THE RELATIVE CARCINOGENIC POTENTIAL OF 50 CHEMICALS THAT MAY BE AIR POLLUTANTS

Final Report

Prepared for:

Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency

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Introduction

As part of the Special Study of Toxics, the Office of Air Quality Planning and Standards of the U.S. Environmental Protection Agency is assessing the potential risk of human cancer associated with emissions of 80-90 pollutants from NESHAPS-type sources. The purpose of this report is to survey the available information on the adverse health effects of 50 pollutants in order to determine the carcinogenic potential of these pollutants. For those pollutants that may have the potential to induce cancer in humans, this report presents unit risk scores that are estimates of the relative carcinogenic potency of those pollutants. The pollutants reviewed are listed in Table 1. This list of chemicals was developed by the Strategies and Air Standards Division of OAQPS from the top 100 compounds in the Argonne prioritization ranking. The list was modified and trimmed to 50 by deleting regulated hazardous air pollutants, compounds included on the list of 37 candidate hazardous air pollutants, and compounds with a known or estimated production volume lower than 50 million pounds per year; and by adding compounds that are among the top 50 high-volume production chemicals in the United States or that were monitored in the ambient air by numerous investigators in a number of locations.

Methods

Clement Associates, Inc., searched a number of on-line data bases and secondary literature resources for information

relevant to the carcinogenic potential of the com pounds in Table 1. Resources screened in this manner are shown in Table 2, which also shows which resources contained information about specific chemicals on the list. Because there was little published information available on the carcinogenic potential of many of the compounds on the list, it was necessary to attempt to identify unpublished and ongoing studies that might provide useful information. Several sources were used in this attempt, including the National Toxicology Program (NTP) Management Status Report of December 6, 1983, the Chemical Information System on-line data file Chemical Carcinogenesis Research Information Service (CCRIS), the TSCA Section 8(e) submission file of EPA, and the Chemical Hazard Information Profiles (CHIPs) prepared by EPA. For five compounds, carcinogenesis bioassays have been completed but not published by the NTP. Clement obtained copies of the draft reports and was able to use them as a basis for assessing the carcinogenic potential of the compounds. In addition, five unpublished carcinogenicity bioassays were obtained from the TSCA Section 8(e) submission file. These were also used to evaluate the carcinogenic potential of the compounds studied. It should be understood that many of these reports are preliminary and Clement did not critically evaluate them to independently assess the accuracy of stated conclusions.

In those cases where quantitative dose-response data were available, Clement calculated an estimated unit risk value

TABLE 1

CHEMICALS REVIEWED FOR CARCINOGENIC POTENTIAL

Chemical Name	CAS Number
Acetic acid	64-19-7
Acetonitrile	75-05-8
Acrylamide	79-06-1
Ammonia	7664-41-7
Barium carbonate	513-77-9
1,3-Butadiene	106-99-0
tert-Butyl alcohol	75-65-0
Carbon disulfide	75-15-0
Carbonyl sulfide	463-58-1
Chlorine	7782-50-5
Chloroacetic acid	79-11-8
Chloroethane (Ethyl chloride)	75-00-3
Chromium	7440-47-3
Copper	7440-50-8
Cumene	98-82-8
Cyclohexane	110-82-8
Dibenzofuran	132-64-9
1,2-Dibromoethane (Ethylene dibromide)	106-93-4
1,2-Dichloroethylene	540-59-0
Diethanolamine	111-42-2
Di(2-ethylhexyl)phthalate (Dioctylphthalate)	117-81-7
Ethylbenzene	100-41-4
Ethyl ester acrylic acid (Ethyl acrylate)	140-88-5
Ethylene	74-85-1
Ethylene glycol	107-21-1
Ethylene glycol monoethyl ether (2-Ethoxyethanol)	110-80-5
Hexahydro-2H-azepin-1-one (Caprolactam)	105-60-2
Isobutyraldehyde	78-84-2
Isopropyl alcohol	67-63-0
4,4'-Isopropylidenediphenol (Bisphenol A)	80-05-7
Melamine	108-78-1
Methanol (Methyl alcohol)	67-56-1
Methyl chloride	74-87-3
Methyl ethyl ketone	78-93-3
Methyl methacrylate	80-62-6
4,4'-Methylenedianiline	101-77-9
Molybdenum trioxide	1313-27-5
Napthalene	91-20-3
Pentachlorophenol	87-86-5
Phthalic anhydride	85-44-9
Propene (Propylene)	115-07-1
Propionaldehyde	123-38-6

TABLE 1 (continued)

Chemical Name	CAS Number
Propylene dichloride	78-87-5
Styrene	100-42-5
Terephthalic acid	100-21-0
Titanium dioxide	13463-67-7
2,4-Toluene diisocyanate	584-84-9
Vinyl acetate	108-05-4
Zinc	7440-66-6
Zinc oxide	1314-13-2

TABLE 2

SOURCES REVIEWED

Compound	RTECS[a]	ACGIH[b]	Patty[c]	NIOSH[d]	AWQC[e]	Drinking Water[f]	IARC[g]	NTP Bioassay		CHIP[j]	CCRIS[k]
								Complete[h]	In Progress[i]		
Acetic acid	X	X	X								
Acetonitrile		X	X	X					X	X	
Acrylamide	X	X	X	X							
Ammonia	X	X	X	X							
Barium carbonate		X	X			X			X		
1,3-Butadiene	X	X	X					X		X	X
tert-Butyl alcohol	X	X	X			X			X		
Carbon disulfide	X	X	X	X		X			X		
Carbonyl sulfide			X								
Chlorine	X	X	X	X							
Chloroacetic acid	X		X						X		
Chloroethane (Ethyl chloride)	X	X	X		X					X	
Chromium	X	X	X	X	X	X	X				
Copper	X	X	X		X	X					
Cumene		X	X								
Cyclohexane	X	X	X								
Dibenzofuran											
1,2-Dibromoethane (Ethylene dibromide)	X	X	X	X			X	X			X
1,2-Dichloroethylene		X	X								
Diethanolamine		X	X						X	X	
Di(2-ethylhexyl)phthalate (Dioctylphthalate)	X		X		X		X	X			X
Ethylbenzene		X	X		X				X		

TABLE 2 (continued)

Compound	RTECS[a]	ACGIH[b]	Patty[c]	NIOSH[d]	AWQC[e]	Drinking Water[f]	IARC[g]	NTP Bioassay: Complete[h]	NTP Bioassay: In Progress[i]	CHIP[j]	CCRIS[k]
Ethyl ester acrylic acid (Ethyl acrylate)	X	X	X				X	X			
Ethylene	X						X				
Ethylene glycol	X	X	X						X		
Ethylene glycol monoethyl ether (2-Ethoxyethanol)		X	X						X	X	
Hexahydro-2H-azepin-1-one (Caprolactam)	X	X				X	X	X			X
Isobutyraldehyde									X		
Isopropyl alcohol	X	X	X	X			X			X	
4,4'-Isopropylidenediphenol (Bisphenol A)	X		X					X			X
Melamine	X							X		X	
Methanol (Methyl alcohol)	X	X	X							X	
Methyl chloride	X	X	X		X	X					X
Methyl ethyl ketone	X	X	X	X							
Methyl methacrylate	X	X	X				X				
4,4'-Methylenedianiline	X	X					X	X			
Molybdenum trioxide	X	X	X						X		
Napthalene	X	X	X		X				X		
Pentachlorophenol	X	X	X		X		X		X		
Phthalic anhydride	X	X	X					X			X
Propene (Propylene)							X	X			
Propionaldehyde			X								
Propylene dichloride	X	X	X		X	X		X			X

TABLE 2 (continued)

Compound	RTECS[a]	ACGIH[b]	Patty[c]	NIOSH[d]	AWQC[e]	Drinking Water[f]	IARC[g]	NTP Bioassay		CHIP[j]	CCRIS[k]
								Complete[h]	In Progress[i]		
Styrene	X	X	X			X	X	X			X
Terephthalic acid	X									X	
Titanium dioxide	X	X	X					X			X
2,4-Toluene diisocyanate	X	X	X				X	X			
Vinyl acetate		X	X	X			X				
Zinc	X		X		X	X					
Zinc oxide	X	X	X	X							X

[a]Registry of Toxic Effects of Chemical Substances data file in the National Library of Medicine On-Line Service.

