71670	Sodium sulfobromophthalein	2.62 x 10 ⁴	>10 ⁵
632791	Tetrabromophthalic anhydride	n.d.	>10 ⁸
	Tetrabromo- <u>o</u> -chlorotoluene	n.d.	>10 ⁵
87105	Tribromsalan	5.11 x 10 ⁷	>10 ⁵

1. Alkyl bromides: 2-Bromo-1,1-dimethoxyethane was eliminated from consideration because it is not produced in quantities greater than 10^5 grams. Carbromal and acetylcarbromal were eliminated because carbromal is currently in the NCI testing program. n-Butyl bromide was eliminated because it was found to be negative in the mouse lung adenoma assay and it was not expected to be active in more extensive testing. Nine alkyl bromides have been tested for carcinogenicity and six of these are carcinogenic. A high percentage of alkyl bromides are mutagenic. Total exposure of the alkyl bromide group as a whole is high (total production or exposure is estimated to be at least 10^{10} grams). Because of the impossibility of performing large-scale carcinogenicity tests on all alkyl bromides, it was recommended that the group as a whole be subject to mutagenicity and carcinogenicity research experiments and that the Department of Labor (OSHA) and NIOSH be advised of the possible hazards of such alkylating agents in the workplace. Little additional information on potential exposure and possible carcinogenicity was available on the alkyl bromides remaining under consideration. Therefore the following four compounds whose structures are fairly representative of the group as a whole and whose potential exposure is estimated to be at least moderate were recommended to the CSWG:

- a) 2,2-Bis(bromomethyl)-1,3-propanediol
- b) 1,3-Dibromopropane
- c) Ethyl bromide
- d) Methyl bromide

2. Vicinal bromides: Three vicinal bromides have been tested for carcinogenic activity. Two of them, 1,2-dibromoethane and 1,2-dibromo-3-chloropropane, were eliminated from consideration as test candidates because they have been shown to be carcinogenic. A third, tris(2,3-dibromopropyl)-phosphate, was recently judged to be carcinogenic on the basis of an NCI bioassay. Therefore, this group is regarded with a relatively high suspicion of carcinogenic activity. Because of its high production (at least 10^9 grams), 2,3-dibromo-1-propanol was nominated to the CSWG. The two remaining vicinal bromides, hexabromocyclododecane and pentabromo-6-chlorocyclohexane, were deferred from further consideration because details of their exposure were not known. It was recommended that Dr. Cameron contact the manufacturers of these potentially hazardous compounds to ascertain the possible workplace exposure.

3. Vinyl bromides: Two vinyl bromides are already on test: vinyl bromide and cytembena. Available information indicates that the production or exposure of the two remaining compounds in this group, 2-bromoethenylbenzene and 2,3-dibromopropylene, is fairly limited. Therefore no further action was recommended for this group.

4. Benzyl bromides: Although all seven of the benzyl bromides tested for carcinogenic activity were found to be positive (they were all bromomethyl analogs of methylated benzanthracene carcinogens), no action was recommended on this group because no chemicals of this type were found to be of environmental or commercial significance.

5. Aryl bromides: These compounds are reasonably important in terms of potential exposure (estimated total production or exposure is at least 10^9 grams) and the aryl bromide structure represents a gap in knowledge of potential carcinogenicity. No compounds of this type are currently on test but

chlorbromuron was dropped from consideration because the related chloro derivative, monuron, is on test. Bromophenyl phenyl ether and 5,13-dibromo-8,16-pyranthredione were eliminated because available information indicated the total production of each was not greater than 10^5 grams per year. Three compounds from this group were nominated:

- a) 1-Amino-2,4-dibromoanthraquinone. Nominated as a representative of the aryl bromides known to be produced in quantities greater than 10^7 grams (its total production was reported as 3.9×10^8 grams in 1974).
- b) Bromobenzene. Nominated as a model compound representative of this group, having a total production of greater than 10^5 grams and known to alkylate cellular macromolecules in the liver via metabolism to the reactive arene oxide.
- c) p-Dibromobenzene. Also nominated as a model compound from this group. Although exact details of its exposure are not known, the extent of exposure is estimated to be high based on its use pattern and the fact that Dow, a major manufacturer, is one of its producers.

6. Polybrominated aromatics: The available data are inadequate to evaluate the potential carcinogenicity of this group of environmentally and commercially important chemicals (estimated total production or exposure is greater than 10^8 grams per year). Eosine acid was eliminated from consideration because previous carcinogenicity tests reported in PHS 149 indicated it to be inactive. Although the polybrominated biphenyls are an important group of chemicals, none were nominated because hexabromobiphenyl currently is being tested for carcinogenic activity by NIEHS. Tetrabromophthalic anhydride (total production $>10^8$ grams) was nominated as a representative compound of the remaining polybrominated aromatics.

