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A STUDY OF ETHERS FOR THE SELECTION OF
CANDIDATES FOR CARCINOGEN BIOASSAY*

Key words: Ethers, Carcinogenicity,
Bioassay, Review

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ABSTRACT

The class of ether compounds was studied in order to nominate chemicals to the National Cancer Institute as candidates for carcinogen bioassay. After application of several qualifying criteria relating to previous, current, or planned carcinogenicity tests and to commercial significance, the preliminary candidate list of 323 chemicals was reduced to a list of 176 chemicals. Based upon consideration of both the suspicion of possible

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carcinogenic activity and evidence indicating potential exposure, the following eight chemicals were nominated: methyleugenol, isoeugenol, 2-isopropoxyphenyl N-methylcarbamate, estragole, 2-hydroxy-4-methoxybenzophenone, tetrahydrofuran, methyl vinyl ether, and diphenyl ether.

INTRODUCTION

As a part of the chemical selection process of the Office for Environmental Cancer, Division of Cancer Cause and Prevention (DCCP) of the National Cancer Institute (NCI), SRI International (SRI) has been conducting, over the past years, systematic studies of classes of chemicals according to use and structural interest in order to nominate chemicals for carcinogenicity testing. Reports on these studies and summary data sheets on the chemicals that are nominated are prepared and are submitted to various committees for evaluation. These documents are first reviewed by the Chemical Selection Working Group (CSWG), an interagency group operating under the auspices of the Office for Environmental Cancer. These reports were also reviewed by the former Chemical Selection Subgroup (CSSG) of the Clearinghouse on Environmental Carcinogens up to May 1980, when the charter for this committee expired and was not renewed. The CSSG was an advisory group to the NCI and consisted of representatives from academia and industry. After consideration by each committee, these reports are revised as necessary in order to incorporate comments, recommendations, and decisions made by each committee. Then the reports are submitted for further evaluation to the National Toxicology Program (NTP) which makes the final decision as to which chemicals are selected for testing for carcinogenicity.

The study of the class of ether compounds for the selection of candidates for carcinogen bioassay was conducted and presented to the CSWG in March 1979. The selection of this class for study was based on consideration of both suspicion of possible carcinogenicity and potential exposure. In general, the

carcinogenicity of ethers has not been studied systematically, although a limited body of carcinogenicity test data was available (e.g., dioxane and dimethoxane), that contributed to structure-activity assessments and the evaluation of the potential carcinogenicity of this class. Although there were no aggregated production figures on the entire class of ether compounds, it was known that they were used extensively as solvents (e.g., dialkyl ethers) and heat transfer media (e.g., diphenyl oxide), and there appeared to be substantial occupational exposure and some consumer exposure.

SCOPE OF THE STUDY

The scope of the study was defined as commercially significant ethers. Ethers are defined as compounds of the general formula R-O-R, Ar-O-R, or Ar-O-Ar, where R is alkyl and Ar is aryl. Excluded from the study as candidates were ethers of uncertain structure and ether derivatives of chemicals belonging to classes of known carcinogens (e.g., aryl amines, aryl nitro compounds, azo dyes, and polycyclic aromatic hydrocarbons). Other ethers were excluded that would be or have been studied more appropriately as part of other class studies (i.e., methoxylated steroids, organometallics, and furans and benzofurans¹). Also excluded from this study were other structures that are not strictly ethers (i.e., lactones, epoxides, anhydrides, nucleosides, and simple sugars). A chemical was defined as being commercially significant if it was included in either the U.S. International Trade Commission's Synthetic Organic Chemicals, U.S. Production and Sales² or in SRI's 1978 Directory of Chemical Producers-U.S.A.³

POTENTIAL CARCINOGENICITY OF ETHER COMPOUNDS

The potential carcinogenicity of ether compounds was evaluated from review articles, compendia, and other reports of experimental data in the open literature. The following sources

of carcinogenicity information were particularly useful: C.E. Searle (ed.), Chemical Carcinogens, ACS Monograph 173⁴; IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man⁵; and NCI Carcinogenesis Technical Report Series.⁶ After the examination of the data reported and judged to be adequate in these sources, the known carcinogenic ether compounds were identified and categorized by structural type (e.g., simple aliphatic, diaryl).

Although the limited data available cannot be used to develop conclusive structure-activity relationships, they suggest structural features that tentatively may be associated with the carcinogenicity of ethers. For example, the three safrole compounds for which adequate test data were found are carcinogenic. These results indicate that the ether moiety may contribute to the carcinogenicity of these compounds, possibly by stabilizing through resonance, the development of an electrophilic species in the propenyl side chain. A preliminary test, in which 3,4,5-trimethoxycinnamaldehyde was found to be carcinogenic while the unsubstituted cinnamaldehyde was inactive⁷, also suggests a role for ether substituents in mediating the formation of incipient electrophilic centers in carcinogenic compounds containing propenyl and related substituents (e.g., safrole).

Two other structural features that may be associated with the carcinogenicity of ethers are alkyl haloether moieties and dioxanes. All of the alkyl haloethers for which adequate data were found are carcinogenic, and two dioxanes (1,4-dioxane and dimethoxane) of the three for which adequate data were found are carcinogenic.

The names, structures, and test results of specific ether compounds for which adequate test data have been reported for an evaluation of carcinogenicity are presented in Table 1.

PRELIMINARY LIST OF CANDIDATE CHEMICALS

A preliminary candidate list was compiled, using the

TABLE 1
CARCINOGENICITY OF ETHERS

A. Positive Results

<u>Name and CAS No.</u>	<u>Structure</u>	<u>Species</u>	<u>Route</u>	<u>Target Organ</u>	<u>Reference</u>
1,4-Dioxane (123-91-1)		Rat	p.o.	Nasal cavity, liver	9,10
		Guinea pig	p.o.	Liver, gall bladder	9
		Mouse	p.o.	Liver	10
		Mouse	skin	Promoter (DMBA as initiator)	9
Dimethoxane (828-00-2)		Rat	p.o.	Liver	11
Griseofulvin (126-07-8)		Mouse	p.o.	Liver	12
		Mouse, infant (M)	s.c.	Liver	12

(continued)

TABLE 1 (continued)