[b]American Conference of Governmental Industrial Hygienists (1980)

[c]Patty (1963)

[d]National Institute of Occupational Safety and Health Criteria for Recommended Standard Documents

[e]U.S. Environmental Protection Agency Ambient Water Quality Criteria Documents

[f]National Academy of Sciences (1977)

[g]International Agency for Research on Cancer Monographs on the Evaluation of the Carcinogenic Effects of Chemicals to Humans

[h]National Cancer Institute and the National Toxicology Program reports on Carcinogenesis Bioassays

[i]National Toxicology Program Management Status Report (1983g)

[j]U.S. Environmental Protection Agency Chemical Hazard Information Profiles

kChemical Carcinogensis Research Information Service data file in the NIH/EPA Chemical Information System

by fitting the data to the one-hit model and obtaining the upper 95% confidence limit for the unit risk. This value has the units $(\mu g/m^3)^{-1}$ and is an estimate of risk at an air concentration of 1 $\mu g/m^3$. Unit risks calculated from studies in which doses were expressed as mg/kg/day were converted to air concentrations by assuming that a 70-kg person inhales 20 m^3 of air per day. Thus, estimated unit risks in $(mg/kg/day)^{-1}$ were multiplied by 2.9×10^{-4} for this conversion. No scaling factors were used to convert unit risks calculated from animal data to values more appropriate to humans.

Results

Table 3 presents unit risk estimates with associated uncertainty scores for 49 chemicals. For many of the chemicals on the list, extensive searching of the sources described in Table 2 failed to indicate any evidence of carcinogenic activity. Therefore, risk values could not be estimated for them in the subsequent analysis. It should be noted that, of the compounds in Table 3 without unit risk estimates, only three, i.e., caprolactam, phthalic anhydride, and propene, have been tested for their carcinogenic potential and even this testing has not been extensive. The 29 compounds from ammonia through zinc oxide have not been tested. Furthermore, three compounds for which unit risks were estimated, i.e., ethylene, diethanolamine, and pentachlorophenol, have not been tested for their carcinogenic potential. For this reason, Clement reviewed the literature for information on the genetic toxicity of these compounds

TABLE 3

ESTIMATED UNIT RISKS FOR
49 POLLUTANTS EMITTED BY NESHAPS-TYPE SOURCES

Compound	Estimated Unit Risk ($\mu g/m3$)-1	Uncertainty Score
Chromium	1.2×10^{-2}	1
1,2-Dibromoethane	2.5×10^{-3}	1
Acrylamide	1.7×10^{-5}	2
4,4'-Methylenedianiline	2.1×10^{-5}	2
Di(2-ethylhexyl)-phthalate	1.3×10^{-7}	2
Methyl chloride	1.4×10^{-7}	2
Propylene dichloride	7.2×10^{-7}	2
4,4'-Isopropylidenedi-phenol	1.4×10^{-6}	3
1,3-Butadiene	4.6×10^{-7}	3
Ethyl ester acrylic acid	5.0×10^{-7}	3
Melamine	4.1×10^{-7}	3
Titanium dioxide	5.6×10^{-7}	3
Ethylene	2.7×10^{-6}	4
Diethanolamine	1.1×10^{-7}	4
Styrene	2.9×10^{-7}	4
Pentachlorophenol	3.9×10^{-7}	4
Terephthalic acid	1.8×10^{-8}	4
Ammonia	NS	4
tert-Butyl alcohol	NS	4
Chlorine	NS	4
Chloroacetic acid	NS	4
Chloroethane	NS	4

TABLE 3 (continued)

Compound	Estimated Unit Risk (μg/m3)-1	Uncertainty Score
1,2-Dichloroethylene	NS	4
Ethylene glycol monoethyl ether	NS	4
Isobutyraldehyde	NS	4
Methanol	NS	4
Methyl methacrylate	NS	4
Molybdenum trioxide	NS	4
Propionaldehyde	NS	4
Vinyl acetate	NS	4
Acetic acid	NS	3
Acetonitrile	NS	3
Barium carbonate	NS	3
Carbon disulfide	NS	3
Carbonyl sulfide	NS	3
Copper	NS	3
Cumene	NS	3
Cyclohexane	NS	3
Dibenzofuran	NS	3
Ethylbenzene	NS	3
Ethylene glycol	NS	3
Isopropyl alcohol	NS	3
Methyl ethyl ketone	NS	3
Naphthalene	NS	3
Zinc	NS	3
Zinc oxide	NS	3
Hexahydro-2H-azepin-1-one	NS	2
Phthalic anhydride	NS	2
Propene (Propylene)	NS	2

and for information on the carcinogenic potential of structurally or pharmacologically similar compounds. This type of information is included in the discussion of the individual compounds in the appendix to this report.

For each compound, an uncertainty score from 1 to 4 was assigned to the unit risk. The criteria for assigning these uncertainty scores are described in Table 4.

The compounds in Table 3 are grouped according to the uncertainty score associated either with the unit risk estimate or with the evidence that the compound is not carcinogenic. Within each uncertainty group, the compounds with unit risk estimates are listed in decreasing order of carcinogenic potency. Those compounds without unit risk estiamtes are listed in alphabetical order within each uncertainty group.

Discussion

Because most of the compounds listed in Table 3 have not been adequately tested for their carcinogenic potential, it is not possible to provide a quantitative basis for ranking these chemicals according to their potential carcinogenic hazard. In Table 5, subjective qualitative judgments have been applied to reorder the chemicals according to their potential carcinogenic risk to humans. In arriving at this ranking three factors were considered: the quantitative unit risk estimate, where available; the weight of the evidence, if any, that a chemical was carcinogenic; and chemical structure and mechanism of toxic action. Chemicals that are grouped together cannot be differentiated on the basis of estimated carcinogenic potency.

TABLE 4

CRITERIA FOR ASSIGNING UNCERTAINTY SCORES

Compounds with Cancer Potency Scores

1--More than one positive study and the potency score is based on a complete risk assessment performed by EPA-CAG using a multistage model

2--One or more positive studies by an appropriate route of administration and the potency score is based on an extrapolation from actual tumor incidence using a one-hit model

3--One positive or suggestive study and the potency score is based on an extrapolation from tumor incidence (may not be statistically significant) using a one-hit model.

