WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF THE CARCINOGENIC RISKS TO HUMANS

Chemicals, Industrial Processes and
Industries Associated with Cancer
in Humans
IARC Monographs, Volumes 1 to 29

IARC MONOGRAPHS SUPPLEMENT 4

IARC, LYON, FRANCE

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SUPPLEMENT 4

Report of an IARC *ad hoc* Working Group
which met in Lyon, 8-12 February 1982
to advise the Director, IARC,
on chemicals, industrial processes and industries
that are carcinogenic for humans

October 1982

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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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NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monograph* series is taken to mean the probability that exposure to a chemical or complex mixture or employment in a particular occupation will lead to cancer in humans.

The fact that a monograph has been prepared on a chemical, complex mixture or occupation does not imply that a carcinogenic hazard is associated with the exposure, only that the published data have been examined. Equally, the fact that a chemical, complex mixture or occupation has not yet been evaluated in a monograph does not mean that it does not represent a carcinogenic hazard.

Anyone who is aware of published data that may alter an evaluation of the carcinogenic risk of a chemical, complex mixture or employment in an occupation is encouraged to make this information available to the Division of Environmental Carcinogenesis, International Agency for Research on Cancer, Lyon, France, in order that the chemical, complex mixture or occupation 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 Division of Environmental Carcinogenesis, so that corrections can be reported in future volumes.

CHEMICALS, INDUSTRIAL PROCESSES AND INDUSTRIES ASSOCIATED WITH CANCER IN HUMANS

INTRODUCTION

The programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans has existed since 1971 and involves the preparation and publication of monographs that evaluate individual chemicals and, more recently, carcinogenic risks resulting from exposures to complex mixtures, since it is in this way that human populations are often exposed. Exposures occurring in the wood and leather industries and in the rubber manufacturing industry were thus the subject of recent IARC monographs. (A full list of *IARC Monographs*, both published and in press, is given in Appendix 1.) The evaluations contained in each volume of monographs are made by independent international Working Groups and provide governments and their advisers with authoritative scientific opinions on which to base preventive measures.

The criteria used for preparing draft monographs, for judging the adequacy of available data and for evaluating carcinogenic risk to humans were first established in 1971, and these criteria (with minor modifications) were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the IARC Monographs. In 1977, a further *ad hoc* Working Group revised the criteria[1], and these have appeared as the Preamble[2] to the Monographs since Volume 17.

The terms *'sufficient evidence'* and *'limited evidence'* of carcinogenicity used in those criteria refer only to the amount of evidence available and not to the potency of the carcinogenic effect nor to the mechanism involved. However, in the case of chemicals for which there is *sufficient evidence* of carcinogenicity in experimental animals, it was considered reasonable to recommend that, for practical purposes, such chemicals be regarded as if they presented a carcinogenic risk to humans. In the case of chemicals for which there is only *limited evidence* of carcinogenicity, further experimental and epidemiological research was deemed to be desirable.

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 purely scientific basis, but only pragmatically. Such a pragmatic correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.

An international *ad hoc* Working Group of 20 experts in cancer research met in Lyon in January 1979 to re-evaluate the epidemiological and experimental carcinogenicity data on 54 chemicals, groups of chemicals or industrial processes which had been evaluated in Volumes 1-20 of the *IARC Monographs*. Of these, 18 chemicals and industrial processes were considered to be carcinogenic for humans. A further 18 chemicals and groups of chemicals were considered to be probably carcinogenic for humans, although the data were considered inadequate to establish a causal association. To reflect different degrees of evidence within the latter group, it was subdivided: six chemicals were found to have

a higher degree of evidence and 12 chemicals a lower degree. Data on the remaining 18 chemicals were considered to be insufficient to allow an evaluation of their carcinogenicity for humans. A report summarizing the background, purpose and overall conclusions of the Working Group, and the evidence on which the evaluation for each chemical was based was published as Supplement 1 of the *IARC Monographs*[3] and as a leading article in *Cancer Research*[4].

In the first 29 volumes of the *IARC Monographs*, 585 chemicals, groups of chemicals, industrial processes and occupational exposures were evaluated or re-evaluated. Previous analyses of these evaluations indicated that for 44 of these, the working groups found that there was positive evidence of or a suspicion of an association with human cancer. For the remaining 541 exposures, epidemiological data were either unavailable or were considered to be inadequate to evaluate carcinogenicity to humans; one exception was fluorides used in drinking-water and dental preparations, for which no evidence of a carcinogenic effect was found. For 147 of the exposures, there was considered to be *sufficient evidence* of carcinogenicity in animals, and for a further 157 exposures there was *limited evidence*. The data were inadequate to evaluate the presence or absence of a carcinogenic effect for the remaining 236 exposures.

A list of all exposures for which it is currently considered that there is *sufficient evidence* of carcinogenicity in experimental animals is given in Appendix 2.

Objective

The aim of the present *ad hoc* Working Group was to update Supplement 1 of the *IARC Monographs*. All chemicals, groups of chemicals, industrial processes and occupational exposures for which some data on carcinogenicity in humans were available were re-evaluated, on the basis both of studies summarized previously in the monographs and of data published subsequently. Similar data from studies on experimental animals and from short-term tests were also summarized.

Short-term tests for the detection of potential chemical carcinogens

The induction of cancer is thought to proceed by a series of steps, some of which have been distinguished experimentally[5-9]. The first step - 'initiation' - is thought to involve damage to DNA resulting in heritable modifications in, or rearrangements of, genetic information. Proliferation of cells whose properties have been permanently altered during initiation (which may involve somatic mutation) is thought to result in the formation of clones of cells whose further progress to malignancy is dependent on a series of events - 'promotion' and 'progression' - the underlying mechanisms of which are largely unknown. Although this is a useful model, it should be kept in mind that the carcinogenic process may not always proceed by such a multi-step mechanism.

The idea that damage to DNA is a critical event in the initiation of carcinogenesis is based on a large body of data which show that many carcinogens are reactive

electrophiles *per se*, or can be readily converted to reactive electrophiles by enzymic pathways characteristic of eukaryotic metabolism[10]. A variety of DNA-carcinogen adducts, formed by reaction of electrophilic moieties with nucleophilic centres in DNA, have been identified in DNA recovered from reactions performed with carcinogens *in vitro*, or from cultured cells or intact organisms treated with carcinogens[8,11,12]. Moreover, the recognition that many classes of carcinogens (including ionizing and ultra-violet radiation and chemicals of a very wide range of structure and reactivity) are mutagenic[13] supports the idea that DNA is a critical target of carcinogenic agents. Assays for mutagenicity and allied effects, such as the induction of DNA repair, the misincorporation of nucleotide triphosphates during in-vitro nucleic acid synthesis, and various manifestations of chromosomal damage, in organisms ranging from bacteriophages to mammals, all exploit this characteristic ability of carcinogens to cause DNA damage or chromosomal anomalies either directly or indirectly. It should be noted, however, that some carcinogens may act by mechanisms that do not involve DNA damage[14] and thus would not cause such genetic effects.

A number of short-term tests for carcinogens employ as endpoints well-defined genetic markers in prokaryotes and lower eukaryotes (e.g., bacteria and fungi) and in mammalian cell lines. Many of these cells do not possess or have lost, following culture, the range of enzyme systems known in intact mammals to metabolize chemically unreactive carcinogens to reactive electrophiles. It is often necessary, therefore, to provide an exogenous source of such activity in the form of a tissue extract or cell feeder-layer or whole-cell systems prepared from mammalian sources[15]. In-vitro metabolic systems may not accurately reflect the fate of a chemical subjected to the checks and balances afforded by absorption, distribution, metabolism and excretion in mammals[15], and this must be borne in mind when evaluating the results from short-term tests which employ in-vitro metabolic activation. In addition, the organization of genetic material and its repair processes in mammalian cells is highly complex and is not fully reflected in some lower biological systems.

Tests have been devised which exploit the useful attributes of microbial or cellular genetic systems without compromising the integrity of mammalian pharmacodynamics and metabolism. Such 'host-mediated' assays involve the inoculation of indicator organisms into mammals (usually rodents) which are then dosed with the test chemical. There are limitations to both the numbers and types of organisms which can be introduced and recovered from dosed animals and to the access of indicator organisms to activated metabolites. Lack of sensitivity may therefore be a problem.

A group of short-term tests use 'transformation' of cultured mammalian cells, rather than manifestation of DNA damage or chromosomal anomalies, as an indicator of carcinogenic potential. Some of the assays also employ an exogenous metabolic activation system. Cell transformation is assessed by scoring characteristic changes in cellular and colonial morphology, or changes in growth characteristics (e.g., growth of colonies in soft agar) following treatment with the test compound. In some protocols, the ability of transformed cells to produce tumours is tested by injecting the cells into appropriate animals.

Manifestations of damage to DNA and other components of the genetic apparatus can also be assayed directly by exposing animals to the test compound and assaying the effect in these animals or in their offspring. For example, the following endpoints can be scored: mutations in the fruit fly, chromosomal anomalies in bone-marrow cells and blood lymphocytes of rodents, and specific-locus mutations in rodents treated with the test agent and in their offspring.

Similar studies may be conducted on cells taken from people exposed to putative chemical carcinogens and by examining the cells for mutation and for chromosomal anomalies either directly or after short-term culture *in vitro*. Samples of sperm from such individuals may also be analysed for morphological abnormalities. Evidence of absorption of putative carcinogens may be adduced from the assay of body fluids and excreta for DNA-damaging activity, using, for example, bacterial mutation assays.

Results from several studies[16,17] of the predictive value of various short-term tests show that some chemicals of proven carcinogenicity in experimental animals are, as far as could be judged, inactive in tests that utilize DNA or chromosomal damage as endpoints. These include, for example, certain hormones, metals, minerals and tumour promoters[14], which do not appear to exert their effects through modifications of DNA that are expressed in the form of mutations or chromosomal anomalies. No well-validated short-term tests for putative promoters are yet available, although several lines of investigation are being pursued[18-21].

Uses of short-term tests

Validated short-term tests of the type described above are useful (a) for predicting potential carcinogenicity in the absence of data on animal carcinogenicity, (b) as a contribution in deciding which chemicals should be tested or retested in animals, (c) for identifying active fractions of complex mixtures containing putative carcinogens, (d) for recognizing active metabolites of known carcinogens in human or animal body fluids, (e) in helping to elucidate mechanisms of carcinogenesis and (f) as additional evidence in interpreting ambiguous data from experimental or epidemiological studies.

In view of the limitations of current knowledge about mechanisms of carcinogenesis, certain cautions should be emphasized: (1) at present, these tests should not be used by themselves to conclude whether or not an agent is carcinogenic; (2) even when positive results are obtained in one or more of these tests, it is not clear that they can be used reliably to predict the relative potencies of compounds as carcinogens in intact animals; (3) since the currently available tests do not detect all classes of agents that are active in the carcinogenic process (e.g., hormones, promoters), one must be cautious in utilizing these tests as the sole criterion for setting priorities in carcinogenesis research and in selecting compounds for animal bioassays.

The present state of knowledge does not permit the selection of a specific test(s) as the most appropriate for identifying all classes of potential carcinogens, although certain systems are more sensitive to some classes. Before the results of a particular test can be considered to be fully acceptable for predicting potential carcinogenicity, certain criteria should be met: (a) the test should have been validated with respect to known animal carcinogens and noncarcinogens, and (b) when possible, a structurally related carcinogen(s) and noncarcinogen(s) should have been tested simultaneously with the chemical in question. The results should have been confirmed in additional test systems. Confidence in positive results is increased if a mechanism of action can be deduced and if appropriate dose-response data are available. Ideally, a compound should be tested in a battery of short term tests. For optimum usefulness, data on purity must be given. For several recent reviews on the use of short-term tests see IARC[15,16], de Serres and Ashby[17], Bartsch *et al.*[22], Hollstein *et al.*[23] and Sugimura *et al.*[21].

METHODS

The data on each chemical were reviewed in detail before the meeting by selected members of the group: the animal studies and short-term test results were evaluated by experimentalists and the human studies by an epidemiologist. During the meeting of the Working Group these assessments were debated and adopted, and overall evaluations of carcinogenicity for humans were made on the basis of the combined evidence from humans and experimental systems (Table 1). Brief descriptions of the data on which the assessments and evaluations were based are given in the section on Results, together with references to the *Monographs* volumes in which they were evaluated previously and, when applicable, to papers published subsequently.

Assessment of evidence for carcinogenicity from studies in humans

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 in space or time 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 before a causal association can be inferred between exposure and cancer in humans:

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 from studies in humans were categorized as:

i. *Sufficient evidence* of carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.
ii. *Limited evidence* of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.
iii. *Inadequate evidence*, which indicates that one of three conditions prevailed: (a) there were few pertinent data; (b) the available studies, while showing evidence of association, did not exclude chance, bias or confounding; (c) studies were available which do not show evidence of carcinogenicity.

Assessment of evidence for carcinogenicity from studies in experimental animals

These assessments were classified into four groups:

i. *Sufficient evidence* of carcinogenicity, which 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 on dose-response effects, as well as information from short-term tests or on chemical structure.

ii. *Limited evidence* of carcinogenicity, which 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 and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumours in mice).

iii. *Inadequate evidence*, which 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; or 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.

iv. *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 carcinogenic and not to the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

Assessment of data from short-term tests

Because of the large number and wide variety of short-term tests that may be relevant for the prediction of potential carcinogens, the data relative to each compound have been summarized in the form of tables. These indicate both the type of test used and the biological complexity of the test system. *'DNA damage'* includes evidence for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria, and a positive response in tests of comparative survival in DNA repair-proficient and DNA repair-deficient bacteria. *'Mutagenicity'* refers to induction of mutations in cultured cells or in organisms (e.g., heritable alterations in phenotype, including forward or reverse point mutations, recombination, gene conversion, and specific-locus mutation). *'Chromosomal anomalies'* refers to the induction of chromosomal aberrations, including breaks, gaps, rearrangements and micronuclei, sister chromatid exchange and aneuploidy. *'Other'* refers to various additional endpoints, including cell transformation (T), i.e., morphological transformation and colony formation in agar; dominant lethal (DL) tests; morphological abnormalities in sperm (SA); and mitochondrial mutation (Mt). The biological systems include: *'Prokaryotes'*, i.e., bacteria, in the presence or absence of an exogenous metabolic activation system, and cellular systems; *'Fungi and green plants'*; *'Insects'*, usually *Drosophila melanogaster*; *'Mammalian cells* (in vitro)';,either rodent or human somatic cells or cell lines in culture; *'Mammals* (in vivo)', studies in which the test compound was administered to intact experimental animals; and *'Humans* (in vivo)', studies of cells from groups of individuals drawn from a population exposed to the substance in question.

In these tables, a '+' indicates that the result was judged by the Working Group to be significantly positive in one or more assays; '-' indicates that it was judged to be negative from an evaluation of one or more assays; and '?' indicates that contradictory results were obtained in assays from different laboratories or in different biological systems, or that the result was judged to be equivocal. The individual tables for each compound are summarized, for purposes of comparison, in Appendix 3.

The overall evidence summarized in the table was adjudged to fall into one of three categories, *sufficient*, *limited* and *inadequate*:

i. *Sufficient evidence*, when there were at least three positive results in at least two of three test systems measuring DNA damage, mutagenicity or chromosomal effects. When two of the positive results were for the same genetic effect, they had to be derived from systems of different biological complexity.
ii. *Limited evidence*, when there were at least two positive results, either for different endpoints or in systems representing two levels of biological complexity.
iii. *Inadequate evidence*, when there were generally negative or only one positive test results. Up to two positive test results were considered inadequate if they were accompanied by two or more negative test results.

The Working Group was unable to define criteria for 'negative' evidence.

In establishing these categories the Working Group gave greater weight to the three primary endpoints - DNA damage, mutagenicity and chromosomal effects - and judgements were made on the quality as well as on the quantity of the evidence. In a minority of cases, strict interpretation of these criteria was tempered by consideration of a variety of other factors (such as the purity of the test compound, problems of metabolic activation, appropriateness of the test system) which, in the judgement of the Working Group, would place a compound in a category above or below that indicated by the summary table.

Evaluation of carcinogenic risk to humans

At present, no objective criteria exist to interpret data from studies in experimental animals or from short-term tests 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. The breadth of the categories of evidence defined above allows substantial variation within each. The decisions reached by the Group regarding overall risk incorporated these differences, even though they could not always be reflected adequately in the placement of an exposure into a particular category, as listed in Table 1.

The chemicals, groups of chemicals, industrial processes or occupational exposures were thus put into one of three groups:

Group 1

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

Group 2

The chemical, group of chemicals, industrial process or occupational exposure is probably carcinogenic to humans. This category includes exposures for which, at one extreme, the evidence of human carcinogenicity is almost *'sufficient'*, as well as exposures for which, at the other extreme, it is inadequate. To reflect this range, the category was divided into higher (*Group A*) and lower (*Group B*) degrees of evidence. Usually, category 2A was reserved for exposures for which there was at least *limited evidence* of carcinogenicity to humans. The data from studies in experimental animals played an important role in assigning studies to category 2, and particularly those in Group B; thus, the combination of *sufficient evidence* in animals and inadequate data in humans usually resulted in a classification of 2B.

In some cases, the Working Group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from Group 2B to 2A.

Group 3

The chemical, group of chemicals, industrial process or occupational exposure cannot be classified as to its carcinogenicity to humans.

RESULTS AND CONCLUSIONS

The assessments of degrees of evidence for carcinogenicity to humans and in experimental animals and for activity in short-term tests, as well as the summary evaluations of carcinogenic risk to humans are given in Table 1.

Group 1: The Working Group concluded that the following 7 industrial processes and occupational exposures and 23 chemicals and groups of chemicals are causally associated with cancer in humans*.

Industrial processes and occupational exposures:

Auramine manufacture
Boot and shoe manufacture and repair (certain occupations)
Furniture manufacture
Isopropyl alcohol manufacture (strong-acid process)
Nickel refining
Rubber industry (certain occupations)
Underground haematite mining (with exposure to radon)

* This list does not include known human carcinogens such as tobacco smoke, betel quid and alcoholic beverages, since they have not yet been covered in the *Monographs* programme.

Chemicals and groups of chemicals:

4-Aminobiphenyl
Analgesic mixtures containing phenacetin[a]
Arsenic and arsenic compounds[a]
Asbestos
Azathioprine
Benzene
Benzidine
N,*N*-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)
Bis(chloromethyl)ether and technical-grade chloromethyl methyl ether
1,4-Butanediol dimethanesulphonate (Myleran)
Certain combined chemotherapy for lymphomas[a] (including MOPP[b])
Chlorambucil
Chromium and certain chromium compounds[a]
Conjugated oestrogens[a]
Cyclophosphamide
Diethylstilboestrol
Melphalan
Methoxsalen with ultra-violet A therapy (PUVA)
Mustard gas
2-Naphthylamine
Soots, tars and oils[a,c]
Treosulphan
Vinyl chloride

Group 2: The following 61 chemicals, groups of chemicals or industrial processes are *probably* carcinogenic to humans

Group 2A

Acrylonitrile
Aflatoxins
Benzo[*a*]pyrene
Beryllium and beryllium compounds[a]
Combined oral contraceptives[a]
Diethyl sulphate
Dimethyl sulphate
Manufacture of magenta[a]
Nickel and certain nickel compounds
Nitrogen mustard
Oxymetholone
Phenacetin
Procarbazine
ortho-Toluidine

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[a] The compound(s) responsible for the carcinogenic effect in humans cannot be specified.
[b] Procarbazine, nitrogen mustard, vincristine and prednisone
[c] Mineral oils may vary in composition, particularly in relation to their content of carcinogenic polycyclic aromatic hydrocarbons.

Group 2B

Actinomycin D
Adriamycin
Amitrole
Auramine (technical grade)
Benzotrichloride
Bischloroethyl nitrosourea (BCNU)
Cadmium and cadmium compounds
Carbon tetrachloride
Chloramphenicol
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)
Chloroform
Chlorophenols (occupational exposure to)[a]
Cisplatin
Dacarbazine
DDT
3,3′-Dichlorobenzidine
Dienoestrol
3,3′-Dimethoxybenzidine (*ortho*-Dianisidine)
Dimethylcarbamoyl chloride
1,4-Dioxane
Direct Black 38 (technical grade)
Direct Blue 6 (technical grade)
Direct Brown 95 (technical grade)
Epichlorohydrin
Ethinyloestradiol
Ethylene dibromide
Ethylene oxide
Ethylene thiourea
Formaldehyde (gas)
Hydrazine
Mestranol
Metronidazole
Norethisterone
Oestradiol-17β
Oestrone
Phenazopyridine
Phenytoin
Phenoxyacetic acid herbicides (occupational exposure to)[a]
Polychlorinated biphenyls
Progesterone
Propylthiouracil
Sequential oral contraceptives[a]
Tetrachlorodibenzo-*para*-dioxin (TCDD)
2,4,6-Trichlorophenol
Tris(aziridinyl)-*para*-benzoquinone (Triaziquone)
Tris(1-aziridinyl)phosphine sulphide (Thiotepa)
Uracil mustard

Group 3: The remaining 64 chemicals, groups of chemicals, industrial processes and occupational exposures could not be classified as to their carcinogenicity to humans.

[a] The compound(s) responsible for the probable carcinogenic effect in humans cannot be specified.

Table 1. Summary evaluations of carcinogenic risk to humans from chemicals, industrial processes and industries* based on evidence for carcinogenicity to humans and to animals and for activity in short-term tests†

Chemical, process or industry	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Evidence for activity in short-term tests	Summary evaluation of carcinogenic risk to humans
Acrylonitrile	limited	sufficient	sufficient	2A
Actinomycin D	inadequate	limited	sufficient	2B
Adriamycin	inadequate	sufficient	sufficient	2B
Aflatoxins	limited	sufficient	sufficient	2A
Aldrin	inadequate	limited	inadequate	3
4-Aminobiphenyl	sufficient	sufficient	sufficient	1
Amitrole	inadequate	sufficient	inadequate	2B
Anaesthetics, volatile	inadequate	inadequate	inadequate	3
Analgesic mixtures containing phenacetin	sufficient	limited	no data	1
Phenacetin	limited	sufficient	limited	2A
Aniline	inadequate	limited	inadequate	3
Arsenic and certain arsenic compounds	sufficient	inadequate	limited	1
Asbestos	sufficient	sufficient	inadequate	1
Auramine (technical grade)	limited	limited	sufficient	2B
Manufacture of auramine	sufficient	-	-	1
Azathioprine	sufficient	limited	sufficient	1
Benzene	sufficient	limited	limited	1
Benzidine	sufficient	sufficient	sufficient	1
Benzidine-based dyes				
Direct Black 38 (technical grade)	inadequate	sufficient	inadequate	2B
Direct Blue 6 (technical grade)	inadequate	sufficient	no data	2B
Direct Brown 95 (technical grade)	inadequate	limited	no data	2B
Beryllium and beryllium compounds	limited	sufficient	inadequate	2A
N,*N*-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	sufficient	limited	limited	1
Bischloroethyl nitrosourea (BCNU)	inadequate	sufficient	sufficient	2B
Bis(chloromethyl)ether and technical-grade chloromethylmethyl ether	sufficient	sufficient	limited	1

* In *IARC Monographs* 1-29, for which data in humans were available

† This table does not include known human carcinogens such as tobacco smoke, betel quid and alcohol beverages, since they have not yet been considered in the *IARC Monographs*.

Chemical, process or industry	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Evidence for activity in short-term tests	Summary evaluation of carcinogenic risk to humans
Bleomycins	inadequate	inadequate	sufficient	3
1,4-Butanediol dimethanesulphonate (Myleran)	sufficient	limited	sufficient	1
Cadmium and cadmium compounds	limited	sufficient	inadequate	2B
Carbon tetrachloride	inadequate	sufficient	inadequate	2B
Certain combined chemotherapy for lymphomas (including MOPP)	sufficient	-	inadequate	1
Chlorambucil	sufficient	sufficient	sufficient	1
Chloramphenicol	limited	inadequate	inadequate	2B
Chlordane/Heptachlor	inadequate	limited	inadequate	3
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)	inadequate	sufficient	sufficient	2B
Chlorinated toluenes (production of):				
Benzyl chloride	inadequate	limited	sufficient	3
Benzoyl chloride	inadequate	inadequate	inadequate	3
Benzal chloride	inadequate	limited	limited	3
Benzotrichloride	inadequate	sufficient	limited	2B
Chloroform	inadequate	sufficient	inadequate	2B
Chlorophenols (occupational exposure to)	limited	-	-	2B
Chloroprene	inadequate	inadequate	sufficient	3
Chromium and certain chromium compounds	sufficient	sufficient	sufficient (Cr VI) inadequate (Cr III)	1
Cisplatin	inadequate	limited	sufficient	2B
Clofibrate	inadequate	limited	inadequate	3
Clomiphene	inadequate	inadequate	no data	3
Cyclamates	inadequate	limited	inadequate	3
Cyclophosphamide	sufficient	sufficient	sufficient	1
2,4-D and esters (See also Phenoxyacetic acid herbicides, occupational exposure to)	inadequate	inadequate	inadequate	3
Dacarbazine	inadequate	sufficient	limited	2B
Dapsone	inadequate	limited	inadequate	3
DDT	inadequate	sufficient	inadequate	2B
ortho-Dichlorobenzene and *para*-Dichlorobenzene	inadequate	inadequate	inadequate	3

Chemical, process or industry	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Evidence for activity in short-term tests	Summary evaluation of carcinogenic risk to humans
3,3′-Dichlorobenzidine	inadequate	sufficient	sufficient	2B
Dichloromethane	inadequate	inadequate	limited	3
Dieldrin	inadequate	limited	inadequate	3
Diethyl sulphate	limited	sufficient	sufficient	2A
3,3′-Dimethoxybenzidine (*ortho*-Dianisidine)	inadequate	sufficient	limited	2B
Dimethylcarbamoyl chloride	inadequate	sufficient	sufficient	2B
Dimethyl sulphate	inadequate	sufficient	sufficient	2A
1,4-Dioxane	inadequate	sufficient	inadequate	2B
Epichlorohydrin	inadequate	sufficient	sufficient	2B
Ethylene dibromide	inadequate	sufficient	sufficient	2B
Ethylene oxide	inadequate	limited	sufficient	2B
Ethylene thiourea	inadequate	sufficient	limited	2B
5-Fluorouracil	inadequate	inadequate	limited	3
Formaldehyde (gas)	inadequate	sufficient	sufficient	2B
Hexachlorocyclohexane	inadequate	limited	inadequate	3
Hydralazine	inadequate	limited	sufficient	3
Hydrazine	inadequate	sufficient	sufficient	2B
Industries				
Boot and shoe manufacture and repair (certain occupations)	sufficient	-	-	1
Carpentry and joinery (certain exposures)	inadequate	-	-	3
Furniture manufacture	sufficient	-	-	1
Leather goods manufacture	inadequate	-	-	3
Leather tanning	inadequate	-	-	3
Lumber and sawmill industry	inadequate	-	-	3
Pulp and paper manufacture (certain exposures)	inadequate	-	-	3
Rubber industry (certain occupations)	sufficient	-	-	1
Iron dextran complex	inadequate	sufficient	inadequate	3
Isonicotinic acid hydrazide	inadequate	limited	limited	3
Lead and lead compounds	inadequate	sufficient (for some salts)	inadequate	3
Manufacture of isopropyl alcohol (strong-acid process)	sufficient	-	-	1
Isopropyl oils	inadequate	inadequate	no data	3
Manufacture of magenta	limited	-	-	2A
Magenta (technical grade)	inadequate	inadequate	inadequate	3
Melphalan	sufficient	sufficient	sufficient	1
6-Mercaptopurine	inadequate	inadequate	sufficient	3

Chemical, process or industry	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Evidence for activity in short-term tests	Summary evaluation of carcinogenic risk to humans
Methotrexate	inadequate	inadequate	sufficient	3
Methoxsalen with ultraviolet A therapy (PUVA)	sufficient	sufficient	sufficient	1
Metronidazole	inadequate	sufficient	limited	2B
Mustard gas	sufficient	limited	sufficient	1
1-Naphthylamine	inadequate	inadequate	sufficient	3
2-Naphthylamine	sufficient	sufficient	sufficient	1
Nickel refining	sufficient	-	-	1
Nickel and certain nickel compounds	limited	sufficient	inadequate	2A
Nitrogen mustard (See also Certain combined chemotherapy for lymphomas)	inadequate	sufficient	sufficient	2A
Oestrogens and progestins				
Combined oral contraceptives	limited*	-	inadequate	2A
Sequential oral contraceptives	limited	-	-	2B
Other oestrogen-progestin combinations	inadequate	-	-	3
Conjugated oestrogens	sufficient	inadequate	inadequate	1
Oestrogens				
Dienoestrol	limited	inadequate	inadequate	2B
Diethylstilboestrol	sufficient	sufficient	inadequate	1
Ethinyloestradiol	inadequate	sufficient	inadequate	2B
Mestranol	inadequate	sufficient	inadequate	2B
Oestradiol-17β	inadequate	sufficient	inadequate	2B
Oestrone	inadequate	sufficient	inadequate	2B
Progestins:				
Chlormadinone acetate	inadequate	limited	inadequate	3
Dimethisterone	inadequate	inadequate	inadequate	3
Ethynodiol diacetate	inadequate	limited	inadequate	3
17α-Hydroxyprogesterone caproate	inadequate	inadequate	no data	3
Lynoestrenol	inadequate	inadequate	inadequate	3
Medroxyprogesterone acetate	inadequate	limited	inadequate	3
Megestrol acetate	inadequate	limited	inadequate	3
Norethisterone	inadequate	sufficient	inadequate	2B
Norethynodrel	inadequate	limited	inadequate	3
Norgestrel	inadequate	inadequate	no data	3
Progesterone	inadequate	sufficient	inadequate	2B

* Sufficient for liver adenomas.

Chemical, process or industry	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Evidence for activity in short-term tests	Summary evaluation of carcinogenic risk to humans
Oxymetholone	limited	no data	no data	2A
Pentachlorophenol (See also Chlorophenols, occupational exposure to)	inadequate	inadequate	inadequate	3
Phenazopyridine	inadequate	sufficient	no data	2B
Phenelzine	inadequate	limited	inadequate	3
Phenobarbital	inadequate	limited	inadequate	3
Phenoxyacetic acid herbicides (occupational exposure to)	limited	-	-	2B
Phenylbutazone	inadequate	no data	inadequate	3
N-Phenyl-2-naphthylamine	inadequate	inadequate	inadequate	3
Phenytoin	limited	limited	inadequate	2B
Polychlorinated biphenyls	inadequate	sufficient	inadequate	2B
Prednisone (See also Certain combined chemotherapy for lymphomas)	inadequate	inadequate	inadequate	3
Procarbazine (See also Certain combined chemotherapy for lymphomas)	inadequate	sufficient	sufficient	2A
Propylthiouracil	inadequate	sufficient	no data	2B
Reserpine	inadequate	limited	inadequate	3
Saccharin	inadequate	limited	inadequate	3
Soots, tars and oils	sufficient	sufficient	-	1
Benzo[*a*]pyrene	inadequate	sufficient	sufficient	2A
Spironolactone	inadequate	limited	no data	3
Styrene	inadequate	limited	sufficient	3
Styrene oxide	inadequate	limited	sufficient	3
Sulfafurazole	inadequate	inadequate	inadequate	3
Sulfamethoxazole	inadequate	limited	inadequate	3
2,4,5-T and esters (See also Phenoxyacetic acid herbicides, occupational exposure to)	inadequate	inadequate	inadequate	3
Tetrachlorodibenzo-*para*-dioxin (TCDD)	inadequate	sufficient	inadequate	2B
Tetrachloroethylene	inadequate	limited	inadequate	3
ortho-Toluidine	inadequate	sufficient	sufficient	2A
Treosulphan	sufficient	no data	inadequate	1
Trichloroethylene	inadequate	limited	inadequate	3
2,4,5-Trichlorophenol (See also Chlorophenols, occupational exposure to)	inadequate	inadequate	no data	3
2,4,6-Trichlorophenol (See also Chlorophenols, occupational exposure to)	inadequate	sufficient	no data	2B

Chemical, process or industry	Evidence for carcinogenicity in humans	Evidence for carcinogenicity in animals	Evidence for activity in short-term tests	Summary evaluation of carcinogenic risk to humans
Tris(aziridinyl)-*para*-benzoquone (Triaziquone)	inadequate	limited	sufficient	2B
Tris(1-aziridinyl)phosphine sulphide (Thiotepa)	inadequate	sufficient	sufficient	2B
Underground haematite mining (with exposure to radon)	sufficient	-	-	I
Haematite	inadequate	inadequate	inadequate	3
Uracil mustard	inadequate	sufficient	sufficient	2B
Vinblastine	inadequate	inadequate	inadequate	3
Vincristine (See also Certain combined chemotherapy for lymphomas)	inadequate	inadequate	inadequate	3
Vinyl chloride	sufficient	sufficient	sufficient	I
Vinylidene chloride	inadequate	limited	sufficient	3

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DESCRIPTIVE SUMMARIES OF THE DATA ON THE BASIS OF WHICH THE CHEMICALS, INDUSTRIAL PROCESSES AND INDUSTRIES WERE EVALUATED FOR CARCINOGENICITY TO HUMANS

ACRYLONITRILE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

As reported previously, 1345 male workers potentially exposed to acrylonitrile and observed for 20 or more years had a greater than expected incidence of lung cancer (8 observed, 4.4 expected) and cancer of the large-intestine (3 observed, 2.2 expected) and prostate (3 observed, 0.9 expected) than other workers in the same company. Mortality from lung cancer was also greater than expected[1,2]. In a similar study, of 1111 male workers exposed to acrylonitrile between 1950 and 1968 and followed for 10 years or more, 5 stomach cancers (1.9 expected), 2 colon cancers (1.1), 2 brain cancers (0.7) and 9 cancers of the respiratory tract (7.6) were observed, 3 of the latter in relatively young men. No allowance was made for latency, however[3]. Two further studies[4,5] are difficult to evaluate because of weaknesses in design and reporting. One of them[5] showed an excess of bronchial cancer (11/5.7) and of tumours of the lymphatic system (4/1.70). Increases in all cancers were seen in three studies: 16/5.8[1,2], 21/18.6[3] and 23/17.5[5].