<u>Name and CAS No.</u>	<u>Structure</u>	<u>Species</u>	<u>Route</u>	<u>Target Organ</u>	<u>Reference</u>
Dihydroxysafrole (94-58-6)		Rat	p.o.	Esophagus	13
		Mouse (M)	p.o.	Liver	13
		Mouse	p.o.	Lung	13
Isosafrole (120-58-1)		Rat	p.o.	Liver	14
		Mouse	p.o.	Liver	14
Safrole (94-59-7)		Rat	p.o.	Liver	15
		Mouse	p.o.	Liver	15
		Mouse, infant (M)	s.c.	Liver, Lung	15
Aramite® (140-57-8)		Rat	p.o.	Liver	16
		Mouse	p.o.	Liver	16
		Dog	p.o.	Gall bladder, biliary duct	16

TABLE 1 (continued)

<u>Name and CAS No.</u>	<u>Structure</u>	<u>Species</u> ^f	<u>Route</u>	<u>Target Organ</u>	<u>Reference</u>
Nafenopin (3771-19-5)		Rat	p.o.	Liver	17
		Mouse	p.o.	Liver	18
Penicillic acid (90-65-3)		Rat	s.c.	Injection site	19
		Mouse	s.c.	Injection site	19
1,2-Bis(chloromethoxy)- ethane (13483-18-6)		Mouse	topical	Skin	20
			s.c.	Injection site	20
			i.p.	Injection site	20
1,2,3-Tris(chloro- methoxy)propane (38571-73-2)		Mouse	topical	Skin	21
			s.c.	Injection site	21
			i.p.	Injection site	21
Bis(2-chloroethyl) ether (111-44-4)		Mouse	p.o.	Liver	22

(continued)

TABLE 1 (continued)

<u>Name and CAS No.</u>	<u>Structure</u>	<u>Species</u>	<u>Route</u>	<u>Target Organ</u>	<u>Reference</u>
Chloromethyl methyl ether (107-30-2)		Mouse	topical	Skin	23
			s.c.	Injection site	
(n.b. The commercial chloromethyl methyl ether tested may be contaminated with bis(chloromethyl)ether that could be at least in part responsible for the carcinogenic activity observed)					
Bis(chloromethyl) ether (432-88-1)		Rat	inhalation	Lung, nasal cavity	24
			s.c.	Injection site	
		Mouse	inhalation	Lung	24
			topical	Skin	
House, infant	s.c.	Lung	24		
1,4-Bis(chloromethoxy methyl)benzene (56894-91-8)		Mouse	topical	Skin	25
			s.c.	Injection site	

TABLE I (continued)

B. Negative Results

<u>Name and CAS No.</u>	<u>Structure</u>	<u>Species</u>	<u>Route</u>	<u>Reference</u>
Dioxathion (78-34-2)		Rat Mouse	p.o. p.o.	26
Rotenone (83-79-4)		Mouse	p.o.	27
Vanillin (121-33-5)		Rat	p.o.	28

(continued)

TABLE 1 (continued)

<u>Name and CAS No.</u>	<u>Structure</u>	<u>Species</u>	<u>Route</u>	<u>Reference</u>
(p-Methoxyphenyl) acetic acid (104-01-8)		Mouse	p.o.	27
p-(Benzyloxy)phenol (103-16-2)		Mouse	p.o.	27
Methoxychlor (72-43-5)		Rat	p.o.	29
		Mouse	p.o.	

substructure search capability of the NIH/EPA Chemical Information System (CIS) to search the U.S. International Trade Commission (ITC) data base⁸ for organic ethers falling within the scope of the study. The ITC data base included chemicals produced or imported in the U.S. from about 1960-1975 and, therefore, was a convenient source of commercially significant ether compounds. By this method, the Chemical Abstracts Service (CAS) Registry Numbers for 313 chemicals were obtained.

To this list of 313 chemicals reported to be produced in the U.S., an additional 10 ethers were added. Seven of these were reported to be imported through the principal U.S. customs districts in quantities exceeding 10,000 pounds per year (4.5×10^6 g) in either 1976 or 1977, and the other three were judged to have potential for human exposure based on information found in SRI chemical information files. Thus, the resulting preliminary candidate list of ethers consisted of 323 chemicals.

A summary of the disposition of these candidates by structural subclass from the preliminary candidate list through nomination is shown in Table 2. The steps used for the evaluation of the candidate chemicals are discussed in the following sections of this report.

QUALIFYING CRITERIA

The preliminary candidate list of 323 ethers was reduced to a final candidate list of 176 chemicals by application of the following qualifying criteria:

Previous Tests

The following nine candidate chemicals were eliminated from further consideration because previous carcinogenicity test results (see Table 1) were judged adequate to preclude the need for further testing by NCI:

TABLE 2

ETHERS CLASS STUDYNumber of Chemicals by Structural Subclass - From Preliminary Candidate List to Nomination

<u>STRUCTURAL SUBCLASS</u>	<u>NUMBER OF CHEMICALS</u>				
	<u>ON PRELIMINARY LIST</u>	<u>ELIMINATED AND BASIS OF ELIMINATION</u>			<u>NOMINATED</u>
		<u>On CBDS List</u>	<u>Failed Other Qualifying Criteria</u>	<u>Considerations of Suspicion and Exposure</u>	
A. Alkoxyphenyl ethers	86	3	36	43	4
B. Extended phenyl ring ethers	26	-	16	9	1
C. Fused aryl ring system ethers	32	-	22	10	-
D. Tetrahydrofurans	7	-	0	6	1
E. Simple aliphatic ethers	46	1	23	21	1
F. Ring-containing aliphatic ethers	11	-	3	8	-
G. Halophenoxyalkyl ethers	38	-	5	33	-
H. Pyrans and benzopyrans	14	-	8	6	-
I. Diaryl ethers	11	-	4	6	1
J. Nitrogen heterocyclic ring systems	39	1	20	18	-
K. Ethers of uncharacterized structure	13	-	5	8	-
Total Compounds	323	5	142	168	8

<u>CAS NO.</u>	<u>NAME</u>	<u>REFERENCE</u>
72-43-5	Methoxychlor	29
78-34-2	Dioxathion	26
103-16-2	p-(Benzyloxy)phenol	27
104-01-8	(p-Methoxyphenyl)acetic acid	27
107-30-2	Chloromethyl methyl ether	23
111-44-4	Bis(2-chloroethyl) ether	22
121-33-5	Vanillin	28
123-91-1	1,4-Dioxane	9,10
140-57-8	Aramite®	16

Prior Considerations and Current Test Status

By matching the CAS Registry Numbers and names of chemicals on the preliminary candidate list against those of chemicals in the NCI Carcinogenesis Bioassay Data System (CBDS) file,³⁰ five chemicals having CBDS numbers assigned to them were eliminated because they have already been selected, are currently on test, or have already been tested in the NCI Bioassay Program. An additional 13 candidate chemicals were eliminated because they had been considered previously and acted upon by the CSWG. The names and CAS Registry Numbers of these 18 candidate chemicals are listed in Table 3.