4--Suggestive evidence of carcinogenicity and the potency score is estimated by analogy to structurally similar compounds

Compounds with No Cancer Potency Scores

1--Compound has been extensively tested for carcinogenic potential and found not to be carcinogenic

2--Compound has been tested in a single bioassay and found not to be carcinogenic

3--Compound has not been tested but, by comparison to structurally similar compounds or from in vitro data, it is not expected to be carcinogenic

4--Compound has not been tested, but, on the basis of either structure or some other toxic effect (mutagenesis, teratogenesis), there is some concern that it may be carcinogenic if adequately tested.

TABLE 5

LISTING OF POLLUTANTS IN DECREASING ORDER OF POTENTIAL CARCINOGENIC RISK TO HUMANS

1,2-Dibromoethane

Acrylamide
Chromium
4,4'-Methylenedianiline

Di(2-ethylhexyl)phthalate
Methyl chloride

Propylene dichloride

4,4'-Isopropylidenediphenol

1,3-Butadiene
Ethyl ester acrylic acid
Melamine
Titanium dioxide

Styrene
Terephthalic acid

Ammonia
Chorine
Chloroacetic acid
Diethanolamine
Ethylene
Isobutyraldehyde
Methyl methacrylate
Pentachlorophenol
Proprionaldehyde

Chloroethane
1,2-Dichloroethylene

Acetic acid
Acetonitrile
Carbon disulfide
Ethylene glycol
Ethylene glycol monoethyl ether
Isopropyl alcohol
Methanol
Methyl ethyl ketone
Molybdenum trioxide
Naphthalene
tert-Butyl alcohol
Vinyl acetate

TABLE 5 (cont'd.)

Barium carbonate
Carbonyl sulfide
Copper
Cumene
Cyclohexane
Dibenzofuran
Ethylbenzene
Zinc
Zinc Oxide

Phthalic anhydride

Hexahydro-2H-azepin-1-one
Propene

Among the chemicals in Table 5 that have been shown to be carcinogenic, chromium is grouped with acrylamide and 4,4'-methylenediamiline because it is unlikely that all the chromium present in air is present as carcinogenic compounds of chromium VI. Insofar as some chromium is present as chromium III or metallic chromium, the risk will be proportionally lower. Some chemicals that were assigned unit risks in Table 3, i.e., diethanolamine, ethylene, and pentachlorophenol, are grouped with chemicals for which no unit risks were estimated, e.g., ammonia and chlorine. This is done because the evidence that diethanolamine, ethylene, and pentachlorophenol are carcinogenic is extremely weak while ammonia, chlorine, chloroacetic acid, isobutyraldehyde, methyl methacylate, and propionaldehyde are irritant gases or volatile liquids that may contribute to an increased incidence of cancer in the upper respiratory tract as a result of long-term low level exposure.

Chloroethane and 1,2-dichloroethylene are placed just below the irritant gases and vapors because their structural relationship to the carcinogenic halogenated hydrocarbons such as vinyl chloride and 1,2-dichloroethylene make them somewhat suspect.

All of the chemicals in the group headed by acetic acid and acetonitrile are unlikely to be carcinogenic but deserve further study because they either are structurally related to known carcinogens (vinyl acetate, naphthalene), are metabolized to carcinogenic intermediates (methanol), are somewhat

irritating vapors (acetic acid, acetonitrile, isopropyl alcohol, methanol, tert-butyl alcohol, vinyl acetate) or they are known to cause other chronic or acute toxic effects that could possibly be interrelated with a carcinogenic response (carbon disulfide, ethylene glycol, ethylene glycol monoethyl ether, methyl ethyl ketone, molybdenum trioxide). The compounds grouped with barium carbonate, on the other hand, are relatively benign and have no known physiological effect.

Phthalic anhydride, though tested and found not to be carcinogenic, can be an upper respiratory irritant and for this reason is placed above hexahydro-2H-azepin-1-one and propene in the ranking.

More detailed discussions of the health effects information on each chemical are included in the appendix to this report.

APPENDIX

Acetic Acid

There is no evidence, in the sources reviewed, that acetic acid is carcinogenic. Occupational exposure to an airborne concentration of 60 ppm for 7-12 years was reported to cause conjunctivitis, bronchitis, pharyngitis, and erosion of exposed teeth but no other more serious effects (ACGIH 1980). No chronic animal studies were found. Acetic acid has been reported to cause mutagenic effects in Drosophila melanogaster and E. coli (RTECS 1983). The molecular structure of acetic acid does not suggest that it is carcinogenic.

Acetonitrile

There is no evidence, in the sources reviewed, that acetonitrile is carcinogenic. No studies on long-term occupational exposure were reported by NIOSH (1978b), and no chronic animal studies have been reported in the sources reviewed. Acetonitrile is currently on study in the National Toxicology Program Research and Testing Program (NTP 1983g).

Acrylamide

There is some evidence to suggest acrylamide is carcinogenic. In a recent study reported by the Dow Chemical Company (1983), statistically significant increased incidences of specific tumors were found in several organs of female rats treated for 2 years with acrylamide. Male and female Fischer 344 rats were divided into two groups of 90 rats/sex/group. Acrylamide was administered to both sexes at doses of 0, 0.01, 0.1, 0.5,

and 2.0 mg/kg of body weight in the drinking water. The tissues affected were the brain, spinal cord, mammary gland, clitoral gland, uterus, oral cavity, pituitary gland, and thyroid gland. There are few reports on long term occupational exposure to acrylamide, and none suggests an increased incidence of cancer related to exposure.

A unit risk was estimated from the reported incidence of uterine adenocarcinomas in the Dow Chemical Company study. The tumor incidences in the groups from the control group to the highest dose group were 1/60, 2/60, 1/60, 0/59, 5/60 (number with tumor/number examined), respectively. The unit risk is 1.7×10^{-5} $(\mu g/m^3)^{-1}$. This represents an isolated report study and has not been fully evaluated. The route of exposure is not completely appropriate for assessing cancer risk via inhalation.

Ammonia

One epidemiological study (reviewed by NIOSH 1974) on chemical workers has suggested an association between occupational exposure to ammonia and cancer morbidity. In two ammonia plants with airborne concentrations of 75-150 ppm, the 10-year cancer morbidity was 1,000-1,250/10,000 for male workers and 370/10,000 for female workers compared to 160/10,000 for the entire factory of 30,000 workers where the ammonia plants were located. Excess neoplasms were noted for the lung, urinary tract, intestinal tract, and lymphatic system. NIOSH (1974) found this study poorly reported and documented and inadequate to support a conclusion that ammonia was the causal factor.

Other epidemiological studies have reported only irritation of the eyes or respiratory tract and have not examined a potential carcinogenic effect. No animal study was found in the sources reviewed that adequately examined the effects of long term exposure to ammonia. Two mutagenicity studies reported by RTECS (1983) indicated positive effects. One study was in rats and another in E. coli.

Barium

There is no evidence, in the sources reviewed, that barium carbonate is carcinogenic. Barium carbonate is a soluble salt and tends to be more acutely injurious than the insoluble salts of barium. There were no animal chronic studies or epidemiological studies found in the sources reviewed. Barium chloride, another soluble barium salt, is currently under study by the National Toxicology Program in a carcinogenicity bioassay (NTP 1983g).