B. Evidence for carcinogenicity to animals (*sufficient*)

In studies on male and female rats, administration orally and by inhalation of acrylonitrile resulted in tumours of the brain, forestomach and Zymbal gland[1]. A presumed follow-up of one of these studies, in which rats were administered acrylonitrile in drinking-water, showed increased incidences of tumours of the central nervous system, Zymbal gland, squamous stomach, tongue, small intestine and mammary gland at all doses tested[6].

C. Evidence for activity in short-term tests (*sufficient*)

Acrylonitrile induced DNA strand breakage *in vitro*[7]. It was mutagenic in bacteria, in the presence or absence of an exogenous metabolic activation system[1,8,10]. Urine from rats exposed to acrylonitrile by i.p. injection was also mutagenic to *Salmonella*[11,12]. It did not induce chromosomal damage or micronuclei in bone-marrow cells of mice exposed *in vivo*[13], but positive results were obtained in rat bone marrow *in vivo*[14] and in Chinese hamster ovary cells cocultivated with rat hepatocytes as an activation system[15]. It induced cell transformation in Syrian hamster embryo cells[7]. Workers exposed to acrylonitrile did not exhibit evidence of increased chromosomal aberrations in peripheral lymphocytes[16].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	+		+	T(+)
Mammals *(in vivo)*			?	
Humans *(in vivo)*			-	

T = cell transformation

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ACTINOMYCIN D (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Second malignant neoplasms have occurred in patients treated for primary neoplasms with actinomycin and radiation and usually, but not always, with other chemotherapeutic agents[1]. The single analytical study available compared survivors of childhood cancer who developed a second neoplasm with comparable matched survivors who did not, and found that more controls had received treatment with actinomycin D than cases, whose second primary tumours included sarcomas, haematological malignancies, thyroid cancer and other solid tumours[2]. [This observation has not been repeated, but is plausible in view of the radiomimetic properties of actinomycin D, the simultaneous exposure to radiation of patients treated with it, and the modal shape of radiation dose-effect curves in certain laboratory systems.]

B. Evidence for carcinogenicity to animals (*limited*)

Actinomycin D produces peritoneal sarcomas in rats, but not in mice, following repeated intraperitoneal injections[3,4]. A low incidence of subcutaneous sarcomas occurred in mice following repeated subcutaneous injections[3]. No tumour was observed in rats after intragastric administration, but the duration of the experiment was short[5].

C. Evidence for activity in short-term tests (*sufficient*)

Actinomycin D was not mutagenic to bacteria[6] but produced mutations in fungi[3,6,7] and *Drosophila*[3,8]. It induced chromosomal aberrations in mammalian cells *in vitro*[3,9-11]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*			+	
Mammals *(in vivo)*				
Humans *(in vivo)*				

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ADRIAMYCIN (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Acute nonlymphocytic leukaemia[1-3] and osteosarcoma[4] have occurred in patients following treatment in which adriamycin was given in combination with radiotherapy and alkylating agents as treatment for primary neoplasms. No epidemiological study of adriamycin as a single agent was available to the Working Group. [See also the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'.]

B. Evidence for carcinogenicity to animals (*sufficient*)

Adriamycin is carcinogenic in rats, producing mammary tumours after a single intravenous injection[5-8] and local sarcomas after single or repeated subcutaneous injections[9,10].

C. Evidence for activity in short-term tests (*sufficient*)

Adriamycin bound non-covalently to DNA[5]. It was mutagenic in bacteria[5,11] and mammalian cells *in vitro*[11,12]. It caused chromosomal anomalies in hamster cells and human lymphocytes *in vitro*[5,13] and in mouse bone-marrow cells *in vivo*[14-16]. Adriamycin induced sister chromatid exchanges *in vitro*[17] and in mouse embryo cells following injections to pregnant females[16]. It produced cell transformation in Fischer rat embryo cells[5]. Patients treated with adriamycin showed significant increases in the incidence of chromosomal aberrations and sister chromatid exchanges[18,19].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		+	+	T(+)
Mammals *(in vivo)*			+	
Humans *(in vivo)*			+	

T = cell transformation

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AFLATOXINS (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

A positive correlation between estimated aflatoxin intake (or the level of aflatoxin contamination of market food samples) of populations and the incidence of primary liver cancer was observed in epidemiological studies undertaken to test this specific hypothesis[1-4]. A few case reports of cancer (not liver cancer) in scientists working with aflatoxin have been published[5,6]. No study has been carried out, however, which could link an increased risk of liver cancer to actual aflatoxin intake in individuals.

B. Evidence for carcinogenicity to animals (*sufficient*)

Aflatoxins produced liver tumours in mice, rats, fish, ducks, marmosets, tree shrews and monkeys after administration by several routes, including orally. Cancers of the colon and kidney were produced in addition in rats[1]. Recent papers have extended these findings. All rats fed 5 mg/kg of diet aflatoxin B_1 for six weeks developed hepatocarcinomas[7]; rats fed peanut oil containing 5-7 μg/kg aflatoxin B_1 developed parenchymal liver damage but no liver-cell tumours[8]. A series of studies[9,10] have established that aflatoxin B_1 can induce liver tumours in monkeys; osteogenic sarcoma, adenocarcinoma of the gall bladder or bile duct, and carcinomas of the pancreas were also observed. Aflatoxin B_1 also induced liver tumours in the subhuman primate tree shrew *Tupaia glis*[11]. The feeding of aflatoxin B_1 to pregnant rats induced liver and other tumours in the mothers and tumours in the progeny[12].

C. Evidence for activity in short-term tests (*sufficient*)

Aflatoxin B_1 is an extremely potent mutagen in the *Salmonella*/ microsome assay[1,13-21]. It induced forward mutations in *S. typhimurium*[22], induction and mutagenesis of prophage

λ in *Escherichia coli* K12[23] and mutations in *Neurospora crassa*[1,24], in V79 Chinese hamster cells[25] following metabolic activation and in *Drosophila* melanogaster[1,26-29]. It induced chromosomal aberrations[30] and sister chromatid exchanges in mammalian cells *in vitro*[31-35], and chromosomal aberrations in mouse bone marrow *in vivo*[36]. It induced DNA repair[1] and mutagenesis in mammalian cells *in vitro*[37] and transformation of Syrian hamster cells[38], guinea-pig cells[39] and 3T3 cells[40]. Aflatoxin B_1 also induced DNA-repair synthesis in human peripheral lymphocytes[41] and formed the same DNA adducts in human cells as in rodent cells[42]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*			+	
Humans *(in vivo)*				

T = cell transformation

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ALDRIN (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Specific mention of aldrin in analytic epidemiological studies is limited to reports of follow-up of a cohort of men employed in its manufacture in a plant where dieldrin, and later endrin and telodrin, were also manufactured[1,2]. In the most recent report, of 166 men exposed to these compounds for more than four years and 15 or more years before the end of follow-up, two cases of cancer were observed. No estimate was provided of the expected number, and description of follow-up was limited[2].

B. Evidence for carcinogenicity to animals (*limited*)

Aldrin has been tested by the oral route in mice and rats. It was carcinogenic in mice, producing malignant liver neoplasms[1,3,4]; and thyroid tumours were found in rats[3]. Three further studies in rats were negative[1,5] and one was inadequate[1].

C. Evidence for activity in short-term tests (*inadequate*)

Aldrin did not produce damage to *Escherichia coli* plasmid DNA[6] and was not mutagenic to *Salmonella typhimurium*[7] or to yeast[8]. It did not induce recessive lethal mutations in *Drosophila melanogaster*[9]. Aldrin was suggested to induce DNA repair in cultured human fibroblasts and lymphocytes[10,11], but it did not elicit unscheduled DNA synthesis in cultured rat hepatocytes[12]. It was claimed to produce chromosomal aberrations in bone-marrow cells of rats and mice exposed *in vivo* and in blood cells of humans *in vitro*[13], but it did not elicit a positive response in the mouse bone-marrow micronucleus test[14]. No data on humans were available. For a recent review, see reference 15.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		-		
Insects		-		
Mammalian cells *(in vitro)*	-		?	
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

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4-AMINOBIPHENYL (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Epidemiological studies, confined to one series of workers exposed occupationally to commercial 4-aminobiphenyl, showed a high incidence of bladder cancer[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

4-Aminobiphenyl is carcinogenic in mice, rats, rabbits and dogs after oral administration, producing cancer principally of the urinary bladder[1].

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

C. Evidence for activity in short-term tests (*sufficient*)

4-Aminobiphenyl elicited DNA repair in cultured rat hepatocytes[2] and was mutagenic in bacteria in the presence of an exogenous metabolic activation system[3,4]. It was also mutagenic in yeast[5]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	+			
Mammals *(in vivo)*				
Humans *(in vivo)*				

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AMITROLE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

A cohort of 348 railroad workers exposed for 45 days or more to amitrole, 2,4-D or 2,4,5-T were studied in a follow-up study. There was a deficit of deaths from all causes (45 observed, 49 expected) but an excess from malignant neoplasms (17 observed, 11.9

expected). Among those exposed to amitrole but not 2,4-D or 2,4,5-T, there were 5 deaths from cancer (2 lung cancers, 1 pancreatic cancer, 1 reticulum-cell sarcoma and 1 maxillary sinus cancer), with 3.3 expected; and 3 deaths with 2.0 expected in those first exposed 10 years or more before death. Among those exposed to amitrole *and* 2,4-D or 2,4,5-T there were 6 deaths from cancer with 2.9 expected, of which all 6, with 1.8 expected ($p < 0.005$), occurred in those first exposed 10 years or more before death. The men were also exposed to other organic (e.g., monurone and diurone) and inorganic chemicals (e.g., potassium chlorate)[1-3]. In a case-control study covering 110 patients with soft-tissue sarcoma and 220 matched controls, one case and one control had been exposed to amitrole[4].

B. Evidence for carcinogenicity to animals (*sufficient*)

Amitrole is carcinogenic in mice[1,5] and rats[1,6,7], producing thyroid and liver tumours following oral or subcutaneous administration.

C. Evidence for activity in short-term tests (*inadequate*)

Amitrole was not mutagenic in the *Salmonella* assay[8,9], was negative in the *Escherichia coli* pol A system[8] and was not mutagenic to *Drosophila melanogaster*[10]. It was mutagenic and produced chromosomal aberrations in fungi[11] and caused cell transformation in the Syrian embryo transformation assay[12]. No chromosomal abnormality was seen in human lymphocytes *in vitro*[13]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		+	+	
Insects		-		
Mammalian cells *(in vitro)*			-	T(+)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

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ANAESTHETICS, VOLATILE* (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Published data on cancer in humans exposed to anaesthetics have come from postal surveys of cancer incidence among working populations and studies of the mortality of anaesthetists. Among the former[1-4], a higher rate of self-reported cancer was found in one study[2] among female operating room personnel than among controls, partly reflecting an excess of leukaemia and lymphoma. In another study[4], a higher rate of cancers was reported by dental assistants with relatively heavy exposure to anaesthetics; the latter reflected a higher prevalence of cervical and uterine cancer in women with a heavier exposure to anaesthetics than in those with a lighter exposure. All these postal surveys had major shortcomings[5], with response rates varying from 55 to 84.5%. Four mortality studies of anaesthetists[6-9] all found a deficiency of deaths from cancer; in only one study[6] was there an excess of deaths from lymphomas and myelomas (17 *versus* 8.9 expected). In a study of the incidence of cancer among offspring born to nurse-anaesthetists[10], three neoplasms occurred in two of 434 children born to anaesthetists who had worked during pregnancy (a neuroblastoma and a carcinoma of the thyroid in one and a carcinoma of the parotid in the other), and one malignancy (leukaemia) occurred among the 261 children born to anaesthetists who had not worked during pregnancy.

B. Evidence for carcinogenicity to animals (*inadequate*)

Isoflurane was reported to induce liver tumours in mice[1]; but no increase in tumour incidence was seen in mice of the same strain exposed by inhalation to isoflurane, enflurane, halothane, methoxyflurane or nitrous oxide both *in utero* and after delivery and examined after 15 months[11]. No carcinogenic effect was seen in rats exposed chronically to a low level of halothane alone or with nitrous oxide[12]. Halothane, enflurane, methoxyflurane and nitrous oxide were not carcinogenic to mice[13].

C. Evidence for activity in short-term tests (*inadequate*)

The following anaesthetics and their metabolites were negative in bacterial mutation assays employing exogenous metabolic activation: halothane and its metabolite 2-chloro-1,1,1-trifluoroethane[14,15]; enflurane; isoflurane; methoxyflurane; nitrous oxide; cyclopropane; diethyl ether[14]. Two other metabolites of halothane, 2-chloro-1,1-difluoroethylene and 2-bromo-2-chloro-1,1-difluoroethylene, were weakly mutagenic to *Salmonella typhimurium* at near-toxic doses in the absence of an exogenous metabolic activation system[15]. Fluroxene and divinyl ether gave positive results in bacterial mutation assays employing exogenous metabolic activation systems[14]. A report that anaesthesiologists working in unscavenged operating rooms produced urine mutagenic to bacteria[16] was not confirmed in a later study using larger numbers of subjects[14]. Halothane induced

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* This heading includes a variety of compounds which cannot be distinguished one from another in the available studies of human exposure. Chloroform and trichloroethylene, which may occur or have occurred in such exposures, are considered separately.

mitotic gene conversion and gene-reversion in *Saccharomyces cerevisiae*[17]. Halothane and methoxyflurane induced aneuploidy and tetraploidy but not chromosomal breakage in *Vicia faba*[18]. Nitrous oxide increased the mutation rate of petal- and stamen-hair cells of *Tradescantia*[19]; it also induced sex-linked recessive mutations in *Drosophila melanogaster*[20]. The slight increases in sex-linked recessive mutations seen following long-term treatment of flies with halothane were considered indicative of a weak mutagenic effect, although of borderline statistical significance[21]. Nitrous oxide, halothane, enflurane, isoflurane and methoxyflurane did not induce sister chromatid exchanges in cultured Chinese hamster CHO cells, in the presence or absence of an exogenous metabolic activation system. In the same study, the three vinyl-containing compounds, divinyl ether, fluroxene and ethyl vinyl ether, all induced sister chromatid exchanges in the presence of an exogenous metabolic activation system[22]. In assays conducted in the absence of such a system, nitrous oxide, halothane and enflurane did not induce 8-azaguanine-resistant mutants in Chinese hamster V79 cells in culture[14]. Exposure of Chinese hamsters or NMRI-strain mice to clinically-used doses of halothane failed to induce structural chromosomal aberrations, micronuclei, sister chromatid exchanges or dominant lethal mutations[23]. The frequencies of sister chromatid exchanges in lymphocytes cultured from peripheral blood of hospital personnel exposed to anaesthetics were lower than those in lymphocytes from an unexposed group[24].

Halothane

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		+	?	
Insects		?		
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*			-	DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

Cyclopropane

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Methoxyflurane

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Isoflurane

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Nitrous oxide

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*		-	-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Enflurane

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		-	-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Fluroxene

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			+	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Divinyl ether

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			+	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Diethyl ether

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects		-		
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

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ANALGESIC MIXTURES CONTAINING PHENACETIN (Group 1) and PHENACETIN (Group 2A)

A. Evidence for carcinogenicity to humans (*sufficient* for analgesic mixtures containing phenacetin; *limited* for phenacetin)

There have been many case reports of renal pelvic cancer associated with abuse of analgesic mixtures containing phenacetin. Cases of other urinary-tract tumours have also been reported in association with analgesic abuse, but analytical studies have been inconclusive[1]. Recently reported studies include case series[2-6], which replicate the association of cancer of the urinary tract, particularly of the renal pelvis, with analgesic abuse nephropathy. These studies are consistent with earlier reports of younger age at onset, higher case fatality rate and greater female susceptibility to analgesic abuse. One case report[7] indicated a progression of only four months from non-detectable to a surgically resectable papillary transitional-cell carcinoma of the renal pelvis. A report of a large-scale computerized drug prescription screening programme found a non-statistically significant deficit of all cancers, an excess of cancer of the mouth floor, a deficit of breast cancer and no reported deviation from expectation of urinary tract cancer for a combination of aspirin-phenacetin-caffeine-butalbital[8]. In a hospital-based study, patients with interstitial nephritis associated with analgesic abuse had a statistically significantly higher prevalence of transitional-cell carcinoma than patients with interstitial nephritis not associated with analgesic abuse (4/48 *versus* 0/98)[9].

B. Evidence for carcinogenicity to animals (*limited* for analgesic mixtures containing phenacetin; *sufficient* for phenacetin)

In one study in rats, phenacetin induced benign and malignant tumours of the urinary tract and of the nasal cavity in males. When given in combination with aspirin and caffeine to rats or mice, no significant association was found between the administration of the mixture and the incidence of tumours. Phenacetin alone enhanced the urinary bladder carcinogenesis of *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine in rats[1]. In a recent study, renal pelvic tumours and urinary bladder tumours were observed in male rats receiving phenacetin alone or in combination with caffeine. Half of the rats treated with phenacetin, phenazone and caffeine in combination developed hepatomas[9].

C. Evidence for activity in short-term tests (*no data* for analgesic mixtures containing phenacetin; *limited* for phenacetin)

Phenacetin was mutagenic to *Salmonella typhimurium* in the presence of hamster liver microsome preparations, but not in the presence of mouse or rat liver preparations[1,10]. *N*-Hydroxyphenacetin, a minor metabolite of phenacetin in humans, was, however, mutagenic to *Salmonella typhimurium* in the presence of rat liver microsomes[1]. The urine of hamsters treated with phenacetin was mutagenic[11]. Phenacetin did not produce recessive lethals in *Drosophila melanogaster*[1]. It produced chromosomal aberrations in Chinese hamster fibroblasts exposed *in vitro*, particularly in the presence of rat liver microsomes[1]. It did not induce micronuclei in mouse erythrocytes exposed *in vivo*[10]; but it produced marginal increases in aberrations and a doubling of sister chromatid exchange frequencies in rat lymphocytes exposed *in vivo*[12]. No data on humans were available.

Phenacetin

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects		-		
Mammalian cells *(in vitro)*			+	
Mammals *(in vivo)*			?	
Humans *(in vivo)*				

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ANILINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

The excess of bladder cancer deaths observed in clusters of cases in workers in the aniline dye industry has been attributed to exposure to chemicals other than aniline. Epidemiological studies of workers exposed to aniline but to no other known bladder carcinogen have shown little evidence of increased risk. These studies are generally methodologically inadequate due to incomplete follow up of workers who left the industry and to absence of estimates of expected numbers of bladder cancers. The most methodologically rigorous study reported one death from bladder cancer in 1223 men producing or using aniline, with 0.83 deaths expected from population rates[1].

B. Evidence for carcinogenicity to animals (*limited*)

Aniline hydrochloride was not carcinogenic to mice when administered orally. In one experiment in rats by dietary administration it produced fibrosarcomas, sarcomas and haemangiosarcomas of the spleen or the peritoneal cavity[1].

C. Evidence for activity in short-term tests (*inadequate*)

Aniline did not induce DNA repair in bacteria or unscheduled DNA synthesis in mammalian cells[1]. It was not mutagenic in bacteria in the presence or absence of an exogenous metabolic activation system[1,2] but was mutagenic in bacteria exposed to urine from rats treated with aniline, or when the bacteria were exposed in the presence of norharman[1]. It was not mutagenic to yeast[1,2] or insects[2] but induced mutations in mouse lymphoma cells *in vitro*[1]. It did not induce chromosomal aberrations in mammalian cells *in vitro*[1], although marginal increases in sister chromatid exchanges were reported[1-3]. It did not induce chromosomal anomalies in rats or in rat bone-marrow cells *in vivo*[1,2] and did not induce cell transformation in Syrian hamster embryo or BHK cells[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	?		
Fungi/Green plants		-		
Insects		-		
Mammalian cells *(in vitro)*	-	+	-	T(-)
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

T = cell transformation

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ARSENIC AND CERTAIN ARSENIC COMPOUNDS (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Exposure to inorganic arsenic compounds in drugs, drinking-water and occupational environments is causally associated with the development of skin cancer in humans. The risk of lung cancer was increased 4 to 12 times in certain smelter workers who inhaled high levels of arsenic trioxide; however, the influence of other constituents in the working environment could not be excluded. Case reports have suggested an association between exposure to arsenic compounds and the occurrence of blood dyscrasias and liver tumours[1].

B. Evidence for carcinogenicity to animals (*inadequate*)†

Information on the carcinogenicity of arsenic compounds in experimental animals was considered inadequate to make an evaluation[1].

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

† Subsequent to the meeting of the present Group, the Secretariat became aware of a paper by Rudnay *et al.* (*Magyar Onkologia*, *25*(2), 73-77, 1981) indicating an increased incidence of lung tumours in mice exposed to arsenic trioxide pre- and post-natally.

C. Evidence for activity in short-term tests (*limited*)

Sodium arsenite induced DNA damage in a *rec* assay[2,3]. Although arsenic has been reported to be mutagenic in *Escherichia coli*[2,3], microbial assays are generally negative for arsenic derivatives[3,4]. It was not mutagenic in mammalian cells *in vitro*[2]. It induced chromosomal anomalies in *Drosophila melanogaster* and in a wide range of mammalian cells[3], including human peripheral leucocytes[2,3,5]. Sodium arsenite caused a slight increase in chromosomal aberrations in bone-marrow cells of mice treated *in vivo* but did not induce dominant lethal mutation[2]. Cytogenetic analysis of people exposed to arsenic showed significant increases of chromosomal aberrations in peripheral blood lymphocytes[3], but the data did not show a strong correlation between aberration frequency and level of exposure[6].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	-		
Fungi/Green plants				
Insects			+	
Mammalian cells *(in vitro)*		-	+	
Mammals *(in vivo)*			?	DL(-)
Humans *(in vivo)*			+	

DL = dominant lethal mutations

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ASBESTOS (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

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 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 cancers occurred in increased incidence 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 people living with asbestos workers. Cigarette smoking and occupational exposure to asbestos fibres increase lung cancer incidence independently; when they occur together, they act multiplicatively[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

All types of commercial asbestos fibre that have been tested are carcinogenic to mice, rats, hamsters and rabbits, producing mesotheliomas and lung carcinomas after inhalation exposure and after administration intrapleurally, intratracheally or intraperitoneally[1].

C. Evidence for activity in short-term tests (*inadequate*)

Asbestos was not mutagenic in *Salmonella typhimurium* or *Escherichia coli*[2]. It has been claimed to be weakly mutagenic in Chinese hamster cells[3], but negative results in rat epithelial cells were published recently[4]. It has been reported that asbestos produces chromosomal anomalies in mammalian cells in culture[5,6], but this may be secondary to toxic damage. No increase in chromosomal anomalies was seen in cultured human cells treated with asbestos[7]. Sister chromatid exchanges were not increased in treated Chinese hamster cells[8]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		-	?	
Mammals *(in vivo)*				
Humans *(in vivo)*				

* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

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AURAMINE (TECHNICAL-GRADE) (Group 2B) and MANUFACTURE OF AURAMINE (Group 1)

A. Evidence for carcinogenicity to humans (*limited* for auramine and *sufficient* for manufacture of auramine)

The manufacture of auramine (which also involves exposure to other chemicals) was judged to be causally associated with an increased incidence of bladder cancer[1] on the basis of one study[2]. An increased risk of bladder cancer was reported to be associated with the manufacture of auramine in two further studies[3,4]. No information on exposure to auramine alone was available to the Working Group.

B. Evidence for carcinogenicity to animals (*limited* for auramine)

Commercial auramine (of unknown purity) is carcinogenic to mice and rats after its oral administration, producing liver tumours, and after its subcutaneous injection in rats, producing local sarcomas[1]. Two-year feeding of technical-grade auramine to rats resulted

in a slight increase in the incidence of liver-cell tumours and of cholangiomas in females receiving the highest dose (200 mg/kg of diet), but no evidence of a dose-response relationship was noted[3].

C. Evidence for activity in short-term tests (*sufficient* for auramine)

Auramine was positive in tests for DNA repair in bacteria and in mammalian cells in culture, in the presence of exogenous metabolic activation[5]. It gave contradictory results in bacterial mutation tests[5]. In one experiment in yeast it was mutagenic in the presence of an exogenous metabolic activation system[6]. In single experiments, auramine induced sister chromatid exchanges in mammalian cells in culture[5] and cell transformation (in BHK21 cells)[5]. It was negative in a micronucleus test in mice[5]. No data on humans were available.

Auramine (technical-grade)

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	?		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	+		+	T(+)
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

T = cell transformation

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AZATHIOPRINE (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Two large prospective epidemiological studies have shown that renal transplant patients (who receive azathioprine and prednisone almost routinely) experience increased incidences of non-Hodgkin's lymphomas, squamous-cell cancers of the skin, hepatobiliary carcinomas and mesenchymal tumours. One study of non-transplant patients treated with azathioprine showed an increased incidence of the same cancers as in transplant recipients, although to a lesser extent, indicating that the presence of the graft may contribute to the higher incidence[1].

B. Evidence for carcinogenicity to animals (*limited*)

Suggestive evidence was obtained that lymphomas are induced in mice after intraperitoneal, subcutaneous or intramuscular injection of azathioprine, and that ear-duct carcinomas are induced in rats after its oral administration. Because of limitations in design and reporting, however, the results were considered to be inconclusive[1].

C. Evidence for activity in short-term tests (*sufficient*)

Azathioprine produced mutations in bacteria, fungi and *Drosophila melanogaster*[1]. Conflicting results have been obtained regarding the induction of chromosomal abnormalities in mammalian cells and in human lymphocytes *in vitro* and regarding dominant lethal effects in mice[1,2]. Azathioprine caused morphological abnormalities in spermatids and increases in micronuclei in mice treated *in vivo*[1]. Lymphocytes from patients treated with this compound showed no chromosomal abnormalities[2].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+		
Insects		+		DL(+)
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*			+	DL(?) SA(+)
Humans *(in vivo)*			-	

DL = dominant lethal mutations ; SA = sperm abnormalities

References

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BENZAL CHLORIDE (Group 3) (See Chlorinated toluenes, production of)

BENZENE (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Several case reports and an epidemiological case-control study suggest a relationship between exposure to benzene and the occurrence of leukaemia. Two cohort studies demonstrated an increased incidence of acute nonlymphocytic leukaemia in workers exposed to benzene. There has been an additional report of a large number of cases of leukaemia (most of which were acute nonlymphocytic) among a group of workers exposed to benzene[1].

B. Evidence for carcinogenicity to animals (*limited*)

No evidence of carcinogenicity was seen in mice that received benzene by skin application. Other experiments in animals were considered to be inadequate to evaluate the carcinogenicity of benzene[1].

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

C. Evidence for activity in short-term tests (*limited*)

Benzene was not mutagenic in bacteria, yeast, *Drosophila melanogaster*, mouse lymphoma cells in culture or mammalian cells *in vivo*[2]. It induced chromosomal anomalies in mammalian cells *in vitro*[2] and in mice and rats but not in Chinese hamsters[3] *in vivo*. It did not induce dominant lethal mutations in mice[2]. Benzene induced chromosomal anomalies in occupationally exposed people[2].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		-		
Insects		-		
Mammalian cells *(in vitro)*		-	+	
Mammals *(in vivo)*		-	+	DL(-)
Humans *(in vivo)*			+	

DL = dominant lethal mutations

References

[1] *IARC Monographs, Suppl. 1*, 24, 1979

2 *IARC Monographs, 29*, 93-148, 1982

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BENZIDINE (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

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

* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

B. Evidence for carcinogenicity to animals (*sufficient*)

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

C. Evidence for activity in short-term tests (*sufficient*)

Benzidine produces indirect evidence of DNA repair in bacteria; there are conflicting reports of its ability to induce DNA repair in mammalian cells *in vitro*[2]. It was mutagenic to bacteria in the presence of an exogenous metabolic activation system[2,3]. There are conflicting reports of its genetic activity: it probably induced mutation, gene conversion and aneuploidy in yeasts[2,3]; one study in *Drosophila melanogaster* was positive for mutations[2] and three others negative[3]. Benzidine induced mutation, sister chromatid exchanges and chromosomal aberrations in mammalian cells treated *in vitro*, in the presence of an exogenous metabolic activation system[3]. There are conflicting reports on its ability to induce chromosomal anomalies in mice treated *in vivo*[3], and it gave inconsistent results in sperm abnormality assays in mice treated *in vivo*[3]. It caused cell transformation (in BHK21 cells)[3]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+	+	
Insects		?		
Mammalian cells *(in vitro)*	?	+	+	T(+)
Mammals *(in vivo)*			?	SA(?)
Humans *(in vivo)*				

T = cell transformation ; SA = sperm abnormalities

References

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[2] *IARC Monographs, 29*, 151-183, 1982

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BENZIDINE-BASED DYES:

DIRECT BLACK 38 (TECHNICAL-GRADE) (Group 2B)
DIRECT BLUE 6 (TECHNICAL-GRADE) (Group 2B)
DIRECT BROWN 95 (TECHNICAL-GRADE) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate* for Direct Black 38, Direct Blue 6 and Direct Brown 95)

The epidemiological data were inadequate to evaluate the carcinogenicity to man of the three benzidine-based dyes, Direct Black 38, Direct Blue 6 and Direct Brown 95. However, a study of silk dyers and painters who had had multiple exposure to benzidine-based and other dyes indicated that those exposures were strongly associated with the occurrence of bladder cancer. Benzidine has been detected in the urine of workers exposed to direct azo dyes[1].

B. Evidence for carcinogenicity to animals (*sufficient* for Direct Black 38 and Direct Blue 6, *limited* for Direct Brown 95)

Commercial *Direct Black 38* is carcinogenic to experimental animals after oral exposure: administration to mice in drinking-water produced liver and mammary tumours; administration to rats in the diet produced hepatocellular carcinomas within 13 weeks. In another study in rats, in which the dye was administered in drinking-water, small numbers of carcinomas were found in the urinary bladder, liver and colon. Commercial material may contain small quantities of two other animal carcinogens, 4-aminobiphenyl and 2,4-diaminobenzene[1].

In a single study, *Direct Blue 6* produced hepatocellular carcinomas in rats within 13 weeks after its oral administration. The commercial product contains small amounts of benzidine[1].

Direct Brown 95 produced neoplastic nodules in the liver and one hepatocellular carcinoma in 10 female rats after its oral administration, in a single study terminated after 13 weeks. The finding of preneoplastic lesions after such a short exposure period indicates a carcinogenic effect similar to that of Direct Black 38 and Direct Blue6[1]. In rats, mice and monkeys, oral administration of Direct Brown 95 is followed by excretion of benzidine in the urine.