U.S. Production Quantities

Investigation of 94 chemicals included in the ITC data base⁸ established that they were not produced in commercial quantities in the U.S. in 1976 or 1977.

A further study of the remaining candidate chemicals established that the commercial significance of another 26 chemicals was marginal. These were chemicals which were produced by only one U.S. company, known to be a small volume manufacturer, and for which annual imports of each chemical through the principal U.S. customs districts were reported to be less than 1,000 pounds (4.5×10^5 g) in 1976 and 1977.

TABLE 3

Candidate Chemicals Eliminated Because of Presence on CBDS List
or Previously Considered by CSWG

<u>CAS NO.</u>	<u>NAME</u>	<u>CBDS</u>	<u>CSWG</u>
50-34-0	Propantheline bromide		X
50-55-5	Reserpine	X	
56-54-2	Quinidine		X
57-22-7	Vincristine		X
59-02-9	Vitamin E		X
61-25-6	Papaverine hydrochloride		X
97-53-0	Eugenol	X	
104-46-1	p-Propenylanisole	X	
108-60-1	Bis(2-chloro-1-methylethyl) ether	X	
121-32-4	Ethyl vanillin	X	
123-11-5	p-Anisaldehyde		X
131-01-1	Deserpidine		X
132-98-9	Phenoxymethyl penicillin, potassium salt		X
147-24-0	Diphenhydramine hydrochloride		X
865-21-4	Vinblastine		X
1504-74-1	o-Methoxycinnamaldehyde		X
2312-35-8	2-(p-t-Butylphenoxy)cyclohexyl-2-propynyl sulfite		X
6591-72-6	Phenoxymethyl penicillin hydrabamine		X

The 120 chemicals in these two categories were eliminated from the candidate list and not considered further in the study.

MEASURES OF POTENTIAL HUMAN EXPOSURE

The 176 remaining candidate chemicals were placed in three categories of potential human exposure based on published data for the quantities imported through the principal U.S. customs districts in 1976 or 1977³¹ and on published data² or estimates of the quantities produced in recent years. Where estimates were made, they were based on the number of companies producing the chemical and whether the companies were major chemical companies or companies known to be small volume manufacturers.³ The three categories of potential human exposure are:

<u>Potential Human Exposure Category</u>	<u>Production + Imports pounds (grams)</u>
High	>100,000 ($>4.5 \times 10^7$)
Moderate	10,000-100,000 (4.5×10^6 - 4.5×10^7)
Low	<10,000 ($<4.5 \times 10^6$)

As an additional measure of potential human exposure, information on the uses of all of the chemicals in the high category was then sought from sources such as the Chemical Economics Handbook,³² the Colour Index,³³ the Kirk-Othmer Encyclopedia of Chemical Technology,³⁴ and the NCI/SRI (Mark II) Exposure-Ranked List.³⁵ Use information was also sought from such sources on those chemicals in the moderate exposure category which had been assigned a high or moderate level of suspicion of carcinogenicity (see below) and those chemicals in the low exposure category which had been assigned a high level of suspicion of carcinogenicity.

SUSPICION OF POSSIBLE CARCINOGENIC ACTIVITY

The list of 176 candidate chemicals was subdivided into 11 chemical structure subclasses covering the range of structural configurations observed in the candidate ethers. This subdivision facilitated attempts to recognize structure-activity relationships among ethers and to identify the best representatives of each subclass.

A priori, each candidate was initially regarded to be of unknown suspicion of possible carcinogenicity because structure-activity relationships were not yet well-defined for ethers. The suspicion for chemicals giving positive results in any previous animal tests was adjusted to high (e.g., estragole). Chemicals having positive in vitro mutagenicity tests (no examples among final candidate chemicals) or considered to be closely related

structurally to known carcinogens and/or mutagens (e.g., isoeugenol by its relationship to isosafrole) were assigned moderate suspicion. A low suspicion was assigned to those chemicals for which positive experimental results were equivocal or for which suspicion was based solely on theoretical considerations (e.g., remote structure-activity relationships and the presence of potentially reactive, non-ether structural groups, such as acyl halides (e.g., 2-phenoxypropanoyl chloride) or double bonds (e.g., rose oxide) that can be epoxidized). No suspicion (i.e., none) was assigned to chemicals predicted to be inactive as carcinogens on the basis of previous animal test results (e.g., diethylene glycol³⁶) or close structural relationships to compounds known to be inactive as carcinogens (e.g., 2,5-dimethoxybenzaldehyde because of its close relationship to vanillin).

NOMINATIONS OF CHEMICALS TO THE CSWG

The final candidate list of 176 chemicals, grouped by structural subclass, is given in Table 4. For each candidate, information on exposure (i.e., U.S. production and imports) and suspicion of carcinogenicity is given; chemicals nominated to the CSWG are indicated. Structures of the nominated chemicals are shown in Table 5. The measures of potential human exposure, the suspicion of carcinogenic activity, and any special considerations were weighed as described below to nominate chemicals from each subclass to the CSWG.