1,3-Butadiene

There is evidence that 1,3-butadiene is carcinogenic. Two separate chronic inhalation studies have recently been completed. One study conducted in rats, sponsored by the International Institute of Synthetic Rubber Producers, Inc., (1982), found significant increased incidences of tumors occurring in a number of tissues. The other study conducted on mice as part of the National Toxicology Program, (NTP 1983a) also found significantly increased incidences of numerous tumors.

No epidemiological studies on cancer morbidity or mortality were found in the sources reviewed.

The mouse study had higher tumor incidences at lower exposure doses than did the rat study, and therefore the unit risk was estimated from data from the mouse study. The mice in the study were exposed to 0, 625, or 1,250 ppm 1,3-butadiene. The incidences of maglignant lymphoma in male mice were 0/50, 23/50, and 29/50 (number with lymphoma/number examined), respectively. The unit risk is 4.6×10^{-7} $(\mu g/m^3)^{-1}$.

Carbon Disulfide

There is no evidence, in the sources reviewed, that carbon disulfide is carcinogenic. Although there have been a number of epidemiological studies conducted on occupationally exposed workers, none have examined or reported any association between exposure and excess cancer incidences. No adequate animal carcinogenicity bioassay were reported in the sources reviewed, but one is now being conducted as part of the National Toxicology Program (NTP 1983g). RTECS (1983) reported one study that found a positive mutagenic effect in the Ames assay and one study that found increased sister chromatid exchanges in human lymphocytes.

Carbonyl Sulfide

There is no evidence, in the sources reviewed, that carbonyl sulfide is carcinogenic. No chronic animal studies or epidemiological studies were found in these sources. The structural

similarities among carbonyl sulfide, carbon dioxide, and carbon disulfide suggest that the carcinogenic potential for carbonyl sulfide is negligible.

Chlorine

There is no evidence, in the sources reviewed, that chlorine is carcinogenic. Epidemiological studies on acutely or chronically exposed people have focused mainly on pulmonary effects and have not examined potential carcinogenic effects. No adequate chronic animal study has been found that could be used to assess chlorine's carcinogenic potential. RTECS (1983) does report one positive mutagenicity study that reported a cytogenetic effect in human lymphocytes.

Chloracetic Acid

There is little evidence, in the sources reviewed, that chloroacetic acid is carcinogenic. In a study with a duration of 200 days reviewed by Patty (1963), rats fed 0.1% chloroacetic acid exhibited no specific lesions. RTECS (1983), however, reported two subcutaneous injection studies in which chloroacetic acid was considered an equivocal tumorigenic agent. RTECS (1983) also reported two studies where chloroacetic acid was considered mutagenic. Chloroacetic acid reacts with sulfhydral groups of essential enzymes (Patty 1963), suggesting that it may be an alkylating agent. If so, it may have a significant carcinogenic potential, but this cannot be determined with the available information.

Chloroethane

There is no current evidence, in the sources reviewed, that chloroethane is carcinogenic. No animal chronic toxicity studies or epidemiological studies were found in these sources. On the basis of structural considerations there is some concern about potential carcinogenic activity. Many congeners of chloroethane, e.g., 1,2-dichloroethane, 1,1,2-trichloroethane, 1,1,2,2-tetrachloroethane, and hexachloroethane, have been found to be carcinogenic in test animals (USEPA 1980a). All these compounds, however, are chlorinated on both carbons, unlike chloroethane. 1,1,1-Trichloroethane did not induce cancer in test animals during a National Cancer Institute bioassay, but the study was considered limited because of mortality, and the compound is being retested. Chloroethane is the only chlorinated ethane not being tested for its carcinogenic potential in the National Toxicology Program (NTP 1983g), presumably because it is felt to have little or no carcinogenic potential.

Chromium

IARC (1980) considers that there is sufficient evidence that certain forms of chromium VI are carcinogenic to rats. These forms include calcium chromate, sintered calcium chromate, lead chromate, strontium chromate, sintered chromium trioxide, and zinc chromate. All except calcium chromate are relatively soluble, and all except lead chromate produced tumors only at the site of injection. Lead chromate-treated animals also had a small number of renal carcinomas that were not observed

in control animals. There were no adequate inhalation or intratracheal injection studies reported by IARC (1980) that showed a positive carcinogenic effect, although many such studies were evaluated.

IARC (1980) also considers that there is sufficient evidence of respiratory carcinogenicity in men occupationally exposed during chromate production. There is also epidemiological evidence to suggest that workers in occupations involving exposure to chromium products are at higher risk of respiratory cancer. Chromium VI compounds probably carry the greatest carcinogenic risk, although the epidemiological evidence is not sufficient to make a distinction between chromium III or VI.

The Cancer Assessment Group of EPA has calculated the unit risk for cancer from chromium exposure as 1.2×10^{-2} $(\mu g/m^3)^{-1}$.

Copper

There is no evidence that copper is carcinogenic. However, no chronic animal studies examining the carcinogenic potential of copper were found. Available evidence on long term oral intake of low (<1mg) concentrations of copper was reported to indicate there was no chronic toxicity to normal humans in a study reviewed by the National Academy of Sciences (1977). RTECS (1983) reports an animal study showing an equivocal tumorigenic effect following intrapleural instillation. The material used in this study was copper slag and copper slag dust, both of which contained substantial amounts of other trace metals

including arsenic, nickel, and chromium, which are known carcinogens (Mackey et al. 1980).

Cumene

There is no evidence, in the sources reviewed, that cumene is carcinogenic. Although some chronic animal toxicity studies have been performed and reported by ACGIH (1980), these studies are not likely to be adequate to assess the carcinogenicity of cumene. Neither ACGIH (1980) nor a review by the National Academy of Sciences (1980) cited epidemiological studies on cumene. There is a lack of useful information on which to assess the carcinogenic potential of cumene, but the similarity in structures of cumene and ethylbenzene would suggest cumene like ethylbenzene is not carcinogenic (see Ethylbenzene).

Cyclohexane

There is no evidence, in the sources reviewed that, cyclohexane is carcinogenic. No animal chronic toxicity studies or epidemiological studies were found. The saturated cyclic structure of cyclohexane suggests that its potential to induce neoplasms is small.

Dibenzofuran

No information was found on dibenzofuran. The polycyclic structure of the compound is similar to that of naphthalene, i.e., they are both planer molecules. As such, the structural considerations used for naphthalene argue against the presumption of carcinogenic activity for dibenzofuran (see Naphthalene).

Further support is contributed by the fact that a lifetime carcinogenesis bioassay of dibenzo-p-dioxin (a structural analogue) in rats and mice was negative (NCI 1979a).

1,2-Dibromoethane

There is substantial evidence that 1,2-dibromoethane is carcinogenic to animals. Both inhalation and gavage oncogenicity studies were positive in mice and rats (NCI 1978, NTP 1982c). NIOSH (1977b) reviewed only one epidemiological study on exposed workers. This study had equivocal findings. The EPA Cancer Assessment Group has calculated the unit risk for carcinogenic potency of 1,2-dibromoethane to be $8.51(mg/kg/day)^{-1}$, which is equivalent to $2.5x10^{-3}$ $(\mu g/m^3)^{-1}$.