C. Evidence for activity in short-term tests (*inadequate* for Direct Black 38, *no data* for Direct Blue 6 and Direct Brown 95)

Direct Black 38 was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic activation system[1]. No data on the mutagenicity of Direct Blue 6 or Direct Brown 95 were available to the Working Group. No data on humans were available.

Direct Black 38

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Reference

[1] *IARC Monographs, 29*, 295-330, 1982

BENZO[*a*]PYRENE (Group 2A) (See Soots, tars and oils)

BENZOTRICHLORIDE (Group 2B) (See Chlorinated toluenes, production of)

BENZOYL CHLORIDE (Group 3) (See Chlorinated toluenes, production of)

BENZYL CHLORIDE (Group 3) (See Chlorinated toluenes, production of)

BERYLLIUM AND CERTAIN BERYLLIUM COMPOUNDS (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

Four early epidemiological studies and three recent ones of occupational exposure to beryllium were considered to provide limited evidence that exposure to beryllium may lead to human lung cancer[1]. The data for most of the studies were derived from two beryllium plants and from the Beryllium Case Registry. Although 55 new cases of beryllium disease were registered between 1973 and 1977[2], no further data were available on the incidence of lung cancer. An analysis of the pathology of the 47 lung cancers noted in one study[3] confirmed the post-mortem diagnosis of lung cancer in 32 of the 37 cases available for review[4]; no one cell type predominated. Of the 47 cases, 21 were noted to have been smokers, but the smoking histories of the other cases were not given.

B. Evidence for carcinogenicity to animals (*sufficient*)

Beryllium compounds are carcinogenic in rats, rabbits and monkeys. Beryllium metal, beryllium-aluminium alloy, beryl ore, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium sulphate (or its tetrahydrate)[1] and beryllium oxide[5] all produce lung tumours in rats exposed by inhalation or intratracheally. Beryllium oxide and beryllium sulphate produce lung tumours in monkeys after intrabronchial implantation or inhalation. Beryllium metal, beryllium carbonate, beryllium oxide, beryllium phosphate, beryllium silicate and zinc beryllium silicate all produce osteosarcomas in rabbits following their intravenous and/or intramedullary administration[1].

C. Evidence for activity in short-term tests (*inadequate*)

Beryllium sulphate did not elicit unscheduled DNA synthesis in mammalian cells in culture. It was not mutagenic in bacteria[1]. There is some evidence that beryllium induces mutation in V79 cells *in vitro*[6], and conflicting evidence that it induces chromosomal aberrations in cultured mammalian cells[1]. It induced cell transformation in Syrian hamster embryo cells[1,7]. It caused misincorporation of nucleotides in an in-vitro DNA-transcription assay[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	-	?	?	T(+)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

References

[1] *IARC Monographs*, *23*, 185-190, 1980

[2] Sprince, N.L. & Kazemi, H. (1980) US Beryllium Case Registry through 1977. *Environ. Res.*, *21*, 44-47

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

A. Evidence for carcinogenicity to humans (*sufficient*)

The administration of chlornaphazine together with radioactive phosphorus (^{32}P-sodium phosphate) caused bladder cancer in 10 of 61 patients treated in this way for polycythemia vera. No case of bladder cancer was found among 46 patients treated with ^{32}P-sodium phosphate alone[1].

B. Evidence for carcinogenicity to animals (*limited*)

Chlornaphazine produces lung tumours in mice following its intraperitoneal injection, and local sarcomas in rats after its subcutaneous administration[1].

C. Evidence for activity in short-term tests (*limited*)

N,N-Bis(2-chloroethyl)-2-naphthylamine was weakly mutagenic in *Salmonella typhimurium*; its activity was substantially increased by the presence of an exogenous metabolic activation system[2]. It was also mutagenic in *Drosophila melanogaster*, producing sex-linked recessive lethal mutations and small chromosome deletions[3]. No data on humans were available.

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

References

[1] *IARC Monographs, Suppl. 1*, p. 26, 1979

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BISCHLOROETHYL NITROSOUREA (BCNU) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

BCNU has been associated in case reports with the development of acute nonlymphocytic leukaemia following its use for the treatment of primary malignant diseases. In all such cases, BCNU was administered with other anticancer therapies known or suspected of being carcinogenic[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

BCNU is carcinogenic to rats, producing tumours of the lung after its intraperitoneal or intravenous administration, and intra-abdominal tumours after its intraperitoneal administration. Tests in mice by intraperitoneal administration and in rats by oral administration could not be evaluated. When tested in mice by skin application together with ultra-violet B irradiation, BCNU caused an earlier appearance of skin tumours[1]. Two studies by skin painting in mice were inadequate[1,2].

C. Evidence for activity in short-term tests (*sufficient*)

BCNU, a directly-acting alkylating agent, reacted with DNA *in vitro* and induced mutations in bacteria and *Drosophila melanogaster* and in mammalian cells *in vitro*[1]. It produced chromosomal aberrations and sister chromatid exchange in bone-marrow cells of mice exposed *in vivo*[3]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*		+		
Mammals *(in vivo)*			+	
Humans *(in vivo)*				

References

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BIS(CHLOROMETHYL)ETHER AND TECHNICAL-GRADE CHLOROMETHYL METHYL ETHER (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Two studies of workers exposed to bis(chloromethyl)ether (BCME) and technical-grade chloromethyl methyl ether (CMME) showed that they had an increased risk of lung cancer, mainly oat-cell carcinoma. Two subsequent studies showed a positive association

* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

between the presence of atypical cells in bronchial excretions and exposure to BCME, which was not related to cigarette smoking. Several studies have demonstrated significant excesses of lung cancer, predominantly oat-cell carcinoma, among workers exposed to BCME or CMME, which were related directly to intensity and duration of exposure. The excesses of mortality from respiratory cancer were most marked among workers under 55 years of age. The evaluation of the carcinogenicity of CMME alone is complicated by the presence in it of 1-8% BCME as a contaminant[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

BCME produces tumours at the site of its administration after exposure by inhalation, skin application or subcutaneous injection, and in rats after inhalation or subcutaneous administration. Technical-grade CMME produces local sarcomas in mice after subcutaneous administration and is an initiator of skin tumours[1].

C. Evidence for activity in short-term tests (*limited*)

BCME is an alkylating agent which forms adducts with DNA *in vitro*[2,3]. It is mutagenic to bacteria in the absence of an exogenous metabolic activation system[4-6]. CMME is mutagenic to bacteria[6]. No data on humans were available.

BCME

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

CMME

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

References

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BLEOMYCINS (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

The development of acute nonlymphocytic leukaemia following the administration of bleomycins with many other cytotoxic agents has been described in patients with Hodgkin's disease or non-Hodgkin's lymphoma. In a small epidemiological study of short duration, no excess of subsequent neoplasms was observed in patients treated with a regimen consisting of bleomycins, adriamycin, vinblastine and dacarbazine[1]. [See also the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'.]

B. Evidence for carcinogenicity to animals (*inadequate*)

The two available studies[1] could not be evaluated because of incomplete reporting.

C. Evidence for activity in short-term tests (*sufficient*)

Bleomycin induced single- and double-strand DNA breaks and chromosomal damage in mammalian cells in culture[2,3]; it was also positive in the inductest in *Escherichia coli*[4]. The compound was negative in the *Salmonella*/microsome mutagenesis assay[1], but reports of the induction of point mutations are contradictory[5]. In *Saccharomyces cerevisiae*, positive[1], negative and antimutagenic effects have been reported; an abstract

reported that it was mutagenic in *Aspergillus nidulans*[6]. It was mutagenic in *Drosophila melanogaster*[1,7]. Bleomycin produced chromosomal aberrations in cultured mammalian cells[2] and in spermatogonia and bone-marrow cells of mice treated *in vivo*[8]. Bleomycin caused cell transformation in C3H 10T½ cells[1]. Lymphocytes and bone-marrow cells from patients treated with bleomycin alone[1,9] or with radiation[10] showed chromosomal aberrations.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	-		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+		+	T(+)
Mammals *(in vivo)*			+	
Humans *(in vivo)*			+	

T = cell transformation

References

[1] *IARC Monographs*, *26*, 97-113, 1981

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BOOT AND SHOE MANUFACTURE AND REPAIR (CERTAIN OCCUPATIONS) (Group 1) (See Industries)

1,4-BUTANEDIOL DIMETHANESULPHONATE (MYLERAN) (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Many cytological abnormalities, including giant nuclei[1], cytomegaly[2] and dysplasia[3] have been observed in leukaemia patients treated with myleran; in one instance, cytomegaly was seen in an infant who was *in utero* during treatment of the mother[4]. A patient treated with myleran for polycythemia vera developed acute and chronic haemolysis, pancytopenia, erythroid hyperplasia, dyserythropoiesis, and circulating normoblasts, all of which reverted to normal after cessation of myleran therapy[5]. Carcinoma of the breast[6] and of the vulva[7] have been seen in association with similar cytological abnormalities in the respective solid tissues. One case of acute nonlymphocytic leukaemia has also been reported in a patient with polycythemia vera treated with myleran[8]. After surgical removal of all visible intrathoracic lung cancer, 726 patients in London were allocated at random to treatment with myleran (243), cyclophosphamide (234) or placebo (249)[9]. After five years, 69 patients who received myleran, 63 who received cyclophosphamide and 85 who received placebo were still alive. By nine years, pancytopenia had developed in 20 of the patients, 19 of whom had received myleran; of these 19, four developed and died from acute nonlymphocytic leukaemia. While none of these were among the 15% of patients treated with myleran who also received radiotherapy and/or other cytotoxic drugs, no relationship was observed between cumulative dose of myleran and either pancytopenia or leukaemia. Solid tumours occurred in 19 other patients in the study but were approximately equally divided among the three drug groups.

B. Evidence for carcinogenicity to animals (*limited*)

Intraperitoneal administration of myleran to mice did not increase the incidence of tumours in two studies[6,10] but induced T-cell lymphoma in male mice in another study[11]; the effect was markedly enhanced by combined administration with chloramphenicol.

This result was confirmed[12], but the experiment could not be evaluated due to incomplete reporting. Intravenous administration of myleran to mice significantly increased the incidence of thymic and ovarian tumours[6], and treatment of mice by an unspecified route induced a variety of pulmonary lesions including a 6% incidence of adenomas[13]. Oral administration to rats of myleran did not increase the incidence of tumours[6], and the incidence of mammary tumours was not increased after intraperitoneal injection, but near lethal doses were used and the animals were followed for only five months[14]. It was reported that intravenous administration of 7% of the LD_{50} dose induced a variety of tumours in male rats, however the experiments could not be evaluated[15].

C. Evidence for activity in short-term tests (*sufficient*)

Myleran is an alkylating agent. It was positive in a test for DNA damage and was mutagenic in *Salmonella typhimurium*[16], *Drosophila melanogaster*[17] and barley[18]. Myleran induced chromosomal aberrations in barley[18] and in intact rodents[19,20] and chromosomal aberrations and sister chromatid exchanges in cultured human cells[21,22]. It induced dominant lethal mutations in a teleost fish[23] and in rodents[24] but was negative in the mouse specific locus test[25]. It induced cell transformation in BHK cells[16]. Myleran induced chromosomal aberrations and sister chromatid exchanges in lymphocytes and bone-marrow cells from patients treated with this drug for chronic myeloid leukaemia[26].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+	+	
Insects		+		
Mammalian cells *(in vitro)*		+	+	T(+)
Mammals *(in vivo)*			+	DL(+)
Humans *(in vivo)*			+	

T = cell transformation ; DL = dominant lethal mutations

References

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CADMIUM AND CERTAIN CADMIUM COMPOUNDS (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

Studies have suggested that human exposure to cadmium (primarily as the oxide) is associated with increased risks of prostatic, respiratory and genito-urinary cancers[1,2], although in some cases the excess risk was not statistically significant. Three further studies have been reported. One is a follow-up of an investigation of 269 cadmium-nickel battery workers and 94 cadmium-copper alloy factory workers[3]. Additional cases of nasopharyngeal, colorectal, prostatic and lung cancer increased the already elevated relative risks. A separate study[4] of 347 cadmium-copper alloy workers exposed to cadmium fume has been reported, in which their mortality is compared with that of workers exposed indirectly to cadmium but also to arsenic. A third group of iron or brass founders was included, and the mortality rates were compared separately with statistics for the general population. The study shows a significant increase in deaths from prostatic, genito-urinary and lung cancers in people working in the vicinity, but not in the cadmium workers themselves. Insufficient information is given regarding the movement of men between or out of the three adjacent plants to assess the relative contribution of arsenic, cadmium or smoking to the results (which run counter to those of most other studies). A preliminary report has been published[5] of a mortality study of 3026 nickel-cadmium battery workers over the period 1923-1975, with an analysis of 659 deaths. The standardized mortality ratio for all cancers was 100, and no statistically significant excess

was noted for cancer at any major site, including the prostate. The limitations and inconsistencies in the epidemiological studies persuaded the Group that it was still far from clear which were the target organs for the putative carcinogenic action of cadmium in humans.

B. Evidence for carcinogenicity to animals (*sufficient*)

Cadmium chloride, oxide, sulphate and sulphide are carcinogenic in rats, causing local sarcomas after their subcutaneous injection. Cadmium powder and cadmium sulphide produce local sarcomas in rats following their intramuscular administration. Cadmium chloride and cadmium sulphate produce testicular atrophy followed by testicular tumours in mice and rats after their subcutaneous administration[1,6]. Administration of up to 50 mg/kg (ppm) cadmium chloride in the diet to rats did not produce tumours[7].

C. Evidence for activity in short-term tests (*inadequate*)

There are conflicting data with regard to the induction by cadmium of DNA damage and mutagenicity in bacteria and yeast[8-10]. Cadmium was not mutagenic in *Drosophila melanogaster*[10]. It produced chromosomal aberrations in human and mammalian cells *in vitro*[11-14]. It did not induce dominant lethal effects or sperm abnormalities in mice[10,15], but cadmium acetate transformed Syrian hamster embryo cells[16]. There was conflicting evidence with regard to the production of chromosomal aberrations in exposed people[1,17].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	?	?		
Fungi/Green plants		?		
Insects		-		
Mammalian cells *(in vitro)*			+	T(+)
Mammals *(in vivo)*				DL(-) SA(-)
Humans *(in vivo)*			?	

T = cell transformation ; DL = dominant lethal mutations; SA = sperm abnormalities

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CARBON TETRACHLORIDE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three case reports describe the occurrence of liver tumours associated with cirrhosis in people who had been exposed to carbon tetrachloride[1]. A mortality study of laundry and dry-cleaning workers exposed to a variety of solvents suggests excesses of respiratory cancers (17 observed, 10.0 expected), cervical cancers (10 observed, 4.8 expected), liver tumours (4 observed, 1.7 expected) and leukaemia (5 observed, 2.2 expected)[2].

B. Evidence for carcinogenicity to animals (*sufficient*)

Carbon tetrachloride is carcinogenic to mice and rats, producing liver neoplasms after its administration by various routes[1,3] and mammary neoplasms in rats following its subcutaneous injection[1]. It also produced liver tumours in trout and hamsters following its oral administration[1], although these studies were not totally adequate.

C. Evidence for activity in short-term tests (*inadequate*)

Carbon tetrachloride was not mutagenic in bacteria[1,4]. It was mutagenic in yeast at almost lethal doses[5]. It did not induce chromosomal damage in cultured rat liver epithelial cells[6] and did not induce unscheduled DNA synthesis in the hepatocytes of rats exposed *in vivo*[7]. Studies of DNA binding were inadequate[1,8,9]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		?		
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*	-			
Humans *(in vivo)*				

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CARPENTRY AND JOINERY (CERTAIN OCCUPATIONS) (Group 3) (See Industries)

CERTAIN COMBINED CHEMOTHERAPY FOR LYMPHOMAS (INCLUDING MOPP) (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Many cases of malignancy have been reported following chemotherapy for Hodgkin's disease and non-Hodgkin's lymphoma[1]. Most have been acute nonlymphocytic leukaemia[1,2], but there have also been cases of non-Hodgkin's lymphoma[1,3-6] and solid tumours[1,7,8]. In 613 consecutive patients with Hodgkin's disease followed for two to ten years after treatment with chemotherapy (152), radiotherapy (117) or chemotherapy plus radiotherapy (344)[9], acute nonlymphocytic leukaemia appeared in 2, 0 and 5 patients, respectively, and solid tumours (central nervous system, thyroid, stomach, lung, nasal) in 1, 0 and 4 of them. The actuarial frequency of leukaemia and of solid tumours five to seven years after therapy was about 2%; while no expected number of second malignancies was computed, it is presumed to be much lower. Of 1094 patients with

Hodgkin's disease treated with MOPP, 31 developed solid tumours (at various sites), a frequency estimated to comprise an actuarial risk of over 5% at 10 years. This risk was consistently higher in subsets receiving combined chemotherapy[10,11]. Five cases of acute nonlymphocytic leukaemia arose after treatment for non-Hodgkin's lymphoma, mostly with MOPP[12], representing an actuarial risk of 4.5% at five years. No expected risk was calculated. No difference between the observed (31) and expected (26) numbers of second malignant neoplasms was found in a review of 630 cases of non-Hodgkin's lymphoma diagnosed from 1968-1978[13]. The cases survived for a total of 2059 person-years beginning six months after diagnosis. No case of acute leukaemia was seen.

B. Evidence for carcinogenicity to animals

No data were available.

C. Evidence for activity in short-term tests (*inadequate*)

An increase in the frequency of sister chromatid exchange was seen in nurses handling cytostatic drugs[14].

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CHLORAMBUCIL (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

At least 46 cases of leukaemia, mostly acute nonlymphocytic, and some solid tumours have been reported to occur in patients treated for nonmalignant disease with courses of chlormabucil, mostly in the absence of radiation or other cytotoxic drugs[1-4]. Following chlorambucil therapy for malignant diseases (mostly Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and ovarian cancer), at least 43 subsequent neoplasms have been reported, of which 40 were acute leukaemia[1,5-7]. In four cases, chlorambucil was the only therapy used[1]. An equivalent number of non-Hodgkin's lymphomas have occurred in patients treated with chlorambucil for chronic lymphatic leukaemia[8], but such occurrences had been recognized before the use of chlorambucil[9] and may therefore reflect the natural history of the underlying disease. Two patients treated with chlorambucil and cyclophosphamide were reported to have developed bladder cancer[1]. Of 300 infants treated with chlorambucil for glomerulonephritis over a 10-year period, two developed acute leukaemia and one a hypernephroma. One of the patients with leukaemia had also received nitrogen mustard. Three of 40 children with severe juvenile arthritis treated with chlorambucil and followed for up to 15 years developed acute nonlymphocytic leukaemia, whereas none occurred in 160 other children not treated with chlorambucil[1].

Excesses of acute leukaemia were reported in a number of epidemiological studies of people treated with chlorambucil, either alone or in combination with other therapies, for both nonmalignant and malignant diseases[1]. Other cancers have also been associated with use of chlorambucil and other agents[1]. An excess of acute leukaemia in association with chlorambucil was seen in a further study[10], in which 431 previously untreated patients with polycythemia vera were given phlebotomy alone, chlorambucil with phlebotomy or radioactive phosphorus with phlebotomy, and followed for a mean of 6.5 years. Of the 26 cases of acute leukaemia that occurred, 16 were in the group receiving chlorambucil. The risk increased with increasing dose and time of treatment.

B. Evidence for carcinogenicity to animals (*sufficient*)

Chlorambucil has been tested in mice and rats by intraperitoneal injection: it produced tumours of the lung in mice and probably produced tumours of the haematopoietic system and ovary in mice and haematopoietic tumours in male rats. It was also tested in a two-stage skin carcinogenesis experiment in mice, in which it had an initiating effect[1].

C. Evidence for activity in short-term tests (*sufficient*)

Chlorambucil is an alkylating agent and interacts with DNA in mammalian cells *in vitro*. It induced mutations in bacteria and fungi in the absence of an exogenous metabolic activation system; it caused chromosomal aberrations in human cells *in vitro* and in rat embryos *in vivo*. Small increases in chromatid-type chromosomal damage have been observed in bone-marrow cells and peripheral lymphocytes from patients treated with chlorambucil for a variety of diseases[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	+		+	
Mammals *(in vivo)*			+	
Humans *(in vivo)*			?	

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CHLORAMPHENICOL (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

Case reports have described leukaemia in patients following chloramphenicol-induced aplastic anaemia[1,2]. A follow-up study described three cases of leukaemia in 126 patients who had had bone-marrow depression following treatment with chloramphenicol[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

No adequate test for the carcinogenicity of chloramphenicol in experimental animals was available[1,3].

C. Evidence for activity in short-term tests (*inadequate*)

Chloramphenicol did not induce DNA damage or mutation in bacteria[1,4]. There is questionable evidence that chromosomal aberrations were induced in human lymphocytes *in vitro*[5,6]. Chloramphenicol did not induce dominant lethal mutations[7] and did not produce chromosomal aberrations in mice *in vivo*[8]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*			-	DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

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CHLORDANE/HEPTACHLOR (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

These compounds were evaluated together because they are structurally similar and because technical-grade chlordane contains 3-10% heptachlor.

Domestic use of chlordane has been reported to be associated with cases of neuroblastoma and acute leukaemia. Aplastic anaemia and blood dyscrasias have also been associated with exposure to chlordane and heptachlor[1]. Follow-up of 16 126 pesticides applicators in the US[2] showed a deficit of deaths from all cancers but small excesses of deaths from cancer of the lung, skin and bladder. These site-specific excesses were no more evident in termite-control workers (with particular exposure to chlordane and heptachlor) than in other pesticide applicators, and did not appear to be related to intensity of exposure or time since first exposure to pesticides. Follow-up of 1403 men in two factories where chlordane, and heptachlor and endrin were manufactured, respectively[3], also showed a deficit of deaths from all cancers and a small excess of lung cancer. The latter did not relate positively to time since first exposure. Neither study documented smoking habits.

B. Evidence for carcinogenicity to animals (*limited*)

Chlordane and heptachlor (which contained about 20% chlordane) were carcinogenic in mice, producing liver neoplasms following their oral administration[1,4]. Data concerning rats were inconclusive[1].

C. Evidence for activity in short-term tests (*inadequate*)

Neither chlordane nor heptachlor was mutagenic in bacterial systems[1], and neither produced breaks in *Escherichia coli* plasmid DNA[5]. Heptachlor was not mutagenic in *Drosophila melanogaster*[1]. Although chlordane and heptachlor were claimed to have produced unscheduled DNA synthesis in human fibroblasts[1], neither compound did so in cultured mouse, rat or hamster hepatocytes[6-8]. Chlordane was claimed to have induced ouabain-resistant mutants in Chinese hamster V79 cells[1] and was possibly weakly mutagenic at the HGPRT locus in cultured rat liver epithelial cells[6]. Chlordane was not mutagenic to human foreskin fibroblasts in a rat hepatocyte-mediated mutagenesis assay[9], and heptachlor was not mutagenic in cultured rat liver epithelial cells[6]. Heptachlor was claimed to have produced chromosomal aberrations in the bone-marrow cells of mice[1]. Chlordane and heptachlor were both negative in dominant lethal tests in mice[1]. No data on humans were available.

Chlordane

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	-	-		
Mammals *(in vivo)*				DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

Heptachlor

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants				
Insects		-		
Mammalian cells *(in vitro)*	-	-	?	
Mammals *(in vivo)*				DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

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1-(2-CHLOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA (CCNU) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Several case reports describe the development of acute nonlymphocytic leukaemia in cancer patients who had received CCNU. With one exception, all such patients had also received other cytotoxic agents and/or irradiation[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

CCNU is carcinogenic in rats following its intraperitoneal or intravenous injection, producing lung carcinomas. It was also tested in mice by intraperitoneal injection: a slight increase in the incidence of lymphomas was observed[1]. In one study by skin application to mice[2], no skin tumour was observed, but the duration of the experiment was inadequate.

C. Evidence for activity in short-term tests (*sufficient*)

CCNU, a directly-acting alkylating agent, reacts with DNA[3]. It induced mutations in bacteria in the absence of an exogenous metabolic activation system and induced mutations in Chinese hamster cells *in vitro*[1]. It induced sister chromatid exchanges in blood lymphocytes from patients treated *in vivo*[1,4].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		+		
Mammals *(in vivo)*				
Humans *(in vivo)*			+	

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CHLORINATED TOLUENES, PRODUCTION OF:

BENZAL CHLORIDE (Group 3)
BENZOTRICHLORIDE (Group 2B)
BENZOYL CHLORIDE (Group 3)
BENZYL CHLORIDE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate* for benzal chloride, benzotrichloride, benzoyl chloride and benzyl chloride)

Six cases of respiratory cancer were reported among workers in two small factories where benzoyl chloride and its chlorinated precursors were produced[1]. As the production processes involved exposures to all four compounds, no evaluation of any one compound alone could be made. However, the epidemiological data provide limited evidence that employment in the production of chlorinated toluenes, which involves potential exposure to each, presents a carcinogenic risk to man.

B. Evidence for carcinogenicity to animals (*sufficient* for benzotrichloride, *limited* for benzyl chloride and benzal chloride and *inadequate* for benzoyl chloride)

Benzyl chloride was tested in mice by skin application and in rats by subcutaneous injection. Sarcomas at the injection site were observed in rats; a few skin carcinomas were observed in a limited number of mice, but their incidence was not statistically significant[1]. *Benzoyl chloride* was tested in two sets of experiments by skin application to female mice. A few skin carcinomas were observed, but their incidence was not statistically significant[1].

In one experiment in which *benzal chloride* was tested by skin application to female mice, it produced squamous-cell carcinomas of the skin. In a concurrent experiment in which it was tested for a shorter duration, a low incidence of skin papillomas was observed[1].

Benzotrichloride was tested in three studies by skin application to female mice. It produced squamous-cell carcinomas of the skin in all three experiments; upper-digestive-tract tumours were also observed in two of the three experiments. An increase in the incidence of tumours at other sites was reported[1].

C. Evidence for activity in short-term tests (*sufficient* for benzyl chloride, *limited* for benzal chloride and benzotrichloride and *inadequate* for benzoyl chloride)

Benzyl chloride, an alkylating agent, produced DNA damage in bacteria and induced unscheduled DNA synthesis in mammalian cells *in vitro*[2]. It was mutagenic in bacteria in the absence of an exogenous metabolic activation system, in mammalian cells *in vitro* and in yeasts[1,2]. There were conflicting results concerning its mutagenicity to *Drosophila melanogaster*[2]. Benzyl chloride alkylated the DNA of brain, testis, liver, lung and spleen of mice given single intravenous injections[1]. It induced chromosomal aberrations and sister chromatid exchanges in rodent cells *in vitro*[1,2] and no chromosomal anomaly but sister chromatid exchanges in human lymphocytes *in vitro*[2]. It transformed Syrian hamster embryo cells[1]. No sperm abnormality was seen in mice *in vivo*, and it was negative in micronucleus tests in mice[2]. No data on humans were available.

Benzoyl chloride did not induce DNA damage in prokaryotes or cause mutations in bacteria in the presence of an exogenous metabolic activation system[1]. No data on humans were available.

Benzal chloride was mutagenic in the *Salmonella typhimurium* assay[1]. Reversion of *Escherichia coli* WP_2 (hcr) and positive results in the *Bacillus subtilis rec* assay have also been reported[1]. No data on humans were available.

Benzotrichloride induced DNA damage in prokaryotes and caused mutations in bacteria in the presence of an exogenous metabolic activation system[1]. No data on humans were available.

Benzyl chloride

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		?		
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*	+		-	DL(-)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations

Benzoyl chloride

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Benzal chloride

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Benzotrichloride

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

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CHLORMADINONE ACETATE (Group 3) (See Oestrogens and progestins)

CHLOROFORM (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

No adequate study has been devoted to chloroform as a cause of human cancer[1]. In two studies of trihalomethane levels in drinking-water supplies and community-based rates of cancer mortality[2,3], correlations were found between these levels and various site-specific cancer mortality rates, especially of bladder cancer, but also of cancer of rectum-intestine and brain, lymphoma and kidney cancer. Since the results were markedly dependent on the different methods used to analyse the data, no causal inference can be made. A mortality study of anaesthesiologists who worked at the time chloroform was used[4] provided no significant information.

B. Evidence for carcinogenicity to animals (*sufficient*)

Chloroform is carcinogenic following its oral administration, producing benign and malignant liver neoplasms in mice, and kidney and thyroid neoplasms in rats[1]. It was tested inadequately by subcutaneous and intraperitoneal injection in mice[1]. No carcinogenic effect was observed in dogs[5].

C. Evidence for activity in short-term tests (*inadequate*)

There was no indication that chloroform binds to DNA[8]. Negative results were obtained with chloroform in a variety of bacterial systems employing DNA repair and mutation as endpoints[1,6-8] and in yeast[8], with the exception of one report[9]. It was inactive in a number of other short-term tests, including tests for mutagenicity in *Drosophila melanogaster*[6], those for chromosomal anomalies in human peripheral blood lymphocytes[10] and the micronucleus test in mouse bone-marrow erythrocytes[8]. Results of tests for cell transformation (in BHK) were equivocal[8]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		-		
Insects		-		
Mammalian cells *(in vitro)*			-	T(?)
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

T = cell transformation

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CHLOROPHENOLS (OCCUPATIONAL EXPOSURE TO) (Group 2B)

Evidence for carcinogenicity to humans (*limited*)

In two case-control studies of soft-tissue sarcoma[1,2] and one of lymphoma[3], exposure to chlorophenols (mainly 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorophenol[4]) was associated with three- to eight-fold increases in risk of those diseases. Cases of soft-tissue sarcoma, apparently substantially in excess of the expected number,

have also been reported in cohorts of men involved in the manufacture of trichlorophenols (mainly, if not entirely, 2,4,5-trichlorophenol)[5-8]. Cases of leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma have also been reported in individuals exposed to pentachlorophenol[9-11]. In all of these studies, exposure to chlorophenols probably involved exposure also to dioxins, as well as to other chemicals. (See also the summaries of data on 2,4,5- and 2,4,6-trichlorophenols and pentachlorophenol.)

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CHLOROPRENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one study, an excess of lung and skin cancers was related to occupational exposure to chloroprene. [The results were inconclusive, since epidemiological measures of cancer frequency were not defined.] In another investigation, no excess of lung or other type of

cancer was reported among chloroprene workers. There is one case report of an angiosarcoma of the liver in a worker exposed to chloroprene[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

A number of experimental studies were considered to be inadequate for an evaluation of the carcinogenicity of chloroprene[1]. In a further study[2], chloroprene was given orally to pregnant rats on the 17th day of gestation, and their offspring were treated weekly from weaning for life with 50 mg/kg bw by stomach tube. The total incidence of tumours was similar in treated and untreated animals.

C. Evidence for activity in short-term tests (*sufficient*)

Chloroprene vapours were weakly mutagenic to *Salmonella typhimurium* TA100 in the presence of an exogenous metabolic activation system[1] and produced a low but statistically significant increase in X-linked recessive lethals in *Drosophila melanogaster*[1,3]. It was not mutagenic to mammalian cells in culture[4]. It has been claimed that chloroprene induced chromosomal aberrations and dominant lethal mutations in rat bone-marrow cells *in vivo*[1]. It induced cell transformation in normal hamster lung cells *in vitro*[5]. Workers exposed to chloroprene exhibited increases in chromosomal aberrations in peripheral lymphocytes. These data and reports of reproductive disturbances in such workers and in their wives suggest that chloroprene is mutagenic to humans[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*		-		T(+)
Mammals *(in vivo)*			?	DL(?)
Humans *(in vivo)*			+	

T = cell transformation ; DL = dominant lethal mutations

References

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CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

An increased incidence of lung cancer has been observed among workers in the chromate-producing industry and possibly also among chromium platers and chromium alloy workers. There is a suggestion that cancers at other sites are also increased in such populations. The chromium compound(s) responsible has not been specified[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Calcium chromate is carcinogenic to rats after its administration by several routes, including intrabronchial implantation. Chromium chromate, strontium chromate and zinc chromate produce local sarcomas in rats at the sites of their application. Inadequate evidence was available for the carcinogenicity in mice and rats of barium chromate, lead chromate, chromic acetate, sodium dichromate and chromium carbonyl[1].

C. Evidence for activity in short-term tests (*sufficient* for Cr VI, *inadequate* for Cr III)

Hexavalent chromium caused DNA damage[2-5] and misincorporation of nucleotides in an in-vitro DNA transcription assay[2]. It was mutagenic in bacteria in the absence of an exogenous metabolic activation system[2,5,6] and mutagenic in fungi[2,5] and in mammalian cells *in vitro*[2,5] and *in vivo*[2]. Potassium dichromate induced dominant lethal mutations in mice treated *in vivo*[7]. Hexavalent chromium caused chromosomal aberrations in mammalian cells *in vitro*[2,5,8] and micronuclei in mice *in vivo*[2]. It produced cell transformation in a number of systems[2,5]. Micronuclei were formed in peripheral lymphocytes from exposed workers[2].