Alkoxyphenyl Ethers

This subclass consisted of 47 candidate chemicals. The following four chemicals, including the lone chemical assigned a high suspicion of possible carcinogenicity (estragole), were nominated:

1. Methyleugenol (CAS No. 93-15-2)

As a 1,2-dimethoxybenzene substituted in the 4-position

TABLE 4

Final Candidate List Grouped by Structure*

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
A. Alkoxyphenyl ethers	88-32-4	3-tert-Butyl-4-methoxyphenol	>4.54x10 ⁶	--	Unknown	
	88-40-4	2-tert-Butyl-5-methylanisole	>2.27x10 ⁶	--	Unknown	
	90-05-1	Guaiacol	>4.54x10 ⁵	1.33x10 ⁸	Unknown	
	91-52-1	2,4-Dimethoxybenzoic acid	>4.54x10 ⁵	--	None	
	93-02-7	2,5-Dimethoxybenzaldehyde	>4.54x10 ⁶	--	None (28)	
	93-14-1	Glycerol guaiacolate	>1.36x10 ⁶	5.48x10 ⁷	Unknown	
	93-15-2	Methyleugenol	>1.81x10 ⁶	--	Moderate (15,37)	X
	93-16-3	1,2-Dimethoxy-4-propenylbenzene	>9.07x10 ⁵	--	Moderate (14,37)	
	93-17-4	(3,4-Dimethoxyphenyl) acetonitrile	>4.54x10 ⁵	--	Unknown	
	93-28-7	Acetyleneugenol	>1.81x10 ⁶	--	Moderate (15,37)	

* Footnotes a-h appear at the end of the table.

(continued)

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to CSWG
	94-86-0	2-Ethoxy-5-propenylphenol	>9.07x10 ⁵	--	Moderate (14,37)	
	97-54-1	Isoeugenol	5.76x10 ⁷	--	Moderate (14,37)	X
	100-06-1	4'-Methoxyacetophenone	9.98x10 ⁶	2.00x10 ⁵	Unknown	
	100-09-4	4-Methoxybenzoic acid	>4.54x10 ⁵	4.25x10 ⁶	None	
	100-66-3	Anisole	>4.54x10 ⁵	1.00x10 ^{6(c)}	Unknown	
	100-84-5	3-Methylanisole	>4.54x10 ⁵	--	Unknown	
	104-27-8	1-(4-Methoxyphenyl)-1-penten-3-one	>4.54x10 ⁵	--	Low (14,37)	
	104-45-0	4-Propylanisole	>9.07x10 ⁵	--	Moderate (13)	
	104-93-8	4-Methylanisole	1.04x10 ⁷	--	Unknown	
	114-26-1	2-Isopropoxyphenyl-N-methyl-carbamate	5.90x10 ^{8(d)}	7.90x10 ⁷	Unknown	
	118-41-2	3,4,5-Trimethoxybenzoic acid	>9.07x10 ⁵	4.50x10 ^{5(c)}	Unknown	
	120-11-6	Benzyl isoeugenol	>9.07x10 ⁵	7.39x10 ^{5(c)}	Moderate (14,37)	
	120-13-8	(4-Ethoxy-3-methoxyphenyl) acetic acid	>4.54x10 ⁵	--	None (27)	
	120-14-9	Veratraldehyde	>1.36x10 ⁶	--	None (28)	
	120-25-2	4-Ethoxy-3-methoxybenzaldehyde	>4.54x10 ⁵	--	None (28)	

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	121-00-6	2-tert-Butyl-4-methoxyphenol	>9.07x10 ⁵	--	Unknown	
	122-35-0	2-Phenoxypropanoyl chloride	>9.07x10 ⁵	--	Low	
	122-48-5	4-Hydroxy-3-methoxybenzyl- acetone	>4.54x10 ⁵	--	Unknown	
	122-59-8	Phenoxyacetic acid	>2.27x10 ⁶	7.02x10 ⁸	None (27)	
	122-94-1	4-Butoxyphenol	>4.54x10 ⁵	--	Unknown	
	135-02-4	2-Anisaldehyde	>2.27x10 ⁶	--	None (28)	
	139-61-7	p-(Cyclohexyloxy)benzoic acid	>4.54x10 ⁵	--	None (27)	
	140-65-8	4-(3-(4-Butoxyphenoxy)propyl)- morpholine	>4.54x10 ⁵	--	Unknown	
	140-67-0	Estragole	>1.36x10 ⁶	--	High (15,37)	X
	150-76-5	4-Hydroxyanisole	>9.07x10 ⁵	--	Unknown	
	150-78-7	1,4-Dimethoxybenzene	>2.27x10 ⁶	5.75x10 ⁵	Unknown	
	151-10-0	1,3-Dimethoxybenzene	>6.80x10 ⁶	--	Unknown	
	579-75-9	2-Methoxybenzoic acid	>4.54x10 ⁵	--	None	
	591-31-1	3-Methoxybenzaldehyde	--	9.03x10 ⁶	None (28)	
	621-59-0	3-Hydroxy-p-anisaldehyde	>9.07x10 ⁵	--	None (28)	
	1321-14-8	Potassium guaiacolsulfonate	>4.54x10 ⁵	6.00x10 ⁶	None	

(continued)

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	1466-76-8	2,6-Dimethoxybenzoic acid	>2.27x10 ⁶	1.00x10 ⁶	Unknown	
	2785-89-9	4-Ethylguaiacol	--	1.60x10 ⁸	Unknown	
	4180-23-8	trans-Anethole	1.10x10 ⁹	6.26x10 ⁶ (e)	Moderate (14,37)	
	7443-25-6	Dimethyl(p-methoxybenzylidene) malonate	>2.27x10 ⁶	--	Low (14,37)	
	10031-82-0	4-Ethoxybenzaldehyde	>4.54x10 ⁵	--	None (27,37)	
	61813-58-9	4-Ethoxy-3-methoxybenzyl alcohol	>4.54x10 ⁵	--	Unknown	
B. Extended phenyl	86-26-0	2-Phenylanisole	>4.54x10 ⁵	--	Unknown	
	131-53-3	2,2'-Dihydroxy-4-methoxy- benzophenone	>2.27x10 ⁶	--	Unknown	
	131-54-4	2,2'-Dihydroxy-4,4'-dimethoxy- benzophenone	>2.27x10 ⁶	--	Unknown	
	131-57-7	2-Hydroxy-4-methoxy-benzophenone	3.60x10 ⁸	--	Unknown	
	554-92-7	Trimethobenzamide hydrochloride	>4.54x10 ⁵	--	Unknown	
	1176-08-5	Phenyltoloxamine citrate	>1.36x10 ⁶	--	Unknown	
	1843-05-6	2-Hydroxy-4-(octyloxy)-benzo- phenone	>4.54x10 ⁶	--	Unknown	

