WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISKS TO HUMANS

Chemicals and Industrial Processes
Associated with Cancer in Humans

IARC Monographs, Volumes 1 to 20

IARC MONOGRAPHS SUPPLEMENT 1

IARC, LYON

SEPTEMBER 1979

WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

CHEMICALS AND INDUSTRIAL PROCESSES ASSOCIATED WITH CANCER IN HUMANS

IARC MONOGRAPHS, Volumes 1 to 20

Report of an IARC ad hoc Working Group which
met in Lyon, 15-17 January 1979 to advise the
Director, IARC, on chemicals carcinogenic for humans

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September 1979

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
LYON

IARC MONOGRAPHS

In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for groups of chemicals to which humans are known to be exposed, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

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IARC MONOGRAPHS Volumes 1-20

Supplement 1

CHEMICALS AND INDUSTRIAL PROCESSES ASSOCIATED WITH CANCER IN HUMANS

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Delete : Foot note 3

Insert [3] Pell, S. Mortality of workers exposed to dimethyl sulphate 1932-1974, submitted to the American Conference of Governmental and Industrial Hygienists, 1976.

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ASSOCIATED WITH CANCER IN HUMANS
Lyon, 15-17 January 1979

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NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monograph* series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical for humans is encouraged to make this information available to the Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, Lyon, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Chemical Carcinogenesis, so that corrections can be reported in future volumes.

CHEMICALS AND INDUSTRIAL PROCESSES ASSOCIATED WITH CANCER IN HUMANS IARC MONOGRAPHS VOLUMES 1-20

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 Volumes 1-20 of the *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. On the basis of evidence from human studies, 18 of the 54 chemicals and 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, it was further subdivided; for six chemicals there was a high degree of evidence, and for 12 there was 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.

This volume includes a cumulative index of chemicals for Volumes 1-20 of the IARC Monographs, as well as an index by possible target organ in humans. A condensed version of this report will appear in the December 1979 issue of Cancer Research.

INTRODUCTION

In 1971 the International Agency for Research on Cancer (IARC) began a programme to prepare monographs on the evaluation of the carcinogenic risk of chemicals to humans (1). The objectives of the Monographs Programme 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 two critera: firstly, there are data related to carcinogenicity in humans or experimental animals; and secondly, there is evidence of human exposure (2).

In the first sixteen 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, more than 350 chemicals were evaluated in Volumes 1-16, while human data were available for only 48 (14%) of them. 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 importanly, they recommend 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 *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 Volume 17 of the Monographs. However, since these criteria were not used for Volumes 1-16, a further *ad hoc* Working Group was convened to re-evaluate the data from animal studies for substances evaluated in those volumes, and to identify those for which there is *sufficient evidence* of carcinogenicity (4).

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 (5).

By the end of 1978, twenty volumes of Monographs had been prepared. Of the 442 chemicals and industrial processes evaluated therein, there is *sufficient evidence* of carcinogenicity in experimental animals for 142 (32%) of them. These chemicals are listed in Table 1. Case reports or epidemiological studies have been published for only 60 of the 442 (14%). Because of time limitations, six compounds with limited data on human carcinogenicity were not considered by the Working Group. These compounds are listed in Table 2, and summaries of the animal and human evidence (without evaluations) are given at the end of the appendix. The Group also did not consider sex hormone preparations (with the exception of diethylstilboestrol), since they had recently been re-evaluated for volume 21. There were thus 54 chemicals and industrial processes with data on carcinogenicity from human and animal studies reviewed by the Working Group.

Table 1. Chemicals evaluated in *IARC Monographs*, Volumes 1-20 for which there is *sufficient evidence* of carcinogenicity in experimental animals[1]

Compound	IARC Monograph volume and page number
A	
Acrylonitrile[1]	*19*, 73
Actinomycins	*10*, 29
Aflatoxins	*10*, 51
ortho-Aminozotoluene	*8*, 61
4-Aminobiphenyl	*1*, 74
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	*7*,143
Amitrole	*7*, 31
Aramite	*5*, 39
Asbestos	*14*
Azaserine	*10*, 73
B	
Benz[*a*]anthracene	*3*, 45
Benzidine	*1*, 80
Benzo[*b*]fluoranthene	*3*, 69
Benzo[*a*]pyrene	*3*, 91
Benzyl violet 4B	*16*,153
Beryllium	*1*, 17
Beryllium oxide	*1*, 17
Beryllium phosphate	*1*, 17
Beryllium sulphate	*1*, 17
Bis(chloromethyl)ether	*4*,231
β-Butyrolactone	*11*,225

[1] Chemicals with data on cancer in humans appear in italics.

Compound	IARC Monograph volume and page number
C	
Cadmium	*2*, 74; *11*, 39
Cadmium chloride	*2*, 74; *11*, 39
Cadmium oxide	*2*, 74; *11*, 39
Cadmium sulphate	*2*, 74; *11*, 39
Cadmium sulphide	*2*, 74; *11*, 39
Calcium chromate	*2*,100
Carbon tetrachloride	*1*, 53; *20*
Chlorambucil	*9*,125
Chlordecone (Kepone)	*20*
Chloroform	*20*
Chromium	*2*,100
Citrus red no. 2	*8*,101
Cycasin	*1*,157; *10*,121
Cyclophosphamide	*9*,135
D	
Daunomycin	*10*,145
N,N'-Diacetylbenzidine	*16*,293
4,4'-Diaminodiphenyl ether	*16*,301
2,4-Diaminotoluene	*16*, 83
Dibenz[*a*,*h*]acridine	*3*,247
Dibenz[*a*,*j*]acridine	*3*,254
Dibenz[*a*,*h*]anthracene	*3*,178
7H-Dibenzo[*c*,*g*]carbazole	*3*,260
Dibenzo[*a*,*e*]pyrene	*3*,201
Dibenzo[*a*,*h*]pyrene	*3*,207
Dibenzo[*a*,*i*]pyrene	*3*,215
1,2-Dibromo-3-chloropropane	*15*,139; *20*
3,3'-Dichlorobenzidine	*4*, 49
3,3'-Dichloro-4,4'-diaminodiphenyl ether	*16*,309
1,2-Dichloroethane	*20*
Diepoxybutane	*11*,115
1,2-Diethylhydrazine	*4*,153
Diethylstilboestrol	*6*, 55; *20*
Diethyl sulphate	*4*,277
Dihydrosafrole	*1*,170; *10*,233
3,3'-Dimethoxybenzidine (*ortho*-Dianisidine)	*4*, 41
para-Dimethylaminoazobenzene	*8*,125
trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	*7*,147
3,3'-Dimethylbenzidine (*ortho*-Tolidine)	*1*, 87
Dimethylcarbamoyl chloride	*12*, 77
1,1-Dimethylhydrazine	*4*,137
1,2-Dimethylhydrazine	*4*,145
Dimethyl sulphate	*4*,271
1,4-Dioxane	*11*,247

Compound	IARC Monograph volume and page number
E	
Ethinyloestradiol	*6*, 77
Ethylene dibromide	*15*,195
Ethylenethiourea	*7*, 45
Ethyl methanesulphonate	*7*,245
F	
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl) thiazole	*7*,151
G	
Glycidaldehyde	*11*,175
H	
Hexachlorobenzene	*20*
Hexamethylphosphoramide	*15*,211
Hydrazine	*4*,127
I	
Indeno[1,2,3-*cd*]pyrene	*3*,229
Iron dextran	*2*,161
Isosafrole	*1*,169; *10*,232
L	
Lasiocarpine	*10*,281
Lead acetate	*1*, 40
Lead phosphate	*1*, 40
Lead subacetate	*1*, 40
M	
Melphalan	*9*,167
Merphalan	*9*,167
Mestranol	*6*, 87
2-Methylaziridine	*9*, 61
Methylazoxymethanol acetate	*1*,164; *10*,131
4,4'-Methylene bis(2-chloroaniline)	*4*, 65
4,4'-Methylene bis(2-methylaniline)	*4*, 73
Methyl iodide	*15*,245
Methyl methanesulphonate	*7*,253
N-Methyl-N'-nitro-N-nitrosoguanidine	*4*,183
Methylthiouracil	*7*, 53
Mirex	*5*,203; *20*

