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An Evaluation of Chemicals and Industrial Processes Associated with Cancer in Humans Based on Human and Animal Data: IARC Monographs Volumes 1 to 20[1]

Report of an IARC Working Group[2,3]

ABSTRACT

An international *ad hoc* Working Group of experts in cancer research met at the International Agency for Research on Cancer (IARC) in January 1979 to evaluate the data on human and experimental animal carcinogenicity for 54 chemicals, groups of chemicals, and industrial processes. Monographs for these chemicals were published in Vols. 1 to 20 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Based on evidence from human studies, 18 of the 54 chemicals or industrial processes are human carcinogens. A further 18 chemicals are probably carcinogenic for humans, although the data were considered not adequate to establish a causal association. To reflect differing degrees of evidence of carcinogenicity within this group, the chemicals were further subdivided, with 6 chemicals exhibiting a high degree of evidence and 12 chemicals exhibiting a lower degree. Data on the remaining 18 chemicals were considered insufficient to allow any evaluation of carcinogenicity. The report summarizes the background, purpose, and overall conclusions of the Working Group. The evidence supporting the evaluations is given in the "Appendix."

INTRODUCTION

In 1971, the International Agency for Research on Cancer (IARC) began a program to prepare monographs on the evaluation of the carcinogenic risk of chemicals to humans (1). The objectives of the Monographs Program are to examine critically the data relating to carcinogenicity for chemicals to which humans are known to be exposed; to evaluate these data with the help of experts in chemical carcinogenesis, epidemiology, and related fields; and to make this information available for the primary prevention of cancer. Selection of chemicals for evaluation is based on 2 criteria: (*a*) there are data related to carcinogenicity in humans or experimental animals; and (*b*) there is evidence of human exposure (4).

In the first 16 volumes of the monographs, the assessments of carcinogenicity in humans and experimental animals were made separately. No attempt was made to estimate carcinogenic risk to humans on the basis of data from experimental animals. However, most of the chemicals evaluated in the monographs had only data from animal studies. Specifically, of more than 350 chemicals evaluated in Vols. 1 to 16, only 48 (about 14%) had any human data. In cases where there was no information available from studies in humans, the IARC was asked repeatedly to consider making an assessment of the carcinogenic risk for humans which was based only on animal data.

An *ad hoc* Working Group met in October 1977 to review the criteria for the assessment of the carcinogenic risk of chemicals to humans (3). The group drafted guidelines for subsequent Working Groups which standardize the evaluations of carcinogenicity studies both in humans and in animals. More importantly, they recommended that in the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity (*i.e.*, a causal association) in animals (2) as if they presented a carcinogenic risk for humans. The use of the expressions "for practical purposes" and "as if they presented a carcinogenic risk" indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a scientific basis, but rather only pragmatically, with the intent of helping regulatory agencies in making decisions related to the primary prevention of cancer.

These guidelines were adopted starting with Vol. 17 of the Monographs. However, since these criteria were not used for Vols. 1 to 16, a further *ad hoc* Working Group was convened to reevaluate the data from animal studies for the chemicals evaluated in those volumes and to identify those for which there is sufficient evidence of carcinogenicity (2). This Working Group did not consider chemicals or industrial processes for which epidemiological data or case reports suggested an association with the occurrence of cancer in humans (6).

By the end of 1978, 20 volumes of the Monographs had been prepared. Of the 442 chemicals, groups of chemicals, and industrial processes evaluated therein, 143 (32%) have sufficient evidence of carcinogenicity in experimental animals, whereas case reports or epidemiological studies have been

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[2] This report was prepared by Ralph Althouse, James Huff, Lorenzo Tomatis, and Julian Wilbourn, International Agency for Research on Cancer. Requests for reprints should be addressed to Dr. L. Tomatis, Chief, Unit of Chemical Carcinogenesis, IARC, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France.

[3] This report results from an *ad hoc* Working Group which met in Lyon on January 15 to 17, 1979, to advise the Director of IARC on chemicals carcinogenic for humans. Working Group members: P. Armitage (University of Oxford, Oxford, U. K.); B. K. Armstrong, Rapporteur (University of Western Australia, Nedlands, Australia); A. L. Brown, Chairman (University of Wisconsin, Madison, Wis.); P. Bogovski (Institute of Experimental and Clinical Medicine, Tallin, U.S.S.R.); P. Cole (Harvard University, Cambridge, Mass.); N. E. Day (International Agency for Research on Cancer, Lyon, France); G. Della Porta (Istituto Nazionale per lo Studio e la Cura del Tumori, Milan, Italy); R. A. Griesemer, Rapporteur (National Cancer Institute, Bethesda, Md.); T. Hirohata (Kurume University, Kurume, Japan); W. J. Hunter (Commission of the European Communities, Luxembourg); S. D. Jayakar (Laboratorio di Genetica Biochimica ed Evoluzionistica, Pavia, Italy); L. Massé (Ecole Nationale de la Santé Publique, Rennes, France); M. C. Pike (University of Southern California Medical School, Los Angeles, Calif.); R. Preussmann (Institut für Toxikologie und Chemotherapie, Heidelberg, Federal Republic of Germany); M. A. Schneiderman (National Cancer Institute, Bethesda, Md.); L. Teppo (Finnish Cancer Registry, Helsinki, Finland); D. B. Thomas (Fred Hutchinson Cancer Research Center, Seattle, Wash.); J. K. Wagoner (Occupational Safety and Health Administration, Washington, D. C.); N. J. Wald, Vice-Chairman (University of Oxford, Oxford, U.K.); I. B. Weinstein (Columbia University, New York, N. Y.).

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published for only 60 of the 442 (14%). Because of time limitations, 6 compounds with limited human evidence were not considered by the Working Group (*o*- and *p*-dichlorobenzene, dichlorobenzidine, phenylbutazone, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *o*- and *p*-toluidine, vinylidene chloride). The group also did not consider sex hormone preparations (with the exception of diethylstilbestrol), since they had recently been reevaluated for Vol. 21. There were thus 54 chemicals and industrial processes with data on carcinogenicity from human and animal studies reviewed by the Working Group. This report summarizes the deliberations and conclusions of this *ad hoc* Working Group.

METHODS

For each chemical, the data were reviewed in detail before the meeting by 2 members of the group, the animal studies by an experimentalist and the human studies by an epidemiologist. Data that had become available since the publication of the relevant monograph were included in this review.

Separate assessments of the human and animal evidence of carcinogenicity were debated and adopted by the Working Group. An overall evaluation of carcinogenicity for humans was made based on the combined evidence. Brief descriptions of the data used to support the assessments and the evaluations appear in the "Appendix." We encourage the reader to consult these notes together with Table 1. For each chemical, the "Appendix" gives references for the appropriate volume in the Monographs series and, where applicable, papers which have been published subsequently.

Assessment of Evidence for Carcinogenicity from Experimental Animal Studies

These assessments were classified in 1 of 5 groups.

"Sufficient Evidence" of Carcinogenicity. There is an increased incidence of malignant tumors: (*a*) in multiple species or strains; (*b*) in multiple experiments (preferably with different routes of administration or using different dose levels); or (*c*) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects as well as information on mutagenicity or chemical structure.

"Limited Evidence" of Carcinogenicity. Data suggest a carcinogenic effect but are limited because: (*a*) the studies refer to a single species, strain, or experiment; (*b*) the experiments are restricted due to inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (*c*) the neoplasms produced often occur spontaneously or are difficult to classify as malignant by histological criteria alone (*e.g.*, lung and liver tumors in mice).

"Inadequate Evidence." Because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or the absence of a carcinogenic effect.

"Negative Evidence." Within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is limited since, in general, studies showing no effect are less likely to be published than those suggesting carcinogenicity.

"No Data." Data were not available to the Working Group.

The categories "sufficient evidence" and "limited evidence" refer only to the strength of the experimental evidence that these chemicals are (or are not) carcinogenic and not to the extent of their carcinogenic activity. The classification for any chemical may change as new information becomes available.