There is no good evidence that *trivalent chromium* causes mutations in bacteria, fungi or mammalian cells in culture or that it transforms mammalian cells *in vitro*[2]. The few positive results in assays for chromosomal aberrations were obtained only with very high doses and could be explained by non-specific toxic effects[9,10]. No data on humans were available.

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

Hexavalent chromium

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*		+	+	T(+)
Mammals *(in vivo)*		+	+	DL(+)
Humans *(in vivo)*			+	

T = cell transformation; DL = dominant lethal mutations

Trivalent chromium

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		?		
Fungi/Green plants		?		
Insects				
Mammalian cells *(in vitro)*		?	?	T(?)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

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CISPLATIN (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

A patient with metastatic seminoma treated with cisplatin, as well as with radiation, bleomycin and vinblastine, developed acute myeloid leukaemia[1].

B. Evidence for carcinogenicity to animals (*limited*)

Cisplatin, tested by intraperitoneal administration in mice, increased the incidence of lung tumours. When it was administered intraperitoneally, alternately with croton oil application to the skin, papillomas and carcinomas of the skin were produced, along with small numbers of internal neoplasms[2].

C. Evidence for activity in short-term tests (*sufficient*)

Cisplatin, a DNA-binding agent, produced DNA damage[3] and mutation in bacteria[2,4-6]. It was also mutagenic in *Drosophila melanogaster*[7] and in mammalian cells *in vitro*[2,8]. It produced chromosomal aberrations in human and rodent cells *in vitro*[2] and sister chromatid exchanges and chromosomal aberrations in mouse bone-marrow cells *in vivo*[2]. It did not induce dominant lethal mutations in mice but induced cell transformation (in Syrian hamster embryo cells)[2]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*		+	+	T(+)
Mammals *(in vivo)*			+	DL(-)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations

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CLOFIBRATE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Available information relating clofibrate to cancer in humans consists of a single case report of an adenocarcinoma of the jejunum in a man who had received clofibrate (among other drugs) for 15 years, and of data from randomized trials of clofibrate in men with elevated serum cholesterol levels[1]. A five-year trial was completed by 3586 men receiving clofibrate, 3608 receiving a high-cholesterol placebo and 3509 given a low-cholesterol placebo. Increased mortality from cancer (mainly gastrointestinal) was observed in the clofibrate group during the trial and in the following year (58 deaths) as compared with that in the high-cholesterol group (42 deaths); this difference is not statistically significant. No excess of cancer was found in two other trials of clofibrate[1].

B. Evidence for carcinogenicity to animals (*limited*)

Clofibrate was tested in two studies by oral administration to male rats; it produced hepatocellular carcinomas. An increased incidence of tumours at sites other than the liver was also observed[1].

C. Evidence for activity in short-term tests (*inadequate*)

Clofibrate was not mutagenic to bacteria[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Reference

[1] *IARC Monographs*, *24*, 39-51, 1980

CLOMIPHENE (Group 3)

A. Evidence for carcinogenicity to humans *(inadequate)*

There are a few case reports of malignant and benign tumours occurring at various sites in patients treated with clomiphene citrate, but there is no evidence of a causal relationship[1,2].

B. Evidence for carcinogenicity to animals (*inadequate*)

Clomiphene citrate was tested in an inadequate experiment in newborn rats by subcutaneous injection; uterine and ovarian tumours were reported[1]. In two subsequent reports[3,4], one-day-old female Sprague-Dawley rats received a single subcutaneous injection of clomiphene citrate (mixed *cis* and *trans* isomers); uterine tumours were reported to have occurred in treated animals. Hilar-cell tumours of the ovary were also reported, but it is not clear whether they occurred in animals treated with clomiphene, nafoxidine, or both. In none of the reports are the numbers of tumours produced by clomiphene given, and none are illustrated.

C. Evidence for activity in short-term tests

No data were available.

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CONJUGATED OESTROGENS (Group 1) (See Oestrogens and progestins)

CYCLAMATES (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

There is no consistent evidence that the risk of cancer is increased among users of artificial sweeteners[1]. Three case-control studies have shown no overall excess of bladder cancer in association with use of artificial sweeteners[2-4]. The largest was a population-based survey in 10 areas of the US, involving interviews with 3010 bladder cancer patients and 5783 controls randomly selected from the areas in which the patients resided[2]. The relative risk of bladder cancer associated with any use of artificial sweeteners was 0.99 (95% confidence limits, 0.89-1.10) among men and 1.07 (0.89-1.29) among women, compared with a risk of 1.0 among non-users. However, significant trends of increasing risk with increasing average daily consumption and with duration of use were observed in certain subgroups, namely female non-smokers (with a low baseline risk of bladder cancer) and male heavy smokers (with a high baseline risk). Since these subgroups were considered *a priori* to be worthy of special attention on the basis of hypotheses derived from animal experimentation, the findings raise the possibility that cyclamates may act as weak carcinogens and/or promoters. In one of the two other studies, a population-based survey of 592 patients with lower-urinary-tract cancer[3], the relative risk among women associated with any use of diet drinks or sugar substitutes was 1.6, and exceeded by two-fold that for non-smokers. The risk for any use among men was 0.8.

B. Evidence for carcinogenicity to animals (*limited*)

Sodium cyclamate has been tested either alone or in combination with other chemicals by several routes of administration. Oral administration at several dose levels to different strains of mice and rats resulted in a few benign and malignant bladder tumours in rats, although their incidence was not statistically different from that in controls; and an increased incidence of lymphosarcomas in female mice in one experiment. Several other experiments in mice, rats, hamsters and monkeys were inadequately conducted and/or reported. A 10:1 mixture of sodium cyclamate:sodium saccharin was given in one multigeneration experiment in mice and in two experiments in rats: transitional-cell carcinomas in the bladder were induced only in male rats of one strain given the highest dose. Instillation of low doses of *N*-nitroso-*N*-methylurea into the bladder of rats fed sodium cyclamate resulted in dose-related induction of transitional-cell neoplasms of the bladder[1]. After subcutaneous injection to rats, no tumours were observed at the site of injection (the only site reported)[1]. A significant increase in the incidence of bladder carcinomas was observed in mice after implantation of a pellet containing sodium cyclamate in the bladder.

Calcium cyclamate did not alter tumour incidence when tested by oral administration in a two-generation experiment in rats but produced local tumours in another experiment following its subcutaneous injection[1].

Cyclohexylamine has been tested by oral administration at several dose levels in different strains of mice and rats, including one multigeneration study in mice. The tumour incidence was similar in treated and control animals[1].

C. Evidence for activity in short-term tests (*inadequate*)

Generally negative results have been obtained with cyclamates in short-term tests[1]. They were not mutagenic in bacteria[5]. Chromosome breaks have been observed in human leucocytes treated with cyclamates *in vitro*[1]. High doses of sodium cyclamate did not produce sister chromatid exchanges in bone-marrow cells of Chinese hamsters exposed *in vivo*[6]. Cyclamates did not transform BHK cells in culture, did not induce sperm abnormalities in mice[1,8,9] and were negative in the dominant lethal test in mice[5,7]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			+	T(-)
Mammals *(in vivo)*			-	DL(-) SA(-)
Humans *(in vivo)*				

T = cell transformation ; DL = dominant lethal mutations ; SA = sperm abnormalities

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CYCLOPHOSPHAMIDE (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

More than 100 case reports were available describing cancer in patients treated with cyclophosphamide for malignant and nonmalignant diseases. Many but not all such patients had also been given other cytostatic drugs and/or radiation. Five epidemiological studies were available in which treated patients with malignant or nonmalignant disease were compared with similarly afflicted controls. These were consistent in demonstrating excesses of various neoplasms, especially of bladder cancer and leukaemia, in the treated groups, although the numbers in all five studies were small[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Cyclophosphamide is carcinogenic to rats after its oral or intravenous administration, producing benign and malignant tumours at various sites, including the bladder. It is carcinogenic to mice following its subcutaneous injection, producing benign and malignant tumours at the site of injection and at distant sites. There was some evidence of its oncogenicity in mice and rats following its intraperitoneal injection[1].

C. Evidence for activity in short-term tests (*sufficient*)

Cyclophosphamide is metabolized to an alkylating intermediate. It produced DNA damage[2,3] and was mutagenic in bacteria, yeast, *Drosophila melanogaster* and human and mammalian cells *in vitro* and in mammalian cells *in vivo*[1,4-6]. It induced chromosomal aberrations in fungi and in mammalian cells *in vitro* and *in vivo*[1]. Cyclophosphamide induced dominant lethal mutations in rodents but not in *Drosophila*[1,2]. It induced cell transformation (in BHK[7] and C3H10T$\frac{1}{2}$ cells)[1], and induced heritable translocation in mice[8]. Chromosomal aberrations were induced in the lymphocytes of patients treated with cyclophosphamide[9].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+	+	
Insects		+		DL(-)
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*		+	+	DL(+)
Humans *(in vivo)*			+	

T = cell transformation; DL = dominant lethal mutations

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2,4-D AND ESTERS (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Cases of soft-tissue sarcoma and lymphoma were reported in men exposed occupationally to 2,4-D and/or its esters and to 2,4,5-T[1,2]. Subsequent case-control studies of people exposed to phenoxyacetic acids gave relative risks of 5.3 (95% confidence limits, 2.4-11.5)[3] and 6.8 (95% confidence limits, 2.6-17.3)[4] for soft-tissue sarcomas and 4.8 (95% confidence limits, 2.9-8.1)[5] for lymphoma. In one of these studies[4], patients who had been exposed to 2,4-D, 4-chloro-2-methyl phenoxyacetic acid or phenoxypropionic acids but not to 2,4,5-T also appeared to be at increased risk of soft-tissue sarcoma (relative risk, 4.2). In the study of lymphoma[5], seven cases and one control were apparently exposed only to 2,4-D [relative risk, 19.6; 95% confidence interval, 4.3-89.8]. Other men in these studies were exposed to a variety of other chemicals, but for none did the relative risk approach those cited above. Follow-up studies of cohorts of men exposed to 2,4-D together with other herbicides and pesticides[6-8] showed evidence (although not entirely consistent and derived from small numbers of cases) of an increased risk of cancer. There was one death from lymphoma among men exposed to phenoxyacetic acids in two of these cohorts but none from soft-tissue sarcoma. [See also the summary of data on 'Phenoxyacetic acid herbicides (occupational exposure)'.]

B. Evidence for carcinogenicity to animals (*inadequate*)

2,4-D and several of its esters were tested in rats and mice by oral administration and in mice by subcutaneous administration. All of these studies had limitations, due either to inadequate reporting or to the small number of animals used. Therefore, although increased incidences of tumours were observed in one study in which rats received 2,4-D orally and in another in which mice received its isooctyl ester by subcutaneous injection, no evaluation of the carcinogenicity of this compound could be made[9].

[Phenoxyacetic acid herbicides have been shown to cause peroxisome proliferation in Chinese hamsters[10]. Certain agents known to cause this proliferation are carcinogenic, and the phenomenon has been suggested to have mechanistic significance in the induction of tumours.]

C. Evidence for activity in short-term tests (*inadequate*)

2,4-D produced unscheduled DNA synthesis in cultured human fibroblasts[11] but not in rat hepatocytes[12]. It was not mutagenic in bacterial systems[9]; however, it has been pointed out[13] that the phenoxy acids occur in their dissociated form at pHs of around 7 and that such compounds with low pK values should be tested at low pH levels. 2,4-D was mutagenic in yeast when tested at low pH[14], but was not active under other conditions, including those of the host-mediated assay[9]. It produced a small increase in recessive lethal mutations and somatic mutations in *Drosophila melanogaster*[15], although in other studies negative results were obtained[9,16]. It was mutagenic for cultured Chinese

hamster cells[17]. Chromosomal anomalies have been observed in plants[9,18], but some of these effects may be the result of general toxicity. 2,4-D has been reported to increase the number of chromatid aberrations and chromosomal aberrations in cultured human lymphocytes[9], but no aberration was detected in bovine peripheral blood cells exposed *in vitro*[9]. Toxic concentrations of 2,4-D produced chromosomal aberrations but did not induce micronuclei in the bone-marrow cells of mice treated *in vivo*[9]. 2,4-D did not induce dominant lethal mutations in mice[9]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		?	?	
Insects		?		
Mammalian cells *(in vitro)*	?	+	?	
Mammals *(in vivo)*			?	DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

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DACARBAZINE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

A single case of acute leukaemia following treatment with dacarbazine in combination with other cytotoxic agents has been reported. In a small epidemiological study of short duration, no excess of subsequent neoplasms was observed in patients treated with a regimen consisting of dacarbazine, adriamycin, bleomycins and vinblastine[1]. [See also the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'.]

B. Evidence for carcinogenicity to animals (*sufficient*)

Following its oral or intraperitoneal administration to rats, dacarbazine produced tumours at various sites, including breast, thymus, spleen and brain, in as little as 18 weeks after initial exposure. After its intraperitoneal administration to mice, dacarbazine produced tumours at various sites, including lung, haematopoietic tissue and uterus[1].

C. Evidence for activity in short-term tests (*limited*)

Dacarbazine is an alkylating agent. In a limited number of assays, it was negative in bacterial mutation tests[1]. It induced sex-linked recessive lethal mutations in *Drosophila melanogaster*[2]. It was mutagenic in mouse lymphoma cells *in vitro* in the presence of an exogenous metabolic activation system[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		?		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*		+		
Mammals *(in vivo)*				
Humans *(in vivo)*				

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DAPSONE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Cases of cancer have been reported in patients treated with dapsone for dermatitis herpetiformis; but the relevant data consist in five studies[1-3] of patients with leprosy, the principal disorder treated with dapsone. In none of these studies was any significant excess of cancer found. In one study[2], mortality from cancer was examined over two time periods, before and after the introduction of dapsone; but no increase was detected.

B. Evidence for carcinogenicity to animals (*limited*)

Dapsone has been tested by oral administration in mice and rats, by intraperitoneal administration in mice and by prenatal and lifetime oral exposure in mice and rats. In three different studies in rats, high doses of dapsone induced mesenchymal tumours of the spleen (and of the peritoneum in two studies) in males. An increased incidence of tumours of the thyroid was found in rats of both sexes in one study and in males in a further study. The experiment in mice involving intraperitoneal administration of dapsone could not be evaluated. The other two experiments did not provide evidence of carcinogenicity[1].

C. Evidence for activity in short-term tests (*inadequate*)

Dapsone was not mutagenic to *Salmonella typhimurium*[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

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DDT (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

In four studies[1-3], tissue levels of DDT were reported to be higher in cancer patients than in subjects dying from other causes; no difference was found in two other studies[1,4]. Serum DDT appeared to be elevated in another study of nine cancer patients[5], but it is

difficult to interpret. In two case-control studies of soft-tissue sarcoma and one of lymphoma[6-8], relative risks for the association of these diseases with exposure to DDT were, respectively, 1.2, 1.3 and 1.6. Some of the men had also been exposed to phenoxyacetic acids and chlorophenols, which gave higher relative risks. A case-control study of colon cancer[9] showed no increased relative risk for exposure to DDT. A small excess of deaths from cancer (3 observed, 1.0 expected) was found in forestry foremen exposed to DDT, 2,4-D and 2,4,5-T[10].

B. Evidence for carcinogenicity to animals (*sufficient*)

DDT is carcinogenic to mice following its oral administration, causing benign and malignant liver neoplasms[1,11] and lymphomas and lung neoplasms[11]. Following its subcutaneous injection to mice, it produced liver tumours[11]. Oral administration to rats caused liver neoplasms[12,13]. Two feeding studies with hamsters were negative[1,14], while feeding studies with dogs and monkeys were inconclusive[1]. DDT slightly increased the incidence of liver neoplasms in rats previously exposed to *N*-nitrosodiethylamine[15].

C. Evidence for activity in short-term tests (*inadequate*)

DDT did not interact with DNA[16] and did not produce unscheduled DNA synthesis in cultured human fibroblasts[17] or rat, mouse or hamster hepatocytes[18,19]. It was not mutagenic to *Salmonella typhimurium*[20-22], to yeast[23], to cultured rat liver epithelial cells[24] or to human fibroblasts in a rat hepatocyte-mediated assay[25]. DDT did not produce chromosomal aberrations in cultured human lymphocytes[26]. It did not produce recessive or dominant lethal mutations in wasps (*Bracon hebetor*)[27] or visible or lethal mutations in mice exposed for five generations[28]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		-		
Insects		-		DL(-)
Mammalian cells *(in vitro)*	-	-	-	
Mammals *(in vivo)*		-		DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

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ortho-DICHLOROBENZENE AND *para*-DICHLOROBENZENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

One report of a series of five cases has suggested an association between leukaemia and exposure to dichlorobenzenes[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

The one available study on *ortho*-dichlorobenzene was inadequate for evaluation. No data on *para*-dichlorobenzene were available.

C. Evidence for activity in short-term tests (*inadequate*)

Neither *ortho*- nor *para*-dichlorobenzene was mutagenic to *Salmonella typhimurium*. A single report described weak mutagenicity of *ortho*- and *para*-dichlorobenzene to *Aspergillus nidulans*. *para*-Dichlorobenzene caused chromosomal anomalies in the root tips of *Vicia faba*[1]. No data on humans were available.

ortho-*Dichlorobenzene*

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		?		
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

para-*Dichlorobenzene*

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		?	+	
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Reference

[1] *IARC Monographs*, *29*, 213-238, 1982

3,3′-DICHLOROBENZIDINE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three retrospective epidemiological studies of workers exposed to 3,3′-dichlorobenzidine gave no evidence of carcinogenicity, but the studies were of insufficient quality or statistical power to permit confident exclusion of this possibility. Because 3,3′-dichlorobenzidine and benzidine may be made in the same plant, dichlorobenzidine may have contributed to the incidence of bladder cancer attributed to benzidine[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

3,3′-Dichlorobenzidine was tested in mice, rats, hamster and dogs by oral administration, in rats by subcutaneous administration and in mice by transplacental exposure. Following its oral administration, it produced liver-cell tumours in mice and hepatocellular carcinomas in dogs, mammary and Zymbal-gland tumours in rats and carcinomas of the urinary bladder in hamsters and dogs. Increased incidences of leukaemias were observed in rats following its oral administration and in mice following transplacental exposure[1].

C. Evidence for activity in short-term tests (*sufficient*)

3,3′-Dichlorobenzidine bound to DNA treated *in vitro*, the binding being greatly enhanced in the presence of an exogenous metabolic activation system[2]. It induced unscheduled DNA synthesis in HeLa cells and was mutagenic to *Salmonella typhimurium*[1]. It induced cell transformation (in the BHK system) in the presence of a hepatic extract[3] and enhanced transformation of rat embryo cells containing Rauscher leukaemia virus[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	+			T(+)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

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DICHLOROMETHANE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A large, occupationally exposed population was investigated in both a proportionate mortality study, with 334 deaths, and in a 13-year cohort mortality study of 751 employees, of whom 252 had at least 20 years of work exposure. Neither method of analysis suggested any association with cancer at any site[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

Dichloromethane was tested in one experiment in male mice by intraperitoneal injection. Although the results were suggestive of an increased incidence of lung tumours, the experiment was inadequate for evaluation[2].

C. Evidence for activity in short-term tests (*limited*)

Dichloromethane did not induce unscheduled DNA synthesis in human or hamster cells *in vitro*[3]. It was mutagenic to *Salmonella typhimurium*[1,4] and to *Drosophila melanogaster*[5] but not to hamster cells *in vitro*[3]. No significant increase in sister chromatid exchanges was seen in mammalian cells *in vitro*[3]. The micronucleus test in mouse bone-marrow cells was negative[5]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*	-	-	-	
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

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DIELDRIN (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Mean tissue levels of dieldrin were reported to be elevated in one necropsy study of 50 cancer patients and 42 comparison subjects[1]. Mean serum levels were also reported to be elevated in eight cancer patients compared with seven controls[2]. Follow-up of some 233 workmen (166 employed for more than four years and followed for 15 or more years) in a plant where aldrin and dieldrin and, later, endrin and telodrin were manufactured showed two deaths from cancer[1,3]. [No estimate was given of the expected number of cancers, and details of follow-up were limited.]

B. Evidence for carcinogenicity to animals (*limited*)

Dieldrin is carcinogenic to mice, producing benign and malignant liver neoplasms following its oral administration[1,4,5]. No carcinogenic effect was observed in feeding studies in rats[1,6,7], trout[8] or hamsters[9]. Feeding studies in dogs and monkeys were considered to be inadequate[1].

C. Evidence for activity in short-term tests (*inadequate*)

Dieldrin did not produce DNA breaks in an *Escherichia coli* plasmid[10]. It was claimed to elicit DNA repair in cultured human fibroblasts[11] and human lymphocytes[12], but it did not do so in cultured rat hepatocytes[13] and did not produce DNA damage in cultured Chinese hamster cells[14]. It was not mutagenic to *Salmonella typhimurium*[15,16], to yeast[17], to *Drosophila melanogaster*[18] or to the wasp *Bracon hebetor*[19]. In a limited study[20], there

was some indication that it was mutagenic to Chinese hamster V79 cells. It produced chromosomal aberrations in human embryonic lung cells *in vitro*[20] and chromosomal damage to mouse bone-marrow cells *in vivo* in one study[21] but not in another[22] and not in Chinese hamster bone-marrow cells[23]. It did not induce cell transformation *in vitro* (in BHK cells)[23]. It was negative in the mouse dominant-lethal test and did not induce mitotic gene conversion in yeast in a host-mediated assay[22]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		-		
Insects		-		
Mammalian cells *(in vitro)*	-	?	?	T(-)
Mammals *(in vivo)*			?	DL(-)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations

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DIENOESTROL (Group 2B) (See Oestrogens and progestins)

DIETHYLSTILBOESTROL (Group 1) (See Oestrogens and progestins)

DIETHYL SULPHATE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

In a historical cohort study of 335 process workers and 408 chemical mechanics and refinery workers at a factory manufacturing isopropyl alcohol and ethanol, an excess mortality (standardized mortality ratio = 504) of upper respiratory (laryngeal) cancer was found (4 cases, 0.8 expected) among process workers and an SMR of 320 among all 743 workers. The cohort spent 20% of its time on the ethanol manufacturing process; but 70% of the time of the four cases was associated with ethanol manufacture. The strong-acid ethanol process produced high concentrations of diethyl sulphate[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Diethyl sulphate is carcinogenic to rats following its subcutaneous administration, producing local tumours; and it is carcinogenic after prenatal exposure, producing tumours of the nervous system. A few tumours of the forestomach occurred in rats given diethyl sulphate by gavage[2].

C. Evidence for activity in short-term tests (*sufficient*)

Diethyl sulphate induced DNA damage in *Bacillus subtilis* and in human fibroblasts in culture and was positive in the phage-induction assay; DNA was bound to 7-ethylguanine in HeLa cells[3]. It was mutagenic to bacteria[3], fungi[3], yeast[3], higher plants[3], *Drosophila melanogaster*[3,4], mammalian cells in culture[3], and mice *in vivo*[3]. Conflicting results were obtained concerning the production of chromosomal anomalies in the bone-marrow cells of mice treated *in vivo*[3]. Dominant lethal mutations were induced in mice[3]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+		
Mammals *(in vivo)*		+	?	DL(+)
Humans *(in vivo)*				

DL = dominant lethal mutations

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DIMETHISTERONE (Group 3) (See Oestrogens and progestins)

3,3′-DIMETHOXYBENZIDINE (*ortho*-DIANISIDINE) (Group 2B)

A. Evidence of carcinogenicity to humans (*inadequate*)

In an English summary of a Russian study, it was stated that there is not a single case on record of an occupational urinary bladder neoplasm produced solely by the effect of dianisidine [3,3′-dimethoxybenzidine][1]. This compound (as well as dichlorobenzidine and *ortho*-toluidine) has been prepared in the same plants as benzidine and may have contributed to the bladder cancer risk observed among benzidine workers[2]. 3,3′-Dimethoxybenzidine has been found in the urine of workers exposed to it[3].

B. Evidence of carcinogenicity to animals (*sufficient*)

Following its oral administration, 3,3′-dimethoxybenzidine produced tumours in rats at various sites, including the bladder, intestine, skin and Zymbal gland, and produced forestomach papillomas in hamsters[3].

C. Evidence for activity in short-term tests (*limited*)

3,3'-Dimethoxybenzidine was negative in the pol A assay[4] but induced unscheduled DNA synthesis in HeLa cells[5] and in primary rat hepatocytes[6]. It was mutagenic in *Salmonella typhimurium*[7-9] and transformed BHK cells *in vitro*[10]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	+			T(+)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

References

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DIMETHYLCARBAMOYL CHLORIDE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

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

B. Evidence for carcinogenicity to animals (*sufficient*)

Dimethylcarbamoyl chloride was tested by skin application and by subcutaneous or intraperitoneal injection in female mice of one strain, in which it induced local tumours[1]. It produced a high incidence of carcinomas of the nasal tract in male rats and hamsters following exposure by inhalation[2].

C. Evidence for activity in short-term tests (*sufficient*)

Dimethylcarbamoyl chloride was highly active in producing DNA damage in the *Escherichia coli* pol A assay, in *rec* assays and in yeast, but negative results were reported in mammalian fibroblasts *in vitro*[3]. It was mutagenic in bacteria[1,3], yeast and mouse lymphoma cells *in vitro* but not in *Drosophila melanogaster*[3]. Chromosomal aberrations were observed in yeast and mammalian cells *in vitro* and *in vivo*[3]. It induced cell transformation (in the BHK assay)[3]. No chromosomal aberration was reported in 10 workers exposed to this compound for 4-17 years[4].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+	+	
Insects		-		
Mammalian cells *(in vitro)*	-	+	+	T(+)
Mammals *(in vivo)*			+	
Humans *(in vivo)*			-	

T = cell transformation

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DIMETHYL SULPHATE (Group 2A)

A. Evidence for carcinogenicity to humans (*inadequate*)

Four cases of bronchial carcinoma were reported in men occupationally exposed to dimethyl sulphate[1]. Additional case reports have since appeared: a case of pulmonary carcinoma in a man exposed for seven years to 'small amounts' of dimethyl sulphate but to larger amounts of dichlorodimethyl ether and monochlorodimethyl ether[2], and a case of choroidal melanoma in a man exposed for six years to dimethyl sulphate[3].

B. Evidence for carcinogenicity to animals (*sufficient*)

Dimethyl sulphate is carcinogenic to rats following its inhalation or subcutaneous injection, producing mainly local tumours, and after prenatal exposure, producing tumours of the nervous system[1].

C. Evidence for activity in short-term tests (*sufficient*)

Dimethyl sulphate is a methylating agent and reacts with nucleic acids *in vitro* and *in vivo*[4]. It induced prophage in bacteria, and indirect evidence of DNA repair in bacteria[4]. It induced DNA repair in cultured mammalian cells[4,5]. It bound covalently to DNA of rats treated *in vivo*[6] and inhibited the synthesis of testicular DNA of mice treated *in vivo*[4]. It was mutagenic to viruses[4], bacteria[4], fungi[4], vascular plants[4], insects[4], fish[4] and cultured mammalian cells[4,7] in the absence of an exogenous metabolic activation system. It induced chromosomal aberrations in vascular plants[4], fish[4] and cultured mammalian cells[4], and provoked sister chromatid exchanges in cultured mammalian cells[4,8]. Dimethyl sulphate was negative in a dominant lethal test in mice[4]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+	+	
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	
Mammals *(in vivo)*	+			DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

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1,4-DIOXANE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

In a mortality study of 165 workers who had been exposed to low concentrations of 1,4-dioxane since 1954, seven deaths had occurred as of 1975, two of them from cancer[1]. [The observation is based on small numbers, short follow-up and low exposure levels.]

B. Evidence for carcinogenicity to animals (*sufficient*)

Administration of 1,4-dioxane in drinking-water at several dose levels to rats and male guinea-pigs produced adenomas and carcinomas in the liver in rats of both sexes and hepatomas in guinea-pigs, carcinomas of the nasal cavity in male and female rats and carcinomas of the gall-bladder in guinea-pigs. No increase in the incidence of tumours was observed in rats following its inhalation. It was active as a promoter in a two-stage study on skin carcinogenesis in mice[1].

C. Evidence for activity in short-term tests (*inadequate*)

1,4-Dioxane did not induce unscheduled DNA repair *in vitro* or *in vivo*[2]. It was not mutagenic in several strains of *Salmonella typhimurium*, either in the presence or absence of an exogenous metabolic activation system[2-4]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	-			
Mammals *(in vivo)*	-			
Humans *(in vivo)*				

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DIRECT BLACK 38 (TECHNICAL-GRADE) (Group 2B) (See Benzidine-based dyes)

DIRECT BLUE 6 (TECHNICAL-GRADE) (Group 2B) (See Benzidine-based dyes)

DIRECT BROWN 95 (TECHNICAL-GRADE) (Group 2B) (See Benzidine-based dyes)

EPICHLOROHYDRIN (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

One study of 863 workers exposed in 1948-1965 to epichlorohydrin in two factories showed an excess of respiratory cancer (the pooled data give 10 observed, 8.74 expected). This difference is significant. Some of the workers had also been engaged in the manufacture of isopropyl alcohol, in which exposure to diisopropylsulphate may occur[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Epichlorohydrin was tested in male rats by oral administration, inducing papillomas and carcinomas of the forestomach[2], and by inhalation, inducing papillomas and carcinomas of the nasal cavity[3]. It was also tested in one strain of female mice by skin application, and by subcutaneous and intraperitoneal injection: it induced subcutaneous sarcomas and was active as an initiator for the skin[4].

C. Evidence for activity in short-term tests (*sufficient*)

Epichlorohydrin is an alkylating agent. It provoked DNA repair in cultured mammalian cells[5]. It was mutagenic in bacteria[4-7], fungi[5-7], vascular plants[7], insects[4,6] and cultured mammalian cells[5] in the absence of an exogenous metabolic activation system. It induced mutations in bacteria in the host-mediated assay in mice[6]. It induced chromosomal aberrations in vascular plants[7] and sister chromatid exchanges[5,8] and chromosomal aberrations[5,9] in cultured mammalian cells. Chromosomal aberrations[10] but not micronuclei[6] were produced in bone-marrow cells of mice treated *in vivo*. It induced cell transformation (in the BHK assay[5]) and morphological abnormalities in mouse sperm[4], but was negative in assays for dominant lethality[4]. In three studies[6,11-14], elevated levels of chromosomal aberrations were observed in peripheral blood lymphocytes of workers occupationally exposed to epichlorohydrin. However, the evidence was insufficient to establish a cause-and-effect relationship between exposure to epichlorohydrin and cytogenetic damage.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+	+	
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*			+	DL(-) SA(+)
Humans *(in vivo)*			?	

T = cell transformation; DL = dominant lethal mutations; SA = sperm abnormalities

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ETHINYLOESTRADIOL (Group 2B) (See Oestrogens and progestins)

ETHYLENE DIBROMIDE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

The only epidemiological study of the carcinogenic effects of ethylene dibromide[1] investigated the mortality of 161 men exposed in two factories since the 1920s and since 1942, respectively. By 1 January 1976, 36 workers had died, seven of them from cancer (expected, 5.8). [The results are uninformative because of the small size of the study.]

B. Evidence for carcinogenicity to animals (*sufficient*)

Ethylene dibromide is carcinogenic to mice and rats following its oral administration, producing squamous-cell carcinomas of the forestomach in animals of both species[1]. It produced skin, lung and forestomach tumours in mice after topical administration[3].