Compound	IARC Monograph volume and page number
Mitomycin C	*10*,171
Monocrotaline	*10*,291
5-(Morpholinomethyl)-3-[(5-nitro-furfurylidene)-amino]-2-oxazolidinone	*7*,161
N	
2-Naphthylamine	*4*, 97
Nickel	*2*,126; *11*, 75
Nickel subsulphide	*2*,126; *11*, 75
Niridazole	*13*,123
5-Nitroacenaphthene	*16*,319
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone	*7*,181
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	*1*,181; *7*,185
Nitrogen mustard and its hydrochloride	*9*,193
Nitrogen mustard N-oxide and its hydrochloride	*9*,209
N-Nitrosodi-*n*-butylamine	*4*,197; *17*, 51
N-Nitrosodiethanolamine	*17*, 77
N-Nitrosodiethylamine	*1*,107; *17*, 83
N-Nitrosodimethylamine	*1*, 95; *17*,125
N-Nitrosodi-*n*-propylamine	*17*,177
N-Nitroso-N-ethylurea	*1*,135; *17*,191
N-Nitrosomethylethylamine	*17*,221
N-Nitroso-N-methylurea	*1*,125; *17*,227
N-Nitroso-N-methylurethane	*4*,211
N-Nitrosomethylvinylamine	*17*,257
N-Nitrosomorpholine	*17*,263
N-Nitrosonornicotine	*17*,281
N-Nitrosopiperidine	*17*,287
N-Nitrosopyrrolidine	*17*,313
N-Nitrososarcosine	*17*,327
O	
Oestradiol-17β	*6*, 99
Oestrone	*6*,123
Oil orange SS	*8*,165
P	
Polychlorinated biphenyls	*18*, 43
Ponceau MX	*8*,189
Ponceau 3R	*8*,199
1,3-Propane sultone	*4*,253
β-Propiolactone	*4*,259
Propylthiouracil	*7*, 67

Compound	IARC Monograph volume and page number
S	
Safrole	*1*,169; *10*,231
Soots, tars and oils	*3*, 22
Sterigmatocystin	*1*,175; *10*,245
Streptozotocin	*4*,221; *17*,337
T	
Testosterone	*6*,209
Thioacetamide	*7*, 77
Thiourea	*7*, 95
Toxaphene	*20*
Tris(aziridinyl)phosphine sulphide (thiotepa)	*9*, 85
Tris(2,3-dibromopropyl)phosphate	*20*
Trypan blue (commercial grade)	*8*,267
U	
Uracil mustard	*9*,235
Urethane	*7*,111
V	
Vinyl chloride	*7*,291; *19*,377

Table 2. Chemicals from IARC Monographs Volumes 1-20 with evidence from human studies which were not considered by the Working Group.

ortho- and *para*-Dichlorobenzene
Dichlorobenzidine
Phenylbutazone
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)
ortho- and *para*-Toluidine
Vinylidene chloride

METHODS

The data on each chemical were reviewed in detail before the meeting by two 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. The reader is encouraged to consult these notes together with the summary Table 3. For each chemical the appropriate volume in the *Monographs* series is given and also, where applicable, papers that have been published subsequently.

Assessment of evidence for carcinogenicity from experimental animal studies

These assessments were classified in five groups:

i. *Sufficient evidence* of carcinogenicity indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains, or (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 tumour, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.

ii. *Limited evidence* of carcinogenicity means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment; or (b) the experiments are restricted by 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 tumours in mice).

iii. *Inadequate evidence* indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect

iv. *Negative evidence* means that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.

v. *No data* indicates that 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 from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the chemical or process.
2. Descriptive epidemiological studies in which the incidence of cancer in human populations was found to vary spatially or temporally with exposure to the agents.
3. Analytical epidemiological (case-control and cohort) studies in which individual exposure to the chemical or group of chemicals was found to be associated with an increased risk of cancer.

Three criteria must be met for a causal association to be inferred between exposure and human cancer (3):

1. There is no identified bias which could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing 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 :

i. *Sufficient evidence* of carcinogenicity indicates a causal association between exposure and human cancer.

ii. *Limited evidence* of carcinogenicity indicates a possible carcinogenic effect in humans, although the data are not sufficient to demonstrate a causal association.

iii. *Inadequate evidence* of carcinogenicity indicates that the data are 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* from animal studies and between *inadequate evidence* and *limited evidence* from 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 both the epidemiological and experimental evidence. Furthermore, the breadth of the categories for human and animal evidence defined above allows substantial variation within each, and the decisions reached by the group regarding overall risk incorporated these differences, even though they could not always be adequately reflected in the placement of a chemical into a particular category in the Table3. The evidence in support of these decisions is summarized in the notes for each chemical in the Appendix.

The chemicals, groups of chemicals, or industrial processes were placed into one of three 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 (group A) or lower (group B) degrees of evidence. The data from experimental animal studies played an important role in assigning chemicals to category 2, and particularly to those in group 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 3.

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[1]

Benzene

Benzidine

N,N-bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)

Bis(chloromethyl)ether and technical grade chloromethyl methyl ether

Chromium and certain chromium compounds[1]

Diethylstilboestrol

Underground haematite mining[1]

Manufacture of isopropyl alcohol by the strong acid process[1]

Melphalan

Mustard gas

2-Naphthylamine

Nickel refining[1]

Soots, tars and mineral oils[1]

Vinyl chloride

The following 18 chemicals and groups of chemicals are *probably carcinogenic for humans* (Group 2)

Group A (six chemicals)

Aflatoxins

Cadmium and certain cadmium compounds[1]

Chlorambucil

Cyclophosphamide

Nickel and certain nickel compounds[1]

Tris(1-aziridinyl)phosphine sulphide (thiotepa)

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[1] The specific compound(s) which may be responsible for a carcinogenic effect in humans cannot be specified precisely.

Group B (12 chemicals)

Acrylonitrile	Dimethylsulphate
Amitrole (aminotriazole)	Ethylene oxide
Auramine	Iron dextran
Beryllium and certain beryllium compounds[1]	Oxymetholone
Carbon tetrachloride	Phenacetin
Dimethylcarbamoyl chloride	Polychlorinated biphenyls

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

Chloramphenicol	Isopropyl oils
Chlordane/heptachlor	Lead and certain lead compounds[1]
Chloroprene	Phenobarbitone
Dichlorodiphenyltrichloroethane (DDT)	N-Phenyl-2-naphthylamine
Dieldrin	Phenytoin
Epichlorohydrin	Reserpine
Haematite	Styrene
Hexachlorocyclohexane (technical grade HCH/lindane)	Trichloroethylene
Isoniazid	Tris(aziridinyl)-*para*-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 haematite, 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 chemical under consideration, the responsible

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[1] The specific compound(s) which may be responsible for a carcinogenic effect in humans cannot be specified precisely.

carcinogen(s) cannot be specified precisely; 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.