B. Iodides

Although present in the environment at much lower levels than the bromides, the organo iodides similarly were divided into the following major groups: alkyl iodides, vinyl iodides, aryl iodides, polyiodinated aromatics, and iodopyrimidines. The chemicals in each of these groups initially considered as test candidates, and their exposure estimates and reported production volumes are listed in Table 2.

1. Alkyl iodides: The alkyl iodides should be viewed as potentially hazardous substances. Of eight that have been tested, six have been found to be carcinogenic. One chemical in this group, methiodal sodium, is on test currently in the NCI bioassay program. The CSWG was alerted to the potential hazards of methyl and ethyl iodides but neither was recommended for test. Both are mutagenic and methyl iodide is a known carcinogen so further testing of it did not seem warranted. Both are reported to be produced in quantities greater than 10^5 grams per year (the annual production of methyl iodide was reported as 8.63×10^6 grams in 1973), but insufficient details of the exposure to ethyl iodide were available

Table 2

IODIDES

<u>CAS No.</u>	<u>Name</u>	<u>Exposure (g/yr)</u>	<u>Production (g/yr)</u>
<u>Alkyl iodides</u>			
75036	Ethyl iodide	n.d.	>10 ⁵
74884	Methyl iodide	n.d.	>10 ⁵
5634399	Organidin	2.52 x 10 ⁶	>10 ⁵
<u>Vinyl iodides</u>			
583879	Iodobrassid	7.16 x 10 ⁵	n.d.
<u>Aryl iodides</u>			
130267	5-Chloro-7-iodo-8-quinolinol	3.22 x 10 ⁶	>10 ⁵
83738	5,7-Diiodo-8-quinolinol	2.57 x 10 ⁶	n.d.
4386350	Merodicein	1.34 x 10 ⁵	n.d.
<u>Polyiodinated aromatics</u>			
13753	Choloxin	4.55 x 10 ⁴	n.d.
55061	Cytomel sodium	4.58 x 10 ³	n.d.
55038	Dathroid	5.1 x 10 ⁴	>10 ⁵
568638	Erythrosine	2.85 x 10 ⁷	9.1 x 10 ⁷
737315	Hypaque sodium	4.67 x 10 ⁷	>10 ⁵
606177	Iodipamide	7.14 x 10 ⁵	n.d.
96833	Iopanoic acid	3.63 x 10 ⁷	>10 ⁵
1225203	Iothalamate sodium	1.07 x 10 ⁶	>10 ⁵
1221563	Ipodate sodium	5.95 x 10 ⁶	n.d.
131497	Renografin	2.5 x 10 ⁷	>10 ⁵
129635	Triotrast	1.16 x 10 ⁷	n.d.
<u>Iodopyrimidines</u>			
54422	2'-Deoxy-5-iodouridine	6.20 x 10 ³	n.d.
3565159	5-Iodo-2-thiouracil	6.72 x 10 ⁴	n.d.

to recommend it as a test candidate. The remaining alkyl iodide found to be of environmental or commercial importance, organidin, was recommended for testing because of its estimated human exposure of 2.52×10^6 grams per year.

2. Vinyl iodides: No vinyl iodides have been tested for carcinogenicity and none are on test currently in the NCI program. Iodobrassicid, the only one found to be of potential environmental or commercial importance, was thought to have a high risk of potential carcinogenic activity but was deferred from further consideration due to its relatively low exposure (7.2×10^5 grams/year) and limited uses as an iodine source and in iodine therapy in veterinary medicine. Definitive data on workplace exposure, if any, are being sought from NIOSH and the Department of Labor.

3. Aryl iodides: The three aryl iodides under consideration because of potential human exposure were all phenols. These were not regarded with a high suspicion of carcinogenic activity and hence were deferred from further consideration for a full carcinogenicity test.

4. Polyiodinated aromatics: These compounds were considered to be of importance because of potential human exposure (estimated total exposure is about 10^6 grams/year) but there were insufficient data available to adequately assess their potential carcinogenicity. Of the two compounds that have been tested for carcinogenicity, one, a polyiodo diethylstilbestrol derivative, was positive and the other, erythrosine, was negative. Hence the latter compound, whose potential exposure is significant (exposure estimated to be 2.85×10^7 grams/year), was not considered further for testing. Two compounds, iopanoic acid and hypaque sodium, were recommended as representative of the remaining polyiodo compounds having potential exposure. Both are used as radiopaque drugs but, according to the FDA, the parenterally administered hypaque sodium is more widely used than the orally administered iopanoic acid.

5. Iodopyrimidines: Neither iodopyrimidine under consideration was recommended for selection because of previous carcinogenicity studies. 5-Iodo-2-thiouracil has been shown to be a thyroid carcinogen in rats. 2'-Deoxy-5-iodouridine has been found negative in a number of carcinogenicity studies.

C. Fluorides

The organo fluorides initially considered because of their potential for human exposure are listed in Table 3. Many of these are fluorinated steroids but estimates of their exposure are not relatively high. The other organo fluorides considered in this study include vinyl fluorides, aryl fluorides, and fluoropyrimidines.