Assessment of Evidence for Carcinogenicity from Human Studies

Evidence of carcinogenicity in humans came from 4 types of studies: (*a*) case reports of individual cancer patients who were exposed to the chemical or process; (*b*) epidemiological studies in which the incidence of cancer in human populations was found to vary spatially or temporally with exposure to the agents; (*c*) epidemiological studies in which individuals with a cancer are compared with a control group free of that cancer to see whether the history of exposure to the presumed causal agent is greater in the cancer patients (*i.e.*, case-control studies); (*d*) epidemiological studies in which individuals with exposure to the presumed causal agent are followed up to see if their cancer incidence is higher than that of individuals without such exposure (*i.e.*, cohort or follow-up studies).

Three criteria must be met to infer a causal association between exposure and human cancer (3): (*a*) there is no identified bias which could explain the association; (*b*) the possibility has been ruled out that the association is due to another uncontrolled variable (often called a confounding variable) that is associated with both the cancer and the presumed causal agent; (*c*) the association is unlikely to be due to chance.

In general, while a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies all show the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity in human studies were categorized as: (*a*) sufficient evidence of carcinogenicity, a causal association between exposure and human cancer; (*b*) limited evidence of carcinogenicity, a possible carcinogenic effect in humans, but data not sufficient to demonstrate a causal association; (*c*) inadequate evidence of carcinogenicity, data qualitatively or quantitatively insufficient to allow any conclusion regarding carcinogenicity for humans.

Dividing lines were by no means firmly drawn between sufficient evidence and limited evidence for animal studies and between inadequate evidence and limited evidence for both human and animal studies. When differences of opinion occurred among the members of the Working Group, the classification was made by majority vote.

Evaluation of the Carcinogenic Risk to Humans

Presently, no objective criteria exist to interpret the animal data directly in terms of human risk. Thus, in the absence of sufficient evidence from human studies, evaluation of the carcinogenic risk to humans was based on consideration of the epidemiological and experimental evidence together. Furthermore, the breadth of the above-defined categories for human and animal evidence allows substantial variation within each, and the decisions reached by the group regarding overall risk incorporated these differences, even though they could not

Table 1

Classification of the degree of evidence of carcinogenicity for humans of chemicals or industrial processes from IARC Monographs, Vols. 1 to 20

Chemical or process	Degree of evidence[a]		Evaluation[b] of carcinogenic risk to humans
	In humans	In experimental animals	
1. Acrylonitrile	Limited	Sufficient	2B
2. Aflatoxins	Limited	Sufficient	2A
3. 4-Aminobiphenyl	Sufficient	Sufficient	1
4. Amitrole (aminotriazole)	Inadequate	Sufficient	2B
5. Arsenic and certain arsenic compounds	Sufficient	Inadequate	1
6. Asbestos	Sufficient	Sufficient	1
7. Auramine[c]	Limited	Limited	2B
8. Manufacture of auramine	Sufficient	Not applicable[d]	1
9. Benzene	Sufficient	Inadequate	1
10. Benzidine	Sufficient	Sufficient	1
11. Beryllium and certain beryllium compounds[e]	Limited	Sufficient	2B
12. *N,N*-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)	Sufficient	Limited	1
13. BCME and technical grade CMME	Sufficient Sufficient	Sufficient Limited	1
14. Cadmium and certain cadmium compounds[e]	Limited	Sufficient	2A
15. Carbon tetrachloride	Inadequate	Sufficient	2B
16. Chlorambucil	Limited	Sufficient	2A
17. Chloramphenicol	Inadequate	No data	3
18. Chlordane and heptachlor	Inadequate	Limited	3
19. Chloroprene	Inadequate	Inadequate	3
20. Chromium and certain chromium compounds[e]	Sufficient	Sufficient	1
21. Cyclophosphamide	Limited	Sufficient	2A
22. DDT	Inadequate	Limited	3
23. Dieldrin	Inadequate	Limited	3
24. Diethylstilbestrol	Sufficient	Sufficient	1
25. Dimethylcarbamoyl chloride	Inadequate	Sufficient	2B
26. Dimethyl sulfate	Inadequate	Sufficient	2B
27. Epichlorohydrin	Inadequate	Limited	3
28. Ethylene oxide	Limited	Inadequate	2B
29. Hematite[f]	Inadequate	Negative	3
30. Underground hematite mining	Sufficient	Not applicable[d]	1
31. HCH (technical HCH and lindane)	Inadequate	Limited	3
32. Iron dextran	Inadequate	Sufficient	2B
33. Isoniazid	Inadequate	Limited	3
34. Isopropyl oils[c, e]	Inadequate	Inadequate	3
35. Manufacture of isopropyl alcohol (strong acid process)	Sufficient	Not applicable[d]	1
36. Lead and certain lead compounds[e]	Inadequate	Sufficient (for some soluble salts)	3
37. Melphalan	Sufficient	Sufficient	1
38. Mustard gas	Sufficient	Limited	1
39. 2-Naphthylamine	Sufficient	Sufficient	1
40. Nickel and certain nickel compounds[c, e]	Limited	Sufficient	2A
41. Nickel refining	Sufficient	Not applicable[d]	1
42. Oxymetholone	Limited	No data	2B
43. Phenacetin	Limited	Limited	2B
44. Phenobarbitone	Limited	Limited	3
45. *N*-Phenyl-2-naphthylamine	Inadequate	Inadequate	3
46. Phenytoin	Limited	Limited	3
47. Polychlorinated biphenyls	Inadequate	Sufficient	2B
48. Reserpine	Inadequate	Inadequate	3
49. Soots, tars, and mineral oils[e]	Sufficient	Sufficient	1
50. Styrene	Inadequate	Limited	3
51. Trichloroethylene	Inadequate	Limited	3
52. Tris(aziridinyl)-*p*-benzoquinone (triaziquone)	Inadequate	Limited	3
53. Tris(1-aziridinyl)phosphine sulfide (thiotepa)	Limited	Sufficient	2A
54. Vinyl chloride	Sufficient	Sufficient	1

[a] For an explanation of the categories of degree of evidence, see "Methods."
[b] For an explanation of the categories of carcinogenic risk to humans, see "Methods."
[c] Please refer to section on industrial processes and to the evaluations in the "Appendix."
[d] It is difficult to expose experimental animals to the same conditions to which workers are exposed; therefore, no animal data are available.
[e] The specific compounds which may be responsible for a carcinogenic effect have not been identified.

always be adequately reflected in the placement of a chemical into a particular category for Table 1. The evidence supporting these decisions is summarized in the notes for each chemical in the "Appendix."

The chemicals, groups of chemicals, or industrial processes were placed into 1 of 3 groups.

Group 1. The chemical, group of chemicals, or industrial process is carcinogenic for humans. This category was used only when there was sufficient evidence to support a causal association between the exposure and cancer.

Group 2. The chemical or group of chemicals is probably carcinogenic for humans. This category includes chemicals for which the evidence of human carcinogenicity is almost sufficient as well as chemicals for which it is only suggestive. To reflect this range, this category has been divided into higher (Subgroup A) or lower (Subgroup B) degrees of evidence. The

data from experimental animal studies played an important role in assigning chemicals to Group 2, particularly to Subgroup B.

Group 3. The chemical or group of chemicals cannot be classified as to its carcinogenicity for humans.