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	2985-59-3	4-(Dodecyloxy)-2-hydroxy- benzophenone	>4.54x10 ⁶	--	Unknown	
	4065-45-6	2-Hydroxy-4-methoxy-5-sulfo- benzophenone	>2.27x10 ⁶	--	Unknown	
	4756-45-0	2-(2-Hydroxy-4-methoxybenzoyl) benzoic acid	--	--	Unknown	
C. Fused aryl ring system ethers	64-86-8	Colchicine	--	--	Unknown	
	82-39-3	1-Methoxyanthraquinone	>2.27x10 ⁶	--	Low (38,39)	
	93-04-9	2-Methoxynaphthalene	>4.54x10 ⁵	1.11x10 ⁷	Unknown	
	93-18-5	2-Ethoxynaphthalene	>4.54x10 ⁵	5.56x10 ⁶	Unknown	
	128-58-5	C.I. Vat Green 1	>4.54x10 ⁶	5.05x10 ⁷	Unknown	
	1078-19-9	6-Methoxy-1-tetralone	--	--	Unknown	
	3263-31-8	C.I. Vat Orange 5	>2.27x10 ⁶	--	Unknown	
	6407-55-2	1,8-Dimethoxyanthraquinone	>2.27x10 ⁶	--	Low (38,39)	
	6448-90-4	1,5-Dimethoxyanthraquinone	>2.27x10 ⁶	--	Low (38,39)	
	55150-29-3	2-Ethoxynaphthoyl chloride	>4.54x10 ⁶	--	Low	
D. Tetrahydrofurans	96-47-9	Tetrahydro-2-methylfuran	--	--	Unknown	

(continued)

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	97-99-4	Tetrahydrofurfuryl alcohol	--	--	Unknown	
	109-99-9	Tetrahydrofuran	>6.81x10 ⁶	3.70x10 ⁷ (f)	Unknown	X
	150-81-2	Tetrahydrofurfuryl oleate	>2.27x10 ⁶	--	Unknown	
	696-59-3	Tetrahydro-2,5-dimethoxyfuran	>2.27x10 ⁶	--	Unknown	
	2455-24-5	Tetrahydrofurfuryl methacrylate	--	--	Unknown	
	22373-78-0	Nonensin sodium salt	>4.54x10 ⁵	--	Unknown	
E. Simple aliphatic ethers	60-29-7	Diethyl ether	3.68x10 ⁹	9.08x10 ⁴ (c)	None	
	76-38-0	Methoxyflurane	>2.27x10 ⁶	--	Moderate (40,41,42)	
	78-51-3	Tri(2-butoxyethyl) phosphate	>2.27x10 ⁶	--	None	
	107-25-5	Methyl vinyl ether	>4.54x10 ⁶	--	Moderate (43)	X
	107-70-0	4-Methoxy-4-methyl-2-pentanone	>2.27x10 ⁶	--	Unknown	
	108-20-3	Isopropyl ether	>4.54x10 ⁶	--	Unknown	
	109-53-5	Isobutyl vinyl ether	>2.27x10 ⁶	--	Moderate (43)	
	109-63-7	Boron fluoride-ethyl ether complex	>2.27x10 ⁶	--	None	
	109-92-2	Ethyl vinyl ether	>2.27x10 ⁶	--	Moderate	

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	110-75-8	2-Chloroethyl vinyl ether	>2.27x10 ⁶	--	Moderate (22,43)	
	111-34-2	Butyl vinyl ether	>4.54x10 ⁶	--	Moderate (43)	
	111-46-6	Diethylene glycol	1.48x10 ¹¹	--	None (36)	
	112-27-6	Triethylene glycol	5.88x10 ¹⁰	--	None (36)	
	112-28-7	3-(3-Methoxypropoxy)-1-propanol	>2.27x10 ⁶	--	Unknown	
	115-10-6	Methyl ether	--	--	None	
	142-96-1	Butyl ether	--	--	Unknown	
	2150-02-9	2,2'-Oxydiethanethiol	>2.27x10 ⁶	--	None	
	5332-73-0	3-Methoxypropylamine	--	--	Unknown	
	7492-67-3	Citronellyl oxycetaldehyde	>9.08x10 ⁵	--	Unknown	
	13133-29-4	Tripropylene glycol, monomethyl ether	>2.27x10 ⁶	--	None	
E. Simple aliphatic ethers	61702-69-0	Hexyl alcohol, propoxylated and sulfated, sodium salt	>2.27x10 ⁶	--	None	
	61702-82-7	Diisooctyl diglycolate	>2.27x10 ⁶	--	None	
F. Ring-containing aliphatic ethers	94-51-9	Dipropandiol dibenzoate	>2.27x10 ⁶	--	Unknown	
	103-50-4	Benzyl ether	>2.27x10 ⁶	--	Unknown	

(continued)

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	122-73-6	Benzyl isopentyl ether	>4.54x10 ⁵	--	Unknown	
	341-69-5	Orphenadrine hydrochloride	>4.54x10 ⁵	--	Unknown	
	523-87-5	Dimenhydrinate	>9.08x10 ⁵	--	Unknown	
	1808-12-4	Bromodiphenhydramine hydrochloride	>4.54x10 ⁵	--	Unknown	
	4682-36-4	Orphenadrine citrate	>4.54x10 ⁵	--	Unknown	
	6652-28-4	Benzoin isopropyl ether	>4.54x10 ⁶	2.27x10 ^{6(c)}	Unknown	
G. Halophenoxyalkyl ethers	58-54-8	Ethacrynic acid	>4.54x10 ⁵	--	Unknown	
	93-65-2	Mecoprop	--	1.99x10 ⁸	Unknown	
	93-72-1	2-(2,4,5-Trichlorophenoxy)- propionic acid	>2.27x10 ⁶	--	Moderate (44,45,46)	
	93-76-5	(2,4,5-Trichlorophenoxy) acetic acid	--	--	Moderate (44,45,46)	
	93-79-8	(2,4,5-Trichlorophenoxy)acetic acid butyl ester	--	--	Moderate (44,45,46)	
	94-11-1	(2,4-Dichlorophenoxy)acetic acid isopropyl ester	--	--	Moderate (44,45,46)	
	94-74-6	(4-Chloro-2-methylphenoxy)- acetic acid	>4.54x10 ⁶	9.58x10 ^{8(c)}	Unknown	