1,2-Dichloroethylene

1,2-Dichloroethylene occurs as two distinct geometric isomers, cis and trans 1,2-dichloroethylene. Neither has been tested for its carcinogenic potential. Evidence for mutagenic activity is equivocal, but neither isomer is a potent mutagen in bacterial assay systems. On the basis of structure-activity considerations, there is some suggestion that the dichloroethylenes may have carcinogenic potential; monochloroethylene (vinyl chloride) is a proven human carcinogen, and 1,1-dichloroethylene and trichloroethylene may induce liver cancer in experimental animals, although the evidence is less than convincing. On the other hand, several investigators have suggested that unsymmetrically halogenated ethylenes, e.g., vinyl chloride and

TCE, are more likely to be metabolically activated to carcinogenic intermediates than are symmetrically substituted ethylenes, e.g., 1,2-dichloroethylene. On this basis it is reasonable to conclude that it is unlikely that cis- and trans-1,2,-dichloroethylene are carcinogenic, but, if they are, they would not be expected to be very potent.

Diethanolamine

There is no evidence, in the sources reviewed, that diethanolamine is carcinogenic. No animal chronic toxicity studies or epidemiological studies were found. The compound is currently under study in the National Toxicology Program in oncogenicity bioassays (NTP 1983g). The animal study has been completed, and the technical report is being drafted. The structure of diethanolamine makes biotransformation to a nitrosoamine possible, although no evidence was found to indicate that this does occur. EPA (1980) did review a study that found nitrosodiethanolamine to be a liver carcinogen in rats. The nitroso-compound was fed to rats intermittently at a dose of 600 mg/kg over a 41-week period. All treated rats developed malignant tumors. Assuming that no hepatocarcinomas occurred in control rats, the calculated unit risk is 1.1×10^{-5} $(\mu g/m^3)^{-1}$. The risk associated with ethanolamine should be much less, so a factor of 100 will be used, making the unit risk 1.1×10^{-7} $(\mu g/m^3)^{-1}$.

Di(2-ethylhexyl)Phthalate

Di(2-ethylhexyl)phthalate was found to cause a significant increase in the incidence of hepatocellular carcinoma in rats and mice during a chronic feeding study conducted by the National Toxicology Program (1982d). Other chronic toxicity studies reviewed by EPA (1980i) in which animals were orally administered di(2-ethylhexyl)phthalate did not indicate that the compound was carcinogenic. The highest dose levels in these negative studies were somewhat lower than the low dose level in the positive study. No adequate epidemiological studies were available for the IARC Working Group to review (IARC 1982). Di(2-ethylhexyl) phthalate was not found to be mutagenic in the reviewed studies.

A unit risk for di(2-ethylhexyl)phthalate was calculated based on hepatocellular carcinomas found in male and female rats in the National Toxicology Program bioassay. The average daily intakes for the three groups were 0, 358, and 724 mg/kg/day. The combined tumor incidences for each of these groups were 3/100, 12/98, and 25/98 (number with tumor/number examined), respectively. The unit risk is 1.3×10^{-7} $(\mu g/m^3)^{-1}$. Since the unit risk was based on a feeding study, there is additional uncertainty with this value.

Ethylbenzene

There was no evidence in the sources reviewed, including a review by the National Academy of Sciences (1980), that ethylbenzene was carcinogenic. Only one long-term study was reviewed

in these sources. This was a 6-month subchronic toxicity study, using guinea pigs, monkeys, and rabbits. There was no evidence that ethylbenzene is carcinogenic, and the study was inadequate to evaluate the compound's carcinogenic potential. EPA (1980e), speculating on the possibility that ethylbenzene was mutagenic or carcinogenic, concluded:

> Gillete, et al. (1974) have reviewed certain considerations of drug toxicity including those related to possible carcinogens. EB or its known metabolites in man and in animals (Bardodej and Bardedjova, 1970; Kiese and Lenk, 1973, 1974; McMahon and Sullivan, 1966) do not fit into any of the presently known physical/chemical catagories of mutagenic and/or carcinogenic agents.

Ethylbenzene was deferred from testing by the National Toxicology Program (NTP 1983g).

Ethyl Ester Acrylic Acid

There is some evidence that ethyl ester acrylic acid is carcinogenic. Four animal chronic toxicity studies have been reported. One study, in which rats ingested the compound in drinking water, found no treatment-related lesions. This study report was reviewed by IARC (1979a) and found to contain insufficient detail to evaluate the finding adequately. Two recent inhalation studies conducted by Dow Chemical's Toxicology Research Laboratory and released by Celanese (1983a, 1983b) also report finding no increased tumor incidences in either mice or rats exposed to ethyl ester acrylic acid. These studies have not yet been critically evaluated, but they do appear to be adequate tests for carcinogenicity. A National Toxicology Program oncogenicity bioassay on mice and rats has been completed and a

draft report prepared (NTP 1983c). In this gavage study, treated male rats and mice had a significantly increased incidence of forestomach squamous cell carcinoma. No epidemiological studies have been found concerning ethyl ester acrylic acid.

Based on the National Toxicology Program bioassay, a unit risk for ethyl ester acrylic acid was estimated. Male rats in this study received doses of 0, 100, or 200 mg/kg/day. The respective tumor incidences for these dose groups were 0/50, 5/50, and 12/50 (number with tumor/number examined). The estimated unit risk is 5.0×10^{-7} $(\mu g/m^3)^{-1}$. Because this value is based on a positive gavage study while inhalation studies were negative, there is uncertainty about how relevant the value is to human inhalation exposure.

Ethylene

There is no evidence, in the sources reviewed, that ethylene is carcinogenic. No chronic toxicity studies in animals or epidemiological studies were found. Although IARC (1979a) indicated that an oncogenicity study in rats was in progress, no report of such a study was found. Ethylene oxide is known to be a metabolite of ethylene (IARC 1979a) and has been shown to be an animal carcinogen. Thus, it is possible that ethylene may also prove to be carcinogenic. The EPA Carcinogen Assessment Group has calculated a unit risk for ethylene oxide of 1.8×10^{-4} $(\mu g/m^3)^{-1}$. Assuming a difference in potency between ethylene and ethylene oxide of 100, the unit risk of ethylene would be 2.7×10^{-6} $(\mu g/m^3)^{-1}$. A recent finding that propylene was

not carcinogenic may suggest, on a structural basis, that ethylene is not carcinogenic (see Propylene).

Ethylene Glycol

There is no evidence, in the sources reviewed, that ethylene glycol is carcinogenic. ACGIH (1980) reviewed some subchronic toxicity studies in animals that did not show neoplastic effects, but these studies are not adequate to assess the carcinogenic potential of ethylene glycol. A report on a 2-year feeding study using a small number of rats did not indicate that ethylene glycol induced an increased incidence of tumors, although this study was not an adequate oncogenicity bioassay. No epidemiological studies were found in the sources reviewed. Ethylene glycol is currently under study by the National Toxicology Program (NTP 1983g), which is conducting a lifetime feeding study in mice.

Ethylene Glycol Monoethyl Ether

There is no evidence, in the sources reviewed, that ethylene glycol monoethyl ether is carcinogenic. One chronic toxicity study in rats was reviewed in several sources. There was no reported increase of tumor incidence in the treated animals, although the study may not have been adequate to assess the carcinogenic potential of the compound. Ethylene glycol monoethyl ether is presently under study in the National Toxicology Program (NTP 1983g). No epidemiological studies were reported in the sources reviewed. Ethylene glycol monoethyl ether has

been found to be teratogenic in experimental animals and epidemiologic evidence suggests an association between exposure of pregnant women to this chemical and birth defects. The relevance of these findings to assessing the potential carcinogenic risk from ethylene glycol monoethyl ether is unclear.