RESULTS AND CONCLUSIONS

The separate evaluations of animal and human evidence are presented in Table 1. The Working Group concluded that the following 18 chemicals, groups of chemicals, and industrial processes are carcinogenic for humans (Group 1):

4-Aminobiphenyl
Arsenic and certain arsenic compounds
Asbestos
Manufacture of auramine[4]
Benzene
Benzidine
N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)
BCME[5] and technical grade CMME
Chromium and certain chromium compounds[4]
Diethylstilbestrol
Underground hematite mining[4]
Manufacture of isopropyl alcohol by the strong acid process[4]
Melphalan
Mustard gas
2-Naphthylamine
Nickel refining[4]
Soots, tars, and mineral oils[4]
Vinyl chloride

The following 16 chemicals and groups of chemicals are probably carcinogenic for humans (Group 2):

Subgroup A (6 Chemicals)

Aflatoxins
Cadmium and certain cadmium compounds[4]
Chlorambucil
Cyclophosphamide
Nickel and certain nickel compounds[4]
Tris(1-aziridinyl)phosphine sulfide (thiotepa)

Subgroup B (12 Chemicals)

Acrylonitrile
Amitrole (aminotriazole)
Auramine
Beryllium and certain beryllium compounds[4]
Carbon tetrachloride
Dimethylcarbamoyl chloride
Dimethyl sulfate
Ethylene oxide
Iron dextran
Oxymetholone
Phenacetin
Polychlorinated biphenyls

The following 18 chemicals and groups of chemicals could not be classified as to their carcinogenicity for humans (Group 3):

Chloramphenicol
Chlordane-heptachlor
Chloroprene
DDT
Dieldrin
Epichlorohydrin
Hemalite
HCH (technical grade HCH-lindane)
Isoniazid
Isopropyl oils
Lead and certain lead compounds[4]
Phenobarbitone
N-Phenyl-2-naphthylamine
Phenytoin
Reserpine
Styrene
Trichloroethylene
Tris(aziridinyl)-*p*-benzoquinone (triaziquone)

Mining and Manufacturing Processes

For some of the chemicals, part or all of the evidence indicating a carcinogenic effect for humans comes from an increased incidence of cancer in individuals involved in the mining or manufacture of these chemicals. There is sufficient evidence that the manufacture of auramine, the underground mining of hematite, the manufacture of isopropyl alcohol by the strong-acid process, and the refining of nickel are carcinogenic to humans, at least in the situations in which they have been studied. Because these occupations include exposure to other factors in addition to the indicated chemical, the responsible carcinogens have not been identified; therefore, the results cannot be generalized to all situations involving these processes. Nonetheless, these processes should be assumed to carry a carcinogenic risk to humans unless proven otherwise.

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   Vol. 2. Some Inorganic and Organometallic Compounds (7 monographs), 181 pp., 1973.
   Vol. 3. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds (17 monographs), 271 pp., 1973.
   Vol. 4. Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents (28 monographs), 286 pp., 1974.
   Vol. 5. Some Organochlorine Pesticides (12 monographs), 241 pp., 1974.
   Vol. 6. Sex Hormones (15 monographs), 243 pp., 1974.
   Vol. 7. Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals (23 monographs), 326 pp., 1974.
   Vol. 8. Some Aromatic Azo Compounds (32 monographs), 357 pp., 1975.
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   Vol. 10. Some Naturally Occurring Substances (32 monographs), 353 pp., 1976.
   Vol. 11. Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics (24 monographs), 306 pp., 1976.

[4] The specific compound(s) which may be responsible for a carcinogenic effect in humans has not been identified.

[5] The abbreviations used are: BCME, bis(chloromethyl) ether; CMME, chloromethyl methyl ether; DDT, dichlorodiphenyltrichloroethane; HCH, hexachlorocyclohexane.

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APPENDIX

Descriptive Evaluations of the Animal and Human Evidence of Carcinogenicity for Chemicals or Industrial Processes Evaluated in Vols. 1 to 20 of the IARC Monographs

1. *Acrylonitrile (Group 2B)*

Acrylonitrile is carcinogenic in rats after p.o. administration and inhalation, producing cancers of the brain, forestomach, and Zymbal's gland (1).

The one available study suggests 4- to 6-fold increases in the rates of lung and colon cancer in men observed for 20 or more years; however, it is limited by the absence of information on smoking and on exposure to other chemicals and by incompleteness of follow-up (1).

1. IARC Monogr., 19: 73–113, 1979.

2. *Aflatoxins (Group 2A)*

Aflatoxins are carcinogenic in mice, rats, fish, ducks, marmosets, tree shrews, and monkeys by several routes of administration (including p.o.), producing mainly cancers of the liver, colon, and kidney (1).

Epidemiological studies have shown a positive correlation between the average dietary concentrations of aflatoxins in populations and the incidence of primary liver cancer. These studies were undertaken to test this specific hypothesis. However, no studies have been carried out which could link an increased risk of liver cancer to actual aflatoxin intake in individuals (1).

1. IARC Monogr., 10: 51–77, 1976.

3. *4-Aminobiphenyl (Group 1)*

4-Aminobiphenyl is carcinogenic in mice, rats, rabbits, and dogs after p.o. administration, producing principally cancer of the urinary bladder (1).

Epidemiological studies, which are confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, show a high incidence of bladder cancer (1, 2).

1. IARC Monogr., 1: 74–79, 1972.
2. Melamed, M. R. Diagnostic cytology of urinary tract carcinoma. Eur. J. Cancer, 8: 287–292, 1972.

4. *Amitrole (Aminotriazole) (Group 2B)*

Amitrole is carcinogenic in mice and rats, producing thyroid and liver tumors following p.o. or s.c. administration (1, 2).

Railroad workers who were exposed to amitrole and other herbicides showed a slight (but statistically significant) excess of cancer when all sites were considered together. Because workers were exposed to several different herbicides, however, no conclusions could be made regarding the carcinogenicity of amitrole alone (1).

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5. *Arsenic and Certain Arsenic Compounds (Group 1)*

Information on the carcinogenicity of arsenic compounds in experimental animals was considered inadequate for evaluation (2).

Skin cancer in humans is causally associated with exposure to inorganic arsenic compounds in drugs, drinking water, and the occupational environment. The risk of lung cancer was increased 4 to 12 times in certain smelter workers who inhaled high levels of arsenic trioxide (2, 4, 7). However, in these studies, the influence of other constituents of the working atmosphere cannot be excluded. Case reports have suggested an association between exposure to arsenic compounds and blood dyscrasias and liver tumors (1, 3, 5, 6).

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6. *Asbestos (Group 1)*

All types of commercial asbestos fibers which have been tested are carcinogenic in mice, rats, hamsters, and rabbits, producing mesotheliomas and lung cancers after inhalation and after intrapleural, intratracheal, and i.p. administration (1).

Occupational exposure to chrysotile, amosite, anthophyllite, and mixtures containing crocidolite has resulted in a high

incidence of lung cancer. A predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also caused an increased incidence of lung cancer. Pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite, and chrysotile asbestos. Gastrointestinal tract cancers were increased in groups exposed occupationally to amosite, chrysotile, or mixed fibers containing crocidolite. An excess of cancer of the larynx was also observed in exposed workers. Mesotheliomas have occurred in individuals living in the neighborhood of asbestos factories and crocidolite mines and in persons living with asbestos workers. Both cigarette smoking and occupational exposure to asbestos fibers independently increase lung cancer incidence. When present together, they act multiplicatively (1).

1. IARC Monogr., *14*: 1–106, 1977.

7. *Auramine (Group 2B)*
8. *and The Manufacture of Auramine*[4] *(Group 1)*

Commercial auramine is carcinogenic in mice and rats after p.o. administration, producing liver tumors, and after s.c. injection in rats, producing local sarcomas (1).

The manufacture of auramine (which involves exposure to other chemicals along with auramine) has been shown in one study to be causally associated with an increase in bladder cancer. The actual carcinogenic compound(s) has not been identified (1).

1. IARC Mongr., *1*: 69–73, 1972.

9. *Benzene (Group 1)*

Benzene has shown no evidence of carcinogenicity when tested in mice by skin application. Other animal experiments were considered to be inadequate to evaluate the carcinogenicity of benzene (3, 5, 7).

Several case reports as well as an epidemiological case control study suggest a relationship between benzene exposure and leukemia (3). Two cohort studies (4, 6) showed an increased incidence of acute nonlymphocytic leukemia in workers exposed to benzene. There has been an additional report of a large number of leukemia cases (most of which were acute nonlymphocytic) among a group of workers exposed to benzene (1, 2).