Table 3. Classification of the degree of evidence of carcinogenicity for humans of chemicals or industrial processes from *IARC Monographs Volumes 1-20*

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[d]	limited	limited	2B
8. Manufacture of auramine	sufficient	not applicable[e]	1
9. Benzene	sufficient	inadequate	1
10. Benzidine	sufficient	sufficient	1
11. Beryllium and certain beryllium compounds[c]	limited	sufficient	2B
12. *N,N*-Bis (2-chloroethyl)-2-naphthylamine (chlornaphazine)	sufficient	limited	1
13. Bis(chloromethyl)ether and technical grade chloromethyl methyl ether	sufficient	sufficient	1
14. Cadmium and certain cadmium compounds[c]	limited	sufficient	2A
15. Carbon tetrachloride	inadequate	sufficient	2B
16. Chlorambucil	limited	sufficient	2A
17. Chloramphenicol	inadequate	no data	3

Table 3 - continued

Chemical or process	Degree of evidence[a]		Evaluation[b] of carcinogenic risk to humans
	In humans	In experimental animals	
18. Chlordane and heptachlor	inadequate	limited	3
19. Chloroprene	inadequate	inadequate	3
20. Chromium and certain chromium compounds[c]	sufficient	sufficient	1
21. Cyclophosphamide	limited	sufficient	2A
22. Dichlorodiphenyltrichloroethane (DDT)	inadequate	limited	3
23. Dieldrin	inadequate	limited	3
24. Diethylstilboestrol	sufficient	sufficient	1
25. Dimethylcarbamoyl chloride	inadequate	sufficient	2B
26. Dimethyl sulphate	inadequate	sufficient	2B
27. Epichlorohydrin	inadequate	limited	3
28. Ethylene oxide	limited	inadequate	2B
29. Haematite[d]	inadequate	negative	3
30. Underground haematite mining	sufficient	not applicable[e]	1
31. Hexachlorocyclohexane (technical HCH & lindane)	inadequate	limited	3
32. Iron dextran	inadequate	sufficient	2B
33. Isoniazid	inadequate	limited	3
34. Isopropyl oils[c,d]	inadequate	inadequate	3

Table 3 - continued

Chemical or process	Degree of evidence[a]		Evaluation[b] of carcinogenic risk to humans
	In humans	In experimental animals	
35. Manufacture of isopropyl alcohol (strong acid process)	sufficient	not applicable[e]	1
36. Lead and certain lead compounds[c]	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,d]	limited	sufficient	2A
41. Nickel refining	sufficient	not applicable[e]	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[c]	sufficient	sufficient	1
50. Styrene	inadequate	limited	3
51. Trichloroethylene	inadequate	limited	3
52. Tris(aziridinyl)*para*-benzoquinone (triaziquone)	inadequate	limited	3

Table 3 - continued

Chemical or process	Degree of evidence[a]		Evaluation[b] of carcinogenic risk to humans
	In humans	In experimental animals	
53. Tris(1-aziridinyl)phosphine sulphide (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] The specific compounds which may be responsible for a carcinogenic effect cannot be specified precisely.

[d] Please refer to section on industrial processes, and to the evaluations in the appendix.

[e] It is difficult to expose experimental animals to the same conditions to which workers are exposed, therefore no animal data are available.

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Volume 4 (1974)	Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents (28 monographs), 286 pages
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APPENDIX

DESCRIPTIVE EVALUATIONS OF THE ANIMAL AND HUMAN EVIDENCE FOR CARCINOGENICITY OF THE CHEMICALS CONSIDERED

1. ACRYLONITRILE (Group 2B)

Acrylonitrile is carcinogenic in rats after oral administration and inhalation, producing cancers of the brain, forestomach, and Zymbal 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].

2. AFLATOXINS (Group 2A)

Aflatoxins are carcinogenic in mice, rats, fish, ducks, marmosets, tree shrews and monkeys by several routes of administration (including) oral), producing mainly cancers of the liver, colon and kidney[2].

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[2].

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[1] IARC Monographs, 19: 73-133, 1979.

[2] IARC Monographs, 10: 51-72, 1976.

3. 4-AMINOBIPHENYL (Group 1)

4-Aminobiphenyl is carcinogenic in mice, rats, rabbits and dogs after oral 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].

4. AMITROLE (AMINOTRIAZOLE) (Group 2B)

Amitrole is carcinogenic in mice and rats, producing thyroid and liver tumours following oral or subcutaneous administration[3,4].

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 the workers were exposed to several different herbicides however, no conclusions could be made regarding the carcinogenicity of amitrole alone[3].

5. ARSENIC AND CERTAIN ARSENIC COMPOUNDS (Group 1)

Information on the carcinogenicity of arsenic compounds in experimental animals was considered inadequate for evaluation[5].

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[5-7].

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[1] IARC Monographs, 1: 74-79, 1972.

[2] Melamed, M.R. (1972) Diagnostic cytology of urinary tract carcinoma. Eur. J. Cancer, 8: 287-292.

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However, the influence of other constituents of the working environment cannot be excluded in these studies. Case reports have suggested an association between exposure to arsenic compounds and blood dyscrasias and liver tumours[1-4].

6. ASBESTOS (Group 1)

All types of commercial asbestos fibres that have been tested are carcinogenic in mice, rats, hamsters and rabbits, producing mesotheliomas and lung carcinomas after inhalation, and after intrapleural, intratracheal and intraperitoneal administration[5].

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 fibres containing crocidolite. An excess of cancer of the larynx was also observed in exposed workers. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and crocidolite mines, and in persons living with asbestos workers. Both cigarette smoking and occupational exposure to asbestos fibres increase lung cancer incidence independently. When present together, they act multiplicatively[5].

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7. AURAMINE (Group 2B) and

8. THE MANUFACTURE OF AURAMINE (Group 1)

Commercial auramine is carcinogenic in mice and rats after oral administration, producing liver tumours, and after subcutaneous injection in rats, producing local sarcomas[1].

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

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[2,3,4].

Several case reports as well as an epidemiological case control study suggest a relationship between benzene exposure and leukaemia[2]. Two cohort studies[5,6] showed an increased incidence of acute non-lymphocytic leukaemia in workers exposed to benzene. There has been an additional report of a large number of leukaemia cases (most of which were acute non-lymphocytic) among a group of workers exposed to benzene[7,8].

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[1] IARC Monographs, 1: 69-73, 1972.

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10. BENZIDINE (Group 1)

Benzidine is carcinogenic in experimental animals after oral and subcutaneous administration, producing liver tumours in rats and hamsters, and bladder cancers in dogs[1].

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[1]. The causal association is strengthened by data which suggest that the incidence of this cancer in workers decreased after a reduction in industrial exposure[2].

11. BERYLLIUM AND CERTAIN BERYLLIUM COMPOUNDS (Group 2B)

Inhalation of beryllium sulphate, beryl ore, and bertrandite produce lung tumours in rats. Beryllium oxide and beryllium sulphate produce lung tumours in monkeys after intrabronchial implantation or inhalation. Zinc beryllium silicate, beryllium metal, and beryllium phosphate all produce bone tumours in rabbits following intravenous injection[3].

Five early epidemiological studies were considered inadequate to evaluate the carcinogenic effects of beryllium. Three recent epidemiological studies[4-6] concerned men occupationally exposed to beryllium, some of whom developed acute beryllium disease. The populations for these studies come from two 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 only became apparent 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

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[1] IARC Monographs, 1: 80-86, 1972.

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the effects of smoking. The study that uses data from the Beryllium Case Registry[1] shows that six of the seven 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.

12. *N,N*-BIS(2-CHLOROETHYL)-2-NAPHTHYLAMINE (CHLORNAPHAZINE) (Group 1)

N,N-Bis(2-Chloroethyl)-2-naphthylamine (chlornaphazine) produces lung tumours in mice following intraperitoneal injection, and local sarcomas in rats after subcutaneous administration[2].

The administration of chlornaphazine together with radioactive phosphorus (^{32}P-sodium phosphate) caused bladder cancer in 10 of 61 patients treated for polycythemia vera. In 46 patients treated with ^{32}P-sodium phosphate alone, no cases of bladder cancer were found[2].

13. BIS(CHROMETHYL)ETHER AND TECHNICAL GRADE CHLOROMETHYL METHYL ETHER (Group 1)

Bis(chloromethyl)ether (BCME) produces tumours at the site of application in mice after administration by inhalation, skin application or subcutaneous injection, and in rats after inhalation and subcutaneous administration. Technical grade chloromethyl methyl ether (CMME) (which is almost always contaminated with BCME) produces local sarcomas in mice after subcutaneous administration, and is also an initiator of skin tumours[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

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[1] Infante, P.F., Wagoner, J.K. & Sprince, N.L. (1979) Mortality patterns from lung cancer and non-neoplastic respiratory disease among white males in the Beryllium Case Registry. Environ. Res. (in press).