Hexahydro-2H-azepin-1-one

There is no evidence, in the sources reviewed, that hexahydro-2H-azepin-1-one (E-caprolactam) is carcinogenic. The National Toxicology Program (1982b) found no evidence that E-caprolactam induced neoplastic effects in mice or rats during a 2-year feeding study. The epidemiology studies reviewed by ACGIH (1980) also found no indication that E-caprolactam caused adverse health effects in occupationally exposed workers. It was not determined whether these studies were adequate to detect increased cancer morbidity or mortality. RTECS (1983) reported one study that found an effect on rat sperm morphology following in vivo exposure to E-caprolactam.

Isobutyraldehyde and Propionaldehyde

Isobutyraldehyde and proprionaldehyde are saturated aliphatic aldehydes, and they have not been studied for their potential to induce cancer or other chronic toxic effects. If these are considered as members of a homologous series beginning with formaldehyde (one carbon), acetaldehyde (two carbons), propionaldehyde (three carbons), and isobutyraldehyde (four carbons), there is some evidence for carcinogenic potential,

because formaldehyde is a confirmed animal carcinogen and acetaldehyde was shown to induce nasal and laryngeal cancer in hamsters exposed by inhalation for 7 hours a day, 5 days a week, for 52 weeks (Feron et al. 1982). However, it is important to note that the concentrations of acetaldehyde to which hamsters were exposed were very high (1,650-2,500 ppm), approximately 100 times greater than the concentrations of formaldehyde that induced cancer in rats. Furthermore, the mechanism by which the lower aldehydes induce cancer is unknown and may be secondary to their irritant properties. Therefore, if propionaldehyde and isobutyraldehyde follow the trend, they would not be expected to induce cancer, and if they did, only at extremely high concentrations. Isobutyraldehyde is presently under study by the National Toxicology Program (NTP 1983g).

Isopropyl Alcohol

There is evidence, in the sources reviewed, that occupational exposure to the strong acid production process of isopropyl alcohol is carcinogenic. This carcinogenic effect has been attributed to isopropyl oils, which are by-products of the production process, and not to isopropyl alcohol. The manufacturing process has been discontinued. Isopropyl oil mixtures have been shown to be tumorigenic in mice, but IARC (1977) did not consider these studies adequate to provide sufficient evidence of carcinogenicity. No chronic toxicity studies on isopropyl alcohol were found in the sources reviewed. One inhalation exposure study on mice, which had a duration of

up to 12 months, did not show an increased incidence in lung tumors; however, this study was not adequate to evaluate the carcinogenicity of isopropyl alcohol. Based on its structure, it is not likely that isopropyl alcohol is carcinogenic.

4,4-Isopropylidenediphenol

There is equivocal evidence, in the sources reviewed, that 4,4-isopropylidenediphenol (bisphenol A) is carcinogenic. Rats fed bisphenol A in a 2-year oncogenicity study developed a higher incidence of leukemias than did the control rats (NTP 1982a). This increase in both male and female rats was not statistically significant, although there was a significant dose-related trend in the male rats. A statistically significant increased incidence in interstitial-cell tumors of the testes was also found in male rats, but was not considered a significant compound-related effect because of the normally high incidence found in aging rats of the strain used. Male mice also had an increased incidence of leukemias/lymphomas, but it was not significant. The National Toxicology Program concluded that there was no convincing evidence that bisphenol A was carcinogenic to rats and mice in this bioassay. However, since increased incidences of leukemia were found in the male and female rats and male mice and a significant dose-related trend was found for this type of neoplasia, a unit risk was calculated using the male rat incidence data. The dietary levels fed to the rats were 0, 1,000, and 2,000 ppm, which gave an average daily dose of 0, 74, and 148 mg/kg/day, respectively. The tumor

incidence data was 13/50, 12/50, and 23/50 (number with leukemia/number examined), respectively. The calculated unit risk is 2.2×10^{-6} ($\mu g/m^3$). Because this value is calculated on nonsignificant incidence data, the uncertainty associated with it is high.

Melamine

A recent 2-year feeding study in rats and mice under supervision of the National Toxicology Program (1983d) found that melamine caused a significantly increased incidence of transitional-cell carcinoma of the bladder in male rats. There were no other tumor incidences that were significantly increased over control values in the male and female rats and mice. In a separate study, reviewed by NTP (1983d), rats of a different strain were fed melamine for 2 years. Benign papillomas in the bladder of some high-dose animals were found, but no malignant tumors were seen. Bladder stones were associated with these benign tumors. Bladder stones were also found in a large number of the high-dose rats of the NTP study. No other information on the carcinogenicity of melamine was found in the sources reviewed except that melamine was not mutagenic in Drosophila melanogaster or several strains of Salmonella typhimurium.

A unit risk for melamine was calculated on the incidence of transitional-cell tumors in the bladder of male rats. These animals were fed diets containing 0, 4,500, and 9,000 ppm melamine, which gave average daily doses of 0, 126, and 263 mg/kg/day, respectively. The tumor incidence was 0/45, 0/50, and 8/49

(number with tumor/number examined), respectively. The calculated unit risk is $4.1 \times 10^{-7} (\mu g/m^3)^{-1}$. Because there are scientists of the opinion that the appearance of bladder tumors in the presence of bladder stones is evidence that the tumorigenic response is secondary to the primary response of bladder stone formation, the use of a nonthreshold model to estimate cancer risk in such a case may be overly conservative and inappropriate.

Methanol

There is no evidence, in the sources reviewed, that methanol is carcinogenic. In one chronic study in dogs, reviewed by ACGIH (1980), no effect was observed, although the study was not an adequate oncogenicity study. Several studies on occupational exposure were also reported by ACGIH (1980), but none appeared to be concerned with cancer morbidity or mortality. Methanol is metabolized to formic acid and formaldehyde. Formaldehyde has been shown to cause cancer in rats. This effect occurs at the site of application, and thus formation within the body from methanol may not be an important factor in the determination of methanol's carcinogenic potential.

Methyl Chloride

Methyl chloride has been tested in a 2-year inhalation bioassay on mice and rats that was sponsored by CIIT (1981). A significantly increased incidence of renal tumors was found in male mice. No increased incidence of any tumor was found

in female mice and male and female rats. There is very little other information on the carcinogenic potential of methyl chloride, in the sources reviewed, except that it has been found to be mutagenic in Salmonella typhimurium (CCRIS 1983).

A unit risk was calculated based on the incidence of renal tumors (cortical adenomas and cortical adenocarcinomas) in the male mice. The mice were exposed to airborne concentrations of 0, 104, 469, and 1,086 mg/m^3 and had tumor inci dences of 0/67, 0/61, 2/57, and 18/82 (number with tumor/number examined), respectively. The calculated unit risk is 1.4×10^{-7} $(\mu g/m^3)^{-1}$.

Methyl Ethyl Ketone

There is no evidence, in the sources reviewed, that methyl ethyl ketone is carcinogenic. No studies werereviewed in these sources that examined the chronic toxicity of the compound in animals or humans. The only aliphatic ketone that has undergone long-term testing is acetone, which was applied to the skin of mice for 1 year without producing tumors (NIOSH 1978a). NIOSH also reported studies showing negative findings in mutagenicity assays of acetone. Although these results are not adequate evidence that acetone is not carcinogenic, they are suggestive. Since acetone and methyl ethyl ketone are structurally very similar they are expected to act in a similar manner.