C. Evidence for activity in short-term tests (*sufficient*)

Ethylene dibromide bound covalently to liver DNA of rats treated *in vivo*[4,5]. It was selectively lethal to DNA-repair-deficient bacteria[2,6], and provoked DNA repair in cultured mammalian cells[6]. It was mutagenic to bacteria[2,6], fungi[2,6], vascular plants[6], insects[7] and cultured mammalian cells[6,8] in the absence of an exogenous metabolic activation system. It induced chromosomal aberrations and sister chromatid exchanges in cultured mammalian cells[6]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	
Mammals *(in vivo)*	+			
Humans *(in vivo)*				

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ETHYLENE OXIDE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Two studies of workers exposed occupationally to ethylene oxide[1,2] have shown increased rates of leukaemia. In one study[1] of 70 workers who had been exposed to ethylene oxide for 4-10 years, three cases of leukaemia were found (0.2 expected); one case had also been exposed to benzene. The other study[2] dealt with the incidence and mortality experience of 89 full-time and 86 intermittently exposed men: the first group had nine tumours (expected, 3.4), including three stomach cancers (0.4 expected) and two leukaemias (0.14 expected). The men had been exposed to a variety of vapours, and hence the results cannot be attributed with certainty to ethylene oxide alone. A third study[3] of 767 men with potential exposure to ethylene oxide showed no significant cancer excess, although nonsignificant excesses, based on small numbers of cases, were seen for pancreatic, bladder and brain cancer and for Hodgkin's disease. [Insufficient allowance was made for latency, and the SMR was only 58, indicating diluting errors in the design of the study.]

B. Evidence for carcinogenicity to animals (*limited*)

Ethylene oxide was tested inadequately in mice by skin painting and in rats by subcutaneous injection[4]. When administered subcutaneously to female mice, it produced sarcomas at the injection site in several animals[5].

C. Evidence for activity in short-term tests (*sufficient*)

Ethylene oxide alkylated the DNA of mammalian cells *in vitro*[4] and *in vivo*[6]. It was mutagenic to bacteria[4,7,8], yeast[4] and Chinese hamster ovary cells *in vitro*[9] and to *Drosophila melanogaster*[4], mice and rats *in vivo*[4]. It induced chromosomal aberrations in *Drosophila*[4] and in rats[4] and mice[10] and induced micronuclei in bone-marrow cells of mice and rats[11]. Dominant lethal mutations were induced in rats[12] and mice[10]. Increases in chromosomal aberrations were seen in peripheral blood lymphocytes of workers exposed occupationally or accidentally to ethylene oxide and other alkane oxides[13-15].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+		
Insects		+	+	
Mammalian cells *(in vitro)*	+	+		
Mammals *(in vivo)*	+	+	+	DL(+)
Humans *(in vivo)*			+	

DL = dominant lethal mutations

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ETHYLENE THIOUREA (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one incidence study[1], 1929 workers were identified as having worked at some time with ethylene thiourea in one of several rubber manufacturing companies. No case of thyroid cancer was reported from this group to the regional cancer registry between 1957 and 1971, although less than one case would have been expected.

B. Evidence for carcinogenicity to animals (*sufficient*)

In three studies, ethylene thiourea produced a high incidence of follicular carcinomas of the thyroid in rats after its oral administration[2-6]. Animals of both sexes were affected, although male rats had a higher incidence. Lower doses produced thyroid follicular hyperplasia. In mice, oral administration of ethylene thiourea produced liver tumours[5]; the thyroids of these animals were not examined. [In dosed rats, either shortened survival due to thyroid tumours or altered body weights may have obscured a potential carcinogenic effect on the liver from ethylene thiourea administration.] A feeding study in hamsters showed no effect[6].

C. Evidence for activity in short-term tests (*limited*)

There are conflicting data on the mutagenicity of ethylene thiourea. In some studies, this compound, at high doses, induced mutation and indirect evidence of DNA repair in bacteria and fungi, in the presence or absence of an exogenous metabolic activation system[7]. Other workers obtained negative results[7]. It did not induce mutation of bacteria in the host-mediated assay[8] and did not induce mutation (sex-linked recessive lethals) in *Drosophila melanogaster* in two separate studies[7,9]. In multiple experiments, this chemical

did not induce mutation in cultured mammalian cells[7], neither did it cause sister chromatid exchange[7], chromosomal aberrations[7,10] or, in most studies, DNA repair[7]. However, it induced cell transformation (in the BHK assay) in the absence of an exogenous metabolic activation system[7]. In experiments in mice *in vivo*, ethylene thiourea did not induce dominant lethal mutations[8,10], bone-marrow micronuclei[7,8] or sister chromatid exchanges[7], morphological abnormalities in sperm[7] or inhibition of testicular DNA synthesis[11]. It did not induce chromosomal aberrations or covalent DNA binding in the bone marrow of rats[10]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	?	?		
Fungi/Green plants	?	?	+	
Insects		-		
Mammalian cells *(in vitro)*	?	-	-	T(+)
Mammals *(in vivo)*	-		-	DL(-)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations

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ETHYNODIOL DIACETATE (Group 3) (See Oestrogens and progestins)

5-FLUOROURACIL (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

5-Fluorouracil has been associated in a few case reports with a variety of subsequent neoplasms. In almost all of the cases, the drug had been given together with other agents known or suspected of being carcinogenic[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

5-Fluorouracil was tested by intravenous administration to mice and rats and by oral administration to rats. No evidence of carcinogenicity was found, but the studies suffered from limitations with regard to duration or dose[1]. It was reported that ingestion of 5-fluorouracil prevented or delayed the appearance of spontaneous mammary and pituitary tumours in old female Wistar-Furth rats[2].

C. Evidence for activity in short-term tests (*limited*)

5-Fluorouracil was not mutagenic and did not induce DNA repair in bacteria[1]. It produced petite mutations in yeast[1]. Chromosomal breakage was seen in CHO[1] and human[3] cells when 5-fluorouracil was added *in vitro* at a high concentration. It induced micronuclei in mouse bone-marrow cells *in vivo*[1]. Inconclusive results were obtained in a mouse specific locus test[4], and it was negative in a sperm abnormality test[5]. Cytotoxic concentrations produced cell transformation (in C3H/10T$\frac{1}{2}$)[1]. A metabolite, 5-fluoro-2′-deoxyuridine, also transformed cells, which produced tumours when injected into

immunosuppressed syngeneic mice[1]. A slight increase in the incidence of chromosomal aberrations was seen in peripheral blood lymphocytes from patients with solid tumours treated with 5-fluorouracil[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants				Mt(+)
Insects				
Mammalian cells *(in vitro)*			?	T(+)
Mammals *(in vivo)*		?	+	SA(-)
Humans *(in vivo)*			?	

Mt = petite mutations in yeast ; T = cell transformation ; SA = sperm abnormalities

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FORMALDEHYDE (GAS) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three epidemiological studies of people exposed to formaldehyde have been published[1]. A proportional mortality study of 1106 morticians showed an excess of skin cancer but no evidence of an elevated risk of nasal or pulmonary neoplasms. Studies of two populations in formaldehyde factories revealed an excess of prostatic cancer in one and of gastrointestinal cancer in the other. Respiratory and nasal cancer mortality was not elevated in either group. No excess of respiratory-tract tumours was noted in a population of British pathologists.

B. Evidence for carcinogenicity to animals (*sufficient*)

Formaldehyde was tested for carcinogenicity by inhalation exposure in two strains of rats and one strain of mice. A significant incidence of squamous-cell carcinomas of the nasal cavity was induced in both strains of rats but not in mice. Another study in mice and one in hamsters by inhalation exposure, one in rats by subcutaneous administration and one in rabbits by exposure in oral tanks were considered inadequate for evaluation[1].

C. Evidence for activity in short-term tests (*sufficient*)

Formaldehyde bound covalently to DNA, formed DNA-protein cross-lilnks[1] and induced single-strand DNA breaks[2]. It gave indirect evidence for DNA repair in bacteria and fungi[1,3] and induced DNA repair in cultured mammalian cells. It was mutagenic to viruses[1], bacteria[1], vascular plants[1], fungi[1] and insects[1] in the absence of an exogenous metabolic activation system. It induced morphological transformation in cultured mammalian cells (C3H/10T½) only after their treatment with a tumour-promoting agent[1]. One laboratory reported that formaldehyde induced dominant lethal mutations in mice[1]. In other studies in mice, it did not induce bone-marrow micronuclei[1,4] or chromosomal aberrations in sperm[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+		
Insects		+		
Mammalian cells *(in vitro)*	+		+	T(?)
Mammals *(in vivo)*			-	DL(?)
Humans *(in vivo)*				

T = cell transformation DL = dominant lethal mutations

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FURNITURE MANUFACTURE (Group 1) (See Industries)

HAEMATITE (Group 3) [See Underground haematite mining (with exposure to radon)]

HEXACHLOROCYCLOHEXANE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three cases of leukaemia were reported in men exposed to γ-hexachlorocyclohexane with or without other chemicals. Cases of aplastic anaemia have also been associated with exposure to this compound[1]. Mean tissue levels of hexachlorocyclohexane were reported in one of three studies of cancer patients to be elevated as compared with those of other subjects at necropsy[2-4]. Mean serum levels of β-hexachlorocyclohexane were not appreciably higher in four cancer patients than in three controls[5]. Exposure to γ-hexachlorocyclohexane was recorded in case-control studies of soft-tissue sarcomas and of lymphomas[6,7], but was insufficiently frequent for any conclusion to be drawn.

B. Evidence for carcinogenicity to animals (*limited*)

Technical, α- and β-hexachlorocyclohexane and lindane (the γ isomer) are carcinogenic to mice when administered orally, producing liver tumours[1,8]; the technical grade also produced lymphoreticular neoplasms[8]. Studies in rats[1,9,10] and dogs[11] were considered to be inadequate. Technical hexachlorocyclohexane and lindane were tested inadequately by skin application[1,8]. Hexachlorocyclohexane increased the incidence of liver neoplasms in rats previously exposed to *N*-nitrosodiethylamine[12].

C. Evidence for activity in short-term tests (*inadequate*)

Lindane did not induce unscheduled DNA synthesis in human fibroblasts[1] or rat hepatocytes[13] but was reported to be weakly active in human lymphocytes[14]. α- and β-Hexachlorocyclohexane and lindane, when tested individually or as a mixture, were not mutagenic to bacteria or yeast and did not selectively kill DNA-repair-deficient strains of bacteria[1,15,16]. Lindane was not mutagenic to *Drosophila melanogaster*[1]. It induced polyploidy, mitotic arrests and some chromosomal aberrations in a number of plant systems[1], and a low frequency of chromosomal anomalies in human lymphocytes[1] and Chinese hamster cells *in vitro*[1]; β-hexachlorocyclohexane but not lindane produced some anomalies in rat bone-marrow cells *in vivo*[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		-	?	
Insects		-		
Mammalian cells *(in vitro)*	-		?	
Mammals *(in vivo)*			?	
Humans *(in vivo)*				

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HYDRALAZINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Two studies suggested an association between exposure to hydralazine and human cancer. One was confined to patients with and without signs of toxicity due to hydralazine, and potential confounding factors were not controlled. The other involved a small number of subjects exposed to hydralazine, and the possibility of selection bias could not be excluded[1].

B. Evidence for carcinogenicity to animals (*limited*)

Hydralazine hydrochloride was tested in one experiment in mice by oral administration. A significant increase in the incidence of lung tumours was reported[1].

C. Evidence for activity in short-term tests (*sufficient*)

Hydralazine binds to DNA. It induced mutation and gave indirect evidence of DNA repair in bacteria in the absence of an exogenous metabolic activation system[1,2]; it also induced DNA repair in cultured mammalian cells[1,3] and in rat hepatocytes[1]. Two major metabolites in man, 3-methyl-*s*-triazolo(3,4-*a*)phthalazine and its hydroxy derivative, were inactive in bacterial tests, either in the presence or absence of an exogenous metabolic activation system[1]. There is also evidence that hydralazine caused chromosomal aberrations in mammalian cells *in vitro*[4] and in rat bone marrow *in vivo*[1]. Hydralazine did not induce DNA damage (as judged by a negative response in an alkaline-elution assay) in liver or lung of mice treated *in vivo*[2]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	+		+	
Mammals *(in vivo)*	-		+	
Humans *(in vivo)*				

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HYDRAZINE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Two reports of cancer mortality in workers exposed to hydrazine have appeared in recent years. One case of choroidal melanoma was observed in a man who had been exposed to hydrazine for six years[1]. A preliminary report of an epidemiological study of men engaged in hydrazine manufacture revealed no unusual excess of cancer[2]; this study included 423 men, with a 64% vital status ascertainment. None of the five cancers reported (3 stomach, 1 prostate, 1 neurogenic) was in the group with highest exposure.

B. Evidence for carcinogenicity to animals (*sufficient*)

Hydrazine is carcinogenic to mice after its oral administration, producing lung, liver and mammary tumours, and after its intraperitoneal administration, producing lung tumours and sarcomas. It is carcinogenic to rats following oral administration, producing lung and liver tumours. In a study reported as an abstract, rats and male hamsters exposed daily by inhalation to 5 ppm (6.5 mg/m^3) hydrazine in air developed nasal tumours. After repeated exposure by inhalation to 1 ppm (1.3 mg/m^3) hydrazine, rats developed nasal turbinate tumours, and female mice developed pulmonary adenomas. The incidence of nasal turbinate tumours in rats was dose-related. The increased tumour incidences in mice and hamsters occurred only with the maximum tolerated dose levels[4].

C. Evidence for activity in short-term tests (*sufficient*)

Hydrazine was mutagenic and gave indirect evidence of DNA repair in bacteria and fungi in the absence of an exogenous metabolic activation system[5]. It did not induce mutation in cultured mammalian cells, either in the presence or absence of metabolic activation[5,6], and conflicting results have been obtained with regard to the induction of chromosomal aberrations, sister chromatid exchanges and DNA repair[5,7]. In two separate studies, hydrazine caused cell transformation (in the BHK assay)[5]. In several experiments in mice, hydrazine did not induce bone-marrow micronuclei or morphological abnormalities in sperm; in one study it did not increase the level of sister chromatid exchanges in bone marrow[5]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+	+	
Insects				
Mammalian cells *(in vitro)*	?	-	?	T(+)
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

T = cell transformation

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17α-HYDROXYPROGESTERONE CAPROATE (Group 3) (See Oestrogens and progestins)

INDUSTRIES:

BOOT AND SHOE MANUFACTURE AND REPAIR (Group 1)

Evidence for carcinogenicity to humans (*sufficient* for certain exposures)

Three cases of mesothelioma were reported among 3806 deaths in shoe workers[1]; and there was an earlier report of a female shoemaker (whose husband was also a shoemaker) who died of mesothelioma[2].

There is sufficient evidence that nasal adenocarcinoma has been caused by employment in the boot and shoe manufacturing and repairing industries. Relative risks well in excess of 10-fold have been reported in the boot and shoe manufacturing industry in England and Italy. The distribution of the cases within the industry suggests strongly that exposure to leather dust plays a role in the association. There is also evidence that an increased risk may exist for other types of nasal cancer for employment in the boot and shoe industries[3].

There is evidence of an increased risk of bladder cancer associated with employment in the leather industry. Although boot- and shoemakers were included in these studies, it is not possible to determine whether the risk related to them in particular or to other occupational subgroups[3].

The occurrence of leukaemia and aplastic anaemia among shoemakers exposed to benzene is well documented[3,4].

Hypothesis-generating surveys have suggested associations between boot and shoe manufacture/repair and cancers of the lung, oral cavity and pharynx and stomach. The same surveys have suggested associations between work in the leather industry (occupation not further specified) and cancer of the larynx and lymphoma. Most of these associations were positive. In view of the design of the pertinent studies, these findings could not be evaluated[3].

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CARPENTRY AND JOINERY (Group 3)

Evidence for carcinogenicity to humans (*inadequate*)

In a case-control study based on an analysis of occupational data in the hospital records of 121 men seen for nasal cancer in British Columbia between 1939 and 1977[1], a relative risk of 2.5 (adjusted for smoking and ethnic origin) was associated with exposure to wood. Most histological types of epithelial tumour, except for transitional tumours, showed an increased risk. Of the 28 wood workers with nasal cancer, 16 worked in the forest industry, 7 were carpenters, 4 were construction workers and 1 was a cabinet-maker.

In France, carpenters were not found to have an increased risk of nasal cancer, but no quantitative data were given[2].

In a national study on the incidence of nasal cancer in England in 1963-1967[3], the occupations of 925 men were studied, using postal questionnaires and data from hospital and death records. Among wood workers, the Standard Incidence Ratios (SIRs) for cabinet- and chairmakers, machinists and 'other' wood workers were, respectively, 966, 616 and 293. For carpenters and joiners, the SIR was 149.

In a study of 1070 white male model makers and pattern makers employed in the Detroit automobile industry[4], cancer experience was studied by matching the listing to the Michigan death registry. Significant excesses of cancers of all sites (40 observed; standardized mortality ratio, 150), cancer of the colon and rectum (11 observed; SMR,

286) and cancer of the salivary gland (2 observed, 0.1 expected; SMR, 2100). Only 75.9% of the workers had been traced to the end of the follow-up period. The excesses of cancers were seen in men exposed for less than 20 years in the industry and not in those exposed for more than 20 years. No information was given about the working conditions of the men.

[The epidemiological data from these studies and those described previously[5] are not sufficient to make a definitive assessment of the carcinogenic risks of employment as a carpenter or joiner. Several studies raise the possibility of an increased risk of Hodgkin's disease. Apart from one anecdotal report, there is no evidence of an association between nasal adenocarcinoma and work as a carpenter. A number of studies suggest an association between work as a joiner and nasal adenocarcinoma, but it is possible that the workers involved may have worked in the furniture industry. The evidence suggesting increased risks of lung, bladder, and stomach cancer comes from large population-based occupational mortality statistical studies and is inadequate to allow an evaluation of risks for these tumours. The one study of model and pattern makers suggesting an increased incidence of cancer of the colon and rectum could not be evaluated.]

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THE FURNITURE AND CABINET-MAKING INDUSTRY (Group 1)

Evidence for carcinogenicity to humans (*sufficient*)

In a study of 25 cases of malignant nasal tumour occurring in Verona during the period 1969-1979[1], all three patients with adenocarcinomas and two of the 13 with other epithelial tumours had been employed in wood processing industries.

A case-control study was reported based on 301 cases of nasal cancer in the Connecticut Tumor Register and controls randomly selected from all deaths in men aged

35 or older in the state. Occupational data were derived from death certificates and from the *Price & Lee City Directory*. Positive associations were found with exposure to cutting oils (odds ratio, 2.8; 1.4-5.7) and wood dust (odds ratio, 4.0; 1.5-10.8). The cases in those exposed to wood dust occured in 2 cabinet-makers, 2 woodworkers, 1 sawmill owner, 2 lumber company workers and 1 pattern maker. It was suggested that cutting oils might be a factor in nasal cancer in turners[2].

Of 149 cases of nasal cancer in French woodworkers[3], 138 were adenocarcinomas. Of the 61 cases observed, 52 were in furniture and cabinet-makers.

A study was made of the incidence and mortality of cancer in 5371 men employed in the Buckinghamshire furniture industry and followed for an average of 19 years since commencing work[4]. The incidence of nasal adenocarcinoma was about 100 times that expected in the local population, and a significant relationship was found between the incidence of the tumour and increasing dustiness of work. For cancer of the bronchus, the Standard Registration Ratio was 82 (61-107) and the Standardized Mortality Ratio (corrected for the Oxford Region) was 79 (59-105), and a significant trend of increasing SMR with increasing dustiness of work was found. A trend of increasing SMR for bronchial cancer with increasing duration of work (not significant) was also found. A sample of the workforce living in 1969 contained a lower percentage of current smokers than the general population, and there were slightly fewer smokers among the men in the dustiest jobs than in the less dusty jobs.

[Epidemiological data reported here and previously[2] provide sufficient evidence that nasal adenocarcinomas have been caused by employment in the furniture making industry. The excess risk occurs (mainly) among those exposed to wood dust. Although the greatest risk is in respect of adenocarcinoma (relative risks in excess of 100 have been reported from England and Denmark), there is suggestive evidence of a slight increase in the risk of other nasal cancers. One study (Esping & Axelson[2]) showed an increased relative risk for lung cancer (based on four cases from one factory), while another[4] (based on 53 cases in 9 factories) showed no increased risk as compared with an external standard but found suggestive trends with increasing dustiness and duration of work. A cohort study of the Danish carpenters' and cabinet makers' union[2] gives SMRs for lung cancer of 96 (men aged 20-64) and 110 (men aged 65-84). Mortality statistics have, in general, shown no increase in lung cancer, and no evaluation of the risk of lung cancer is possible.]

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LEATHER GOODS MANUFACTURE (Group 3)

Evidence for carcinogenicity to humans (*inadequate*)

A few cases of leukaemia have been reported following exposure to benzene (a known human carcinogen[1]) during the manufacture of leather goods other than boots and shoes. The few cases of nasal cancer reported are insufficient to make an association with employment in the manufacture of leather goods (other than boots and shoes or tanning)[2].

[A positive association between bladder cancer and employment in the leather industry (not further specified) is supported by a number of studies, but the specific role of the production of leather goods (other than boots and shoes or tanning) cannot be evaluated. The suggested associations between employment in the leather industry (not further specified) and cancers of the lung, larynx, oral cavity and pharynx, kidney and lymphomas come from hypothesis-generating surveys. They do not refer specifically to workers engaged in the production of leather goods (other than boots and shoes or tanning).]

References

[1] *IARC Monographs*, *29*, 93-148, 1982

[2] *IARC Monographs*, *25*, 279-292, 1980

THE LEATHER TANNING AND PROCESSING INDUSTRIES (Group 3)

Evidence for carcinogenicity to humans (*inadequate*)

Very few reports of epidemiological studies or cases deal specifically with workers engaged in leather tanning and processing. There is no evidence to suggest an association between leather tanning and nasal cancer[1,2]. The suggested associations between employment in the leather industry (not further specified) and cancer of the lung, larynx, buccal cavity, pharynx and kidney and lymphomas come from hypothesis-generating surveys. They do not refer specifically to workers in tanneries. A positive association between employment n the leather industry (not further specified) and bladder cancer is supported by a number of studies. The only study that dealt specifically with leather tanners, however, revealed a relative risk of 1.5, which is not statistically significant[1].

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THE LUMBER AND SAWMILL INDUSTRIES (INCLUDING LOGGING) (Group 3)

Evidence for carcinogenicity to humans (*inadequate*)

In a case-control study based on an analysis of occupational data in the hospital records of 121 men seen for nasal cancer in British Columbia between 1939 and 1977, a relative risk of 2.5 (adjusted for smoking and ethnic origin) was found to be associated with exposure to wood. Most histological types of epithelial tumour, except for transitional tumours, showed an increased risk. Of the 28 wood workers with nasal cancer 16 worked in the forest industry, 7 were carpenters, 4 were construction workers and 1 was a cabinet-maker[1].

In a proportional mortality study of the causes of death of 375 of 1030 union-affiliated Swedish lumberjacks who died between 1968 and 1977, there were fewer deaths from cancer than expected (Proportional Mortality Ratio, 88; 95% confidence limits, 69-111). A marked deficiency of lung cancer deaths (Standardized Mortality Ratio, SMR, 33) and excesses of kidney cancer (SMR 193, 92-407) and of cancers of the lymphatic and haemopoietic system (SMR 191, 105-349) were found. No information was given about the histology of these two groups of tumours. The mortality experience of Swedish males during that period was used as the standard of comparison[2].

A case-control study of Hodgkin's disease, using death certificates from North Carolina counties with a 'significant proportion' of the population employed in the furniture industry and lumbering, showed an excess risk only among occupational groups with exposure to wood and paper. Carpenters and lumberers had a relative risk of 4.2 for Hodgkin's disease (1.4-12.5)[3].

[The epidemiological data reported here and previously[4] are not sufficient to make a definite assessment of the carcinogenic risks of employment in the lumber and sawmill industries. Some studies suggest that the incidences of nasal cancers and Hodgkin's disease may be increased. It is not known whether some nasal cancer patients described as working in lumber and sawmill industries may have worked in furniture manufacture. The hypothesized link to Hodgkin's disease is not adequately supported. Soft-tissue sarcomas and histiocytic lymphomas have been reported following exposures to chlorophenols and phenoxy herbicides; although the risk to sawmill and lumber workers was not quantified directly, the use pattern of chlorophenols suggests that sawmill workers in this study were at increased risk for both of these malignancies. Stomach cancer incidence was slightly elevated among these occupational groups in six mortality series; however, this might be related to nonoccupational factors.]

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THE PULP AND PAPER INDUSTRY (Group 3)

Evidence for carcinogenicity to humans (*inadequate*)

A case-control study of the paternal occupations of 692 children who died of cancer in Massachusetts showed that paternal employment as a paper or pulp mill worker was associated with tumours of the brain and other parts of the nervous system (6 cases observed; relative risk, 2.8); however, as a large number of comparisons were made, this may well be a chance finding[1].

Several studies suggest that an increased risk of lymphoproliferative neoplasms, particularly Hodgkin's disease and perhaps leukaemia, may be linked to employment in the paper and pulp industries[2].

Excess incidences of oral and pharyngeal and/or laryngeal cancers were reported in two studies designed to generate hypotheses but have not been evaluated in independent studies. There appears to be no overall increased risk of lung cancer among paper workers; the excess risk of lung cancer observed in some subgroups of workers in two of the studies cannot be evaluated[2].

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THE RUBBER INDUSTRY (Group 1)

Evidence for carcinogenicity to humans (*sufficient* for certain exposures)

A large number of retrospective follow-up studies of cohorts of rubber workers and case-control studies of individuals with cancer have been conducted in the US, the UK, Switzerland, Canada, Sweden and Finland. These studies indicate that an excess incidence of bladder tumours occurred in the UK, which was probably associated with

exposure to aromatic amines of workers employed before 1950. The evidence is less strong for US workers. US workers, however, showed increased rates of lymphatic leukaemia, probably due to exposure to organic solvents. Stomach and lung cancer rates were elevated in both the US and UK studies. There is limited evidence that other cancers (skin, colon, prostate, lymphoma) are associated with work in the industry. Cancers of the brain, thyroid, pancreas and oesophagus have also been reported[1].

Reference

[1] *IARC Monographs, 28,* 1982

IRON DEXTRAN COMPLEX (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In an early case report[1], an undifferentiated soft-tissue sarcoma developed in a woman who received multiple injections of iron dextran. In a report on diagnoses of sarcoma of the buttock[2], four of 196 cases had been given intramuscular injections of iron. In three of the cases, an interval of at least two years had elapsed. [A selective tendency to register cases of sarcoma preferentially, if they had received iron injections, may have introduced bias.] A review[3] showed that in the 20 years since the introduction of iron dextran, nine malignancies had been described in five reports during 1960-1976. One was a metastatic carcinoma at the site of an iron injection given a few months earlier; two were thought to be foreign-body reactions to fat necrosis. It was also observed that in Greenberg's[2] data, each of the recorded tumours was of a different histological type. A spindle-cell fibrosarcoma of the buttock was reported 14 years after a course of four injections of iron dextran[4].

B. Evidence for carcinogenicity to animals (*sufficient*)

Iron dextran complex is carcinogenic to mice and rats after repeated subcutaneous or intramuscular injections, producing local tumours at the injection site[1]. [The Working Group noted that iron dextran accumulates at the site of injection in rodents, in contrast to its rapid dispersal after injection in human beings.]

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal anomaly was observed in human lymphocytes treated *in vitro*[5]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

References

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ISONICOTINIC ACID HYDRAZIDE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Several early studies did not show a significant excess of cancer among patients treated with isonicotinic acid hydrazide (isoniazid)[1]. A study of tuberculosis patients, most of whom were followed for more than 19 years, showed a slight excess of respiratory cancers in patients treated with this drug [relative risk, RR, 1.4; 95% confidence interval, 1.03-1.96, calculated by the Secretariat] and a deficit in patients not treated with isoniazid [RR, 0.3; 95% confidence interval, 0.06-0.91, 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 the respiratory tract. The excess was mainly for deaths within four years of the start of 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[2]. More recent studies of mortality from cancer among patients treated with isoniazid have shown no excess of lung cancer, or of cancer as a whole, that could be attributed to treatment[3-5]. Of four recent studies of cancer incidence[4-7] in patients with tuberculosis, one[6] showed a greater excess of lung cancer among men exposed to isoniazid (RR, 3.4, based on 88 cases) than among the unexposed (RR, 2.6, based on 18 cases), but this was not statistically significant. The corresponding numbers for women

were 4.6, based on 14 cases exposed, and 0.5, based on a single case not exposed. Three other studies showed no evidence of a higher incidence of lung cancer or of cancer as a whole in patients treated with isoniazid than in those not treated[4,5,7]. Three case-control studies concerning, respectively, bladder and kidney cancers[8], bladder cancer[9] and cancer in children[10] showed no conclusive evidence of a risk associated with isoniazid.

B. Evidence for carcinogenicity to animals (*limited*)

Isonicotinic acid hydrazide produces lung tumours in mice after its oral, intraperitoneal or subcutaneous administration. Studies in rats and hamsters were considered to be inadequate[1].

C. Evidence for activity in short-term tests (*limited*)

Isoniazid did not cause misincorporation of nucleotides on synthetic polyribonucleotides but induced DNA binding *in vitro*[11]. At very high doses, in the absence of an exogenous metabolic activation system, it induced mutation and indirect evidence of DNA repair in bacteria[12,13] and mitotic gene conversion in fungi[14]. Isoniazid induced DNA repair in cultured mammalian cells only in the presence of divalent copper and manganese[12]. In one study, it caused specific-locus mutations in mice treated early in embryogenesis *in vivo*[13]. Isoniazid did not produce dominant lethal mutations in mice[13]. It did not induce micronuclei or chromosomal aberrations in the bone marrow of rats[15] or Chinese hamsters[13], or chromosomal aberrations in the germ cells of male Chinese hamsters[16]. It was positive in host-mediated assays using mice, Chinese hamsters, guinea-pigs and Syrian hamsters, causing mutations in bacteria[13]; it has been concluded that this activity was due in part to the formation of hydrazine. Isoniazid (98% pure) caused DNA damage (as judged by a positive effect in an alkaline-elution test) in lung DNA (but not liver DNA) of mice treated *in vivo*[17]. There was no evidence of cytogenetic damage in the cultured peripheral lymphocytes of patients undergoing treatment or prophylaxis with isoniazid[13].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	-			
Mammals *(in vivo)*	?	+	-	DL(-)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

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ISOPROPYL OILS (Group 3) [See Manufacture of isopropyl alcohol (strong-acid process)]

LEAD AND LEAD COMPOUNDS (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three epidemiological studies of workers exposed to lead and lead compounds were available[1]. Excesses of digestive and respiratory cancers were seen in one study of lead smelter workers and battery plant operators and an insignificant excess of skin cancer in workers exposed to tetraethyllead. Since then, there has been a case report[2] of a renal carcinoma in a lead smelter worker, which was similar in appearance to lead-induced tumours in animals. A follow-up of the smelter and battery plant employees has been extended[3-5], showing an excess of respiratory cancer (24 observed, 21 expected) in battery workers; information on smoking was not available.

B. Evidence for carcinogenicity to animals (*sufficient* for some salts)

Lead acetate, lead subacetate and lead phosphate are carcinogenic to rats and lead subacetate to mice, producing renal tumours after their oral or parenteral administration. Gliomas occurred in rats given lead acetate or lead subacetate by the oral route. Lead subacetate produced an increased incidence of lung adenomas in mice after its intraperitoneal administration[1]. Lead dimethyldithiocarbamate was not carcinogenic to mice or rats after its oral administration[5]. Other lead salts and lead tetraalkyls have not been tested adequately[1]. [The Working Group noted that although soluble lead salts have been shown to be carcinogenic to experimental animals, human beings are exposed primarily to metallic lead and lead oxide.]

C. Evidence for activity in short-term tests (*inadequate*)

Soluble salts of lead caused misincorporation of nucleotides in an in-vitro DNA transcription assay and have been shown to form stable complexes with DNA. Mutagenicity assays of lead salts in bacteria and fungi were negative, as were assays for differential survival, an indirect measure of DNA repair. Lead salts induced mutation and chromosomal aberrations in vascular plants. Assays of soluble lead salts for chromosomal aberrations and sister chromatid exchanges in cultured mammalian cells gave conflicting results. Positive results were obtained in a cell-transformation assay (in Syrian hamster embryo cells). In-vivo studies of lead salts have given contradictory results: chromosomal aberrations have been reported in the bone marrow of mice and rats dosed with lead salts and in cultured peripheral lymphocytes recovered from monkeys fed lead with a low-calcium diet. Other studies using rodents were negative. A sperm abnormality test and a dominant lethal mutation test in mice were both negative. Tetraethyllead did not induce dominant lethal mutations in mice[1]. Cytogenetic studies of people exposed to lead have given conflicting results: seven studies were negative and nine were positive[1,6]. A single study of sister chromatid exchange in cultured peripheral lymphocytes from people exposed to lead was negative[6].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	?	-		
Fungi/Green plants		?	?	
Insects				
Mammalian cells *(in vitro)*			?	T(+)
Mammals *(in vivo)*			?	DL(-) SA(-)
Humans *(in vivo)*			?	