[2] IARC Monographs, 4: 119-124, 1974.

[3] IARC Monographs, 4: 231-245, 1974.

to BCME[1,2] which was not related to cigarette smoking. Several studies have demonstrated a significant excess of lung cancer among BCME- or CMME-exposed workers[2-5] 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% of BCME as a contaminant.

14. CADMIUM AND CERTAIN CADMIUM COMPOUNDS (Group 2A)

Cadmium chloride, oxide, sulphate, and sulphide are carcinogenic in rats causing local sarcomas after subcutaneous injection. Cadmium powder and cadmium sulphide produce local sarcomas in rats following intramuscular administration. Cadmium chloride and cadmium sulphate produces testicular tumours in mice and rats following subcutaneous administration[6].

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[6]. A later study[7] showed a slight but not statistically significant increase in prostate cancer in battery plant workers (2 observed vs. 1.2 expected) and cadmium alloy workers (4 observed, vs. 2.69 expected).

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[1] Frost, J.K., Gupta, P.K., Erozam, Y.F., Carter, D., Hollander, D.H. & Levin, M.L. (1973) Pulmonary cytology alterations in toxic environmental inhalation. Hum. Pathol., 4: 521-536.

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[3] Sakabe, H. (1973) Lung cancer due to exposure to bis(chloromethyl) ether. Ind. Health, 11: 145-148.

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[7] Kjellström, T., Friberg, L. & Rahnster, B. (1979) Mortality and cancer morbidity among cadmium-exposed workers: a preliminary report. Environ. Health Perspect., 28: 199-204.

A case-control study[1] 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.

15. CARBON TETRACHLORIDE (Group 2B)

Carbon tetrachloride is carcinogenic in mice and rats, producing liver tumours after administration by various routes. It also produced liver tumours in trout and hamsters following oral administration[2].

Three case reports describe liver tumours associated with cirrhosis in humans exposed to carbon tetrachloride[2].

16. CHLORAMBUCIL (Group 2A)

Chlorambucil is carcinogenic in rats and mice following intraperitoneal injection, producing lymphomas in rats, and lymphosarcomas, ovarian tumours, and lung tumours in mice[3].

Case reports have shown an association between chlorambucil treatment and development of leukaemia[3]. Women with ovarian cancer treated with a variety of alkylating agents, including chlorambucil, subsequently had an increased incidence of leukaemia[4]. Two cases of leukaemia and one case of renal clear-cell carcinoma have been reported in children treated for glomerulonephritis with chlorambucil[5].

17. CHLORAMPHENICOL (Group 3)

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

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[1] Kolonel, L.N. (1976) Association of cadmium with renal cancer. Cancer, 37: 1782-1789.

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Case reports have described leukaemia in patients following chloramphenicol-induced aplastic anemia. A follow-up study described three cases of leukaemia in 126 patients who had bone marrow depression following treatment with chloramphenicol[1].

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 tumours following oral administration. The data for rats are inconclusive[2].

In one report, 5 out of 14 children with neuroblastoma had prenatal and/or postnatal exposure to chlordane. Exposure was not ascertained for the remaining 9 children. In an epidemiological study, three persons with acute leukaemia were found to have been exposed to chlordane (which contained 3% to 7% heptachlor)[2].

19. CHLOROPRENE (Group 3)

Tests for the carcinogenicity of chloroprene in animals were considered inadequate for evaluation[3].

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[3].

20. CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS (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

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[1] IARC Monographs, 10: 85-98, 1976.

[2] IARC Monographs, 20: 1979 (in press).

[3] IARC Monographs, 19: 131-156, 1979.

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[1,2,3].

There is an increased incidence of lung cancer among workers in the chromate-producing industry[1,4-7] and possibly also among chromium platers[8,9] and chromium alloy workers[10]. There is also a suggestion of increased incidence of cancers at other sites[8,10]. The chromium compound(s) responsible has not been specified precisely.

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3 Lane, B.P. & Mass, M.J. (1977) Carcinogenicity and cocarcinogenicity of chromium carbonyl in heterotopic tracheal grafts. Cancer Res., 37: 1476-1479.

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5 Langard, S. & Norseth, T. (1975) A cohort study of bronchial carcinomas in workers producing chromate pigments. Br. J. Ind. Med., 32: 62-65.

6 Ohsaki, Y., Abe, S., Kimura, K., Tsuneta, Y., Mikami, H. & Murao, M. (1978) Lung cancer in Japanese chromate workers. Thorax, 33: 372-374.

7 Taylor, F.H. (1966) The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. Am. J. Public Health, 56: 218-229.

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10 Pokrovskaya, L.V. & Shabynina, N.K. (1973) Carcinogenous hazards in the production of chromium ferroalloys. Gig. Tr. Prof. Zabol., 10: 23-26.

21. CYCLOPHOSPHAMIDE (Group 2A)

Cyclophosphamide is carcinogenic in mice and rats following intraperitoneal injection, in rats following intravenous injection and in mice following subcutaneous injection. Dosages used were comparable to those used in clinical practice. It produced mainly lung and lymphoreticular tumours, but tumours of the liver and reproductive organs, sarcomas and squamous-cell carcinomas of the skin[1] and bladder tumours[2] were also observed.

There are a number of case reports of bladder cancer and acute myeloid leukaemia 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 non-lymphocytic leukaemia following treatment with alkylating agents, including cyclophosphamide[3].

22. DICHLORODIPHENYLTRICHLOROETHANE (DDT) (Group 3)

Dichlorodiphenyltrichloroethane (DDT) is carcinogenic in mice causing liver tumours following oral administration[4]. Non-metastasizing liver tumours occur in rats fed DDT[5,6]

The epidemiological studies available were considered to be inadequate to allow an evaluation of the carcinogenicity of DDT[4].

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[1] IARC Monographs, 9: 135-156, 1975.

[2] Schmähl, D. & Habs, M. (1979) Carcinogenic action of low-dose cyclophosphamide given orally to sprague-dawley rats in a lifetime experiment. Int. J. Cancer, 23: 706-712

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[4] IARC Monographs, 5: 83-124, 1974.

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23. DIELDRIN (Group 3)

Dieldrin is carcinogenic in mice, causing a dose-related increase in liver tumours following oral 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 an evaluation of carcinogenicity[1].

24. DIETHYLSTILBOESTROL (Group 1)

Diethylstilboestrol is carcinogenic in mice, rats, hamsters, frogs[3], and squirrel monkeys, producing tumours principally in oestrogen-responsive tissues[4].

Diethylstilboestrol causes clear-cell carcinoma of the vagina in females exposed *in utero*[4,5]. The evidence for an association with other human cancers is either limited (endometrium)[6] or inadequate (breast[6], ovary[7]).

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[1] IARC Monographs, 5: 125-156, 1974.

[2] Stevenson, D.E., Thorpe, E., Hunt, P.F. & Walker, A.I.T. (1976) The toxic effects of dieldrin in rats: a reevaluation of data obtained in a two-year feeding study. Toxicol. Appl. Pharmacol., 36: 247-254.

[3] Khudoley, V.V. (1976) Carcinogenic action of diethylstilbestrol on frogs. Exp. Biol. Med., 81: 898-900.

[4] IARC Monographs, 6: 55-76, 1974. (IARC Monographs, 21: in preparation)

[5] Herbst, A.L., Cole, P., Colton, T., Robboy, S.J. & Scully, R.E. (1977) Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. Am. J. Obstet. Gynecol., 128: 43-50.

[6] Bibbo, M., Haenszel, W.M., Wied, G.L., Hubby, M. & Herbst, A.L. (1978) A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. N. Engl. J. Med., 298: 763-767.