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7. Ward, J. M., Weisburger, J. H., Yamamoto, R. S., Benjamin, T., Brown, C. A., and Weisburger, E. K. Long-term effect of benzene in C57BL/6N mice. Arch. Environ. Health, *30*: 22–25, 1975.

10. *Benzidine (Group 1)*

Benzidine is carcinogenic in experimental animals after p.o. and s.c. administration, producing liver tumors in rats and hamsters and bladder cancers in dogs (2).

Case reports and follow-up studies of workers provide sufficient evidence that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer (2). This association is strengthened by data which suggest that the incidence of this cancer in workers decreased after a reduction in industrial exposure (1).

1. Ferber, K. H., Hill, W. J., and Cobb, D. A. An assessment of the effect of improved working conditions on bladder tumor incidence in a benzidine manufacturing facility. Am. Ind. Hyg. Assoc. J., *37*: 61–68, 1976.
2. IARC Monogr., *1*: 80–85, 1972.

11. *Beryllium and Certain Beryllium Compounds*[4] *(Group 2B)*

Beryllium sulfate, beryl ore, and bertrandite produce lung tumors in rats following inhalation. Beryllium oxide and beryllium sulfate produce lung tumors in monkeys following intrabronchial implantation or inhalation. Zinc beryllium silicate, beryllium metal, and beryllium phosphate all produce bone tumors in rabbits following i.v. injection (1).

Five early epidemiological studies were considered inadequate to evaluate the carcinogenic effects of beryllium (1). Three recent epidemiological studies (2–4) concerned men occupationally exposed to beryllium, some of whom developed acute beryllium disease. The populations for these studies come from 2 beryllium refining and smelting plants, and both show a 1.5- to 2-fold increase in lung cancer mortality. The statistically significant excess of lung cancer mortality was limited to men employed for less than 1 year and became apparent only after a follow-up of 15 years or more. There was no increase in risk with increased duration of employment. None of the studies adequately consider the effects of smoking. The study that used data from the Beryllium Case Registry (2) shows that 6 of the 7 lung cancer deaths were in men whose exposure to beryllium was through refining and smelting; thus, none of the studies can rule out the effects of factors other than beryllium in the working environment.

1. IARC Monogr., *1*: 17–28, 1972.
2. Infante, P. F., Wagoner, J. K., and Sprince, N. L. Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the beryllium case registry. Environ. Res., in press, 1979.
3. Mancuso, T. F. Occupational lung cancer among beryllium workers. Environ. Res., in press, 1979.
4. Wagoner, J. K., Bayliss, D. L., and Infante, P. F. Beryllium: an etiologic agent in the induction of lung cancer, non-neoplastic respiratory disease and heart disease among industrially exposed workers. Environ. Res., in press, 1979.

12. *N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine) (Group 1)*

N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine) produces lung tumors in mice following i.p. injection and local sarcomas in rats after s.c. administration (1).

The administration of chlornaphazine together with radioactive phosphorus (sodium [^{32}P]phosphate) caused bladder cancer in 10 of 61 patients treated for *polycythemia vera*. In 46 patients treated with sodium [^{32}P]phosphate alone, no cases of bladder cancer were found (1).

1. IARC Mongr., *4*: 119–124, 1974.

13. *BCME and Technical Grade CMME (Group 1)*

BCME produces tumors at the site of application in mice after administration by inhalation, skin application, and s.c. injection and in rats after inhalation and s.c. administration.

Technical grade CMME (which is almost always contaminated with BCME) produces local sarcomas in mice after s.c. administration and is also an initiator of skin tumors (3).

Two studies of workers exposed to BCME and technical grade CMME showed an increased risk of lung cancer, mainly oat cell carcinoma (3). Two subsequent studies have shown a positive association between atypical cells in bronchial excretions (abnormal pulmonary cytology) and exposure to BCME (2, 4) which was not related to cigarette smoking. Several studies have demonstrated a significant excess of lung cancer among BCME- or CMME-exposed workers (1, 4–6) which was directly related to intensity and duration of exposure. Oat cell carcinoma was the predominant histological type of lung cancer. The excess respiratory cancer mortality was most marked in workers under 55 years of age. The evaluation of CMME alone is complicated by the presence of 1 to 8% BCME as a contaminant.

1. Albert, R. E., Pasternack, B. S., Shore, R. E., Lippmann, N. N., and Ferris, B. Mortality patterns among workers exposed to chloromethyl ethers—a preliminary report. Environ. Health Perspect., *11*: 209–214, 1975.
2. Frost, J. K., Gupta, P. K., Erozam, Y. F., Carter, D., Hollander, D. H., and Levin, M. L. Pulmonary cytology alterations in toxic environmental inhalation. Hum. Pathol., *4*: 521–536, 1973.
3. IARC Monogr., *4*: 231–245, 1974.
4. Lemen, R. A., Johnson, W. M., Wagoner, J. K., Archer, V. E., and Saccomanno, G. Cytologic observations and cancer incidence following exposure to BCME. Ann. N. Y. Acad. Sci., *271*: 71–80, 1976.
5. Pasternack, B. S., Shore, R. E., and Albert, R. E. Occupational exposure to chloromethyl ethers. J. Occup. Med., *19*: 741–746, 1977.
6. Sakabe, H. Lung cancer due to exposure to bis(chloromethyl) ether. Ind. Health, *11*: 145–148, 1973.

14. Cadmium and Certain Cadmium Compounds (Group 2A)

Cadmium chloride, oxide, sulfate, and sulfide are carcinogenic in rats, causing local sarcomas after s.c. injection. Cadmium powder and cadmium sulfide produce local sarcomas in rats following i.m. administration. Cadmium chloride and cadmium sulfate produce testicular tumors in mice and rats following s.c. administration (1).

Early studies suggested that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate cancer in humans. In addition, one of these studies suggested an increased risk of respiratory tract cancer (1). A later study (2) showed a slight but not statistically significant increase in prostate cancer in battery plant workers (2 observed *versus* 1.2 expected) and cadmium alloy workers (4 observed *versus* 2.69 expected). A case-control study (3) of renal cancer patients showed a 2.5-fold increased risk associated with occupational cadmium exposure. This relative risk doubled when cigarette smoking was included.

1. IARC Monogr., *11*: 39–74, 1976.
2. Kjellström, T., Friberg, L., and Rahnster, B. Mortality and cancer morbidity among cadmium-exposed workers: a preliminary report. Environ. Health Perspect., *28*: 199–204, 1979.
3. Kolonel, L. N. Association of cadmium with renal cancer. Cancer (Phila.), *37*: 1782–1789, 1976.

15. Carbon Tetrachloride (Group 2B)

Carbon tetrachloride is carcinogenic in mice and rats, producing liver tumors after administration by various routes. It also produced liver tumors in trout and hamsters following p.o. administration (1).

Three case reports describe liver tumors associated with cirrhosis following exposure to carbon tetrachloride (1).

1. IARC Monogr., *20*. In press, 1979.

16. Chlorambucil (Group 2A)

Chlorambucil is carcinogenic in rats and mice following i.p. injection, producing lymphomas in rats and lymphosarcomas, ovarian tumors, and lung tumors in mice (1).

Case reports have shown an association between chlorambucil treatment and development of leukemia (1). Women with ovarian cancer treated with a variety of alkylating agents, including chlorambucil, subsequently had an increased incidence of leukemia (3). Two cases of leukemia and one case of renal clear cell carcinoma have been reported in children treated for glomerulonephritis with chlorambucil (2).

1. IARC Monogr., *9*: 125–134, 1975.
2. Lenoir, G., Guesry, P., Kleinknecht, C., Gagnadoux, M. F., and Broyer, M. Complications extra-gonadiques du chlorambucil chez l'enfant (à propos de 300 observations de néphropathies glomérulaires traitées). Arch. Fr. Pediatr., *34*: 795–807, 1977.
3. Reimer, R. R., Hoover, R., Fraumeni, J. F., Jr., and Young, R. C. Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., *297*: 177–181, 1977.