T = cell transformation; DL = dominant lethal mutations; SA = sperm abnormalities

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LYNOESTRENOL (Group 3) (See Oestrogens and progestins)

MAGENTA (TECHNICAL-GRADE) (Group 3) (See Manufacture of magenta)

MANUFACTURE OF AURAMINE (Group 1) [See Auramine (technical-grade)]

MANUFACTURE OF ISOPROPYL ALCOHOL (STRONG-ACID PROCESS) (Group 1) and ISOPROPYL OILS (Group 3)

A. Evidence for carcinogenicity to humans (*sufficient* for manufacture of isopropyl alcohol by the strong-acid process, *inadequate* for isopropyl oils)

An increased incidence of cancer of the paranasal sinuses was observed in workers at factories manufacturing isopropyl alcohol by the strong-acid process[1,2]. The risk of laryngeal cancer may also have been elevated in these workers[1]. It is unclear whether the risk of cancer is due to diisopropyl sulphate, which is an intermediate in the process, to isopropyl oils, which are formed as by-products, or to other factors. Epidemiological data concerning the manufacture of isopropyl alcohol by the weak-acid process are insufficient for an evaluation of carcinogenicity[1].

B. Evidence for carcinogenicity to animals (*inadequate* for isopropyl oils)

Isopropyl oils formed during the strong-acid process for synthesis of isopropyl alcohol were tested in mice by skin application, inhalation exposure and subcutaneous injection; isopropyl oils formed during the weak-acid process were tested in mice by skin application and subcutaneous injection. Although an increased incidence of lung tumours was observed following inhalation or subcutaneous injection of isopropyl oils formed during the strong-acid process, all of the studies had some limitations due to short duration or incomplete reporting and to the unknown, variable composition of the materials tested[1].

C. Evidence for activity in short-term tests

No data were available.

References

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MANUFACTURE OF MAGENTA (Group 2A) and MAGENTA (TECHNICAL-GRADE) (Group 3)

A. Evidence for carcinogenicity to humans (*limited* for manufacture of magenta, *inadequate* for magenta)

The manufacture of magenta (which also involves exposure to other chemicals) was shown in one study to be causally associated with an increased incidence of bladder cancer[1]. The carcinogenic compound(s) involved has not been specified.

B. Evidence for carcinogenicity to animals (*inadequate* for magenta)

Subcutaneous administration of para-magenta, a component of commercial magenta, induced local sarcomas in rats. In one limited study in mice, there was no increase in tumour incidence following oral administration of commercial magenta[1]. Oral administration of magenta or para-magenta to hamsters for life at the maximum tolerated dose did not result in the development of tumours attributable to the treatment[2].

C. Evidence for activity in short-term tests (*inadequate* for magenta)

Magenta gave indirect evidence of DNA repair in *Escherichia coli*[3]. It was mutagenic in *Salmonella typhimurium* in the presence of a hamster liver microsomal activation system[4]. It did not induce cell transformation (in the Syrian hamster assay)[5] and did not produce recombination in *Saccharomyces cerevisiae*[6]. Magenta was inadequately tested for chromosomal anomalies in Chinese hamster cells *in vitro*[7]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		-		
Insects				
Mammalian cells *(in vitro)*			?	T(-)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

References

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MEDROXYPROGESTERONE ACETATE (Group 3) (See Oestrogens and progestins)

MEGESTROL ACETATE (Group 3) (See Oestrogens and progestins)

MELPHALAN (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Case reports of second primary malignancies (mainly acute leukaemia) have been made for patients treated with melphalan. Epidemiological studies showed substantially increased rates of leukaemia in patients treated with this drug for multiple myeloma and ovarian cancer. Some of these patients were also given other alkylating agents and ionizing radiation; however, sufficient numbers of the patients received melphalan alone for it to be implicated as a causal factor. Additionally, the incidence of acute leukaemia in patients with multiple myeloma has increased since the introduction of melphalan therapy[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

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

C. Evidence for activity in short-term tests (*sufficient*)

Melphalan is an alkylating agent. It reacted directly with DNA and produced mutations in bacteria in the presence or absence of an exogenous metabolic activation system[2]. It induced chromosomal aberrations and sister chromatid exchanges in mammalian cells *in vitro*[3] and *in vivo*[4]. Melphalan produced chromosome damage in lymphocytes of patients treated therapeutically[4,5].

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		+	+	
Mammals *(in vivo)*		+	+	
Humans *(in vivo)*			+	

References

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6-MERCAPTOPURINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A small number of case reports document the occurrence of acute nonlymphocytic leukaemia in patients who received 6-mercaptopurine for both neoplastic and non-neoplastic disorders[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

6-Mercaptopurine was tested by intraperitoneal administration and by skin painting (followed by croton oil) in mice and by intraperitoneal, subcutaneous and intravenous injection in rats. Limitations to the data in all the reports precluded evaluation of the possible carcinogenicity of 6-mercaptopurine[1].

C. Evidence for activity in short-term tests (*sufficient*)

6-Mercaptopurine was mutagenic without metabolic activation in *Salmonella typhimurium*[1] and gave indirect evidence of DNA repair in bacteria[2]. Increases in chromosomal aberrations were found in human peripheral lymphocytes exposed *in vitro*[1]. It was reported in an abstract that 6-mercaptopurine was negative in the mouse heritable translocation test[3]. It was mutagenic to mammalian cells in culture[4,5]. Cytotoxic concentrations did not produce cell transformation in C3H/10T½ cells[1]. It produced dominant lethal effects *in vivo* in male mice[6] but not in male rats[7], and chromosomal aberrations in rodents *in vivo*[1]. Increases in chromosomal aberrations were observed in the peripheral lymphocytes of patients treated with 6-mercaptopurine[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		+	+	T(-)
Mammals *(in vivo)*			+	DL(?)
Humans *(in vivo)*			+	

T = cell transformation ; DL = dominant lethal mutations

References

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MESTRANOL (Group 2B) (See Oestrogens and progestins)

METHOTREXATE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A number of cases have been reported of malignancies developing in patients treated with methotrexate, often in combination with other agents, for psoriasis[1] or previous cancer[1-5]. No excess of cancer was found in two epidemiological studies of patients who received methotrexate for psoriasis or as treatment for choriocarcinoma[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

Methotrexate was tested by oral administration in mice and hamsters, by intraperitoneal injection in mice and rats, and by intravenous injection in rats. One study in mice by oral administration showed a high incidence of lung carcinomas, but the study design did not include matched controls. No other study revealed a carcinogenic effect, but the significance of several was limited because of deficiencies in experimental design or reporting of data[1].

C. Evidence for activity in short-term tests (*sufficient*)

Methotrexate was not mutagenic in *Salmonella typhimurium*[1] but was mutagenic in the folate-requiring organism *Streptococcus faecium*[6]. It did not induce prophage in *Escherichia coli*[6]. A three- to four-fold increase in recombination found in *E. coli* was attributed to inhibition of DNA synthesis[6]. Methotrexate also induced recombination in yeast[6]. Several studies have established that it induced chromosomal aberrations in mammalian cells, including cell cultures and mouse germ cells *in vivo*[1]. It was positive in the micronucleus test in human bone marrow[7] and in the L5178Y/TK$^{+/-}$ mouse cell culture mutagenesis assay[8]. It induced dominant lethal mutations in mice and transformed C3H/10T$\frac{1}{2}$ cells[1]. Methotrexate induced chromosomal aberrations in the bone-marrow cells of treated patients[1,6].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	?		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*		+	+	T(+)
Mammals *(in vivo)*			+	DL(+)
Humans *(in vivo)*			+	

T = cell transformation DL = dominant lethal mutations

References

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METHOXSALEN WITH ULTRA-VIOLET A THERAPY (PUVA) (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

This topic has been reviewed[1]. Methoxsalen and long-wave ultra-violet (A) light (PUVA) treatment has been associated with the development of squamous-cell carcinoma in two patients with mycosis fungoides[2], with haematopoietic neoplasms in two patients, with basal-cell skin cancer in another, and with squamous-cell skin cancer in a cohort study of patients with psoriasis. In none of these reports could the possible effects of methoxsalen alone be distinguished from those of long-wave ultra-violet light or of the combination of the two. Methoxsalen alone did not alter the incidence of skin cancer over two years in two small controlled trials of its use as a putative prophylactic for this disease[3]. In a case-control study of patients with psoriasis treated with PUVA, the relative risk of skin carcinoma was 2.4 in comparison with unmatched controls and 4.7 in comparison with matched controls (95% confidence limits, 2.2-10.0)[4]. A follow-up study for 3.6 years of 525 patients with psoriasis treated with PUVA showed one skin cancer, which was probably already present before treatment commenced[5]. [The study lacked adequate statistical power to detect an association.]

B. Evidence for carcinogenicity to animals (*sufficient*)

Methoxsalen has not been tested alone by skin application and was inadequately tested in mice by oral and by intraperitoneal administration. When it was tested in combination with long-wave ultra-violet light in mice by oral and intraperitoneal administration and by skin application, it increased the incidences of epidermal and dermal tumours[3,6].

C. Evidence for activity in short-term tests (*sufficient*)

Methoxsalen forms cyclobutane mono- and di-adducts with pyrimidine bases of DNA under ultra-violet irradiation[3]. Methoxsalen plus ultra-violet light (PUVA) caused DNA damage in bacteria and in mammalian and human cells *in vitro*[3,7]. PUVA was weakly mutagenic to bacterial cells and to human cells exposed *in vitro*[3]. In the presence of near ultra-violet light (320-400 nm), methoxsalen was a powerful mutagen in a variety of prokaryotes and eukaryotes, including mammalian cells exposed *in vitro*[1,3,8]. It produced chromosomal aberrations in mammalian cells *in vitro* and *in vivo*[3,9]. Cell transformation was demonstrated in various cell systems[3]. There are conflicting data with regard to the induction of chromosomal aberrations in man. More point mutations (increased incidence of 6-thioguanine-resistant lymphocytes) were observed in patients treated with psoralen drugs and ultra-violet irradiation than in healthy controls[3].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*			+	
Humans *(in vivo)*		+	?	

T = cell transformation

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METRONIDAZOLE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

Two epidemiological studies[1,2] of women treated with metronidazole showed an excess of cancers of the uterine cervix, a neoplasm that has risk factors in common with vaginal trichomoniasis, the main indication in women for treatment with this drug. In one study[1], a greater excess of cervical cancer was observed in women with trichomoniasis who were not exposed to metronidazole. An excess of lung cancer (4 observed, 0.6 expected) seen in one study[1] was not found in the other[2] (2 observed, 2.6 expected); in neither study was there a significant excess of non-uterine cancers.

B. Evidence for carcinogenicity to animals (*sufficient*)

Metronidazole is carcinogenic to mice and rats. After its oral administration it significantly increased the incidence of lung tumours in mice of both sexes and of lymphomas in female mice[3], and of mammary[3,4], pituitary, testicular and liver tumours in rats[4].

C. Evidence for activity in short-term tests (*limited*)

Following its reduction, metronidazole interacts with DNA. One or more of its metabolites was mutagenic to *Salmonella typhimurium*, *Escherichia coli* and other bacterial species[3,5-7]; and urine from mice treated with metronidazole was mutagenic to bacteria, the activity being due largely to the metabolite 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole[8]. Neither this metabolite nor the parent compound induced chromosomal damage in human lymphocytes exposed *in vitro*[9]. It did not induce mutations in conidia of *Neurospora crassa*, but induced mutations in growing cells and produced gene conversion in baker's yeast[5,10]. Metronidazole was not mutagenic to *Drosophila*[5,11]. It did not induce sister chromatid exchanges in hamster BHK[12], Chinese hamster CH0[12] or human cells exposed *in vitro*[13]; it appears to be equally ineffective in inducing chromosomal aberrations in mammalian, including human, cells in culture[9,14]. One report described chromosome breaks in bone-marrow cells of treated mice[15], but metronidazole was ineffective in inducing micronuclei in mouse bone-marrow cells *in vivo*[14]. Urine, but not blood, from humans treated with metronidazole was mutagenic to bacteria[3], the hydroxyethyl metabolite being the major active component. Studies on bone-marrow cells from 39 patients and on blood lymphocytes from more than 50 patients being treated with metronidazole for a variety of conditions showed no significant increase in chromosomal damage expressed either as sister chromatid exchange or as gross chromosomal aberrations[16-18].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		-		DL(-)
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*			?	
Humans *(in vivo)*			-	

DL = dominant lethal mutations

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MUSTARD GAS (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Several studies have shown increased mortality from respiratory cancer among people exposed to mustard gas. Mortality was greater among those with chronic occupational exposure than among those exposed sporadically[1].

B. Evidence for carcinogenicity to animals (*limited*)

Mustard gas is carcinogenic to mice, the only species tested, producing lung tumours after its inhalation or intravenous injection and local sarcomas after its subcutaneous injection[1].

C. Evidence for activity in short-term tests (*sufficient*)

Mustard gas, an alkylating agent, reacts with DNA of prokaryotes and eukaryotes *in vitro* and *in vivo*[2,3]. It was mutagenic to yeast and *Drosophila melanogaster*[2,3], to mouse lymphoma cells *in vitro* and in the mouse host-mediated assay[2]. It produced chromosomal aberrations in lymphocytes of rats treated *in vivo* and in mouse lymphoma cells in the host-mediated assay[2]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+			
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	
Mammals *(in vivo)*	+		+	DL(+)
Humans *(in vivo)*				

DL = dominant lethal mutations

* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

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MYLERAN (Group 1) (See 1,4-Butanediol dimethanesulphonate)

1-NAPHTHYLAMINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

An excess of bladder cancer was observed in workers exposed to commercial 1-naphthylamine for five or more years who had not also been engaged in the production of 2-naphthylamine or benzidine. However, as commercial 1-naphthylamine made at that time may have contained 4-10% 2-naphthylamine, it is not possible to assess the carcinogenicity of 1-naphthylamine alone[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

No carcinogenic effect of 1-naphthylamine was observed in hamsters following its oral administration; results obtained in mice following its oral or subcutaneous administration were inconclusive[1]. No tumour was induced in rats after skin application of 1-naphthylamine[2]. No tumour was observed in mice fed diets containing 1-naphthylamine for one year; however, the period of observation was too short, since the animals were killed at the end of treatment[3]. No carcinogenic effect was observed in dogs fed 1-naphthylamine for 109 months[4]; and no bladder or other tumour was observed in dogs fed 1-naphthylamine for nine years[5].

C. Evidence for activity in short-term tests (*sufficient*)

1-Naphthylamine was mutagenic and gave indirect evidence of DNA repair in bacteria and fungi in the presence of an exogenous metabolic activation system. It was not mutagenic to *Drosophila melanogaster* in two separate studies. In cultured mammalian cells supplied with an exogenous metabolizing system, 1-naphthylamine induced mutation at three different loci, sister chromatid exchanges, chromosomal aberrations and DNA repair; however, it was negative in assays for cell transformation (BHK)[6]. In four different studies, 1-naphthylamine did not induce micronuclei in the bone marrow of mice

treated *in vivo*[6,7] and did not produce sperm abnormalities in two studies in mice[8,9]. Results of an assay *in vivo* for sister chromatid exchanges in mice were equivocal[6]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+		
Insects		-		
Mammalian cells *(in vitro)*	+	+	+	T(-)
Mammals *(in vivo)*			-	SA(-)
Humans *(in vivo)*				

T = cell transformation; SA = sperm abnormalities

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2-NAPHTHYLAMINE (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or as an impurity in other compounds, is causally associated with the occurrence of bladder cancer[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

2-Naphthylamine is carcinogenic, producing urinary bladder carcinomas in hamsters, dogs and non-human primates and hepatomas in mice, after its oral administration[1].

C. Evidence for activity in short-term tests (*sufficient*)

2-Naphthylamine induced DNA damage and mutation in fungi[2] and in bacteria[3-5] in the presence of an exogenous metabolic activation system. It induced mutations in *Drosophila melanogaster*[6]. In mammalian cells in culture it induced DNA damage, mutation, chromosomal aberrations, sister chromatid exchanges and transformation (BHK, hamster and rat embryo)[7-9]. Conflicting evidence was obtained in the micronucleus test in mice *in vivo*[6]. It did not induce sperm abnormalities in mice[6]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+		
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*			?	SA(-)
Humans *(in vivo)*				

T = cell transformation SA = sperm abnormalities

* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

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NICKEL AND CERTAIN NICKEL COMPOUNDS (Group 2A) and NICKEL REFINING (Group 1)

A. Evidence for carcinogenicity to humans (*limited* for nickel and certain nickel compounds, *sufficient* for nickel refining)

Early epidemiological studies of populations of workers exposed to nickel or nickel compounds clearly demonstrated excess incidences of cancers of the nasal cavity, the lung and, possibly, the larynx. However, the carcinogen(s) responsible could not be specified. Nickel carbonyl was considered unlikely to be involved in view of experience at a South Wales refinery[1]. Later studies have shed little further light. A study of 814 male workers at a gas diffusion plant who were exposed to pure nickel dust revealed no increased mortality from respiratory-tract cancers in comparison with that of a control group[2]. Similar negative results came from a matched case referent study of aircraft engine workers exposed to oxides, chlorides and alloys of nickel[3]. A mortality study of nickel alloy manufacturers exposed to nickel and nickel oxides but not to nickel subsulphide was similarly negative[6]. Each of these studies involved relatively small

numbers of subjects, and follow-up exceeded 15 years in only one[2]. Two studies of sinonasal cancer mortality did not reveal a risk from exposure to nickel in recent times[5,6]. It is still not possible to state with certainty which specific nickel compounds are human carcinogens, although metallic nickel seems less likely to be so than nickel subsulphide or nickel oxides.

B. Evidence for carcinogenicity to animals (*sufficient* for nickel and certain nickel compounds)

Nickel subsulphide is carcinogenic in rats after exposure by inhalation, producing lung cancer[1]. It produced malignant tumours in rats also after its insertion into heterotransplanted tracheas[7] and after its intramuscular[1,8,9], intrarenal[10,11], intratesticular[12] and intraocular[13] administration. Nickel compounds (nickel powder, subsulphide, oxide, hydroxide and carbonate, and nickelocene and nickel-iron sulphide matte) produce local sarcomas in mice, rats, hamsters and rabbits when given intramuscularly[1,8,14-16]. Intravenous administration of nickel carbonyl produced increased incidences of various tumours in rats[1], and inhalation of nickel carbonyl produced a low incidence of lung tumours in rats[1]. Nickelous acetate administered intraperitoneally to mice produced an excess of lung adenomas and carcinomas[17].

C. Evidence for activity in short-term tests (*inadequate* for nickel and certain nickel compounds)

Soluble nickel salts caused infidelity of DNA synthesis and transcription in an *in vitro* system[18]. Nickel salts gave negative results in mutagenicity tests using bacteriophage and in assays for mutagenicity and differential survival (indirect tests for DNA repair) employing bacteria[18]. Soluble nickel salts induced cytological abnormalities in a vascular plant[18], and, at high doses and after long treatment times, slight increases in chromosomal aberrations in cultured mammalian cells[1,18]. Nickel subsulphide[19] and nickelous chloride[20] caused slight increases in sister chromatid exchange frequencies in cultured mammalian cells. Nickel subsulphide induced cell transformation in cultured mammalian cells (C3H/10T$\frac{1}{2}$[19] and Syrian hamster embryo[21]). Nickel sulphate, subsulphide, selenite and powder caused cell transformation in Syrian hamster embryo cells[21-23]. In tests conducted *in vivo*, nickel sulphate did not induce chromosomal aberrations in the bone marrow or germ cells of male rats[18]. Cultured peripheral lymphocytes from workers exposed to nickel compounds in a refinery contained more chromatid gaps than lymphocytes from unexposed people, but there was no significant difference in other chromosomal aberrations or in sister-chromatid exchanges between the exposed and control groups[24].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants			?	
Insects				
Mammalian cells *(in vitro)*		?	?	T(+)
Mammals *(in vivo)*			-	SA(-)
Humans *(in vivo)*			-	

T = cell transformation; SA = sperm abnormalities

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NITROGEN MUSTARD (Group 2A)

A. Evidence for carcinogenicity to humans (*inadequate*)

Many cases of acute nonlymphocytic leukaemia have been reported in patients with Hodgkin's disease and other solid tumours treated with nitrogen mustard in combination with other cytotoxic drugs and/or radiation[1]. Various solid tumours have been reported

in similar patients[2-6]. Squamous-cell carcinomas have been recorded to occur following long-term topical therapy with nitrogen mustard for mycosis fungoides[7]; some of these secondary skin malignancies appeared at sites not commonly so affected[8]. [See also the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'.]

B. Evidence for carcinogenicity to animals (*sufficient*)

Nitrogen mustard, administered mainly as the hydrochloride, is carcinogenic to mice and rats. After its subcutaneous, intravenous or intraperitoneal administration, it produced mainly lung tumours and lymphomas in mice. Intravenous injection of nitrogen mustard to rats induced tumours in different organs[9]. Application by skin-painting produced local tumours in mice[10].

C. Evidence for activity in short-term tests (*sufficient*)

Nitrogen mustard was mutagenic in bacteriophage in the absence of an exogenous metabolic activation system[11] and induced mutation and indirect evidence of DNA repair in bacteria[9,11,12] and fungi[9,11]. It was mutagenic to vascular plants[9,11], insects[11] and cultured mammalian cells[11]. Nitrogen mustard induced chromosomal aberrations in vascular plants[11], and DNA repair[13], sister chromatid exchanges[14] and chromosomal aberrations[11] in cultured mammalian cells. It bound covalently to the DNA of various organs of mice and rats treated *in vivo*[15], and gave positive results in a dominant lethal mutation assay in mice[9,11]. It induced chromosomal aberrations in the bone marrow of mice[11] and rats[11] and bone-marrow micronuclei in mice treated *in vivo*[16]. It was positive in a sperm abnormality test in mice[17]. Nitrogen mustard induced chromosomal aberrations in cultured peripheral lymphocytes from patients undergoing chemotherapy[18].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants	+	+	+	
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	
Mammals *(in vivo)*	+		+	DL(+) SA(+)
Humans *(in vivo)*			+	

DL = dominant lethal mutations; SA = sperm abnormalities

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NORETHISTERONE (Group 2B) (See Oestrogens and progestins)

NORETHYNODREL (Group 3) (See Oestrogens and progestins)

NORGESTREL (Group 3) (See Oestrogens and progestins)

OESTRADIOL-17β (Group 2B) (See Oestrogens and progestins)

OESTROGENS AND PROGESTINS:

COMBINED ORAL CONTRACEPTIVES (Group 2A)

A. Evidence for carcinogenicity to humans (*limited, sufficient* for liver adenomas)

General conclusions on the carcinogenicity of oral contraceptives were reached by an earlier Working Group[1].

Since benign liver tumours were first associated with use of oral contraceptives[1], more than 250 cases have been reported[2], particularly in relation to long-term use. These tumours tend to have distinctive histological features: in one study, hepatic-cell adenomas occurred only in users, and vascular changes were more marked than in non-users[3]. There have also been case reports of hepatic carcinoma, cholangiocarcinoma and angiosarcoma in users[2,4-7]. Two instances of recurrence of hepatic cancer, after 3.5 and 6 years, were reported in women who continued to use oral contraceptives.

In epidemiological studies, four malignant and one benign *hepatic tumours* were seen during 1950-1959 before oral contraceptives were available; whereas between 1968 and 1977, two of 11 cases with malignant tumours and 10 of 15 with benign tumours were oral contraceptive users[8]. Current oral contraceptive use was reported in 13 of 18 cases of benign liver tumour and two of 11 cases of malignant liver tumour[9].

In a case-control study, use of combination oral contraceptives for at least one year was associated with a relative risk for *endometrial cancer* of 0.5 (95% confidence limits,

0.1-1.0)[10]. In another such study, relative risks for endometrial cancer after use of these contraceptives for less than one year, one to two years, and three or more years were, respectively, 1.1, 0.6 and 0.3 ($p < 0.05$). For any use, regardless of duration, the relative risk estimate was 0.4 (95% confidence limits, 0.2-0.8)[11].

In a case-control study of *ovarian cancer* in patients under the age of 50, a relative risk of 0.7 was estimated for use of oral contraceptives for seven months or more[12]. In studies of use for any length of time of combination oral contraceptives, relative risks for ovarian cancer (with 95% confidence limits) were estimated as 0.8 (0.4-1.5)[13], 0.5 (0.2-1.5)[14] and 0.6 (0.4-0.9)[15]. A relative risk of 0.6 ($p = 0.04$) was reported for women who had used these contraceptives for four or more years[16]. In general, the reduced risk was related to duration of use, but this trend was not statistically significant.

In case-control studies of *breast cancer* cases, relative risk estimates for oral contraceptive use were at or below unity[17-19]. In a study of breast cancer in relation to use of oral contraceptives before or after first full-term pregnancy, use following the pregnancy was not significantly associated. For use lasting 1-48 months, 49-96 months and 97 or more months before the pregnancy, the relative risks were, respectively, 1.0, 2.3 and 3.5 ($p = 0.009$)[20]. [Since age at first pregnancy was not allowed for, the associations were probably confounded.] In cohort studies of cases of breast cancer who had taken oral contraceptives during the year before diagnosis and controls with breast cancer but who had never taken oral contraceptives, the recurrence rate among controls was significantly higher than that among cases, using life-table methods ($p < 0.01$ - < 0.04)[21-22]. A cohort study based on computer files of a health plan, from which prescriptions and diagnoses were available, showed relative risk estimates (with 90% confidence limits) of 4.0 (1.8-9.0) and 15.5 (5.2-46.0) for premenopausal women aged 46-50 and 51-55, respectively[23]. [The method used to estimate premenopausal status was considered to be inadequate.] In a recent report, relative risk estimates (with 95% confidence limits) for current and former users of oral contraceptives were 1.3 (0.7-2.2) and 1.1 (0.7-1.9), respectively. In the age group 15-34 years, these values were 2.8 (1.0-8.0)[24]. A further study showed the relative risk for breast cancer for use at any time of oral contraceptives to be 1.0 (95% confidence limits, 0.6-1.6)[25]. In a large follow-up study over 6.5 years, these values were estimated to be 0.8 (0.7-1.1), and the risk was not significantly higher in any subgroup[26].

In a case-control study of *fibroadenoma of the breast*, relative risks of 0.7, 1.7 and 0.7 ($p = 0.4$) were estimated for three grades of increasing degree of atypia[27].

In two follow-up studies of patients with *pituitary adenoma*, of six cases identified, one was taking an oral contraceptive at the time of diagnosis and two were former users. The periods of observation (about 120 000 person-years for current users, 43 000 for former users and 160 000 for non-users) suggest that there was no substantial increase in incidence attributable to use of oral contraceptives[28].

In a case-control study (by postal inquiry) of *malignant melanoma*, the overall relative risk for any use of oral contraceptives was estimated to be 1.1 (95% confidence limits, 0.7-1.8); the values for five or more years' use were 1.6 (0.8-3.0)[29]. Analysis of data from another study[25] showed that the incidence of malignant melanoma was lower among users of oral contraceptives than among non-users[29].

B. Evidence for carcinogenicity to animals

[See the summaries of data on individual compounds found in combined oral contraceptives - ethinyloestradiol, mestranol, chlormadinone acetate, dimethisterone, ethynodiol diacetate, lynoestrenol, megestrol acetate, norethisterone, norethynodrel and norgestrel.]

C. Evidence for activity in short-term tests (*inadequate*)

A study of 15 women taking a combined oral contraceptive (d-norgestrel/ethinyl oestradiol) indicated a 75% increase in the incidence of sister chromatid exchanges in peripheral lymphocytes when compared with those of 15 controls[30]. [Smoking histories were not mentioned.] A study of 52 women taking combined oral contraceptives (progestins and oestrogens) in which smoking was controlled for showed no increase in sister chromatid exchanges in comparison with 63 controls[31].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*			-	

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SEQUENTIAL ORAL CONTRACEPTIVES (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

There is some evidence of an excess of endometrial cancer in women who use sequential oral contraceptives, and particularly a preparation that contains a relatively large amount of the most potent oestrogen (100 μg ethinyloestradiol) and only a weak progestogen (25 mg dimethisterone)[1]. A relative risk of 7.3 (95% confidence limits, 1.4-38.8) was reported for use of the same preparation[2]. [This finding is in contrast to a reduction in the risk of endometrial cancer found in association with use of combination oral contraceptives. See above.]

B. Evidence for carcinogenicity to animals

No data were available.

C. Evidence for activity in short-term tests

No data were available.

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OTHER OESTROGEN-PROGESTIN COMBINATIONS (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A group of 168 hospitalized postmenopausal women were divided into 84 matched pairs. One group was treated with 2.5 mg conjugated oestrogen and 10 mg medroxyprogesterone daily for seven days of each month for 10 years. At the end of the study, no excess of either breast or endometrial cancer had been noted[1]. [The power of the study to detect an excess was limited.] Similar conclusions were reached in two other studies[2,3].

B. Evidence for carcinogenicity to animals

No data were available.

C. Evidence for activity in short-term tests

No data were available.

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CONJUGATED OESTROGENS (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

An earlier working group concluded that studies in humans strongly suggest that the administration, specifically of conjugated oestrogens, is causally related to an increased incidence of endometrial carcinoma. The evidence as to whether the risk of breast cancer is also increased was considered to be inconclusive[1].

Cases of *liver tumour* have been reported to be associated with use of non-contraceptive oestrogens. A hepatic adenoma was reported in a 52-year-old woman who took conjugated oestrogens daily for three years; a haemangioendothelial sarcoma of the liver was reported in a man who received stilboestrol daily for nine years as treatment for prostatic cancer[3].

In two case-control studies of *endometrial cancer*, similar rates of use of intravaginal oestrogen creams were reported by cases (7%) and controls (8%)[4]. Evaluation of specimens of endometrial cancers showed that those from oestrogen users were more highly differentiated than those from non-users[5]. The association between endometrial cancer and oestrogen use was present within strata classified according to weight, blood pressure, parity, smoking status, age at menopause and history of cholecystectomy[6]. An overall relative risk for use of conjugated oestrogens was estimated to be 3.9 (95% confident limits, 2.5-6.2); for use that ceased at least two years before diagnosis and that lasted at least five years, the estimate was 3.3 (1.4-8.0)[7]. When oestrogen use had lasted more than 3.5 years, relative risks (with 95% confidence limits) in comparisons with community and hospital controls were 3.6 (1.9-6.8) and 4.1 (1.8-9.6), respectively[8]. An overall relative risk of 2.9 (1.7-5.1) was also reported for any use of conjugated oestrogens; for use that lasted five or more years, the estimate was 8.6 (3.2-23)[9]. In a study of slides from patients with endometrial cancer, oestrogen use was highest (63%) when the endometrium distant from the cancer was proliferative, lowest when it was secretory or atrophic (0%) and intermediate for other endometrial findings (25%) ($p < 0.001$)[10]. An evaluation of necropsies performed on 8998 women showed the prevalence of unsuspected endometrial cancer to be 27 per 10 000, considerably higher than the incidence rate of five cases per 10 000 per year recorded in the Connecticut State Tumor Registry[11]. [The study was considered to be invalid because a prevalence rate was compared with an incidence rate[12].]

A relative risk for *epithelial ovarian cancer* from any use of oestrogen replacement therapy was estimated to be 0.9 (95% confidence limits, 0.5-1.6)[13].

Use mainly of conjugated oestrogens for seven or more years resulted in a relative risk for *breast cancer* of 1.8 ($p = 0.02$); in women with intact ovaries, a total cumulative dose of more than 1500 mg gave a relative risk of 2.5 (95% confidence limits, 1.2-5.6), but no association was evident for lower doses. For women whose ovaries had been removed no association was seen, regardless of the total dose[14]. A case-control study was made of patients with breast cancer and controls drawn from a breast cancer screening programme and who had undergone menopause either naturally or surgically. For those who were naturally menopausal, the overall relative risk estimate (with 95% confidence limits) for oestrogen use (mostly conjugated oestrogens) was 1.2 (0.9-1.5); for those who were menopausal because of bilateral oophorectomy, the estimate was 1.5 (0.9-2.8). Among the latter, the relative risk estimates for use of oestrogens for less than 5 years,

5 to 9 years and 10 or more years were 1.4, 1.6 and 1.7, respectively ($p = 0.08$)[15]. [It was considered that the data may have been biased by selective recruitment for screening.] Another study reported that all relative risks for breast cancer from oestrogen use that were based on studies of reasonable numbers were at or below unity regardless of dosage, duration of use, menopausal status or type of menopause[16]. The medical records of cases of breast cancer and of controls who were members of a health plan were abstracted by reviewers who were unaware of whether a subject was a case or a control. The relative risk for any use of conjugated oestrogens was 1.4 (95% confidence limits, 1.0-2.0). The risk was approximately doubled for ten or more recorded prescriptions, for intervals of five or more years between the first and last prescription, and for a usual daily dose of 1.25 mg or more[17].