Methyl Methacrylate

There is no evidence, in the sources reviewed, that methyl methacrylate is carcinogenic. No animal chronic toxicity studies

or epidemiological studies were found in these sources. Methyl methacrylate is structurally similar to ethyl acrylate. Ethyl acrylate has been shown to be carcinogenic in one of several chronic studies. Based on this, methyl methacrylate should also be considered to be a possible carcinogen. A structure-activity relationship has been developed for the acute toxicity of the alkyl acrylates (Autian 1975). Methyl methacrylate is much less potent than ethylacrylate. Because the qualitative evidence for the carcinogenicity of methyl methacrylate is so weak, a unit risk will not be calculated.

4,4-Methylenedianiline

There are several animal studies that examined the carcinogenic effect of 4,4-methylenedianiline (IARC 1974). In a subcutaneous injection study, the compound produced an increased incidence of benign and malignant tumors. A recently released National Toxicology Program bioassay of 4,4-methylenedianiline dihydrochloride found the compound to be carcinogenic to both mice and rats (NTP 1983e). ACGIH (1980) reviewed one study on workers exposed to the compound at levels of 0.03-3.8 ppm that showed no increased mortality or morbidity, but a structurally similar compound, 4,4-methylene bis(2-methylaniline), was found to be associated with an increased incidence of mortality from urinary bladder cancer in dye stuff factory workers.

A unit risk for 4,4-methylenedianiline was calculated on an increased incidence of thyroid follicular-cell adenoma or carcinoma found in female rats in the NTP study. These

rats were given 4,4-methylenedianiline dihydrochloride in their drinking water and received an average lifetime daily dose of 0, 6.4, or 12.2 mg/kg/day. (These doses have been converted to actual doses of 4,4-methylene dianiline and not its dihydrochloride salt). The tumor incidences in these dose groups were 0/47, 4/47, and 19/48 (number with tumors/number examined), respectively. The calculated unit risk is 2.1×10^{-5} $(\mu g/m^3)^{-1}$.

Molybdenum Trioxide

There is some evidence, in the sources reviewed, that molybdenum trioxide may be carcinogenic. RTECS (1983) cites a study by Stoner et al. (1976) in which molybdenum trioxide significantly increased the incidence of lung adenomas in strain A mice after 19 subcutaneous injections over a 30-week period. The same study cites a personal communication that a molybdenum compound was found carcinogenic when administered by intramuscular injection to rats. No other information on the carcinogenc potential of molybdenum trioxide was found in the sources reviewed.

Although, there is a possibility that molybdenum trioxide is carcinogenic there is insufficient information on which to calculate a unit risk. The strain A lung adenoma bioassay is not an actual oncogenicity bioassay and therefore should not be used for unit risk calculations.

Naphthalene

There is little evidence, in the sources reviewed, that naphthalene is carcinogenic. EPA (1980g) has reviewed several

animal studies that examined the carcinogenicity of naphthalene. Two studies reported by the same researcher found increased incidences of lymphosarcomas or leukemia in treated rats. Because of defects in these studies EPA (1980g) concluded that they could not be used as a basis for a naphthalene water criterion. The other animal chronic studies gave negative results. Two mutagenicity studies reviewed by EPA (1980g) found that naphthalene did not produce a mutagenic effect in E. coli or several strains of Salmonella typhimurium. A study of workers (USEPA 1980g) exposed to naphthalene and coal tar for up to 32 years found several cases of malignant tumors, but this study had no control population and confounding factors do not allow any finding on association between naphthalene exposure and cancer. Naphthalene is currently undergoing oncogenicity testing by the National Toxicology Program (NTP 1983g). On the basis of structure-activity considerations, naphthalene would not be expected to be carcinogenic. Among the unsubstituted polycyclic aromatic hydrocarbons with fewer than four condensed rings that have been tested, none has shown tumorigenic activity (Santodonato et al. 1981). Although benzene is a proven leukemogen, this property appears to be extremely structure specific in that such very close structural analogs as toluene, phenol, and monochlorobenzene appear not to have the capacity to induce tumors.

Pentachlorophenol

There is no evidence, in the sources reviewed, that pentachlorophenol is carcinogenic. Studies on workers who treated wood with pentachlorophenol preservatives were reviewed by EPA (1980h). There was no mention of an increased incidence in cancer morbidity or mortality in these reviews. The studies may not have examined that aspect of the workers health since only clinical chemistry information was given. No other epidemiological study was found in the sources review. Chronic feeding studies of commercial grade pentachlorophenol in both mice and rats have been reviewed by EPA (1980h) and IARC (1979b). In both species there were no increased incidences of tumors. A subcutaneous injection study, of the same commercial product, using two strains of mice was also reviewed by IARC (1979b). The male mice of one strain were found to have a significantly greater incidence of hepatocellular carcinomas compared to the control mice. Although there was a positive response in this study it is an inadequate study on which to evaluate the carcinogenicity of pentachlorophenol. The animals received only one injection of compound and the compound was not pure, containing the known carcinogens trichlorophenol and hexachlorodibenzodioxins (NCI 1979e, NTP 1980).

Because pentachlorophenol is structurally related to 2,4,6-trichlorophenol, which was found to be carcinogenic in rats and mice (NCI 1979e) it may also be carcinogenic. Therefore, a unit risk for pentachlorophenol will be derived from tumor

incidence data of hepatocellular adenomacarcinoma in male mice. In this study the animals were fed diets containing the compound. These diets delivered average daily doses of 0, 620, 1,240 mg/kg/day to the mice. The respective tumor incidences are (number with tumor/number examined) 4/20, 32/49, and 39/47. The unit risk is 3.9×10^{-7} $(\mu g/m^3)^{-1}$. There is a great deal of uncertainty in this value, because it not based on a pentachlorophenol study and because the trichlorophenol used may have been contaminated with polychlorinated dibenzodioxins, which can induce hepatocellular carcinomas at very low dose levels.

Phthalic Anhydride

There is no evidence, in the sources reviewed, that phthalic anhydride is carcinogenic. No epidemiological studies were found that examined cancer mortality or morbidity in exposed populations. The National Cancer Institute conducted oncogenicity bioassays of phthalic anhydride on mice and rats (NCI 1979b). The feeding study found that phthalic anhydride was not carcinogenic to either species under the condition of the bioassays. The compound is highly reactive and probably reacts with water to form phthalic acid. Because the lungs may be more sensitive to an effect by phthalic anhydride, the negative finding in the feeding still leaves uncertainty about its possible effect via inhalation.

Propene

There is no evidence, in the sources reviewed, that propene is carcinogenic. IARC (1979a) had insufficient information available for review and evaluation of propene toxicity. The National Toxicology Program has just completed chronic inhalation studies in rat and mice on propene. The report of these studies is in final preparation. No significantly increased tumor incidences were found (NTP 1983f).

Propionaldehyde

See Isobutyraldehyde and Propionaldehyde.

Propylene Dichloride

There is evidence that propylene dichloride is carcinogenic. The findings of a 2-year gavage study in mice and rats by the National Toxicology Program (1983b) suggest that propylene dichloride is a carcinogen in mice. There was a significant increased incidence in liver tumors (adenomas and carcinomas combined) in both male and female mice. Other tumors in rats and mice may have also been compound related. No epidemiological studies on cancer morbidity or mortality of exposed populations were found in the sources reviewed.