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	94-75-7	(2,4-Dichlorophenoxy)acetic acid	>4.54x10 ⁶	2.71x10 ^{9(c)}	Moderate (44,45,46)	
	94-79-1	(2,4-Dichlorophenoxy)acetic acid, sec-butyl ester	>2.27x10 ⁶	--	Moderate (44,45,46)	
	94-80-4	(2,4-Dichlorophenoxy)acetic acid, butyl ester	>4.54x10 ⁶	--	Moderate (44,45,46)	
	94-81-5	4-(2-Methyl-4-chlorophenoxy)-butyric acid	--	6.27x10 ⁷	Low	
	94-82-6	4-(2,4-Dichlorophenoxy)butyric acid	>2.27x10 ⁸	3.91x10 ⁸	Low (44,45,46)	
	1049-20-7	4-Bromoanisole	>2.27x10 ⁶	--	Unknown	
	120-36-5	2-(2,4-Dichlorophenoxy)-propionic acid	--	1.05x10 ⁸	Moderate (44,45,46)	
	120-39-8	(2,4,5-Trichlorophenoxy)acetic acid, pentyl ester	--	--	Moderate (44,45,46)	
	533-23-3	(2,4-Dichlorophenoxy)acetic acid ethyl ester	--	--	Moderate (44,45,46)	
	1918-00-9	3,6-Dichloro-2-methoxybenzoic acid	>2.27x10 ⁶	--	None	
	1928-43-4	(2,4-Dichlorophenoxy)acetic acid 2-ethylhexyl ester	--	--	Moderate (44,45,46)	

(continued)

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	1928-47-8	(2,4,5-Trichlorophenoxy)acetic acid 2-ethylhexyl ester	--	--	Moderate (44,45,46)	
	1929-73-3	(2,4-Dichlorophenoxy)acetic acid 2-butoxyethyl ester	>2.27x10 ⁶	--	Moderate (44,45,46)	
	2008-39-1	(2,4-Dichlorophenoxy)acetic acid dimethylamine salt	9.67x10 ⁹	--	Moderate (44,45,46)	
	2008-46-0	(2,4,5-Trichlorophenoxy)acetic acid triethylamine salt	>2.27x10 ⁶	--	Moderate (44,45,46)	
	2545-59-7	(2,4,5-Trichlorophenoxy)acetic acid butoxyethyl ester	>2.27x10 ⁶	--	Moderate (44,45,46)	
	2675-77-6	1,4-Dichloro-2,5-dimethoxybenzene	>2.27x10 ⁶	--	Unknown	
	2702-72-9	(2,4-Dichlorophenoxy)acetic acid sodium salt	>2.27x10 ⁶	--	Moderate (44,45,46)	
	3599-58-4	(2,4-Dichlorophenoxy)acetic acid compounded with 2-aminoethanol	>2.27x10 ⁶	--	Moderate (44,45,46)	
	3766-27-6	(2,4-Dichlorophenoxy)acetic acid lithium salt	>2.27x10 ⁶	--	Moderate (44,45,46)	
	25168-15-4	(2,4,5-Trichlorophenoxy)-acetic acid isooctyl ester	--	--	Moderate (44,45,46)	
	25168-26-7	(2,4-Dichlorophenoxy)acetic acid isooctyl ester	2.91x10 ⁹	--	Moderate (44,45,46)	

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	27613-72-5	(2,4,5-Trichlorophenoxy)- acetic acid butoxypoly- propylene glycol ester	>2.27x10 ⁶	--	Moderate (44,45,46)	
	53467-11-1	2,4-Dichlorophenoxyacetic acid, butoxypolypropyleneglycol ester	>2.27x10 ⁶	--	Moderate (44,45,46)	
	61792-07-2	(2,4,5-Trichlorophenoxy)- acetic acid 1-methylpropyl ester	--	--	Moderate (44,45,46)	
	61886-39-3	2-Chloro-p-diisopropoxybenzene	--	5.00x10 ⁵	Unknown	
H. Pyrans and benzo- pyrans	118-71-8	3-Hydroxy-2-methylpyrone	>4.54x10 ⁵	--	Unknown	
	3717-88-2	Flavoxate hydrochloride	>4.54x10 ⁵	--	Low (47)	
	4940-11-8	Ethyl maltol	--	--	Unknown	
	6038-78-4	Ethomoxane hydrochloride	>4.54x10 ⁵	--	Low (9,10)	
	16409-43-1	Rose oxide	>2.27x10 ⁶ (g)	--	Low	
	61886-45-1	Cromolyn sodium with lactose	--	9.67x10 ⁵ (c)	Unknown	
I: Diaryl ethers	80-51-3	4,4'-Oxybis(benzenesulfonyl hydrazide)	>4.54x10 ⁵	--	Low (48)	
	82-07-5	Xanthonic acid	>2.27x10 ⁶	00	Unknown	

(continued)

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	82-17-7	1,8-Diphenoxyanthraquinone	>4.54x10 ⁵	--	Unknown	
	82-21-3	1,5-Diphenoxyanthraquinone	>2.27x10 ⁶	--	Unknown	
	101-84-8	Diphenyl ether	>4.54x10 ⁵	6.31x10 ⁷ (h)	Unknown	
	121-63-1	4,4'-Oxybis(benzenesulfonyl chloride)	>4.54x10 ⁵	--	Unknown	
	28299-41-4	Dimethyldiphenyl ether	--	1.04x10 ⁸	Unknown	
J. N-Heterocyclic ring systems	57-94-3	Tubocurarine	>4.54x10 ⁵	--	Unknown	
	61-12-1	Dibucaine hydrochloride	>4.54x10 ⁵	--	Low (49)	
	76-57-3	Codeine	>9.07x10 ⁵	--	Unknown	
	91-53-2	Ethoxyquin	>2.27x10 ⁶	5.78x10 ⁸	Low (49)	
	101-37-1	Triallyl cyanurate	>2.27x10 ⁶	--	Unknown	
	115-37-7	Thebaine	>1.36x10 ⁶	--	Unknown	
	118-08-1	Hydrastine	>4.54x10 ⁵	--	Low (11)	
	124-90-3	Oxycodone hydrochloride	>4.54x10 ⁵	--	Unknown	
	125-30-4	Ethylmorphine hydrochloride	>4.54x10 ⁵	--	Unknown	
	125-69-9	Dextromethorphan hydrobromide	>4.54x10 ⁵	--	Unknown	

Table 4 (continued)

Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	132-17-2	Benztropine mesylate	>4.54x10 ⁵		--	Unknown
	143-71-5	Dihydrocodeinone bitartrate	>1.36x10 ⁶	--	Unknown	
	562-10-7	Doxylamine succinate	>9.07x10 ⁵	--	Unknown	
	633-65-8	Berberine hydrochloride	>4.54x10 ⁵		--	Low (11)
	5667-46-9	Dioxyline phosphate	>4.54x10 ⁵		--	Low (49)
	7388-44-5	Bis(methoxymethyl)-(oxydi- methylene)urea	>4.54x10 ⁵	--	Unknown	
	25333-72-6	Oxycodone terephthalate	>4.54x10 ⁵	--	Unknown	
	61886-51-9	7-Chloro-4-hydroxyquinidine hydrochloride	>2.27x10 ⁶	--	Low (49)	
K. Ethers of unchar- acterized struc- ture	9004-82-4	Sodium lauryl sulfate ethoxylate	5.13x10 ⁹	--	None (50)	
	9011-16-9	Methyl vinyl ether-maleic anhydride copolymer	>4.54x10 ⁵	--	Unknown	
	27028-82-6	Triethanolamine lauryl ether sulfate	>9.07x10 ⁵	--	Unknown	
	31800-88-1	Octyl phosphate, ethoxylated	>2.27x10 ⁶	--	Unknown	
	32612-48-9	Ammonium lauryl polyethoxy- sulfate	>2.27x10 ⁶	--	Unknown	

(continued)

Table 4 (continued)

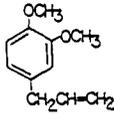
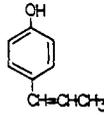
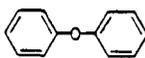
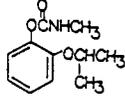
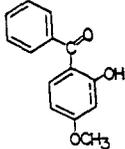
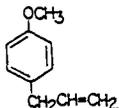
Subclass	CAS No.	Name	Production (g/yr) ^(a)	Imports (g/yr) ^(a)	Suspicion of Carcinogenicity ^(b)	Nomination to to CSWG
	51407-12-6	2-Ethylhexanol, ethoxylated and phosphated	>9.07x10 ⁵	--	Unknown	
	54116-08-4	Tridecyl alcohol, ethoxylated and sulfated, sodium salt	>2.27x10 ⁶	--	Unknown	
	61702-79-2	Tridecyl alcohol, ethoxylated and sulfated, ammonium salt	>4.54x10 ⁵	--	Unknown	

Footnotes

- (a) Reported 1977 data unless otherwise noted. Imports data are for principal U.S. customs districts only.
- (b) Suspicion of carcinogenicity is based on consideration of structure, previous carcinogenicity test results, and mutagenicity data, as described in the text. References are to studies of the carcinogenicity or mutagenicity of the candidate chemical or a structurally related chemical.
- (c) Reported 1976 data
- (d) Estimated 1978 consumption
- (e) Reported 1974 data
- (f) Reported 1975 data
- (g) Estimated annual U.S. consumption in fragrances
- (h) Reported 1978 data

TABLE 5

NOMINATIONS

CAS NO.	NAME	STRUCTURE
93-15-2	Methyleugenol	
97-54-1	Isoeugenol	
101-84-8	Diphenyl ether	
107-25-5	Methyl vinyl ether	$\text{CH}_2=\text{CHOCCH}_3$
109-99-9	Tetrahydrofuran	
114-26-1	2-Isopropoxyphenyl-N-methylcarbamate	
131-57-7	2-Hydroxy-4-methoxybenzophenone	
140-67-0	Estragole	

with a 2-propenyl moiety, methyleugenol was regarded with a moderate suspicion of carcinogenic activity because of its structural resemblance to the known carcinogen, safrole.¹⁵ Also, the related compound eugenol was reported to be producing positive results in a current NCI bioassay.⁵¹ Methyleugenol is believed to have potential for considerable human exposure based on the fact that in 1975 U.S. consumption of methyleugenol as a fragrance was reported to have been 2.3×10^7 g, and because it is used as a food flavoring agent and an insect attractant.

2. Isoeugenol (CAS No. 97-54-1)

Because of substitution in the 4-position with the 1-propenyl moiety, this 2-methoxyphenol is related to the carcinogen isosafrole¹⁴ and thus was judged to have a moderate suspicion of carcinogenicity. Also, the 2-propenyl isomer, eugenol, was reported to be producing positive results in a current NCI bioassay.^{51,52}

3. 2-Isopropoxyphenyl-N-methylcarbamate (CAS No. 114-26-1)

This compound was nominated largely on the basis of its potential exposure. Structurally it is not related to any known carcinogen and is considered a gap in knowledge. It is believed to have potential for considerable human exposure based on the fact that 1978 U.S. consumption was estimated as 5.9×10^8 g, 1977 U.S. imports were at least 7.9×10^7 g, and it is used as an insecticide.

4. Estragole (CAS No. 140-67-0)

This compound was nominated primarily because it was regarded with a high suspicion of probable carcinogenic activity. Structurally, it is related to the known carcinogen, safrole.¹⁵ In preliminary carcinogenicity studies (that were not extended to an adequate bioassay

according to the current NCI protocol), estragole produced significant incidences of hepatocellular carcinomas in preweanling mice following subcutaneous injection.³⁷ Additional testing is recommended to confirm these studies and to examine further the carcinogenicity of propenyl-substituted alkoxyphenyl ethers. It is believed to have considerable potential for human exposure based on the fact that three U.S. manufacturers have reported production in recent years and it is used as a food flavoring agent and as a fragrance.

Extended Phenyl Ring Ethers

This subclass consisted of ten candidate chemicals from which the following single compound was nominated:

2-Hydroxy-4-methoxybenzophenone (CAS No. 131-57-7)

This chemical was nominated largely on the basis of exposure, being representative of the several benzophenone derivatives used as UV stabilizers. Structurally it is a gap in knowledge and judged to be of unknown suspicion of carcinogenicity. It is believed to have potential for considerable human exposure based on the fact that in 1977 U.S. production amounted to 3.6×10^8 g (largest in this subclass) and it is used as a UV stabilizer in plastics and as a sunscreensing agent.

Fused Aryl Ring System Ethers

No chemicals were nominated from this subclass of 10 candidates. Of the five candidate chemicals judged to have a moderate potential for human exposure, two were deferred from further consideration at this time because they are high molecular weight polyaromatic dyes whose relative importance as dyes was judged to be more reliably determined as part of the scheduled class study on dyes and pigments. None of the remaining

candidates (three of moderate exposure, five of low exposure) was nominated because the suspicion of possible carcinogenic activity was considered either low or unknown.