In a cohort study, women treated for five or more years with replacement oestrogens (mostly conjugated oestrogens) and untreated women were followed up. Expected numbers were derived from the Third National Cancer Survey. There were 11 cases of uterine cancer, which yielded a relative risk of 9.3 (95% confidence limits, 4.7-16.7). For breast cancer, the relative risk was 1.1 (not significant)[18]. Computer files on members of a health plan were used to identify prescriptions of replacement oestrogens and cases of breast cancer in women between the ages of 45 and 64 years. Among those with a natural menopause, the relative risk estimate for current oestrogen use was 3.4 (90% confidence limits, 2.1-5.6). In the age group 45-54 years, the corresponding estimate was 10.2 (4.5-23), and that for 55-64 years was 1.9 (1.0-3.5). No analogous association was present among surgically menopausal women[19]. [The method used to estimate menopausal status was considered to be inadequate.] The same health plan membership was analysed in another study: Among women of all ages, the incidence of breast cancer was stable until 1977, after which it declined among those between the ages of 45 and 54. The decline corresponded with a drop in oestrogen prescriptions after 1977[20]. In 31 oestrogen users, six oestrogen and progestogen users and 79 non-hormone users followed up over a three-year period, breast cancer rates were found to be highest among the latter[21]. [Important confounding factors were not controlled for.] Of diabetic women who participated in a randomized controlled trial during pregnancy, 80 were given large doses of stilboestrol and ethisterone, and 76 were given a placebo. After 27 years, 14 (18%) of the exposed and two (3%) of the non-exposed had developed tumours, mainly benign, of the reproductive tract. Breast cancer developed in four of the exposed and in none of the non-exposed women[22].

In a case-control study of testicular cancer, the relative risk for a history of hormone treatment during the mother's pregnancy was 5.0 (one-sided $p = 0.11$). The cancers included embryonal-cell carcinomas, seminomas, teratomas, choriocarcinomas and interstitial-cell carcinomas[23].

A large number of studies of adenocarcinoma of the endometrium thus suggest that use of conjugated oestrogens causes the disease. For breast cancer, the evidence is conflicting, both overall and within subgroups.

B. Evidence for carcinogenicity to animals (*inadequate*)

Conjugated oestrogens have been tested in only one experiment in rats by oral administration. The data were judged insufficient to evaluate their carcinogenicity[1].

C. Evidence for activity in short-term tests (*inadequate*)

A commercial preparation of conjugated oestrogens was not mutagenic to bacteria. It did not induce chromosomal aberrations in human lymphoblastoid cells *in vitro* or in Chinese hamster V79 cells exposed in diffusion chambers implanted into mice after oestrogen treatment[24]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

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OESTROGENS:

DIENOESTROL (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

An earlier working group considered that the administration of oestrogens is causally related to an increased incidence of endometrial carcinoma and that there was no evidence that dienoestrol is different from other oestrogens in this respect[1]. Herbst *et al.*[2] first reported in 1979 on the types of oestrogen to which cases in the Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females had been exposed. Diethylstilboestrol, dienoestrol (very closely related compounds chemically) and hexoestrol had been prescribed to almost two-thirds of the mothers during the index pregnancies. Survey data[2,3] suggest that exposure to these oestrogens in a putative group of controls would have been well below 5%. Other reports from the registry have broadly confirmed the original observations[4-6]. [The Working Group considered that the fact that dienoestrol is structurally related to diethylstilboestrol and is also a metabolite of that compound added to the weight of evidence from epidemiological studies that dienoestrol should be classified as having 'limited' evidence of carcinogenicity.]

B. Evidence for carcinogenicity to animals (*inadequate*)

Dienoestrol was tested in female guinea-pigs by subcutaneous injection and in female mice by intravaginal administration. Although pointing to the induction of 'uterine tumours' in guinea-pigs and ovarian tumours in mice, these experiments were insufficient to evaluate the carcinogenicity of this compound[1].

C. Evidence for activity in short-term tests (*inadequate*)

Dienoestrol was not mutagenic to bacteria. One paper reported a small increase in sister chromatid exchanges in cultured human fibroblasts, but this has not been confirmed[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*				
Humans *(in vivo)*				

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DIETHYLSTILBOESTROL (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Diethylstilboestrol causes clear-cell carcinoma of the vagina in females exposed *in utero*. The evidence for an association with other types of cancer is either limited (endometrium) or inadequate (breast, ovary)[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Diethylstilboestrol is carcinogenic to mice, rats, hamsters, frogs and squirrel monkeys, producing tumours principally in oestrogen-responsive tissues[1].

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

C. Evidence for activity in short-term tests (*inadequate*)

Diethylstilboestrol did not elicit unscheduled DNA synthesis in a variety of mammalian cells[2,3] and did not induce mutations in a wide variety of bacterial systems[3] or in mammalian cells in culture[4,5]. Studies on mutation in fungi are equivocal[2]. There is a single report that it produced chromosomal anomalies in yeast[2]. Conflicting data have been reported with regard to the induction of chromosomal aberrations and sister chromatid exchanges in mammalian cells *in vitro* and of chromosomal anomalies in mouse bone-marrow *in vivo*[2,3,6]. Diethylstilboestrol induced cell transformation in a variety of cell systems[2], and dominant lethal mutations were induced in mice by the diphosphate[3]. Sperm abnormalities were induced in mice[7]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		?	?	
Insects				
Mammalian cells *(in vitro)*	-	-	?	T(+)
Mammals *(in vivo)*			?	DL(+) SA(+)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations; SA = sperm abnormalities

References

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ETHINYLOESTRADIOL (Group 2B)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*sufficient*)

Ethinyloestradiol was tested in mice, rats, dogs and monkeys by oral administration and in rats by subcutaneous injection; in most studies it was administered in combination with progestins. When administered alone to mice, it increased the incidence of pituitary tumours and of malignant mammary tumours in both males and females and produced malignant tumours of the uterus and its cervix in females. In rats, it increased the incidence of benign liver-cell tumours in both males and females and produced malignant liver-cell tumours in females. When it was given in combination with certain progestins, excess incidences of malignant tumours of the uterine fundus were observed in female mice and of benign and/or malignant mammary tumours in male rats; in female rats, the combinations reduced but did not prevent the incidence of malignant liver-cell tumours when compared with that produced by ethinyloestradiol alone. In dogs, no tumour that could be attributed to the treatment was found. The study in monkeys was still in progress at the time of reporting: no tumour had been found after five years of observation. Mammary fibroadenomas were produced in female rats following subcutaneous injection of a combination of ethinyloestradiol with megestrol acetate[1].

Rats fed 0.06-0.08 mg/kg ethinyloestradiol in the diet for two years (about 100 times the human dose) had no overall increase in tumour incidence; however, both males and females had increased incidences of liver neoplastic nodules and pituitary chromophobe adenomas, and males had an increased incidence of mammary tumours[2]. Mammary adenocarcinomas were observed in 90% of rats given 1 mg ethinyloestradiol implanted as a pellet. Concomitant exposure to X-rays synergistically increased the number of tumours per rat and shortened the latency of their appearance[3]. Dietary administration to rats of daily doses of 0.075 mg ethinyloestradiol and 6 mg norethindrone for 12 months starting at four weeks of age resulted in hyperplastic nodules of the liver in all animals and hepatocellular carcinomas in 5.6%[4]. Oral administration of ethinyloestradiol to male rats promoted the development of preneoplastic liver lesions initiated by *N*-nitrosodiethylamine[5].

C. Evidence for activity in short-term tests (*inadequate*)

Ethinyloestradiol did not induce mutations in *Salmonella typhimurium* or *Escherichia coli* K12 in the presence of a liver microsomal system[1,6], in *Drosophila melanogaster*[7], or in mice treated *in vivo*[8]. No chromosomal effect was observed in treated human lymphocyte cultures[1] or Chinese hamster V79 cells[9]. Increases of up to 75% were seen in sister chromatid exchanges in blood lymphocytes of women taking oral contraceptives containing 150 μg d-norgestrel and 30-50 μg ethinyloestradiol[10]. [Such small increases observed in a study in which smoking history was not controlled for are not considered to be indicative of an action of a mutagen.]

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects		-		
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*		-		
Humans *(in vivo)*			-	

References

[1] *IARC Monographs*, *21*, 233-255, 1979

[2] Schardein, J.L. (1980) Studies of the components of an oral contraceptive agent in albino rats. I. Estrogenic component. *J. Toxicol. environ. Health*, *6*, 885-894

[3] Holtzman, S., Stone, J.P. & Shellabarger, C.J. (1981) Synergism of estrogens and X-rays in mammary carcinogenesis in female ACI rats. *J. natl Cancer Inst.*, *67*, 455-459

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[5] Cameron, R., Imaida, K. & Ito, N. (1981) Promotive effects of ethinyl estradiol in hepatocarcinogenesis initiated by diethylnitrosamine in male rats. *Gann*, *72*, 339-340

[6] Dayan, J., Crajer, M.C., Bertozzi, S. & Lefrancois, S. (1980) Application of the *Salmonella typhimurium* microsome test to the study of 25 drugs belonging to 5 chemical series. *Mutat. Res.*, *77*, 301-306

[7] Parádi, E. (1981) Mutagenicity of some contraceptive drugs in *Drosophila melanogaster*. *Mutat. Res.*, *88*, 175-178

[8] Wallace, M.E., Badr, F.M. & Badr, R.S. (1979) Studies in mice on the mutagenicity of two contraceptive drugs. *J. med. Genet.*, *16*, 206-209

[9] Drevon, C., Piccoli, C. & Montesano, R. (1981) Mutagenicity assays of estrogenic hormones in mammalian cells. *Mutat. Res.*, *89*, 83-90

[10] Krishna Murthy, P.B. & Prema, K. (1979) Sister-chromatid exchanges in oral contraceptive users. *Mutat. Res.*, *68*, 149-152

MESTRANOL (Group 2B)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*sufficient*)

Mestranol was tested in mice, rats, dogs and monkeys by oral administration; in most studies it was administered in combination with progestins. When administered alone, it increased the incidences of pituitary tumours in both sexes of one strain of mice and increased the incidence of malignant mammary tumours in castrated males of two further strains and in males and females of another strain. It also produced an increased incidence of malignant mammary tumours in female rats. Studies in monkeys are still in progress; although no tumours have been observed after seven years, no conclusive evaluation can yet be made. In experiments in which mestranol was administered to female mice in combination with norethynodrel, pituitary tumours and vaginal and cervical squamous-cell carcinomas were produced; in male mice, an increased incidence of mammary tumours was observed following administration of mestranol in combination with norethynodrel or ethynodiol diacetate. Combinations with norethynodrel or norethisterone resulted in an excess of benign liver-cell tumours in male rats and increased the incidence of malignant mammary tumours in rats of both sexes. In monkeys given these combinations as well as combinations with norethynodrel or ethynodiol diacetate, no mammary nodule was observed after five and seven years of experimentation, respectively. This experiment is still in progress. It was also tested in combination with norethynodrel by subcutaneous administration in mice, rats and hamsters; it produced an increased incidence of mammary tumours in female mice[1].

Feeding of mestranol or mestranol plus norethynodrel to rats following partial hepatectomy and treatment with *N*-nitrosodiethylamine promoted the development of putative preneoplastic lesions in the liver observed after four or nine months. On the basis of experiments with norethynodrel alone, the authors ascribed this effect to mestranol[2]. No significant increase in mammary tumour occurrence was seen in dogs treated with mestranol[3]. Oral administration to dogs of daily doses of 0.02 or 0.05 mg/kg bw for seven years did not produce malignant mammary tumours. When given in various combinations with progestins, it induced malignant mammary tumours after five years of treatment[1,4].

Mice injected subcutaneously with Enovid (mestranol and norethynodrel) developed small cervical cancers. When mixed in the diet, Enovid caused cervical cancers in one strain of mice and pituitary tumours in another[5]. Rats fed *ortho*-Novum (mestranol and norethisterone) for eight months did not develop liver tumours. Tumours occurred when the animals were fed a non-tumorigenic dose of *N*-2-acetylaminofluorene for one month before administration of the contraceptive for seven months.

C. Evidence for activity in short-term tests (*inadequate*)

No mutation was induced in *Drosophila melanogaster*[7] or in mice *in vivo*[8] after treatment with mestranol. It has been reported to be ineffective in inducing chromosomal aberrations in human leucocytes exposed in culture[1]. Dominant lethal mutations were induced in female mice treated with mestranol[1]. No cytogenetic change was reported in lymphocytes obtained from women taking oestrogen/progestin contraceptives containing mestranol[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects		-		
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*		-		DL(+)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

References

[1] *IARC Monographs*, *21*, 257-278, 1979

[2] Yager, J.D., Jr & Yager, R. (1980) Oral contraceptive steroids as promoters of hepatocarcinogenesis in female Sprague-Dawley rats. *Cancer Res.*, *40*, 3680-3685

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[5] Dunn, T.B. (1979) Cancer and other lesions in mice receiving estrogens. *Recent Results Cancer Res.*, *66*, 175-192

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OESTRADIOL-17β (Group 2B)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*sufficient*)

Oestradiol-17β and its esters were tested in mice, rats, hamsters, guinea-pigs and monkeys by subcutaneous injection or implantation and in mice by oral administration. Its subcutaneous administration resulted in increased incidences of mammary, pituitary, uterine, cervical, vaginal and lymphoid tumours and interstitial-cell tumours of the testis in mice. In rats, there was an increased incidence of mammary and/or pituitary tumours. In hamsters, a high incidence of malignant kidney tumours occurred in intact and castrated males and in ovariectomized females, but not in intact females. In guinea-pigs, diffuse fibromyomatous uterine and abdominal lesions were observed. Oral administration of oestradiol-17β to mice led to an increased mammary tumour incidence. Subcutaneous injections in neonatal mice resulted in precancerous and cancerous cervical and vaginal lesions in later life and an increased incidence of mammary tumours[1].

Implantation of a pellet of oestradiol-17β into the spleen of mice in proximity to a transplanted one-day-old testis in a castrated isologous recipient induced Leydig-cell tumours in the grafts. Pellets placed subcutaneously in six-week-old mice caused Leydig-cell tumours in testes *in situ* and in testes transplanted into the spleen and mammary glands[2]. Feeding of oestradiol-17β to mice for two years resulted in the development of osteosarcomas in the calvaria of three; one of the tumours metastasized[3]. Dietary administration of this oestrogen to female mice bearing the mammary tumour virus shortened the time to appearance of mammary tumours and induced cervical adenosis and carcinomas[4].

C. Evidence for activity in short-term tests (*inadequate*)

No mutation was induced in Chinese hamster V79 cells[5], and no chromosomal anomaly was observed in mouse bone-marrow cells *in vivo* or in human lymphocytes *in vitro*[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		-	-	
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

References

[1] *IARC Monographs*, *21*, 279-326, 1979

[2] Huseby, R.A. (1980) Demonstration of a direct carcinogenic effect of estradiol on Leydig cells of the mouse. *Cancer Res.*, *40*, 1006-1013

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OESTRONE (Group 2B)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*sufficient*)

Oestrone was tested in mice by oral administration; in mice, rats and hamsters by subcutaneous injection and implantation; and in mice by skin painting. Its administration resulted in an increased incidence of mammary tumours in mice; in pituitary, adrenal and mammary tumours, as well as bladder tumours in association with stones, in rats; and in renal tumours in both castrated and intact male hamsters. Oestrone benzoate increased the incidence of mammary tumours in mice following its subcutaneous injection[1].

C. Evidence for activity in short-term tests (*inadequate*)

Chromosomal aberrations were observed in bone-marrow cells of rats given intraperitoneal injections of oestrone[2]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*			+	
Humans *(in vivo)*				

References

[1] *IARC Monographs, 21,* 343-362, 1979

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PROGESTINS:

CHLORMADINONE ACETATE (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to anima's (*limited*)

Chlormadinone acetate was tested in mice, rats and dogs by oral administration. When given alone to dogs, it produced mammary tumours. When given to mice in combination with mestranol, it increased the incidence of pituitary tumours in animals of both sexes; in combination with ethinyloestradiol, it increased the incidence of mammary tumours in intact and castrated male mice of one hybrid strain[1].

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal effect was observed in human lymphocytes treated with chlormadinone acetate *in vitro*[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Reference

[1] *IARC Monographs*, *21*, 365-375, 1979

DIMETHISTERONE (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*inadequate*)

Dimethisterone was tested in dogs in combination with ethinyloestradiol by oral administration. No increase in the incidence of mammary tumours was found[1].

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal effect was observed in human lymphocytes treated with dimethisterone *in vitro*[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*				

Reference

[1] *IARC Monographs, 21*, 377-385, 1979

ETHYNODIOL DIACETATE (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*limited*)

Ethynodiol diacetate was tested in mice, rats and monkeys alone or in combination with oestrogens by oral administration. In castrated male mice, it increased the incidence of mammary tumours, and in male rats it produced benign mammary tumours. In combination with oestrogens, it increased the incidence of pituitary tumours in mice and of malignant mammary tumours in male and female rats. The study in monkeys is still in progress[1].

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal damage was seen in rats fed ethynodiol diacetate, and no chromosomal anomaly was seen in lymphocytes from women who had taken oral contraceptives containing ethynodiol diacetate and mestranol. No significant effect on the frequency of abnormal karyotypes or on sex ratio was seen in abortuses of women who had taken oral contraceptives containing ethynodiol diacetate[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*			-	
Humans *(in vivo)*			-	

Reference

[1] *IARC Monographs*, *21*, 387-398, 1979

17α-HYDROXYPROGESTERONE CAPROATE (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*inadequate*)

17α-Hydroxyprogesterone caproate was tested in rabbits by repeated subcutaneous injection, with inconclusive results[1]. It was reported in an abstract to have accelerated the growth of cervical tumours in mice[2].

C. Evidence for activity in short-term tests

No data were available.

References

[1] *IARC Monographs*, *21*, 399-406, 1979

[2] Urmancheeva, A.F., Novikova, A.I. & Anicimov, V.N. (1981) Stimulating effect of pregnancy on the growth of cervical cancer (Russ.). *Akush. Ginekol. (Moscow)*, *1*, 53-55

LYNOESTRENOL (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*inadequate*)

Lynoestrenol was tested by oral administration in mice and rats, alone or in combination with mestranol. It did not increase the incidence of tumours[1].

C. Evidence for activity in short-term tests (*inadequate*)

Dominant lethal mutations were induced when mice were fed lynostrenol with mestranol. No significant effect on the frequency of abnormal karyotypes or on sex ratio was seen in abortuses of women who had taken oral contraceptives containing lynoestrenol[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				DL(+)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

Reference

[1] *IARC Monographs*, *21*, 407-415, 1979

MEDROXYPROGESTERONE ACETATE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

The results of one epidemiological study of the development of breast nodules and two others of dysplasia and of carcinoma *in situ* of the uterine cervix in women given medroxyprogesterone acetate were conflicting and difficult to interpret because of methodological problems[1]. In a study of 30 patients with breast cancer and 179 controls enrolled at a family planning clinic, use at some time of medroxyprogesterone acetate was reported by five cases (17%) and 32 controls (18%), giving a relative risk of 1[2]. [No confidence limits were given. Potential confounding was not controlled for.]

B. Evidence for carcinogenicity to animals (*limited*)

Medroxyprogesterone acetate produced mammary tumours in dogs following its intramuscular injection[1]. After four years of treatment with the human contraceptive dose, a dose-related incidence of mammary nodules was seen in dogs. The incidence of mammary dysplasia at that time was comparable with that in dogs given progesterone at 25 times the luteal phase levels[3]. Female dogs treated with medroxyprogesterone acetate for at least one year had a distinct increase in incidence of large and small mammary nodules as compared with control animals. The large nodules were usually identified as neoplastic on histological examination[4]. In a review of published and unpublished data on the effects of medroxyprogesterone acetate, malignant mammary tumours, other breast pathology and liver adenoma were reported to have occurred in dogs[5].

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal aberration was seen in bone-marrow cells of rats treated *in vivo*[1], or in peripheral lymphocytes of women taking this compound[6].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*			-	
Humans *(in vivo)*			-	

References

[1] *IARC Monographs*, *21*, 417-429, 1979

[2] Greenspan, A.R., Hatcher, R.A., Moore, M., Rosenberg, M.J. & Ory, H.W. (1980) The association of depo-medroxyprogesterone acetate and breast cancer. *Contraception*, *21*, 563-569

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[5] Minkin, S. (1980) Depo-Provera: A critical analysis. *Women Health*, *5*, 49-69

[6] Matton-Van Leuven, M.-T., Thierry, M. & de Bie, S. (1974) Cytogenetic evaluation of patients in relation to the use of oral contraception. *Contraception*, *10*, 25-38

MEGESTROL ACETATE (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*limited*)

Megestrol acetate was tested alone or with ethinyloestradiol in mice, rats and dogs by oral administration and in rats by subcutaneous administration. It produced mammary tumours in dogs when tested alone and in mice when tested in combination with ethinyloestradiol. Experiments in which it was tested in rats in combination with ethinyloestradiol were negative or inadequate[1].

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal effect was observed in human lymphocytes treated with megestrol acetate *in vitro*. No significant effect on the frequency of abnormal karyotypes or on sex ratio was seen in abortuses of women who had taken oral contraceptives containing this progestin[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*			-	

Reference

[1] *IARC Monographs*, *21*, 431-439, 1979

NORETHISTERONE (Group 2B)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*sufficient*)

Norethisterone and its acetate, alone or in combination with oestrogens, were tested in mice, rats and dogs by oral administration and in mice by subcutaneous implantation. When administered alone to mice, norethisterone increased the incidence of benign liver-cell tumours in males and of pituitary tumours in females and produced granulosa-cell tumours of the ovary in females. Administration of norethisterone acetate alone increased the incidence of benign liver-cell tumours in male mice. In male rats, administration of norethisterone alone increased the incidence of benign liver-cell tumours. Norethisterone in combination with mestranol, or the acetate in combination with ethinyloestradiol, increased the incidence of pituitary tumours in mice of both sexes; norethisterone in combination with ethinyloestradiol increased the incidence of pituitary tumours in female mice. In combination with mestranol it increased the incidence of benign liver-cell tumours in male rats and of malignant mammary tumours in animals of both sexes. Norethisterone acetate in combination with ethinyloestradiol increased the incidence of benign mammary tumours in male rats in one study and increased the incidence of benign liver-cell and mammary tumours in rats of both sexes in a further study. A study in dogs in which norethisterone acetate is being given in combination with ethinyloestradiol is still in progress[1]. Rats fed 3-4 mg/kg norethisterone acetate (about 100 times the human dose) for two years had an increase in neoplastic nodules of the liver; an increased incidence of uterine polyps was seen in females[2]. In rats given weekly intramuscular injections for 104 weeks of norethisterone enanthate at doses of 10, 30 or 50 mg/kg bw (20, 60 and 100 times the human contraceptive dose), there was a dose-related increase in tumours of the pituitary glands in males, whereas in females there was no effect with the lowest dose and even a reduction of tumours with the higher doses. The incidence of benign mammary tumours was increased in males at all doses, but there was little effect on the females; malignant mammary tumour incidence was greatly increased in both males and females given the two higher dose levels, and the increase was related to dose. A dose-related increase in the incidence of liver tumours was also seen in both males and females. Oral administration of norethisterone acetate in the diet at 100 times the usual human dose for 104 weeks resulted in a slight increase in the incidence of carcinomas of the uterus. The effect was greatly increased if ethinyloestradiol was also added to the diet[3].

Administration to female rats of norethisterone plus mestranol at a dose calculated to be 100 times the human contraceptive dose for eight months did not produce liver tumours. Multiple neoplastic nodules of the liver and hepatocellular carcinomas occurred when animals were fed a non-tumorigenic dose of *N*-2-acetylaminofluorene for one month before administration of the contraceptive for seven months[4]. Administration to female rats of daily oral doses of 6 mg norethisterone acetate and 0.075 mg ethinyloestradiol for 12 months starting at four weeks of age resulted in hyperplastic nodules of the liver in all animals and a hepatocellular carcinoma in one[5].

C. Evidence for activity in short-term tests (*inadequate*)

No chromosomal abnormality was seen in bone-marrow cells of mice treated with norethisterone *in vivo*. Dominant lethal mutations were seen in mice given norethisterone acetate but not in mice given short-term treatment with norethisterone and ethinyloestradiol. No chromosomal effect was seen in cultured human lymphocytes or in lymphocytes from women who had taken oral contraceptives containing norethisterone[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*			-	DL(?)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

References

[1] *IARC Monographs*, *21*, 441-460, 1979

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NORETHYNODREL (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*limited*)

Norethynodrel was tested in mice, rats and monkeys, alone or in combination with mestranol, by oral administration. It was also tested alone in mice by subcutaneous implantation, and in combination with mestranol in mice, rats and hamsters by subcutaneous injection. When given alone, it increased the incidence of pituitary tumours in mice of both sexes and of mammary tumours in castrated males of one strain; it also increased the incidence of liver-cell, pituitary and mammary tumours in male rats. When given in combination with mestranol, it increased the incidences of pituitary, mammary, vaginal and cervical tumours in female mice, of pituitary tumours in male mice, of mammary tumours in castrated male mice, of benign liver-cell tumours in male rats and of malignant mammary tumours in rats of both sexes. The study in hamsters was of too short duration to be considered for evaluation. Oral administration of norethynodrel in combination with mestranol to *Macaca mulatta* monkeys for five years did not increase the incidence of mammary tumours; the study is still in progress[1].

Feeding of norethynodrel to rats following partial hepatectomy and treatment with *N*-nitrosodiethylamine (5 mg/kg bw) by gavage 24 hours later increased the number of putative precursor lesions of hepatocarcinogenesis four months later, but there was no significant difference by nine months. One hepatocellular carcinoma was found at nine months in a rat that received this treatment[2].

C. Evidence for activity in short-term tests (*inadequate*)

Norethynodrel did not induce mutations in bacteria, and no chromosomal anomaly was seen in human lymphocytes treated *in vitro* or in bone-marrow cells of rats treated *in vivo*. A significant increase in chromosomal anomalies was seen in the lymphocytes of infants whose mothers had taken oral contraceptives containing norethynodrel[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		-		
Mammals *(in vivo)*		-		
Humans *(in vivo)*			+	

References

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NORGESTREL (Group 3)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*inadequate*)

Norgestrel was tested in mice and rats, alone or in combination with ethinyloestradiol, by oral administration. There was no increase in the incidence of tumours in either species[1].

C. Evidence for activity in short-term tests

No data were available.

Reference

[1] *IARC Monographs*, *21*, 479-490, 1979

PROGESTERONE (Group 2B)

A. Evidence for carcinogenicity to humans

No data were available.

B. Evidence for carcinogenicity to animals (*sufficient*)

Progesterone was tested by subcutaneous and by intramuscular injection in mice, rats, rabbits and dogs and by subcutaneous implantation in mice and rats. It was tested alone in mice and dogs; in rats and rabbits it was given in combination with other sex hormones. When given alone, progesterone increased the incidences of ovarian, uterine and mammary tumours in mice. Neonatal treatment with progesterone enhanced the

occurrence of precancerous and cancerous lesions of the genital tract and increased mammary tumorigenesis in female mice[1]. Dogs treated with progesterone for four years at 1-25 times the luteal phase levels in that species developed mammary dysplasia and a dose-related incidence of mammary gland nodules[2].

C. Evidence for activity in short-term tests (*inadequate*)

Chromosomal abnormalities were induced in meiotic germ cells of female hamsters and of male dogs treated with progesterone *in vivo*, and in cultured human embryonic fibroblasts and renal epithelia treated *in vitro*. No anomaly was seen in human lymphocytes treated *in vitro*[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*			+	
Humans *(in vivo)*				

References

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OESTRONE (Group 2B) (See Oestrogens and progestins)

OXYMETHOLONE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

Although ten cases of liver-cell tumour have been reported in patients with aplastic anaemia, Fanconi's anaemia or paroxysmal nocturnal haemoglobinuria treated for long periods with oxymetholone alone or in combination with other androgenic drugs, a causal relationship could not be established[1].

Multiple hepatomas were reported in a patient with Fanconi's anaemia treated for nine months with oxymetholone; cases of benign hepatoma, peliosis hepatis, primary hepatocellular carcinoma and hepatic cholangiosarcoma have also been linked to use of androgens, mostly oxymetholone. The majority of the reports have involved patients with Fanconi's anaemia[2-6], but liver tumours have also occurred following treatment for aplastic anaemia[4,7,8], panmyelopathy[9] and refractory megaloblastic anaemia[10]. Usually androgens were given for years, but cancer has occurred after as little as two months[6]. There have been well-documented instances of remission following the withdrawal of oxymetholone[8,9,11]. In one case, multiple hepatomas, peliosis hepatis, multiple pancreatic islet-cell tumours, and a renal medullary interstitial tumour were found at autopsy after a five-year course of therapy with androgens [type unspecified] and prednisone[7]. Myeloid leukaemia complicating Fanconi's anaemia has also been reported in association with oxymetholone use[11-13], and there has been one case report of paroxysmal nocturnal haemoglobinuria in which a myeloproliferative disorder developed after oxymetholone therapy[14].

B. Evidence for carcinogenicity to animals

No data were available.

C. Evidence for activity in short-term tests

No data were available.

References

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PENTACHLOROPHENOL (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Pentachlorophenol has been mentioned specifically only in reports of two cases of Hodgkin's disease[1] and seven cases of leukaemia[2] in individuals who used it as a wood preservative or handled wood to which it had been applied and of two cases of non-Hodgkin's lymphoma of the skin in men employed in its manufacture[3]. Generic reference to chlorophenols (which probably included pentachlorophenol[4]) has also been made in three case-control studies which showed relative risks of 6.6 and 3.3 for soft-tissue sarcomas and of 7.6 (heavy exposure) and 2.2 (light exposure) for lymphomas in association with exposure to chlorophenols[5-7]. In none of these studies could exposure to pentachlorophenol be distinguished from exposure to dioxins. In some, exposure to other related and unrelated chemicals also occurred.

B. Evidence for carcinogenicity to animals (*inadequate*)

Pentachlorophenol was tested in one experiment in two strains of mice and in one experiment in rats by oral administration at dose levels sufficiently high to cause mild toxicity; no carcinogenic effect was seen in either species. Pentachlorophenol was also tested in two strains of mice by subcutaneous injection of single doses; it produced hepatomas in males of one strain[8].

C. Evidence for activity in short-term tests (*inadequate*)

Pentachlorophenol was not mutagenic in a host-mediated assay in the presence of an exogenous metabolic activation system or in *Drosophila melanogaster*, but mutagenicity was elicited in fungi[8]. There was some indication of a positive response in a spot test for somatic mutation[9]. In a single study of six workers exposed to pentachlorophenol, there was no evidence for the induction of chromosomal aberrations[8].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		+		
Insects		-		
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*		?		
Humans *(in vivo)*			-	

References

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PHENACETIN (Group 2A) (See Analgesic mixtures containing phenacetin)

PHENAZOPYRIDINE (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one limited epidemiological study, no significant excess of any cancer was observed among 2214 patients receiving phenazopyridine and followed for periods of three to seven-and-a-half years[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Phenazopyridine hydrochloride was tested in mice and rats by oral administration and in mice by intraperitoneal administration. After its oral administration, it significantly increased the incidence of hepatocellular adenomas and carcinomas in female mice. In male and female rats, it induced tumours of the colon and rectum[1].

C. Evidence for activity in short-term tests

No data were available.

Reference

[1] *IARC Monographs*, *24*, 163-173, 1980

PHENELZINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A liver angiosarcoma was reported in one person who had taken phenelzine for six years preceding tumour diagnosis[1].

B. Evidence for carcinogenicity to animals (*limited*)

Phenelzine sulphate was tested in mice by oral administration of 0.015% in the drinking-water for life. Incidences of lung and blood vessel tumours were significantly increased in female but not in male mice[1].