[7] Hoover, R., Gray, L.A. & Fraumeni, J.F. Jr. (1977) Stilboestrol (diethylstilboestrol) and the risk of ovarian cancer. Lancet, ii: 533-534.

25. DIMETHYLCARBAMOYL CHLORIDE (Group 2B)

Dimethylcarbamoyl chloride is carcinogenic in mice, producing local carcinomas after application to the skin and local sarcomas after subcutaneous or intraperitoneal injection[1].

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

26. DIMETHYL SULPHATE (Group 2B)

Dimethyl sulphate is carcinogenic in rats after inhalation or subcutaneous injection, producing mainly local tumours, and after prenatal exposure, producing tumours of the nervous system[2].

Four bronchial carcinomas have been reported in men occupationally exposed to dimethyl sulphate[2]. In an epidemiological study six cancer deaths were found *versus* 2.4 expected; three of these were cancers of the respiratory tract (1.02 expected)[3]. Neither the respiratory tract cancers nor the cancer rate at all sites are statistically significantly increased.

27. EPICHLOROHYDRIN (Group 3)

Epichlorohydrin produces local sarcomas in mice following subcutaneous injection, and was active as an initiator in a two-stage carcinogenesis study in mice[4].

Among men exposed to epichlorohydrin for 15 years or more at 2 plants there was an increased number of deaths due to respiratory cancer (8 observed, 4.7 expected) and leukaemia (2 observed, 0.4 expected)[5]. 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 since smoking habits were not considered in the analysis.

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[1] IARC Monographs, 12: 77-84, 1976.

[2] IARC Monographs, 4: 271-276, 1974.

[3] Pell, S. (1979 - submitted for publication) Mortality of workers exposed to dimethyl sulphate, 1932-1974. Am. Ind. Hyg. Assoc. J.

[4] IARC Monographs, 11: 131-139, 1976.

[5] Enterline, P.E. & Henderson, V.L. (1979) Updated mortality in workers exposed to epichlorohydrin. J. Occup. Med. (in press)

28. ETHYLENE OXIDE (Group 2B)

Solutions of ethylene oxide have been tested inadequately in mice by skin application and in rats by subcutaneous injection. No experiments involving inhalation were available[1].

Two studies of human populations exposed occupationally to ethylene oxide[2,3] have shown increased rates of leukaemia. One of these studies also showed increased rates of gastric cancer. These increases cannot confidently be attributed to ethylene oxide alone however, since the workers were also exposed to other chemicals.

29. HAEMATITE (Group 3) AND

30. UNDERGROUND HAEMATITE MINING (Group 1)

No carcinogenic effects were observed in mice, hamsters, or guinea-pigs given ferric oxide intratracheally[4].

Underground haematite miners have a high incidence of lung cancer, whereas surface haematite miners do not. It is not known whether this excess risk may be due to haematite; to radon (a known lung carcinogen); to inhalation of ferric oxide or silica; or to a combination of these or other factors. Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer, while other studies have not[4,5]. The influence of factors in the workplace other than ferric oxide cannot be eliminated.

31. HEXACHLOROCYCLOHEXANE (TECHNICAL HCH AND LINDANE) (Group 3)

Technical HCH, α- and β-HCH and lindane (γ-HCH) are carcinogenic in mice when administered orally, producing liver tumours. Studies in rats were considered inadequate[6].

Approximately 30 cases of aplastic anaemia, and 3 cases of acute myeloid leukaemia have been reported following exposure to HCH or lindane. A study of 285 workers exposed to many pesticides (including HCH and lindane) showed an apparent excess of lung tumours and one case of leukaemia; however, this cannot be attributed to exposure to HCH or lindane alone[6].

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[1] IARC Monographs, 11: 157-168, 1976.

[2] Hogstedt, C., Rohlén, O., Berndtsson, B.S., Axelson, O. & Ehrenberg, L. (1978) Kohortstudie av dödsorsaker hos anställda i etylenoxid-framställning. Läkartidningen, 75: 3285-3287.

[3] Hogstedt, C., Malaqvist, N. & Wadman, B. (1979) Leukemia in workers exposed to ethylene oxide. JAMA, 241: 1132-1133.

[4] IARC Monographs, 1: 29-39, 1972.

[5] Axelson, O. & Sjoberg, A. (1979) Cancer incidence and exposure to iron oxide dust. J. Occup. Med., 21: 419-422.

[6] IARC Monographs, 20: 1979 (in press).

32. IRON DEXTRAN (Group 2B)

Iron dextran is carcinogenic in mice and rats after subcutaenous or intramuscular injection, producing local tumours[1].

There have been case reports of sarcomas associated with injections of iron dextran[1,2]. The tumours appeared at the probable site of the injections, and the similarity of the local effect in humans and animals was noted.

33. ISONIAZID (Group 3)

Isoniazid produces lung tumours in mice after oral, intraperitoneal, or subcutaneous administration. Studies in rats and hamsters were considered inadequate[3].

Several early studies failed to show a significant excess of cancer among patients treated with isoniazid[3]. A study of tuberculosis patients[4], most of whom were followed for more than 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 was mainly for deaths within 4 years of the start of isoniazid therapy. No dose response effect was seen either for total consumption or 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. In a case-control study[5] of patients with bladder cancer it was found 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.

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[1] IARC Monographs, 2: 161-178, 1973.

[2] Greenberg, G. (1976) Sarcoma after intramuscular iron injection. Br. Med. J., ii: 1508-1509.

[3] IARC Monographs, 4: 159-172, 1974.

[4] Stott, H., Peto, J., Stephens, R. & Fox, W. (1976) An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. Tubercle, 57: 1-15.

[5] Miller, C.T., Neutel, C.I., Nair, R., Marrett, L.D., Last, J.M. & Collins, W.E. (1978) Relative importance of risk factors in bladder carcinogenesis. J. Chronic. Dis., 31: 51-56.

34. ISOPROPYL OILS (Group 3) AND

35. 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 subcutaneous 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].

36. LEAD AND CERTAIN LEAD COMPOUNDS (Group 3)

Basic lead acetate is carcinogenic in rats and mice after oral administration, producing renal tumours. Lead acetate, lead subacetate, and lead phosphate are carcinogenic in rats, producing renal tumours after oral, intraperitoneal or subcutaneous administration[2]. Other lead salts have been inadequately tested[3,4]. 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[2]. One prospective study of mortality in workers in lead smelters and battery plants showed respectively a 30% and 11% increased mortality from all malignant neoplasms[5]. The findings were statistically significant only in the smelter workers. An excess of tumours was seen in the respiratory, urinary, and digestive system, although none of these were significantly increased when considered alone. A study of tetraethyllead workers is inadequate because only workers who remained employed during the study period were included[6].

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[1] IARC Monographs, 15: 223-243, 1977.

[2] IARC Monographs, 1: 40-50, 1972.

[3] Coogan, P., Stein, L., Hsu, G. & Hass, G. (1972) The tumorigenic action of lead in rats. Lab. Invest., 26: 473.

[4] Ito, N. (1973) Experimental studies on tumors of the urinary system of rats induced by chemical carcinogens. Acta Pathol. Jpn, 23: 87-109.

[5] Cooper, W.C. & Gaffy, W.R. (1975) Mortality of lead workers. J. Occup. Med., 17: 100-107.

[6] Robinson, T.R. (1976) The health of long service tetraethyl lead workers. J. Occup. Med., 18: 31-40.

(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).

37. MELPHALAN (Group 1)

Melphalan is carcinogenic in mice and rats following intraperitoneal injection, producing lymphosarcomas, a dose-related increase in lung tumours in mice, and peritoneal sarcomas in rats[1].

Case reports of second primary malignancies (mainly acute leukaemia) in patients treated with melphalan have been published[1-5]. Epidemiological studies showed substantially increased rates of leukaemia in patients treated with melphalan for multiple myeloma[6] and ovarian cancer[7,8]. 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 leukaemia in patients with multiple myeloma has increased since the introduction of melphalan therapy[9].