17. Chloramphenicol (Group 3)

No data were available on the carcinogenicity of chloramphenicol in experimental animals.

Case reports have appeared describing patients with leukemia who had previously had chloramphenicol-induced aplastic anemia. A follow-up study described 3 cases of leukemia in 126 patients who had bone marrow depression following treatment with chloramphenicol (1).

1. IARC Monogr., *10*: 85–98, 1976.

18. Chlordane and Heptachlor (Group 3)

These compounds are considered together, because they are structurally similar and because they are often contaminated one with the other.

Chlordane and heptachlor (which contained about 20% chlordane) are carcinogenic in mice, producing liver tumors following p.o. administration. The data for rats are inconclusive (1).

In one report, 5 of 14 children with neuroblastoma had prenatal and/or postnatal exposure to chlordane. Possible exposure in the remaining 9 children was not ascertained. Three persons with acute leukemia were found to have been exposed to chlordane (which contained 3 to 7% heptachlor) (1).

1. IARC Monogr., *20*: In press, 1979.

19. Chloroprene (Group 3)

Tests for the carcinogenicity of chloroprene in animals were considered inadequate for evaluation (1).

Epidemiological reports regarding cytogenic effects and reproductive disturbances in workers exposed to chloroprene, and in their wives, are consistent with experimental evidence that chloroprene is mutagenic. Several epidemiological studies regarding the carcinogenicity of chloroprene are inconclusive. There is one case report of angiosarcoma of the liver in a worker exposed to chloroprene (1).

1. IARC Monogr., 19: 131–158, 1979.

20. Chromium and Certain Chromium Compounds[4] (Group 1)

Calcium chromate is carcinogenic in rats after administration by several routes, including intrabronchial implantation. Chromium chromate, strontium chromate, and zinc chromate produce local sarcomas in rats at the sites of application. The evidence for the carcinogenicity in mice and rats of barium chromate, lead chromate, chromic acetate, sodium dichromate, and chromium carbonyl is inadequate (2–4).

There is an increased incidence of lung cancer among workers in the chromate-producing industry (1, 2, 5, 6, 9) and possibly also among chromium platers (8, 10) and chromium alloy workers (7). There is also a suggestion of increased incidence of cancers at other sites (7, 8). The chromium compound(s) responsible is not known.

1. Davies, J. M. Lung-cancer mortality of workers making chrome pigments. Lancet, 1: 384, 1978.
2. IARC Monogr., 2: 100–125, 1973.
3. Ivankovic, S., and Preussmann, R. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in sub-acute and long-term feeding experiments in rats. Food Cosmet. Toxicol., 13: 347–351, 1975.
4. Lane, B. P., and Mass, M. J. Carcinogenicity and cocarcinogenicity of chromium carbonyl in heterotopic tracheal grafts. Cancer Res., 37: 1478–1479, 1977.
5. Langard, S., and Norseth, T. A cohort study of bronchial carcinomas in workers producing chromate pigments. Br. J. Ind. Med., 32: 62–65, 1975.
6. Ohsaki, Y., Abe, S., Kimura, K., Taunata, Y., Mikami, H., and Murao, M. Lung cancer in Japanese chromate workers. Thorax, 33: 372–374, 1978.
7. Pokrovskaya, L. V., and Shabynina, N. K. Carcinogenous hazards in the production of chromium ferroalloys. Gig. Tr. Prof. Zabol., 10: 23–26, 1973.
8. Royle, H. Toxicity of chromic acid in the chromium plating industry (1). Environ. Res., 10: 39–53, 1975.
9. Taylor, F. H. The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. Am. J. Public Health, 56: 218–229, 1966.
10. Waterhouse, J. A. H. Cancer among chromium platers. Br. J. Cancer, 32: 262, 1975.

21. Cyclophosphamide (Group 2A)

Cyclophosphamide is carcinogenic in mice and rats following i.p. injection, in rats following i.v. injection, and in mice following s.c. injection. Dosages used were comparable to those used in clinical practice. It produced mainly lung and lymphoreticular tumors, but also tumors of the liver and reproductive organs, sarcomas, squamous cell carcinomas of the skin (1), and bladder tumors (3).

There are a number of case reports of bladder cancer and acute myeloid leukemia in persons treated with cyclophosphamide for a variety of medical conditions (1). A prospective epidemiological study of women with ovarian cancer showed an increase of acute nonlymphocytic leukemia following treatment with alkylating agents, including cyclophosphamide (2).

1. IARC Monogr., 9: 135–158, 1975.
2. Reimer, R. R., Hoover, R., Fraumeni, J. F., Jr., and Young, R. C. Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., 297: 177–181, 1977.
3. Schmahl, D., and Habs, M. Carcinogenic action of low-dose cyclophosphamide given orally to Sprague-Dawley rats in a lifetime experiment. Int. J. Cancer, 23: 706–712, 1979.

22. DDT (Group 3)

DDT is carcinogenic in mice, causing liver tumors following p.o. administration (2). Nonmetastasizing liver tumors occur in rats fed DDT (1, 3).

The epidemiological studies available were considered to be inadequate to allow an evaluation of the carcinogenicity of DDT (2).

1. Cabral, J. R. P., Hall, R. K., and Shubik, P. Effects of long-term DDT intake in rats. Abstract presented at 20th Congress of the European Society of Toxicology, West Berlin, June 25 to 28, 1978.
2. IARC Monogr., 5: 83–124, 1974.
3. Rossi, L., Ravera, M., Repetti, G., and Santi, L. Long-term administration of DDT or phenobarbital-Na in Wistar rats. Int. J. Cancer, 19: 179–185, 1977.

23. Dieldrin (Group 3)

Dieldrin is carcinogenic in mice, causing a dose-related increase in liver tumors following p.o. administration. Feeding studies in rats have shown no carcinogenic effect (1, 2).

A study of workers exposed to dieldrin involved too few subjects and insufficient follow-up time to allow any conclusion (1).

1. IARC Monogr., 5: 125–156, 1974.
2. Stevenson, D. E., Thorpe, E., Hunt, P. F., and Walker, A. I. T. The toxic effects of dieldrin in rats: a reevaluation of data obtained in a two-year feeding study. Toxicol. Appl. Pharmacol., 38: 247–254, 1976.

24. Diethylstilbestrol (Group 1)

Diethylstilbestrol is carcinogenic in mice, rats, hamsters, frogs (6), and squirrel monkeys, producing tumors principally in estrogen-responsive tissues (4, 5).

Diethylstilbestrol causes clear cell carcinoma of the vagina in females exposed *in utero* (2, 4, 5). The evidence for an association with other human cancers is either limited [endometrium (1)] or inadequate [breast (1), ovary (3)].

1. Bibbo, M., Haenszel, W. M., Wied, G. L., Hubby, M., and Herbst, A. L. A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. N. Engl. J. Med., 298: 763–767, 1978.
2. Herbst, A. L., Cole, P., Colton, T., Robboy, S. J., and Scully, R. E. Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. Am. J. Obstet. Gynecol., 128: 43–50, 1977.
3. Hoover, R., Gray, L. A., and Fraumeni, J. F., Jr. Stilbestrol (diethylstilbestrol) and the risk of ovarian cancer. Lancet, 2: 533–534, 1977.
4. IARC Monogr., 6: 55–76, 1974.
5. IARC Monogr., 21: in press, 1979.
6. Khudoley, V. V. Carcinogenic action of diethylstilbestrol on frogs. Bull. Exp. Biol. Med., 81: 898–900, 1976.

25. Dimethylcarbamoyl Chloride (Group 2B)

Dimethylcarbamoyl chloride is carcinogenic in mice, producing local carcinomas after skin application and local sarcomas after s.c. or i.p. injection (1).