Tetrahydrofurans

Tetrahydrofuran was the lone nomination from this subclass of seven candidates:

Tetrahydrofuran (CAS No. 109-99-9)

The nomination was based largely on potential for considerable human exposure based on its production by three major U.S. chemical companies, one of which had an estimated capacity of 4.5×10^9 g in 1978. Tetrahydrofuran is considered to be of unknown suspicion of carcinogenicity on the basis of structure-activity relationships.

Simple Aliphatic Ethers

Included in this subclass of 22 candidate chemicals are the simple dialkyl ethers (e.g., diethyl ether) and the haloethers (e.g., methoxyflurane). Although diethyl ether is known to have a high potential for exposure based on the number of major manufacturers that produce it and its widespread uses, it was rejected for nomination because of a lack of suspicion of carcinogenic activity. Also, diethyl ether is a member of the class of volatile anesthetics which was considered and dropped from further study by the CSWG on April 18, 1977 because this class is under the regulatory jurisdiction of the Food and Drug Administration (FDA). Although the haloethers were regarded with moderate suspicion of possible carcinogenicity, the only candidate with considerable potential for human exposure is methoxyflurane. Since it also is a volatile anesthetic, it was not nominated for reconsideration by the CSWG. A single nomination resulted from review of the remaining candidates in this subclass.

Methyl vinyl ether (CAS No. 107-25-5)

This compound was assigned a moderate level of suspicion of carcinogenicity because of the known carcinogenicity of a number of vinyl compounds (e.g., vinyl chloride, acrylonitrile, and vinyl carbamate) and the known mutagenicity of divinyl ether.⁴³ This chemical was nominated (instead of ethyl vinyl ether) because of its commercial importance as a monomer and comonomer (in combination with maleic anhydride) and its reported production by two major U.S. chemical companies.

Ring-containing Aliphatic Ethers

This subclass consisted of eight candidate chemicals. Structurally, all are gaps in knowledge and judged to be of unknown suspicion of carcinogenicity. None of the candidates was estimated to have sufficient potential for exposure to warrant nominating for test.

Halophenoxyalkyl Ethers

This subclass of 33 candidate chemicals included 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and related compounds. These chemicals were viewed with a moderate suspicion of possible carcinogenicity on the basis of previous limited animal test results reported for 2,4-D, 2,4,5-T, and their esters.^{44,45,46} These tests, although inadequate for a conclusive evaluation of carcinogenicity, did indicate an increased incidence of tumors at various sites in mice after oral and subcutaneous administration. Since a rebuttal proposal against reregistration (RPAR) had been issued by the U.S. Environmental Protection Agency (EPA) for 2,4,5-T, this compound and its salts and esters were deferred from nomination pending the outcome of the EPA ruling. The status of 2,4-D at the EPA at that time was unclear. It had been a pre-RPAR candidate, but its candidacy was still under

review. Therefore, 2,4-D and its salts and esters were also deferred from nomination. The remaining candidates in this subclass were not judged to be substantially different from 2,4-D or 2,4,5-T to warrant further action until the EPA review of these compounds was completed.

Pyrans and Benzopyrans

No candidates were nominated to the CSWG from this subclass of six chemicals. All of the candidates were judged to be of unknown or low suspicion of carcinogenicity, and none was regarded to be of sufficient interest to warrant testing on the basis of structure. Also, none of the candidates was estimated to have significant potential for human exposure.

Diaryl Ethers

This subclass consisted of seven candidates, of which one, diphenyl ether, was nominated to the CSWG.

Diphenyl Ether (CAS No. 101-84-8)

This chemical was nominated as a representative of the diaryl ethers on the basis of its potential exposure and as a model compound for carcinogenicity testing from a subclass that is essentially a gap in knowledge. It is believed to have potential for considerable human exposure based on the fact that U.S. imports were 6.3×10^7 g in 1978 and two major U.S. chemical companies produce this chemical.

N-Heterocyclic Ring Systems

No candidates were nominated to the CSWG from this subclass of 18 chemicals because: (1) suspicion of carcinogenicity was assigned to the candidates on the basis of functionalities other than ethers (e.g., suspicion of ether-substituted quinolines was based on the presence of the quinoline moiety), (2) the structural

TABLE 6

Selection Decisions for Nominated Chemicals

Compound,	CSWG			CSWG ^a	
	Selected	Priority	Deferred	Rejected	Priority
Methyleugenol	X	Moderate			7.0
Isoeugenol	X	Low-Moderate			4.3
2-Isopropoxyphenyl N-methylcarbamate			X		b
Estragole	X	High			3.1
2-Hydroxy-4-methoxybenzophenone	X	Moderate			3.4
Tetrahydrofuran	X	High			5.2
Methyl vinyl ether	X	High			c
Diphenyl ether			X		b

^a The priority ranking was done using a linear (1 to 10) scale of progressive priority. The final score of a particular chemical represents the arithmetic mean of the Subgroup members present and casting votes.

^b This compound was deferred pending the results of industry testing and, hence, was not reviewed by the CSSG.

^c Subsequently (8/23/79), data from industry was presented to the CSWG. Upon evaluation of this data, the chemical was rejected because it is readily hydrolyzed and has limited exposure.

classes to which the ethers belonged had already been considered by the CSWG (e.g., substituted quinidines were excluded as nominations because quinidine itself recently was selected by the CSWG as a result of the Chronic Drugs Class Study), or (3) the chemicals were to be considered more appropriately in an upcoming class study (e.g., the scheduled class study on alkaloids will cover morphines containing ether moieties).

Ethers of Uncharacterized Structure

This class consisted of eight candidates, of which none was nominated to the CSWG. Only one candidate, sodium lauryl sulfate ethoxylate, was considered to have significant potential for human

exposure, but it was not nominated because it was assigned no suspicion of carcinogenicity, based on negative results of a mouse skin tumorigenicity assay.⁵⁰ None of the other candidates was judged to be of sufficient interest on either an exposure or a structure basis to warrant nomination.

SELECTION DECISIONS

The selection decisions made by the CSWG and CSSG on the eight nominated chemicals are shown in Table 6.

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