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[1] IARC Monographs, 9: 167-180, 1975.

[2] Bell, R., Sullivan, J.R., Fone, D.J. & Hurley, T.H. (1976) Carcinoma of the breast. Occurrence after treatment with melphalan for multiple myeloma. J. Assoc. Off. Anal. Chem., 236: 1609-1610.

[3] Burton, I.E., Abbot, C.R., Roberts, B.E. & Antonis, A.H. (1976) Acute leukaemia after four years of melphalan treatment for melanoma. Br. Med. J., i: 20.

[4] Buskard, N.A., Boyes, D.A. & Grossman, L. (1977) Plasma cell leukemia following treatment with radiotherapy and melphalan. Can. Med. Assoc. J., 117: 788-789.

[5] De Bock, R.F.K. & Peetermans, M.E. (1977) Leukaemia after prolonged use of melphalan for non-malignant disease. Lancet, i: 1208-1209.

[6] Law, I.P. & Blom, J. (1977) Second malignancies in patients with multiple myeloma. Oncology, 34: 20-24.

[7] Reimer, R.R., Hoover, R., Fraumeni, J.F. Jr & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., 297: 177-181.

[8] Einhorn, N. (1978) Acute leukemia after chemotherapy (melphalan). Cancer, 41: 444-447.

[9] Adamson, R.H. & Sieber, S.M. (1977) Antineoplastic agents as potential carcinogens. In: Hiatt, H., Watson, J. & Winsten, J. eds, Origins of Human Cancer, Cold Spring Harbour Laboratory, pp. 429-444.

38. MUSTARD GAS (Group 1)

Mustard gas is carcinogenic in mice, the only species tested, after inhalation or intravenous injection producing lung tumours, and after subcutaneous 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].

39. 2-NAPHTHYLAMINE (Group 1)

2-Naphthylamine is carcinogenic, producing urinary bladder carcinomas in hamsters, dogs, and non-human primates, and hepatomas in mice, after oral administration[2].

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[2].

40. NICKEL, CERTAIN NICKEL COMPOUNDS (Group 2A) AND 41. NICKEL REFINING (Group 1)

Nickel subsulphide is carcinogenic in rats by inhalation, producing lung cancer. Nickel compounds (nickel powder, subsulphide, oxide carbonate, and nickelocene) produced local sarcomas in mice, rats and hamsters when given intramuscularly. Inhalation of nickel carbonyl produced a low incidence of lung tumours in rats[3].

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[3].

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[1] IARC Monographs, 9: 181-192, 1975.

[2] IARC Monographs, 4: 97-111, 1974.

[3] IARC Monographs, 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 tumours 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 tumours could be related to hepatic damage known to be caused by oxymetholone. Alternatively, patients with congenital anaemias may be at higher risk of developing these tumours, and this risk may become manifest during the extended survival resulting from oxymetholone treatment[1].

43. PHENACETIN (Group 2B)

Rats fed a diet containing phenacetin had an excess of nasal and urinary tract tumours[2]. *N*-hydroxyphenacetin (a possible metabolite of phenacetin) produced liver carcinomas in rats following oral administration[3].

Several studies indicate that the chronic abuse of analgesic mixtures containing phenacetin 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[3]. These compounds contain phenacetin with other anti-inflammatory drugs (often salicylates or antipyrine (phenazone)) and caffeine.

44. PHENOBARBITONE (Group 3)

Phenobarbitone sodium is carcinogenic, producing benign and malignant liver-cell tumours in mice and benign liver-cell tumours in rats after oral administration[4].

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[1] IARC Monographs, 13: 131-139, 1977.

[2] Isaka, H., Yoshii, H., Otsuji, A. et al. (1979) Tumours of Sprague-Dawley rats induced by long-term feeding of phenacetin. Gann, 70: 29-36.

[3] IARC Monographs, 13: 141-155, 1977.

[4] IARC Monographs, 13: 157-181, 1977.

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[1]. A further follow-up[2] of the patients from this study (who were hospitalized for long periods for the treatment of epilepsy) showed an excess of brain tumours, even more than 10 years after the diagnosis of epilepsy (12 observed versus 4.3 expected), and an increase in liver tumours (11 observed versus 2.8 expected). However, eight of the 11 liver tumour patients also received Thorotrast, a known liver carcinogen. Furthermore, the appearance of brain tumours in these patients is difficult to interpret, because they may be due to the underlying medical condition, rather than to the drugs *per se*. No excess of malignancies of any other sites were seen. In another epidemiological study[3] significantly more mothers of children with brain tumours 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).

45. *N*-PHENYL-2-NAPHTHYLAMINE (Group 3)

N-Phenyl-2-naphthylamine was tested inadequately in mice by oral administration or by single subcutaneous injection. In a biotransformation study, 0.02% of a measured dose of *N*-phenyl-2-naphthylamine was converted metabolically to 2-naphthylamine in dogs[4].

No excess of bladder tumours 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 tumours. In the latter study, exposure was to several compounds, which probably included *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[4].

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[1] IARC Monographs, 13: 157-181, 1977.

[2] Clemmesen, J. & Hjalgrim-Jensen, S. (1978) Is phenobarbital carcinogenic? A follow-up of 8078 epileptics. Exotoxicol. Environ. Safety, 1, 457-470.

[3] Gold, E., Gordis, L., Tonascia, J. & Szkio, M. (1978) Increased risk of brain tumors in children exposed to barbiturates. J. Natl Cancer Inst., 61: 1031-1034.

[4] IARC Monographs, 16: 325-341, 1978.

46. PHENYTOIN (Group 3)

Phenytoin is carcinogenic in mice after oral administration or by intraperitoneal injection, producing lymphomas and leukaemias[1].

There are case reports and epidemiological studies of lymphomas occurring in patients that received phenytoin[1]; however, no excess of lymphomas was reported in a follow-up study of epilepsy patients, many of whom received phenytoin along with other anti-epileptic drugs[2]. Three recent papers[3,4,5] report one case of malignant mesenchymoma and two cases of neuroblastoma in children with phenytoin-induced malformations. An epidemiological study[6] 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 cases reported a history of epilepsy, no differences were seen in the proportion of epileptic mothers who took either phenytoin or phenobarbitone. An excess of lymphomas (6 observed, 4 expected) was seen in children of epileptic mothers, but the occurrence of brain tumours was not reported (see also Phenobarbitone).

47. POLYCHLORINATED BIPHENYLS (Group 2B)

Certain polychlorinated biphenyls are carcinogenic in mice and rats after oral administration, producing liver tumours[7]

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[7].

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[1] IARC Monographs, 13: 201-225, 1977.

[2] Clemmesen, J. & Hjalmgrim-Jensen, S. (1978) Is phenobarbital carcinogenic: a follow-up of 8078 epileptics. Exotoxicol. Environ. Safety, 1: 457-470,

[3] Pendergrass, T.W. & Henson, J.W. (1976) Fetal hydantoin syndrome and neuroblastoma. Lancet, ii, 150.

[4] Sherman, S. & Roizen, N. (1976) Fetal hydantoin syndrome and neuroblastoma. Lancet, ii, 517.

[5] Blattner, W.A., Henson, D.E., Young, R.C. & Fraumeni, J.F. Jr, (1977) Malignant mesenchymoma and birth defects. Prenatal exposure to phenytoin. JAMA, 238: 334-335.

[6] Sanders, B.M. & Draper, G.J. (1979) Childhood cancer and drugs in pregnancy. Br. Med. J., i: 717-718.

[7] IARC Monographs, 18: 43-103, 1978.

48. RESERPINE (Group 3)

Reserpine has been tested inadequately in mice and rats by oral administration[1].

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 who had taken 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 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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[1] IARC Monographs, 10: 217-229, 1976.