A study of humans exposed to dimethylcarbamoyl chloride was considered inadequate due to the small number of people observed (1).

1. IARC Monogr., 12: 77–84, 1976.

26. Dimethyl Sulfate (Group 2B)

Dimethyl sulfate is carcinogenic in rats after inhalation or s.c. injection, producing mainly local tumors, and after prenatal exposure, producing tumors of the nervous system (1).

Four bronchial carcinomas have been reported in men occupationally exposed to dimethyl sulfate (1). In an epidemiological study, 6 cancer deaths were found against 2.4 expected, 3 of which were cancers of the respiratory tract (1.02 expected) (2). Neither of these differences was statistically significant.

1. IARC Monogr., 4: 271–276, 1974.
2. Pell, S. Mortality of workers exposed to dimethyl sulfate, 1932–1974. Submitted to the American Conference of Governmental and Industrial Hygienists, 1976.

27. Epichlorohydrin (Group 3)

Epichlorohydrin produces local sarcomas in mice following s.c. injection and was active as an initiator in a 2-stage carcinogenesis study in mice (2).

Men exposed to epichlorohydrin for 15 years or more at 2 plants showed an increased number of deaths due to respiratory cancer (8 observed, 4.7 expected) and leukemia (2 observed, 0.4 expected) (1). This excess was not statistically significant and furthermore cannot be attributed confidently to epichlorohydrin exposure alone, since these men were exposed to other chemicals, and cigarette smoking was not considered in the analysis.

1. Enterline, P. E., and Henderson, V. L. Updated mortality in workers exposed to epichlorohydrin. J. Occup. Med., in press, 1979.
2. IARC Monogr., 11: 131–139, 1976.

28. Ethylene Oxide (Group 2B)

Solutions of ethylene oxide have been tested inadequately in mice by skin application and in rats by s.c. injection. No experiments involving inhalation were available (3).

Two studies of human populations exposed occupationally to ethylene oxide (1, 2) have shown increased rates of leukemia. One of these studies also showed increased rates of gastric cancer. This increase cannot be confidently attributed to ethylene oxide alone, however, since the workers were exposed to other chemicals as well.

1. Hogstedt, C., Malmqvist, N., and Wadman, B. Leukemia in workers exposed to ethylene oxide. J. Am. Med. Assoc., 241: 1132–1133, 1979.
2. Hogstedt, C., Rohlén, O., Berndtsson, B. S., Axelson, O., and Ehrenberg, L. Kohortstudie av dödsorsaker hos anställda i etylenoxidframställning. Läkartidningen, 75: 3285–3287, 1978.
3. IARC Monogr., 11: 157–167, 1976.

29. Hematite[4] (Group 3)
30. and Underground Hematite Mining (Group 1)

No carcinogenic effects were observed in mice, hamsters, or guinea pigs when ferric oxide was given intratracheally (2).

Underground hematite miners have a high incidence of lung cancer, whereas surface hematite miners do not. It is not known whether this excess risk may be due to hematite, to radon (a known lung carcinogen), to inhalation of ferric oxide or silica, or to a combination of these or other factors (1). Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer while others have not (1, 2). The influence of factors in the workplace other than ferric oxide cannot be eliminated.

1. Axelson, O., and Sjoberg, A. Cancer incidence and exposure to iron oxide dust. J. Occup. Med., 21: 419–422, 1979.
2. IARC Monogr., 9: 29–39, 1972.

31. HCH (Technical HCH and Lindane) (Group 3)

Technical HCH, α- and β-HCH, and lindane (γ-HCH) are carcinogenic in mice when administered p.o., producing liver tumors. Studies in rats were considered inadequate (1).

Approximately 30 cases of aplastic anemia and 3 cases of acute myeloid leukemia following exposure to HCH or lindane have been reported. A study of 285 workers exposed to many pesticides (including HCH and lindane) showed an apparent excess of lung tumors and one case of leukemia; however, this cannot be attributed to HCH or lindane exposure alone (1).

1. IARC Monogr., 20: in press, 1979.

32. Iron Dextran (Group 2B)

Iron dextran is carcinogenic in mice and rats after s.c. or i.m. injection, producing local tumors (2).

There have been case reports of sarcomas associated with injections of iron dextran (1, 2). These appeared in the area which was probably the site of the injections, and the similarity of the local effect in humans and animals was noted.

1. Greenberg, G. Sarcoma after intramuscular iron injection. Br. Med. J., 2: 1508–1509, 1976.
2. IARC Monogr., 2: 161–178, 1973.

33. Isoniazid (Group 3)

Isoniazid produces lung tumors in mice after p.o., i.p., and s.c. administration. Studies in rats and hamsters were considered inadequate (1).

Several early studies failed to show a significant excess of cancer among patients treated with isoniazid (1). A study of tuberculosis patients (3) followed for a mean of over 19 years showed a slight excess of respiratory cancers in patients treated with isoniazid (relative risk, 1.4; 95% confidence limits, 1.03 to 1.96 calculated by the Secretariat) and a deficit in patients not treated with isoniazid (relative risk, 0.3; 95% confidence interval, 0.06 to 0.91 calculated by the Secretariat). Although the numbers are small, the effect was similar in both groups examined and was not seen for cancers at sites other than respiratory. The excess is mainly for deaths within 4 years of the start of isoniazid therapy. No dose-response effect was seen either for total consumption or for maximum daily dose. The striking differences in mortality between patients treated earlier in the study and those treated later and the uncertain relationship of tuberculosis to lung cancer in the absence of isoniazid therapy make these data difficult to evaluate. A case-control study (2) of patients with bladder cancer reported that an excess of female cases but a deficit of male cases had previously taken isoniazid compared to controls without bladder cancer. However, the numbers were small, and the results were not statistically significant.

1. IARC Monogr., 4: 159–172, 1974.
2. Miller, C. T., Nautal, C. I., Nair, R., Merrett, L. D., Last, J. M., and Collins, W. E. Relative importance of risk factors in bladder carcinogenesis. J. Chronic Dis., 31: 51–56, 1978.
3. Stott, H., Peto, J., Stephens, R., and Fox, W. An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. Tubercle, 57: 1–15, 1976.

34. Isopropyl Oils (Group 3)
35. and The Manufacture of Isopropyl Alcohol (Strong-Acid Process) (Group 1)

Isopropyl oils, formed during the manufacture of isopropyl alcohol by both the strong-acid and the weak-acid processes, were tested inadequately in mice by inhalation, skin application, and s.c. administration. Isopropyl oils (strong-acid process) were also tested inadequately in dogs by inhalation and by instillation into the sinuses (1).

An increased incidence of cancer of the paranasal sinuses

has been found in workers in factories manufacturing isopropyl alcohol by the strong-acid process in which isopropyl oils were formed as by-products (1).

1. IARC Monogr., *15*: 223–243, 1977.

36. Lead and Certain Lead Compounds[4] (Group 3)

Basic lead acetate is carcinogenic in rats and mice after p.o. administration, producing renal tumors. Lead acetate, lead subacetate, and lead phosphate are carcinogenic in rats, producing renal tumors after p.o., i.p., or s.c. administration (3). Other lead salts have been inadequately tested (1, 4). No studies of organic lead compounds in animals were available.

An early epidemiological study provided no evidence that exposure to lead or lead compounds caused cancer in humans (3). One prospective study of mortality in workers in lead smelters and battery plants showed, respectively, 30 and 11% increased mortality from all malignant neoplasms (2). The findings were statistically significant only in the smelter workers. An excess of tumors was seen in the respiratory, urinary, and digestive systems, although none were significantly increased when considered alone. A study of tetraethyl lead workers is inadequate because only workers who remained employed during the study period were included (5).

(The Working Group noted that, while human exposure was mainly to metallic lead, the animal carcinogenicity data concerned soluble lead salts. Thus, even with sufficient evidence in animals, lead and lead compounds were classified in Group 3.)