An estimated unit risk was derived for propylene dichloride based on male mouse liver tumor data from the NTP study. The mice received doses of 0, 125, or 250 mg/kg/day, and the respective tumor incidences for these doses were 18/50, 25/49, 32/80 (number with tumor/number examined). The unit risk is 7.2×10^{-7}

Styrene

There is some evidence, in the sources reviewed, that styrene is carcinogenic. IARC (1979a) reviewed a study on cancer mortality of chemical workers producing styrene monomer. Three leukemias and two lymphomas were found among 104 deaths studied, which indicated to the study authors that further studies were needed. IARC (1979a) found that this study failed to identify clearly the population at risk and that there was no comparison to a control population. A National Cancer Institute report (1979c) on an oncogenicity bioassay in rats and mice concluded that there was no convincing evidence that styrene was carcinogenic to rats or mice under the conditions of the bioassay. There was, however, an increased incidence of a combination of lung adenomas and carcinomas in male mice, which was considered to be suggestive evidence. IARC (1982) states that "there is limited evidence in humans and animals that acrylonitrile, epichlorohydrin and styrene are carcinogenic." Thus, a unit risk for styrene was calculated on the incidence of mouse lung tumors in the National Cancer Institute's bioassay. The mice were given daily doses of 0, 150, and 300 mg/kg/day by gavage. The respective tumor incidences for these dose groups were 0/20, 6/44, and 9/43 (number with tumor/number examined). The calculated unit risk is 2.9×10^{-7} $(\mu g/m^3)^{-1}$. There is uncertainty in this value since the tumor incidences used were not considered sufficient evidence that styrene induced a carcinogenic response.

Terephthalic Acid

There is some evidence that terephthalic acid is carcinogenic. EPA (1982b) reviewed a study citing another study that showed that terephthalic acid induced bladder and ureteral neoplasms in both male and female rats in a 2-year feeding study. Rats fed a dietary level of 5% terephthalic acid had tumors and bladder stones, while those fed a dietary level of 1% did not. The study reviewed by EPA (1982b) showed that only the treated rats with bladder stones developed hyperplasia of the transitional epithelium in the urinary bladder. This suggests that hyperplasia and possibly neoplasms would not be induced by terephthalic acid without irritation from bladder calculi. As with melamine a causal association has still not been shown. Therefore, a unit risk was estimated for terephthalic acid. Because the chronic toxicity study was not in the published literature, information from the study was taken from the study reviewed by EPA (1982b) (Chin et al. 1981) and assumptions were made. Two dietary levels were mentioned, 1% and 5%. It is assumed that a control gorup was also included. No tumor incidence was mentioned so it was assumed that no tumors occurred in the control or low-dose groups and a 10% incidence was found in the high-dose group. Dietary levels of 1% and 5% approximate a daily intake for rats of 490 and 2,450 mg/kg/day, respectively. The calculated risk based on these assumptions is 1.8×10^{-8} $(\mu g/m^3)^{-1}$. There is a large degree of uncertainty associated with this value.

Tert-Butyl Alcohol

There is no evidence, in the sources reviewed, that tert-butyl alchol is carcinogenic. No animal chronic-toxicity studies were cited in these sources except for a skin painting promotion study in mice in which tert-butyl alcohol failed to increase carcinogenic activity after an initiating dose of 4-nitroquinoline-1-oxide (reviewed by NAS 1977). No epidemiological studies concerning cancer morbidity or mortality were found in the sources reviewed. Tert-butyl alcohol is currently under study by the National Toxicology Program (NTP 1983g).

Titanium Dioxide

There is some evidence, in the sources reviewed, that titanium dioxide is carcinogenic. RTECS (1983) cites two studies, from the same source, that indicate that titanium dioxide has a tumorigenic effect when injected intramuscularly. E.I. DuPont (1983) reported the preliminary results of a 2-year inhalation study in rats. They report that at the highest airborne concentration used, significantly increased incidences of lung squamous cell carcinoma and bronchioalveolar adenoma were found. On the other hand, the National Cancer Institute reported (1979d) on a 2-year feeding study in mice and rats that found that titanium dioxide was not carcinogenic under the conditions of the bioassay. There was, however, a dose-related increase in the incidence of C-cell adenomas or carcinomas in the thyroid of female rats, although the increase was not statistically significant.

Because there was a positive finding in the 2-year inhalation study, a unit risk for titanium was calculated. The unit risk was based on the incidence of squamous cell carcinoma in the lung. The rats in this study were exposed to airborne concentrations of 0, 10, 50, and 250 mg/m^3. The corresponding incidence data were 0, 0, 0, and "about 10%," respectively. The unit risk is 5.6×10^{-7} $(\mu g/m^3)^{-1}$.

2,4-Toluene Diisocyanate

There is some evidence, in the sources reviewed, that 2,4-toluene diisocyanate is carcinogenic. A National Toxicology Program 2-year gavage study in mice and rats using a mixture of toluene diisocyanates, 86% 2,4-isomer and 14% 2,6-isomer, found dose-related increased incidences of tumors in several tissues (NTP 1982e). The low- and high-dose rats received 30 and 60 mg/kg/day, respectively, and the low- and high-dose mice received 120 and 240 mg/kg/day, respectively. No other animal chronic toxicity studies or epidemiological studies on cancer morbidity or mortality were reported in the sources reviewed. A list of tumor incidences found at a statistically significant higher level in treated rats and mice from the NTP study is given below:

Species	Tumor	Dose		
		Control	Low	High
Rat	Subcutaneous fibromas and fibromas	3/50	6/50	12/50
	Pancreatic acinar-cell adenomas	1/47	3/47	7/49
Mouse	Hemangiomas and hemangio-sarcomas	0/50	1/50	5/50
	Hepatocellular adenomas	2/50	3/50	12/50

Vinyl Acetate

There is no evidence, in the sources reviewed, that vinyl acetate is carcinogenic. No epidemiological studies on cancer morbidity or mortality of exposed populations were found in these sources. NIOSH (1978c) reviewed only one animal study that examined the carcinogenic potential of vinyl acetate. This inhalation study found vinyl acetate did not cause an increased incidence of tumors. The adequacy of the study is questionable because of the high mortality rate of treated rats during the 1st year. Vinyl acetate was not mutagenic to Salmonella typhimurium in the presences or absence of a metabolic activating system.

Vinyl acetate is structurally similar to many known cancer producing agents, e.g., vinyl chloride, vinyl bromide, acrylonitrile, and vinyl carbamate. Therefore, even though no unit risk

will be calculated for the compound, there is an uncertainty about its carcinogenic potency.

Zinc

There is no evidence, in the sources reviewed, that zinc is carcinogenic, although it was reported to induce testicular tumors in rats after direct injection of zinc salt into the testes (EPA 1980j). EPA (1980j) states that "zinc is of interest with regard to cancer since zinc seems to be indirectly involved by being important for the growth of tumors." There is also no indication zinc is mutagenic.

Zinc Oxide

There is no evidence, in the sources reviewed, that zinc oxide is carcinogenic. No animal chronic toxicity studies or epidemiological studies on cancer morbidity or mortality were found in these sources. The National Toxicology Program has deferred the testing of zinc oxide in its bioassay program (NTP 1983g).

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