[2] Lilienfeld, A.M., Chang, L., Thomas, D.B. & Levin, M.L. (1975) Rauwolfia derivatives and breast cancer. Johns Hopkins Med. J., 139: 41-50.

[3] Armstrong, B., Skegg, D., White, G. & Doll, R. (1976) Rauwolfia derivatives and breast cancer in hypertensive women. Lancet, ii: 8-12.

[4] Aromaa, A., Hakama, M., Hakulinen, T., Saxen, E., Teppo, L. & Idänpään-Heikkilä, J. (1976) 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.

[5] Christopher, L.J., Crooks, J., Davidson, J.F., Erskine, Z.G., Gallon, S.C., Moir, D.C. & Weir, R.D. (1977) A multi-centre study of rauwolfia derivatives and breast cancer. Eur. J. Clin. Pharmacol., 11: 409-417.

[6] Kodlin, D. & McCarthy, N. (1978) Reserpine and breast cancer. Cancer, 41: 761-768.

[7] Williams, R., Feinleib, M., Connor, R. & Stegens, N. (1978) 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.

[8] Kewitz, H., Jesdinsky, H., Schröter, P. & Lindtner, E. (1977) Reserpine and breast cancer in women in Germany. Eur. J. Clin. Pharmacol., 11: 79-83.

49. SOOTS, TARS AND MINERAL OILS (Group 1)

Soots, coal-tars, creosote oils, shale oils and cutting oils are carcinogenic in experimental animals after skin painting or subcutaneous injection[1].

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[1]. Recent epidemiological data have supported these conclusions[2-7]. This effect may be due to the presence of polycyclic aromatic hydrocarbons in these materials.

50. STYRENE (Group 3)

Styrene produces lung tumours in mice following oral administration[8,9].

Three deaths from leukaemia and 2 from lymphoma have been reported in workers exposed to styrene, benzene and butadiene; however, these deaths cannot be attributed to styrene exposure alone[8].

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[1] IARC Monographs, 3: 22-42, 1973.

[2] Decoufle, P. (1978) Further analysis of cancer mortality among workers exposed to cutting oil mist. J. Natl Cancer Inst., 61: 1025-1030.

[3] Hammond, E.C., Selikoff, I.J., Lawther, P.L. & Seidman, H. (1976) Inhalation of benzpyrene and cancer in man. Ann. N.Y. Acad. Sci., 271: 116-124.

[4] McMicheal, A.J., Spirtas, R., Gamble, J.F. & Tousey, P.M. (1976) Mortality among rubber workers: Relationship to specific jobs. J. Occup. Med., 18: 178-185.

[5] Redmond, C.K., Strobino, B.R. & Cypress, R.H. (1976) Cancer experience among coke byproduct workers. Ann. N.Y. Acad. Sci., 271: 102-115.

[6] Andjelkovich, D., Taulbee, J., Symons, M. & Williams, T. (1977) Mortality of rubber workers with reference to work experience. J. Occup. Med., 19: 397-405.

[7] Wigle, D.T. (1977) Bladder cancer: Possible new high-risk occupation. Lancet, ii: 83-84.

[8] IARC Monographs, 19: 231-274, 1979.

[9] National Cancer Institute (1979) Bioassay of styrene for possible carcinogenicity. Tech. Rep. Series No. 185 DHEW Pub. No. (NIH) 79-1741, Washington, D.C.

51. TRICHLOROETHYLENE (Group 3)

Trichloroethylene is carcinogenic in mice after oral administration, producing hepatocellular carcinomas and lung tumours[1].

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

52. TRIS(AZIRIDINYL)-*para*-BENZOQUINONE (TRIAZIQUONE) (Group 3)

Tris(aziridinyl)-*para*-benzoquinone (triaziquone) is carcinogenic in rats after intravenous or combined intravenous and intraperitoneal injection, producing a variety of malignant tumours[2].

The four available case reports were inadequate to evaluate the carcinogenicity of triaziquone[2].

53. TRIS(1-AZIRIDINYL)PHOSPHINE SULPHIDE (THIOTEPA) (Group 2A)

Tris(1-aziridinyl)phosphine sulphide (thiotepa) is carcinogenic in mice and rats after administration by various routes, producing a variety of malignant tumours[3,4].

There are several reports and epidemiological studies suggesting the development of acute non-lymphocytic leukaemia in patients treated with thiotepa for ovarian and other malignant tumours[3,5].

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[1] IARC Monographs, 20: 1979 (in press).

[2] IARC Monographs, 9: 67-73, 1975.

[3] IARC Monographs, 9: 85-94, 1975.

[4] National Cancer Institute, Bioassay of Thiotepa for possible carcinogenicity. Tech. Rep. Series No. 58, DHEW Pub. No. (NIH) 78-1308, Washington, D.C., 168 pp.

[5] Reimer, R.R., Hoover, R., Fraumeni, J.F. Jr & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. N. Engl. J. Med., 297: 177-181.

54. VINYL CHLORIDE (Group 1)

Vinyl chloride is carcinogenic in mice, rats and hamsters after administration orally or by inhalation, producing tumours at several sites, including angiosarcomas of the liver[1].

Vinyl chloride causes angiosarcomas of the liver, and tumours of the brain, lung, and haematolymphopoietic system in humans[1]. Reports of increases in digestive system, urinary system and breast tumours (in women) are inadequate to evaluate carcinogenicity for these sites[1].

ADDITIONAL CHEMICALS WITH EVIDENCE FROM HUMAN STUDIES

A. *ortho*- AND *para*-DICHLOROBENZENE

No adequate data on the carcinogenicity of *ortho*- or *para*-dichlorobenzene in experimental animals were available[2].

There is one report of four cases of leukaemia and one case of "myeloproliferative syndrome" occurring in subjects exposed to *ortho*- or *para*-dichlorobenzene as a solvent for other chemicals or in chlorinated benzene mixtures. The authors state that there was no evidence of exposure to benzene[2].

B. 3,3'-DICHLOROBENZIDINE

3,3'-Dichlorobenzidine is carcinogenic in rats, hamsters and dogs. In rats it produced tumours of the skin, mammary gland, zymbal gland and haematopoietic tissues following oral or subcutaneous administration[3,4]. In dogs and hamsters, it produced malignant tumours of the liver and bladder following oral administration[3,5].

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[1] IARC Monographs, 19: 377-437, 1979.

[2] IARC Monographs, 7: 231-244, 1974.

[3] IARC Monographs, 4: 49-55, 1974.

[4] Stula, E.F., Sherman, H., Zapp, J.A., Jr. & Wesley Clayton, J., Jr. (1975) Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline) and 4,4'-methylene-bis(2-methylaniline). Toxicol. appl. Pharmacol., 31: 159-176.

[5] Stula, E.F., Barnes, J.R., Sherman, H., Reinhardt, C.F. & Zapp, J.A., Jr. (1978) Liver and urinary bladder tumours in dogs from 3,3'-dichlorobenzidine. J. Environm. Path. Tox., 1: 475-490.

In three epidemiological studies[1,2,3], no bladder tumours were reported in men occupationally exposed to dichlorobenzidine; however, the numbers of exposed workers followed up in each study was small (35, 175 and 87), and few of the workers had been observed for more than 15 years after first exposure (most had been observed for 10 years or less). None of these investigations used a study design or method of statistical analysis which was adequate to rule out a carcinogenic effect.

C. PHENYLBUTAZONE

No adequate data on the carcinogenicity of phenylbutazone in experimental animals were available[4].

There are at least 23 case reports of leukaemia occurring in patients after treatment with phenylbutazone. In a follow-up study of 25 patients who developed bone marrow depression following phenylbutazone treatment, one died of myeloproliferative disease (probably leukaemia)[4].

D. 2,3,7,8-TETRACHLORODIBENZO-*para*-DIOXIN (TCDD)

Rats fed 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin developed a variety of malignant tumours, mainly of the respiratory tract, sebaceous glands, liver and bile ducts [5,6,7].