The available information was not adequate to assess the potential carcinogenicity of the organo fluorides under consideration. There are numerous studies on the effects of fluoro substitution on the carcinogenicity of known aromatic carcinogens (e.g., acetylaminofluorene, polycyclic aromatic hydrocarbons) but these compounds bear little resemblance to the organo fluorides of environmental or commercial significance. Because of the relative lack of reactivity of most fluorene-carbon bonds and an absence of sufficient details to indicate

significant human exposure to these organo fluorides, none were recommended for consideration at present by the CSWG. Instead, the following recommendations were made:

1. Research should be encouraged on the mutagenicity and carcinogenicity of fluoro compounds as a group and of 5-fluorouracil in particular;
2. Further details on the production and workplace exposure of the vinyl fluorides should be sought from NIOSH and DuPont (a major manufacturer of some of these compounds).

IV. SUMMARY OF ACTIONS BY CSWG

From a group of some 80 environmentally significant organobromides, the class working group nominated 11 for consideration by the CSWG. Of these 11, the CSWG decided to select eight for testing. The class working group identified some 20 environmentally significant organoiodides and nominated three of these for consideration by the CSWG. Of these three, the CSWG decided to select two for testing. No organofluorides were nominated. (See Table 4)

The data on which the CSWG based their decisions are found on the accompanying summary sheets, along with a summary of the considerations on which the final decision was based (see Action by CSWG).

Table 3
FLUORIDES

CAS No.	Name	Exposure (g/yr)	Production (g/yr)
<u>Steroids</u>			
76437	Androfluorone	9.48×10^4	$>10^5$
987246	Betamethasone acetate	6.79×10^3	$>10^5$
151735	Betamethasone disodium phosphate	6.79×10^3	n.d.
2152445	Betamethasone 17-valerate	9.36×10^4	$>10^5$
50022	Dexamethasone	4.99×10^4	$>10^5$
2392394	Dexamethasone disodium phosphate	5.22×10^4	$>10^5$
67732	Fluocinolone acetonide	1.58×10^4	n.d.
127311	Fluohydrocortisone	7.3×10^1	n.d.
514363	Fluorocortisone acetate	1.32×10^3	$>10^5$
426131	Fluorometholone	7.83×10^2	$>10^5$
53349	Fluprednisolone	7.83×10^2	$>10^5$
1524885	Flurandrenolide	2.37×10^4	n.d.
2002291	Locacorten	2.21×10^3	n.d.
1597826	Paramethasone acetate	6.51×10^3	n.d.
124947	Triamcinolone	1.73×10^5	$>10^5$
76255	Triamcinolone acetonide	2.71×10^5	$>10^5$
67787	Triamcinolone diacetate	2.09×10^5	$>10^5$
5611518	Triamcinolone hexacetonide	3.41×10^4	n.d.
<u>Vinyl fluorides</u>			
	Chloropentafluoropentene	n.d.	$<10^5$
79389	Chlorotrifluoroethylene	n.d.	$>10^5$
79356	1,1-Dichloro-2,7-difluoroethylene	n.d.	$>10^5$
75387	1,1-Difluoroethylene	n.d.	$>10^5$
75025	Fluoroethylene	n.d.	$>10^5$
116154	Hexafluoropropene	n.d.	$>10^5$
360894	Perfluoro-2-butene	n.d.	$<10^5$
116143	Tetrafluoroethylene	n.d.	7.8×10^9
<u>Aryl fluorides</u>			
1172185	Fluorazepam hydrochloride	1.77×10^6	$>10^5$
52868	Haldol	3.53×10^4	n.d.
548732	Ipapsine	1.33×10^2	n.d.
<u>Fluoropyrimidines</u>			
51218	5-Fluorouracil	6.96×10^5	n.d.

Table 4

SUMMARY OF ACTIONS BY CSWG

Chemicals Nominated	Action by CSWG	
	Selected	Not Selected
<u>Alkyl bromides</u>		
2,2-Bis-(bromomethyl)-1,3-propandiol	X	
1,3-Dibromopropane	X	
Ethyl bromide	X	
Methyl bromide		X
<u>Vicinal bromides</u>		
2,3-Dibromo-1-propanol	X	
<u>Vinyl bromides</u>		
none		
<u>Benzyl bromides</u>		
none		
<u>Aryl bromides</u>		
1-Amino-2,4-dibromoanthraquinone	X	
Bromobenzene	X	
Chlorbromuron		X
p-Dibromobenzene	X	
<u>Polybrominated aromatics</u>		
Tetrabromophthalic anhydride		X
<u>Alkyl iodides</u>		
Organidin	X	
<u>Vinyl iodides</u>		
none		
<u>Aryl iodides</u>		
none		
<u>Polyiodinated aromatics</u>		
Diatrizoate sodium (Hypaque)	X	
Iopanoic acid		X
<u>Iodopyrimidines</u>		
none		
<u>Fluorides (all)</u>		
none		