1. Coogan, P., Stein, L., Hau, G., and Hasa, G. The tumorigenic action of lead in rats. Lab. Invest., *26*: 473, 1972.
2. Cooper, W. C., and Gaffy, W. R. Mortality of lead workers. J. Occup. Med., *17*: 100–107, 1975.
3. IARC Monogr., *1*: 40–50, 1972.
4. Ito, N. Experimental studies on tumors of the urinary system of rats induced by chemical carcinogens. Acta Pathol. Jpn., *23*: 87–109, 1973.
5. Robinson, T. R. The health of long service tetraethyl lead workers. J. Occup. Med., *18*: 31–40, 1976.

37. Melphalan (Group 1)

Melphalan is carcinogenic in mice and rats following i.p. injection, producing lymphosarcomas, a dose-related increase in lung tumors in mice, and peritoneal sarcomas in rats (1).

Case reports of second primary cancers (mainly acute leukemia) in patients treated with melphalan have been published (2–5, 7). Epidemiological studies showed substantially increased rates of leukemia in patients treated with melphalan for multiple myeloma (8) and ovarian cancer (6, 9). Some of these patients were also treated with other alkylating agents and ionizing radiation; however, sufficient numbers of patients were treated with melphalan alone to implicate it as the causal factor. Additionally, the incidence of acute leukemia in patients with multiple myeloma has increased since the introduction of melphalan therapy (1).

1. Adamson, R. H., and Sieber, S. M. Antineoplastic agents as potential carcinogens. *In*: H. Hiatt, J. Watson, and J. Winsten (eds.), Origins of Human Cancer, pp. 429–444. Cold Spring Harbor, N. Y.: Cold Spring Harbor Laboratory, 1977.
2. Bell, R., Sullivan, J. R., Fone, D. J., and Hurley, T. H. Carcinoma of the breast. Occurrence after treatment with melphalan for multiple myeloma. J. Assoc. Off. Anal. Chem., *235*: 1609–1610, 1976.
3. Berton, I. E., Abbot, C. R., Roberts, B. E., and Antonis, A. H. Acute leukemia after four years of melphalan treatment for melanoma. Br. Med. J., *1*: 20, 1976.
4. Buskard, N. A., Boyes, D. A., and Grossman, L. Plasma cell leukemia following treatment with radiotherapy and melphalan. Can. Med. Assoc. J., *117*: 788–789, 1977.
5. De Bock, R. F. K., and Peetermans, M. E. Leukemia after prolonged use of melphalan for non-malignant disease. Lancet, *1*: 1208–1209, 1977.
6. Einhorn, N. Acute leukemia after chemotherapy (melphalan). Cancer (Phila.), *41*: 444–447, 1978.
7. IARC Monogr., *9*: 167–180, 1975.
8. Law, I. P., and Blom, J. Second malignancies in patients with multiple myeloma. Oncology (Basel), *34*: 20–24, 1977.
9. Reimer, R. R., Hoover, R., Fraumeni, J. F., Jr., and Young, R. C. Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., *297*: 177–181, 1977.

38. Mustard Gas (Group 1)

Mustard gas is carcinogenic in mice, the only species tested, after inhalation or i.v. injection, producing lung tumors, and after s.c. injection, producing local sarcomas (1).

Several studies have shown an increased mortality from respiratory tract cancer among individuals exposed to mustard gas. This mortality was greater in those with chronic occupational exposure than in those with sporadic exposure (1).

1. IARC Monogr., *9*: 181–192, 1975.

39. 2-Naphthylamine (Group 1)

2-Naphthylamine is carcinogenic, producing urinary bladder carcinomas in hamsters, dogs, and nonhuman primates and hepatomas in mice after p.o. administration (1).

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or when present as an impurity in other compounds, is causally associated with bladder cancer (1).

1. IARC Monogr., *4*: 97–111, 1974.

40. Nickel, Certain Nickel Compounds[4] (Group 2A)
41. and Nickel Refining (Group 1)

Nickel subsulfide is carcinogenic in rats after inhalation, producing lung cancer. Nickel compounds (nickel powder, subsulfide, oxide, carbonate, and nickelocene) produced local sarcomas in mice, rats, and hamsters when given i.m. Nickel carbonyl produced a low incidence of lung tumors in rats following inhalation (1).

Epidemiological studies have demonstrated increased incidences of cancer of the nasal cavity, lung, and possibly larynx in workers in nickel refineries. It is not possible, however, to state with certainty which specific nickel compound(s) is carcinogenic for humans (1).

1. IARC Monogr., *11*: 75–112, 1976.

42. Oxymetholone (Group 2B)

No data from experimental animal studies were available to the Working Group (1).

Ten cases of liver cell tumors have been reported in patients with blood disorders treated for long periods with oxymetholone alone or in combination with other androgenic drugs; however, a causal relationship cannot be established. The increased risk of liver cell tumors could be related to hepatic damage known to be caused by oxymetholone. Alternatively, patients with congenital anemias may be at higher risk

of developing these tumors, and this risk may become manifest during the extended survival resulting from oxymetholone treatment (1).

1. IARC Monogr., 13: 131–139, 1977.

43. Phenacetin (Group 2B)

Rats fed a diet containing phenacetin developed nasal and urinary tract tumors (2). *N*-Hydroxyphenacetin (a possible metabolite of phenacetin) produced liver carcinomas in rats following p.o. administration (1).

Several studies indicate that the chronic abuse of analgesic mixtures is associated with papillary necrosis of the kidney and suggest a relationship between papillary necrosis and the subsequent development of transitional cell carcinoma of the renal pelvis (1). These compounds contain phenacetin with other antiinflammatory drugs (often salicylates or antipyrine) and caffeine.

1. IARC Monogr., 13: 141–155, 1977.
2. Isaka, H., Yoshii, H., Otsuji, A., Koike, M., Nagai, Y., Koura, M., Sugiyasu, K., and Kanabayashi, T. Tumors of Sprague-Dawley rats induced by long-term feeding of phenacetin. Gann, 70: 29–36, 1979.

44. Phenobarbitone (Group 3)

Phenobarbitone sodium is carcinogenic, producing benign and malignant liver cell tumors in mice and benign liver cell tumors in rats after p.o. administration (3).

A possible relationship between anticonvulsant therapy in which phenobarbitone was included and the occurrence of cancer in humans has been investigated in one epidemiological study and reported in several case studies. In most instances, phenobarbitone was given in conjunction with other drugs, in particular phenytoin (3). A further follow-up (1) of the patients from this study (who were hospitalized for long periods for the treatment of epilepsy) showed an excess of brain tumors, even more than 10 years after the diagnosis of epilepsy (12 observed *versus* 4.3 expected), and an increase in liver tumors (11 observed *versus* 2.8 expected). Eight of the 11 liver tumor patients received Thorotrast, a known liver carcinogen, however. Furthermore, the origin of the brain tumors in these patients is difficult to interpret, because the occurrence may be due to the underlying medical condition rather than the drugs *per se*. No excess of cancers of any other sites were seen. In another epidemiological study (2), significantly more mothers of children with brain tumors used "barbiturates" (unspecified) when compared with the mothers of children with other cancers, but not when compared with the mothers of normal children. The reason these drugs were given was not specifically stated (see also "Phenytoin").

1. Clemmesen, J., and Hjalgrim-Jensen, S. Is phenobarbital carcinogenic? A follow-up of 8078 epileptics. Ecotoxicol. Environ. Safety, 1: 457–470, 1978.
2. Gold, E., Gordis, L., Tonascia, J., and Szklo, M. Increased risk of brain tumors in children exposed to barbiturates. J. Natl. Cancer Inst., 61: 1031–1034, 1978.
3. IARC Monogr., 13: 157–181, 1977.

45. *N*-Phenyl-2-naphthylamine (Group 3)

N-Phenyl-2-naphthylamine was tested inadequately in mice by p.o. administration or by single s.c. injection. In a biotransformation study, 0.02% of a measured dose of *N*-phenyl-2-naphthylamine was converted metabolically to 2-naphthylamine in dogs (1).