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[1] Gadian, T. (1975) Carcinogens in industry, with special reference to dichlorobenzidine. Chemistry and Industry, 821-831.

[2] Gerarde, H.W., Gerarde, D.F. (1974) Industrial experience with 3,3'-Dichlorobenzidine: An epidemiological study of a chemical manufacturing plant. J. Occ. Med., 16: 322-344.

[3] MacIntyre, I. (1975) Experience of tumours in a British plant handling 3,3'-Dichlorobenzidine. J. Occ. Med., 17: 23-26.

[4] IARC Monographs, 13: 183-199, 1977.

[5] IARC Monographs, 15: 41-102, 1977.

[6] Van Miller, J.P., Lalich, J.J. & Allen, J.R. (1977) Increase incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Chemosphere, 6: 537-544.

[7] Kociba, R.J., Keys, D.G., Beyer, J.E., Carreon, R.M., Wade, C.E., Dittenber, D.A., Kalnins, R.P., Franson, L.E., Park, C.N., Barbard, S.D., Hummel, R.A. & Humiston, C.G. (1978) Results of a two-year chronic and oncogenicity toxicity study of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in rats. Toxicol. appl. Pharmacol., 46: 279-303.

Two bronchogenic carcinomas were reported (*versus* 0.12 expected, calculated by the Monograph Working Group) in a study of workers exposed to TCDD; however smoking habits were not reported, only 55 of the 78 workers were traced, and they were only followed for five or six years. A study in Viet-Nam showed an increase in the proportion of liver cancer patients admitted to Hanoi hospitals during 1962 to 1968 - a period during the war in which herbicides (some containing TCDD) were being used[1,2].

E. *ortho*-TOLUIDINE

ortho-Toluidine is carcinogenic in mice and rats following its oral administration as the hydrochloride. It produced a variety of malignant tumours in rats including sarcomas of the spleen, fibromas of the subcutaneous and mammary tissues, mesotheliomas of the abdominal cavity and carcinomas of the urinary bladder. In mice it produced haemangiosarcomas at various sites and liver tumours[3,4].

Four epidemiological studies were available for review. Three of them deal with bladder tumours in workers who had exposures to many substances (including known bladder carcinogens) as well as to *ortho*-toluidine, and the results of these studies are equivocal. Another study appeared to involve occupational exposure to toluidines specifically; it was suggestive of a carcinogenic effect, but the information presented in the paper was insufficient to allow evaluation[3].

F. VINYLIDENE CHLORIDE

Vinylidene chloride induced malignant tumours, including angiosarcomas, after inhalation in rats and mice. However, the results were not statistically significant. The preliminary results of another inhalation study in mice indicate the induction of kidney tumours in male animals, although the study had not been completed at the time of reporting. Other inhalation studies in rats and hamsters, as well as an oral study in rats is still in progress and cannot be evaluated[5].

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[1] IARC Monographs, 15: 41-102, 1977.

[2] International Agency for Research on Cancer (1978) Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans. IARC Intern. Tech. Rep. No. 78/001, Lyon, France.

[3] IARC Monographs, 16: 349-366, 1978.

[4] National Cancer Institute (1979) Bioassay of *o*-toluidine hydrochloride for possible carcinogenicity. Tech. Rep. Ser. No. 153, DHEW Publication, No. (NIH) 79-1709.

[5] IARC Monographs, 19: 452-453, 1979.

One epidemiological study of 138 workers exposed to vinylidene chloride showed no excess of cancer deaths, however only five deaths in all had occurred in the group. Another study of 629 workers (who were exposed to vinyl chloride and acrylonitride as well as to vinylidene chloride) showed seven deaths due to malignant neoplasms (4.4 expected). Among workers aged 35-39 two bronchial carcinomas were reported (0.08 expected). However, no information on the smoking habits of these men was presented[1]

[1] IARC Monographs, 19: 452-453, 1979.

CUMULATIVE INDEX TO IARC MONOGRAPHS VOLUMES 1-20 ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Numbers underlined indicate volume, and numbers in italics indicate page. References to corrigenda are given in parentheses. Compounds marked with an asterisk (*) were considered by the Working Groups, but monographs were not prepared because adequate data on their carcinogenicity were not available. Chemicals with data on carcinogenicity in humans appear in italics.

INDEX OF CHEMICALS FROM MONOGRAPHS VOLUMES 1-20
BY POSSIBLE TARGET ORGANS IN HUMANS

NOTE: Chemicals with *sufficient evidence* of carcinogenicity for the stated organ system appear in *italics*. The listing of all other chemicals for each target site indicates only that this organ system was mentioned in the literature, and does not imply a causal association between the substance and tumours of the organ listed.

TARGET SITE (ICD 8th CODE)	IARC REFERENCE
Nose and nasal sinus (160)	
Chromium and certain chromium compounds	*2*,100
Isopropyl oils	*15*,223
Manufacture of isopropyl alcohol	*15*,223
Mustard gas	*9*,181
Nickel and certain nickel compounds	*11*, 75
Nickel refining	*11*,
Larynx (161)	
Asbestos	*14*,
Isopropyl oils	*15*,223
Manufacture of isopropyl alcohol	*15*,223
Mustard gas	*9*,181
Nickel and certain nickel compounds	*11*, 75
Nickel refining	*11*, 75
Soots, tars and mineral oils	*2*, 22
Lung - trachea, bronchus (162)	
Acrylonitrile	*19*, 73
Amitrole	*7*, 31
Arsenic and certain arsenic compounds	*2*, 48
Asbestos	*14*
Beryllium and certain beryllium compounds	*1*, 17
BCME and CMME	*4*,231
Cadmium and certain cadmium compounds	*11*, 39
Chloroprene	*19*,131
Chromium and certain chromium compounds	*2*,100
Dimethyl sulphate	*4*,271
Epichlorohydrin	*11*,131
Haematite (ferric oxide)	*1*, 29
Underground mining of haematite	*1*, 29
Hexachlorocyclohexane	*20*
Isoniazid	*4*,159
Lead and certain lead compounds	*1*, 40
Mustard gas	*9*,181
Nickel and certain nickel compounds	*11*, 75
Nickel refining	*11*, 75
Soots, tars and mineral oils	*3*, 22
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	*15*, 41
Vinyl chloride	*19*,377
Vinylidene chloride	*19*,439

TARGET SITE (ICD 8th CODE)	IARC REFERENCE
Bladder (188) (continued)	
2-Naphthylamine	*4*, 97
Phenacetin	*13*,141
N-Phenyl-2-naphthylamine	*14*,325
ortho and *para*-toluidine	*16*,347
Soots, tars and mineral oils	*3*,
Kidney (189)	
Cadmium and certain cadmium compounds	*11*, 39
Lead and certain lead compounds* (urinary tract)	*1*, 40
Phenacetin	*13*,141
Central nervous system (191-192)	
Chlordane and heptachlor	*20*
Phenobarbitone	*13*,159
Phenytoin	*17*,202
Vinyl chloride	*19*,377
Haematolymphopoietic system (200-207)	
Arsenic and certain arsenic compounds	*2*, 48
Benzene	*7*,203
Chlorambucil	*9*,125
Chloramphenicol	*10*, 85
Chlordane and heptachlor	*20*
Chloroprene	*19*,131
Cyclophosphamide	*9*,135
ortho- and *para*-Dichlorobenzene	*7*,231
Epichlorohydrin	*11*,131
Ethylene oxide	*11*,157
Hexachlorocyclohexane	*20*
Melphalan	*9*,167
Oxyphenbutazone	*13*,131
Phenobarbitone	*13*,159
Phenylbutazone	*13*,183
Phenytoin	*13*,201
Styrene	*19*,231
Trichloroethylene	*11*,263
Tris(1-aziridinyl)phosphine sulphide (thiotepa)	*9*, 85
Vinyl chloride	*19*,377