No excess of bladder tumors was found in men in a rubber-processing factory with known exposure to *N*-phenyl-2-naphthylamine (which contained small amounts of 2-naphthylamine). However, a different study of rubber workers (who were not exposed to 2-naphthylamine) did show an increase of bladder tumors. In the latter study, the exposure was to several compounds, which probably included exposure to *N*-phenyl-2-naphthylamine. These findings do not permit an assessment of the carcinogenicity of *N*-phenyl-2-naphthylamine. There is limited evidence from one study of 19 human volunteers that 0.03% of a single 10-mg dose of *N*-phenyl-2-naphthylamine was converted to 2-naphthylamine, a known bladder carcinogen (1).

1. IARC Monogr., 16: 325–341, 1978.

46. Phenytoin (Group 3)

Phenytoin is carcinogenic in mice after p.o. administration or by i.p. injection, producing lymphomas and leukemias (3).

There are case reports and epidemiological studies of lymphomas occurring in patients that received phenytoin (3); however, no excess of lymphomas was reported in a follow-up study of epilepsy patients, many of whom received phenytoin along with other antiepileptic drugs (2). Three recent papers (1, 4, 6) report one case of malignant mesenchymoma and 2 cases of neuroblastoma in children with phenytoin-induced malformations. An epidemiological study (5) looked at the frequency of use of phenytoin and of phenobarbitone in mothers of children with childhood cancers compared with mothers of normal children. While more mothers of cancer patients reported a history of epilepsy, no differences were seen in the proportion of epileptic mothers taking either phenytoin or phenobarbitone. An excess of lymphomas (6 observed with 4 expected) was seen in children of epileptic mothers, but the occurrence of brain tumors was not reported (see also "Phenobarbitone").

1. Blattner, W. A., Henson, D. E., Young, R. C., and Fraument, J. F., Jr. Malignant mesenchymoma and birth defects. Prenatal exposure to phenytoin. J. Am. Med. Assoc., 238: 334–335, 1977.
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3. IARC Monogr., 13: 201–225, 1977.
4. Pendergrass, T. W., and Henson, J. W. Fetal hydantoin syndrome and neuroblastoma. Lancet 2: 150, 1976.
5. Sanders, B. M., and Draper, G. J. Childhood cancer and drugs in pregnancy. Br. Med. J., 1: 717–718, 1979.
6. Sherman, S., and Rotzen, N. Fetal hydantoin syndrome and neuroblastoma. Lancet, 2: 517, 1976.

47. Polychlorinated Biphenyls (Group 2B)

Certain polychlorinated biphenyls are carcinogenic in mice and rats after p.o. administration, producing liver tumors (1).

A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Arochlor 1254, a mixture of polychlorinated biphenyls (1).

1. IARC Monogr., 18: 43–103, 1978.

48. Reserpine (Group 3)

Reserpine has been tested inadequately in mice and rats by p.o. administration (4).

Thirteen case-control studies were available to the Working Group (1–8). Most report a relative risk of between 1 and 2 for breast cancer associated with the use of reserpine. Patients taking reserpine for more than 5 years had slightly higher relative risks. In 11 of the 13 studies, the relative risks were not statistically significant, although pooling of the studies gave a summary relative risk of 1.2 with 95% confidence intervals of 1.1 to 1.4. The possibility of confounding due to several medical care variables could not be excluded; hence, none of the studies, either singly or pooled, provide conclusive evidence of a causal association.

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2. Aromaa, A., Hakama, M., Hakulinen, T., Saxen, E., Teppo, L., and Idänpään-Heikkila, J. Breast cancer and use of rauwolfia and other antihypertensive agents in hypertensive patients: a nationwide case-control study in Finland. Int. J. Cancer, *18*: 727–738, 1976.
3. Christopher, L. J., Crooks, J., Davidson, J. F., Erskine, Z. G., Gallon, S. C., Moir, D. C., and Weir, R. D. A multi-centre study of rauwolfia derivatives and breast cancer. Eur. J. Clin. Pharmacol., *11*: 409–417, 1977.
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8. Williams, R., Feinleib, M., Connor, R., and Stegens, N. Case-control study of antihypertensive and diuretic use by women with malignant and benign breast lesions detected in a mammography screening program. J. Natl. Cancer Inst., *61*: 327–335, 1978.

49. Soots, Tars, and Mineral Oils[4] (Group 1)

Soots, coal tars, creosote oils, shale oils, and cutting oils are carcinogenic in experimental animals after skin painting or s.c. injection (4).

Occupational exposure to coal soot, coal tar, and pitch, coal tar fumes, and some impure mineral oils causes cancer of several sites, including skin, lung, bladder, and gastrointestinal tract (4). Recent epidemiological data have supported these conclusions (1–3, 5–7). This effect may be due to the presence of polycyclic aromatic hydrocarbons in these materials.

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2. Decoufle, P. Further analysis of cancer mortality among workers exposed to cutting oil mist. J. Natl. Cancer Inst., *61*: 1025–1030, 1978.
3. Hammond, E. C., Selikoff, I. J., Lawther, P. L., and Seidman, H. Inhalation of benzpyrene and cancer in man. Ann. N. Y. Acad. Sci., *271*: 116–124, 1976.
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50. Styrene (Group 3)

Styrene produces lung tumors in mice following p.o. administration, (1, 2).

Three deaths from leukemia and 2 deaths from lymphoma have been reported in workers exposed to styrene, benzene, and butadiene; however, these deaths cannot be attributed to styrene exposure alone (1).

1. IARC Monogr., *19*: 231–274, 1979.
2. National Cancer Institute. Bioassay of styrene for possible carcinogenicity. Tech. Rep. Ser. No. 185, DHEW Publication No. (NIH) 79-1741. Washington, D. C.: United States Government Printing Office, 1979.

51. Trichloroethylene (Group 3)

Trichloroethylene is carcinogenic in mice after p.o. administration, producing hepatocellular carcinomas and lung tumors (1).

An epidemiological study of mortality in men occupationally exposed to trichloroethylene showed no excess of cancer deaths (1).

1. IARC Monogr., *20*: in press, 1979.

52. Tris(aziridinyl)-p-benzoquinone (Triaziquone) (Group 3)

Tris(aziridinyl-*p*-benzoquinone (triaziquone) is carcinogenic in rats after i.v. or combined i.v. and i.p. injection, producing a variety of malignant tumors (1).

The 4 available case reports were inadequate to evaluate the carcinogenicity of triaziquone (1).

1. IARC Monogr., *9*: 67–73, 1975.

53. Tris(1-aziridinyl)phosphine sulfide (Thiotepa) (Group 2A)

Tris(1-aziridinyl)phosphine sulfide (thiotepa) is carcinogenic in mice and rats after administration by various routes, producing a variety of malignant tumors (1, 2).

There are several reports and epidemiological studies suggesting the development of acute nonlymphocytic leukemia in patients after thiotepa therapy for ovarian and other malignant tumors (1, 3).

1. IARC Monogr., *9*: 85–94, 1975.
2. National Cancer Institute. Bioassay of thiotepa for possible carcinogenicity. Tech. Rep. Ser. No. 68, DHEW Publication No. (NIH) 78-1308, 186 pp. Washington, D.C.: United States Government Printing Office, 1978.
3. Reimer, R. R., Hoover, R., Fraumeni, J. F., Jr., and Young, R. C. Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., *297*: 177–181, 1977.

54. Vinyl Chloride (Group 1)

Vinyl chloride is carcinogenic in mice, rats, and hamsters after administration p.o. and by inhalation, producing tumors at several sites including angiosarcomas of the liver (1).

Vinyl chloride causes angiosarcomas of the liver and tumors of the brain, lung, and hemolymphopoietic system in humans (1).

1. IARC Monogr., *19*: 377–437, 1979.

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