C. Evidence for activity in short-term tests (*inadequate*)

Phenelzine produced indirect evidence of DNA damage[1] and mutation in bacteria[1-3]. It did not induce DNA damage (as judged by lack of activity in the alkaline elution test) in liver or lung of mice treated *in vivo*[3]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*	-			
Humans *(in vivo)*				

References

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PHENOBARBITAL (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Phenobarbital has been associated with an increased frequency of several cancers, but epidemiological data to evaluate its carcinogenicity to humans were considered to be limited[1].

Excesses of brain cancer have now been reported in three studies of epileptics, most of whom were treated with phenobarbital, often in combination with phenytoin or other drugs[2-4]. The role of anticonvulsant therapy in the origin of brain cancer is not clear, however, since the tumours may be related to the underlying medical condition rather than to use of the drugs *per se*. In the largest study[2,5], the relative brain cancer excess within the first 10 years of admission to an epilepsy clinic was 12-fold (based on 45 cases observed, 3.8 expected), but it decreased steadily with duration of follow-up to 1.3-fold

(2 observed, 1.5 expected) for cancers occurring 30 or more years after admission, suggesting that the therapy was unlikely to have initiated the tumour development. A case/control study[6] involving 84 children with brain cancer reported a two-fold increase in these tumours associated with prenatal or childhood exposure to barbiturates (mostly phenobarbital[7]). In a survey[8] of 11 169 pairs, consisting of childhood cancer cases and matched controls, epilepsy was reported more frequently among the mothers of cancer cases (39 cases, compared with 22 controls). Review of available antenatal records indicated use of phenobarbital by two-thirds and phenytoin by somewhat more than one-third of the epileptic mothers during pregnancy. The number of brain tumours among the 39 cancers was not reported.

Lung cancer was reported in significant excess (standardized mortality ratio, 1.7, based on 87 cases) during 1969-1976 among members of a prepaid health plan identified as users of phenobarbital, phenobarbital sodium or secobarbital sodium during 1969-1973[9]. Increases were associated with the three drugs separately, were found in both men and women, were only partly accounted for by cigarette smoking, and remained when tumours diagnosed within two years of prescription of the drugs were excluded. There was no apparent relation with duration of use. Increases in lung cancer incidence have also been observed in the two cohort studies of epileptics that reported data on this cancer[2,4], but the effects of smoking were not known. The elevations in risk in these cohort studies were smaller than in the first study (relative risk, 1.3, based on 65 cases [$p < 0.05$] in one[2], and 1.4, based on 23 deaths in the other[4]).

Liver cancers occurred excessively (13 observed, 3.4 expected) in one study of epileptics[2]. All but three of the tumours, mostly angiosarcomas or cholangiocarcinomas[2,5], occurred in individuals who had been exposed to thorotrast, a known liver and biliary carcinogen, during angiography. Whether the concomitant anticonvulsant therapy enhanced the development of thorotrast-induced malignancies is unknown.

B. Evidence for carcinogenicity to animals (*limited*)

Phenobarbital is carcinogenic, producing benign and malignant hepatocellular neoplasms in mice and benign hepatocellular neoplasms in rats after its oral administration[1]. Experiments with mice and rats in which phenobarbital was studied for its promoting activity included comparison groups given phenobarbital alone. Oral administration of phenobarbital enhanced the incidence of liver neoplasms in mice previously administered *N*-nitrosodimethylamine[10] and in rats previously administered *N*-2-acetylaminofluorene[11,12], *N*-nitrosodiethylamine[13,14], 2-methyl-*N*,*N*-dimethyl-4-aminoazobenzene[15] or benzo[*a*]pyrene[16].

C. Evidence for activity in short-term tests (*inadequate*)

Phenobarbital was not mutagenic in *Salmonella typhimurium*[1] and did not elicit DNA repair in cultured rat liver cells[17]. There is a single report that it has weak mutagenicity in *Drosophila melanogaster*[1]. It did not induce cell transformation (in the BHK assay)[18]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects		?		
Mammalian cells *(in vitro)*	-			T(-)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

References

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PHENOXYACETIC ACID HERBICIDES (OCCUPATIONAL EXPOSURE TO) (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

In two case-control studies of soft-tissue sarcoma[1,2] and one of lymphoma[3], exposure to phenoxyacetic acids (mainly 2,4,5-T, 2,4-D and MCPA) was associated with five- to eight-fold increases in risk of these diseases. Exposure to 2,4-D and/or MCPA, but not 2,4,5-T, also gave increased relative risks. (TCDD was said not to be a contaminant in these exposures[2,3].) Cases of soft-tissue sarcoma have also been reported in men involved in or associated with the manufacture of 2,4,5-T[4,5]. In most of these studies, exposure to 2,4,5-T probably also involved exposure to TCDD. [See also the summaries of data on 2,4-D, 2,4,5-T and TCDD.]

B. Evidence for carcinogenicity to animals

[See the summaries of data on 2,4-D and 2,4,5-T.]

[Phenoxyacetic acid herbicides have been shown to cause peroxisome proliferation in Chinese hamsters[6]. Certain agents known to cause this proliferation are carcinogenic, and the phenomenon has been suggested to have mechanistic significance in the induction of tumours.]

C. Evidence for activity in short-term tests

[See the summaries of data on 2,4-D and 2,4,5-T.]

References

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PHENYLBUTAZONE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Cases have been reported of leukaemia occurring in patients following phenylbutazone therapy, but their significance cannot be evaluated, given the widespread use of phenylbutazone[1]. No significant excess of leukaemia during 1969-1976 was observed among 3660 members of a prepaid health plan prescribed phenylbutazone during 1969-1973[2].

B. Evidence for carcinogenicity to animals

No data were available.

C. Evidence for activity in short-term tests (*inadequate*)

Phenylbutazone would appear to be inactive in inducing mutations in bacteria[1,3], and it did not induce non-disjunction or crossing-over in *Aspergillus nidulans* in the absence of an exogenous metabolic activation system[1]. There are conflicting data as to its ability

to induce chromosomal damage in mammalian, including human, cells cultured *in vitro*[1,4]. There are consistent reports of an absence of any chromosome-damaging effect on the bone-marrow cells of hamsters or rats and on germ cells of male mice *in vivo*[1]. It was inactive in a dominant lethal test in mice[1]. There are two reports that it did not cause chromosomal damage in bone-marrow cells of treated patients and one report of the presence of chromosomal aberrations in lymphocytes from such patients[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants			-	
Insects				
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*			-	DL(-)
Humans *(in vivo)*			?	

DL = dominant lethal mutations

References

[1] *IARC Monographs*, *13*, 183-200, 1977

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N-PHENYL-2-NAPHTHYLAMINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

No excess of bladder tumours was found among men in a rubber processing factory with known exposure to *N*-phenyl-2-naphthylamine (which contained small amounts of 2-naphthylamine); however, another study of rubber workers (who were not exposed to 2-

naphthylamine) did show an increased incidence of bladder tumours. In the latter study, the men were exposed to several compounds, which probably included *N*-phenyl-2-naphthylamine. There is limited evidence from one study of 19 human volunteers that up to 0.03% of a single 10-mg dose of *N*-phenyl-2-naphthylamine is converted to 2-naphthylamine, a known bladder carcinogen[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

N-Phenyl-2-naphthylamine was tested in mice by oral and by single subcutaneous administration and in a small number of dogs by oral administration. Oral administration in mice produced a statistically significant increase in the incidence of all tumours, and in particular of hepatomas, in males of one of the two strains tested. Subcutaneous administration of this compound produced a significant increase in the total incidence of tumours in females of one strain and of hepatomas in males of the other strain[1]. Hamsters administered *N*-phenyl-2-naphthylamine intragastrically for life at the maximum tolerated dose did not develop tumours that could be attributed to treatment[2]. Pregnant mice were given the compound intragastrically from the 1st to the 18th day of pregnancy, and the offspring were then treated postnatally for 7 or 13 months. The tumour incidences were 8% in controls and 5-22% in treated groups[3]. [The Working Group noted the short period of observation.] In a biotransformation study in dogs, 0.02% of a measured dose of *N*-phenyl-2-naphthylamine was converted metabolically to 2-naphthylamine[1].

C. Evidence for activity in short-term tests (*inadequate*)

N-Phenyl-2-naphthylamine was not mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic activation system[4]. It was reported in an abstract to be mutagenic to *S. typhimurium* in the presence of norharman[5]. It did not induce cell transformation (in the BHK assay)[6]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				T(-)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

References

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PHENYTOIN (Group 2B)

A. Evidence for carcinogenicity to humans (*limited*)

Cancer, mostly neuroblastoma and tumours of neural crest origin, has been reported in six children aged three years or less who had been diagnosed as having an unusual constellation of congenital abnormalities (foetal hydantoin syndrome) thought to be induced by prenatal exposure to phenytoin[1-6]. Although the number of patients is small, the concordance of rare events suggests that phenytoin may be a transplacental carcinogen in humans. There is also one report of malignant mesenchymoma in a patient with phenytoin-associated malformations[7]. In a large case-control study[8] of 11 169 pairs, consisting of childhood cancer cases (about 8% of which would have been neuroblastomas[9]) and matched controls, epilepsy was reported among the mothers of 39 cancer cases compared with 22 controls. Review of available antenatal records indicated use during pregnancy of phenytoin by 37% and of phenobarbital by 67% of the case mothers, but no information on the number of neuroblastomas among the cases was given.

There have been several case reports of lymphomas among individuals under phenytoin therapy, and several reviews of series of lymphoma patients have revealed increased mention of prior phenytoin use[1]. No significant excess of lymphoma, however, was reported in two follow-up studies of epilepsy patients: the observed and expected numbers of lymphoma-leukaemia were 23 and 23.7 in the larger survey[10], and 6 and 4.7 in the smaller survey[11]. An excess of brain and other neurological tumours during 1969-1976 (8 observed, 0.5 expected) was reported among people prescribed phenytoin during 1969-1973[12]. The excess is similar to that reported among epileptics [see summary of data on phenobarbital] and may reflect the underlying disease rather than use of the drug *per se*.

B. Evidence for carcinogenicity to animals (*limited*)

Phenytoin and its sodium salt are carcinogenic in mice after their oral or intraperitoneal administration, producing lymphomas and leukaemias[1,13,14]. The effects of oral administration varied with the strain of mouse: no effect was observed in the resistant C3Hf strain; in C57BL strain, thymic lymphomas were produced in 12% of the treated mice, starting at about eight months of age, as compared with 4% in control mice starting at about 18 months of age; 25% of SJL/J mice had thymic lymphomas early in the study, but late in the study the majority of both treated and control SJL/J mice had extrathymic tumours. The experiments were complicated by the use of a liquid diet. Studies by oral administration in rats were considered to be inadequate[1].

C. Evidence for activity in short-term tests (*inadequate*)

Phenytoin did not cause structural chromosomal anomalies in rats treated *in vivo* and did not induce dominant lethal mutations in mice. There are conflicting reports with regard to the induction of chromosomal aberrations in human lymphocytes exposed *in vitro* to toxic levels of phenytoin[1]. No chromosomal damage was found in lymphocytes or bone-marrow cells from a large series of patients receiving phenytoin[15,16]. [Conflicting findings of small, but significant, increases in aberration frequencies in cultured blood lymphocytes from patients treated with phenytoin may reflect the actions of other drugs, or be the indirect consequence of folate deficiency, which is a known side effect and which is itself a condition that increases aberration frequencies[1].]

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*			-	DL(-)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

References

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POLYCHLORINATED BIPHENYLS (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

A slight increase in the incidence of cancer, particularly melanoma of the skin, was reported in a small group of men exposed to Aroclor 1254, a mixture of polychlorinated biphenyls[1]. A study[2] of 2567 workers employed in two electrical capacitor manufacturing

plants where polychlorinated biphenyls were used (39 018 person-years) and which had been in operation since 1938 and 1946, respectively, showed no excess of all cancers (39 observed, 43.8 expected). However, there were slight, non-significant excesses of rectal cancer (4 observed, 1.19 expected) and liver cancer (3 observed, 1.07 expected). No case of melanoma was reported. A study of 1310 workers with at least six months' exposure to polychlorinated biphenyls in a capacitor manufacturing plant showed an excess of all cancers among male workers (8 observed, 3.3 expected; $p < 0.04$). The excess was due mainly to cancers of the digestive system and of the lymphatic and haematopoietic tissues. Among female workers, there were six cases of cancer (2.3 expected, not significant), of which two were lymphatic or haematopoietic cancers (0.45 expected)[3].

B. Evidence for carcinogenicity to animals (*sufficient*)

Certain polychlorinated biphenyls are carcinogenic to mice and rats after their oral administration, producing benign and malignant liver neoplasms[1]. Oral administration of polychlorinated biphenyls increased the incidence of liver neoplasms in rats previously exposed to *N*-nitrosodiethylamine[4,5].

C. Evidence for activity in short-term tests (*inadequate*)

4-Chlorobiphenyl and Aroclor 1221 were mutagenic to *Salmonella typhimurium*; other mixtures of polychlorinated biphenyls were inactive[1,6,7]. Clophen 30 and Clophen 50 produced no genetic effect in *Drosophila melanogaster*[1]. Aroclor 1254 did not produce dominant lethal mutations in rats, and Aroclor 1242 did not produce chromosomal abnormalities in rat bone marrow or spermatogonia[1]. Aroclor 1254 did not elicit unscheduled DNA synthesis in cultured rat hepatocytes[7] and did not produce chromosomal aberrations in cultured human lymphocytes[1]. Kaneclor-500 did not induce micronuclei in mouse bone marrow *in vitro*[8]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		?		
Fungi/Green plants				
Insects		-		
Mammalian cells *(in vitro)*	-		-	
Mammals *(in vivo)*			-	DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

References

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PREDNISONE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

An increased risk of cancer has been linked to combination chemotherapy, which often includes prednisone [see the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'], but no adequate data were available to evaluate the carcinogenicity of prednisone alone[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

Prednisone was tested in mice and rats by intraperitoneal administration. Little or no carcinogenic effect was observed, but the studies suffered from limitations in design and reporting[1].

C. Evidence for activity in short-term tests (*inadequate*)

Prednisone was not mutagenic in *Escherichia coli*; it caused no chromosomal damage when administered to rats. No chromosomal damage was detected in peripheral lymphocytes of patients treated with prednisone[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*			-	
Humans *(in vivo)*			-	

Reference

[1] *IARC Monographs*, *26*, 293-309, 1981

PROCARBAZINE (Group 2A)

A. Evidence for carcinogenicity to humans (*inadequate*)

An increased risk of cancer has been linked to combination chemotherapy, which often includes procarbazine [see the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'], but no adequate data were available to evaluate the carcinogenicity of procarbazine alone[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Procarbazine hydrochloride is carcinogenic to mice and rats. Repeated intraperitoneal injections produced malignant tumours of the nervous system and haematopoietic system in mice and rats of both sexes and adenocarcinomas of the mammary gland in rats only. Repeated intravenous injections induced malignant tumours in different organs of rats. Oral administration produced pulmonary tumours and leukaemias in mice and mammary tumours in rats. Leukaemias were induced in rhesus and cynomolgus monkeys after administration of procarbazine by multiple routes in the same animal[1].

C. Evidence for activity in short-term tests (*sufficient*)

Procarbazine was positive in the phage-induction test. It was mutagenic in bacteria[1,2], yeast[1], *Drosophila melanogaster*[1,3], mouse lymphoma cells *in vitro*[1] and mammalian cells *in vivo*[1]. It was positive in the heritable translocation test in mice[4] and in the specific-locus somatic mutation assay (spot test) in mice[5]. It produced chromosomal abnormalities in

Drosophila[1,6] and in mammalian cells *in vivo*[1,7]. It induced dominant lethal mutations in *Drosophila*[1] and in mice, and sperm abnormalities in mice[1,7]. Chromosomal aberrations were observed in bone-marrow and lymph-node cells from patients treated with procarbazine[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+	+	DL(+)
Mammalian cells *(in vitro)*		+		
Mammals *(in vivo)*		+	+	DL(+) SA(+)
Humans *(in vivo)*			+	

DL = dominant lethal mutations; SA = sperm abnormalities

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PROGESTERONE (Group 2B) (See Oestrogens and progestins)

PROPYLTHIOURACIL (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one survey of 331 hyperthyroid patients treated with antithyroid drugs, including propylthiouracil, and later with thyroidectomy, four thyroid cancers (an excess of unspecified proportion) were diagnosed more than one year after the beginning of drug therapy[1]. There has been one case report of acute myeloblastic leukaemia following propylthiouracil treatment[2].

B. Evidence for carcinogenicity to animals (*sufficient*)

Propylthiouracil produced thyroid tumours in mice, rats, hamsters and guinea-pigs and pituitary adenomas in mice after its oral administration[3].

C. Evidence for activity in short-term tests

No data were available.

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RESERPINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Fourteen case-control and two cohort studies on the relationship of reserpine to breast cancer were available to the Working Group[1-3]. Between and within studies, estimates of

relative risk for different measures of reserpine use varied from as low as 0.6 to over 3. Many of the positive findings were not coherent with one another; and the studies considered to be the most satisfactory, methodologically, showed little or no evidence of an increased risk.

B. Evidence for carcinogenicity to animals (*limited*)

Reserpine was tested in two experiments in mice by oral administration; in one experiment it induced malignant mammary tumours in females and carcinomas of the seminal vesicles in males. It was tested in three experiments in rats by oral administration; in one experiment, it increased the incidence of pheochromocytomas in males[1]. When reserpine was administered either prior to and concurrent with or following treatment with 3-methylcholanthrene, it had a protective effect against the induction of mammary tumours in rats[4].

C. Evidence for activity in short-term tests (*inadequate*)

Reserpine was negative in the *rec*-assay[5] and was not mutagenic in *Salmonella typhimurium*[1,5]. It did not elicit unscheduled DNA synthesis in cultured rat hepatocytes[6] and did not produce chromosomal aberrations in human lymphocyte cultures[1,5,6], in Chinese hamster cells *in vitro* or in bone-marrow cells from rats treated *in vivo*[5,6]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*	-		-	
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

References

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SACCHARIN (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

There is no consistent evidence that the risk of cancer is increased among users of saccharin[1]. Three case-control studies have shown no overall excess of bladder cancer in association with use of artificial sweeteners, nearly all of which contained saccharin[2-4]. The largest of these studies was a population-based survey in 10 areas of the US, involving interviews with 3010 bladder cancer patients and 5783 controls randomly selected from the areas in which the patients resided[2]. The relative risk of bladder cancer associated with any use of artificial sweeteners was 0.99 (95% confidence limits, 0.89-1.10) among men and 1.07 (0.89-1.29) among women, compared with a risk of 1.0 among non-users. However, significant trends of increasing risk with increasing average daily consumption and with duration of use were observed in certain subgroups, namely female non-smokers (with a low baseline risk of bladder cancer) and male heavy smokers (with a high baseline risk). Since these subgroups were considered *a priori* to be worthy of special attention on the basis of hypotheses derived from animal experimentation, the findings raise the possibility that saccharin may act as a weak carcinogen and/or promoter. In one of the other two studies, a population-based survey of 592 patients with lower-urinary-tract cancer[3], the relative risk among women associated with any use of diet drinks or sugar substitutes was 1.6 and exceeded by two-fold that for non-smokers. The risk for any use among men was 0.8.

B. Evidence for carcinogenicity to animals (*limited*)

Saccharin or sodium saccharin has been tested, either alone or in combination with other chemicals, by several routes of administration. (a) It was tested by oral administration of several dose levels to different strains of mice and rats, including several multigeneration studies[1]. In one study in mice and in one in rats the tumour incidence was similar in treated and control animals. In one single-generation study and two two-generation studies in rats, a significant increase in the incidence of bladder tumours was

observed in males treated with high doses[1,5]. Several experiments in mice, rats, hamsters and monkeys were considered inadequate for evaluation. A 10:1 mixture of sodium cyclamate:sodium saccharin was given in one multigeneration experiment in mice and in two experiments in rats[1]. Transitional-cell carcinomas of the bladder were induced only in male rats of one strain given the highest dose. Pretreatment with a single instillation into the bladder of a low dose of *N*-nitroso-*N*-methylurea or feeding of *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide and subsequent oral administration of saccharin increased the incidence of bladder neoplasms in female and male rats, respectively[1]. Commercial saccharin preparations enhanced lung tumour induction in mice when given before or during urethane administration[5]. (b) Saccharin and sodium saccharin were also tested by insertion into the urinary bladder of mice, inducing bladder neoplasms[1]. (c) Experiments in which it was given by skin application or intraperitoneal administration could not be evaluated[1].

ortho-Toluenesulphonamide increased the incidence of bladder neoplasms in one out of three experiments in rats following its oral administration[1].

C. Evidence for activity in short-term tests (*inadequate*)

Saccharin was not mutagenic[1,6-8] and did not induce DNA repair in bacteria[9]. It produced genetic effects in yeast[10]; it was not mutagenic to *Drosophila melanogaster*[6]; it was reported to be mutagenic in mouse lymphoma cells in the presence of a liver homogenate[1]. Conflicting results were obtained with regard to chromosomal anomalies in cells *in vitro*[1,11]: saccharin caused chromosomal aberrations in cultured Chinese hamster cells[1] and a low level of sister chromatid exchanges in cultured lymphocytes and hamster cells[1,12]. No anomaly was seen in cells from animals treated *in vivo*[1,6]. It showed no covalent binding to DNA of rat bladder or liver[1]. It did not produce transformation in mouse embryo fibroblasts (C3H/10T$\frac{1}{2}$)[11], but at high concentrations it enhanced the transformation of these cells by 3-methylcholanthrene[1]. No sperm abnormality was seen in mice[13]. There were conflicting data concerning the production of dominant lethal mutations in mice[1], and conflicting results in the specific-locus somatic mutation test (spot-test) conducted in mice *in vivo*: in one study[14], positive but non-dose related effects were obtained; while negative results were obtained in single-dose experiments reported in another study[15]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	-	-		
Fungi/Green plants		+		
Insects		-		
Mammalian cells *(in vitro)*		?	?	T(-)
Mammals *(in vivo)*	-	?	-	DL(?) SA(-)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations; SA = sperm abnormalities

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SOOTS, TARS AND OILS (Group 1)* and BENZO[*a*]PYRENE (Group 2A)

A. Evidence for carcinogenicity to humans (*sufficient* for soots, tars and oils; *inadequate* for benzo[*a*]pyrene)

Occupational exposure to coal-soot, coal-tar and pitch, coal-tar fumes and some impure mineral oils causes cancer at several sites including skin, lung, bladder and gut. Recent epidemiological studies support these conclusions[1].

Mineral oils vary in their carcinogenicity and in their composition[2]. Most of the studies linking cancer, including skin cancer and especially of the scrotum, with exposure to mineral oils were undertaken at a time before solvent-refined oils were in common use. Three more recent studies have shown no increased cancer risk among people exposed to mineral oil mists[3-5].

The carcinogenic effects of soots, tars and oils may be due to the presence of polycyclic aromatic hydrocrbons, of which benzo[*a*]pyrene has been the most widely studied. Assessment of the risk due to exposure to benzo[*a*]pyrene, however, is difficult, since human populations are also exposed simultaneously to mixtures of other compounds of known or possible carcinogenicity, including (but not limited to) other polycyclic aromatic hydrocarbons. Therefore, although there are several studies in which benzo[*a*]pyrene was measured as an indication of exposure to the mixture of compounds in soots, tars and oils, the epidemiological data were considered inadequate to evaluate the carcinogenicity of benzo[*a*]pyrene itself.

B. Evidence for carcinogenicity to animals (*sufficient* for soots, tars and oils and for benzo[*a*]pyrene)

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

C. Evidence for activity in short-term tests (*sufficient* for benzo[*a*]pyrene)

The complexity of the mixtures constituting soots, tars and oils precluded any useful evaluation of their activity in short-term tests.

Benzo[*a*]pyrene, an indirect carcinogen which undergoes metabolism to a reactive electrophile capable of binding covalently to DNA[6], has been used extensively as a model carcinogen and as a positive control in a variety of short-term tests[7,8]. It was active in assays for bacterial DNA repair, bacteriophage induction and bacterial mutation[7,8]; mutation in *Drosophila melanogaster*[8]; DNA binding, DNA repair, sister chromatid exchange, chromosomal aberration, point mutation and transformation in mammalian

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* Categorized as Group 1 by the earlier Working Group, and data on humans and on animals not reevaluated by the present Group.

cells in culture[7,8]; and in tests in mammals *in vivo*, including DNA binding, sister chromatid exchange, chromosomal aberration, sperm abnormality and the somatic specific locus (spot) test[7,8].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	T(+)
Mammals *(in vivo)*	+	+	+	SA(+)
Humans *(in vivo)*				

T = cell transformation; SA = sperm abnormalities

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SPIRONOLACTONE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Five cases of breast cancer were reported in women who had used a drug containing spironolactone. Four analytical studies, however, showed no consistent evidence of an association[1].

B. Evidence for carcinogenicity to animals (*limited*)

Spironolactone was tested by oral administration in two experiments in rats. An increased incidence of thyroid and testicular tumours was reported in one experiment but not in another experiment of longer duration with lower doses[1].

C. Evidence for activity in short-term tests

No data were available.

Reference

[1] *IARC Monographs*, *24*, 259-274, 1980

STYRENE (Group 3) and

STYRENE OXIDE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate* for styrene and for styrene oxide)

Some studies have suggested an association between leukaemia and, possibly, lymphomas and exposure to styrene. In a mortality analysis of 2904 workers exposed to low or moderate levels of styrene (not exceeding 100 ppm), 6 cases of leukaemia (3.4 expected; standardized mortality ratio, 176) and 7 cases of lymphoma (5.3 expected; SMR, 132) were observed. When the incidence was analysed, 7 cases of lymphatic leukaemia (1.64 expected), 4 cases of 'all other leukaemia' (2.89 expected) and 4 cases of multiple myeloma (1.55 expected) were found. However, 6 of the leukaemia cases occurred in a group with concomitant exposure to colourants; moreover, a subset of the cohort had also been exposed to benzene in the past[1]. There is an anecdotal report of three deaths from leukaemia and two from lymphoma among a group of workers exposed to styrene, benzene and butadiene, but the study population was ill defined[2]. Two other studies that attempted to investigate this problem[3,4] are uninformative because of diluting errors in design and analysis.

B. Evidence for carcinogenicity to animals (*limited* for styrene and for styrene oxide)

Styrene has been tested by oral administration to mothers and offspring of two strains of mice and one strain of rats. In mice, it increased the incidence of lung tumours in offspring of one strain after administration of high doses, and slightly increased the incidence of liver-cell tumours in male offspring of the other strain after use of a low dose. In rats, no statistically significant increase in tumour incidence was observed[2]. In experiments by oral administration to young adult mice and another strain of rats, a positive, dose-related association between exposure to styrene and frequency of lung tumours was observed only in male mice[5]. A solution of 30% β-nitrostyrene and 70% styrene was tested by oral administration in one strain of rats and one strain of mice at several dose levels. It increased the incidence of lung tumours in the group of male mice given the low dose[6].

Styrene oxide induced neoplasms of the forestomach following its oral administration at two dose levels in one strain of rats[7]. In skin painting experiments, no increase in the incidence of skin tumours was observed in two strains of mice[8].

C. Evidence for activity in short-term tests (*sufficient* for styrene and for styrene oxide

Conflicting results have been obtained with *styrene* in bacterial mutation assays[2,9-11]; positive results were obtained in the presence of an exogenous metabolic activation system and in experiments in which the chemical was applied as a vapour. Styrene did not induce DNA repair in human EUE cells *in vitro* and did not induce mutation or gene conversion in fungi[9], even when they were supplied with an exogenous metabolizing system, unless the dose of styrene was very high. Very high doses of styrene also gave positive results in host-mediated assays using mice[2]. It induced chromosomal aberrations in a vascular plant[12]. In cultured mammalian cells supplied with a metabolizing system, styrene did not induce DNA repair[9] or mutation[2], but did produce chromosomal aberrations[12,13] and sister chromatid exchanges[14], the latter only in the presence of an epoxide hydrase inhibitor. Styrene induced mutation in *Drosophila melanogaster*[15], the mutation yield being increased by pretreating the flies with phenobarbital. Inhalation of styrene by mice resulted in the formation of sister chromatid exchanges in alveolar macrophages and bone-marrow and in regenerating liver cells[16]; however, no chromosomal aberration was induced in the bone marrow of mice exposed to single doses given by gavage or in Chinese hamsters exposed by inhalation[17].

Several studies have shown an increase in chromosomal aberrations in cultured peripheral lymphocytes of workers exposed to high levels of styrene[2,18-23]. In one study, a slight increase in sister chromatid exchanges was also noted[18]. No increase in chromosomal aberrations was seen in workers exposed to low levels of styrene[20].

Styrene oxide was mutagenic in bacteria[8,24,25] and fungi[8] in the absence of an exogenous metabolic activation system; it induced chromosomal aberrations in a vascular plant[12] and mutation in *Drosophila melanogaster*[15]. In a host-mediated assay in mice, it induced gene conversion but not point mutation in a yeast[8]. In cultured mammalian cells, styrene oxide induced mutation[8,9,26], sister chromatid exchanges[14], chromosomal aberrations[12,27] and DNA repair[9]. In one study, styrene oxide given to mice at a dose approaching the maximum tolerated failed to induce dominant lethal mutation, bone-marrow chromosomal aberrations or micronuclei, or translocations in premeiotic germ cells[27]. In another study, it induced chromosomal aberrations in the bone marrow of mice[9], but not in hamsters[28]. No data on humans were available.

Styrene

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		?	+	
Insects		+		
Mammalian cells *(in vitro)*	-	-	+	
Mammals *(in vivo)*			?	
Humans *(in vivo)*			+	

Styrene oxide

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+	+	
Insects		+		
Mammalian cells *(in vitro)*	+	+	+	
Mammals *(in vivo)*			?	DL(?)
Humans *(in vivo)*				

DL = dominant lethal mutations

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SULFAFURAZOLE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

No significant association with cancer at any site was observed during 1969-1976 among 11 659 members of a prepaid health plan prescribed sulfafurazole during 1969-1973, but no other epidemiological data to evaluate its carcinogenic potential to humans were available[1].

B. Evidence for carcinogenicity to animals (*inadequate*)

Sulfafurazole was tested in rats by oral administration; no increase in tumour incidence was observed[1].

C. Evidence for activity in short-term tests (*inadequate*)

No adequate data were available.

Reference

[1] *IARC Monographs*, *24*, 275-284, 1980

SULFAMETHOXAZOLE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Increased incidences of nasopharyngeal carcinoma (3 observed, 0.1 expected) and cervical cancer (7 observed, 2.2 expected) were observed during 1969-1976 among 1709 members of a prepaid health plan who had been prescribed sulfamethoxazole during 1969-1973, but the study was conducted to generate hypotheses rather than to make inferences about the relationship of the use of a wide variety of drugs and the development of cancer[1].

B. Evidence for carcinogenicity to animals (*limited*)

Sulfamethoxazole produced thyroid tumours in rats following its oral administration; no information on other tumour types was reported[1].

C. Evidence for activity in short-term tests (*inadequate*)

Sulfamethoxazole, tested in combination with trimethoprim, did not induce chromosomal aberrations in cultured human cells. Lymphocytes from children and adults treated with sulfamethoxazole in combination with trimethoprim showed no increase in chromosomal aberrations[1].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*			-	
Mammals *(in vivo)*				
Humans *(in vivo)*			-	

Reference

[1] *IARC Monographs, 24*, 285-295, 1980

2,4,5-T AND ESTERS (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

2,4,5-T and its esters were mentioned specifically (in association with 2,4-D) in case reports of soft-tissue sarcomas and lymphomas related to exposure to phenoxyacetic acids[1,2] and in subsequent case-control studies[3-5] that showed increased risks of these tumours with exposure to 2,4,5-T and 2,4-D, both with and without concomitant exposure to chlorophenols. The relative risks associated with exposure to phenoxyacetic acid herbicides (mainly 2,4,5-T and 2,4-D) were 5.3 (95% confidence limits, 2.4-11.5) and 6.8 (2.6-17.3) for soft-tissue sarcomas and 4.8 (2.9-8.1) for lymphomas. The 2,4,5-T was almost certainly contaminated with tetrachlorodibenzo-*para*-dioxin (TCDD). The effects of exposure to 2,4,5-T (in association with 2,4,5-trichlorophenol, TCDD and, usually, other chemicals) were also assessed in several cohort studies of chemical manufacturers and other exposed workers[6-9]. In the last three studies, a total of 18 cancers were observed and 18.5 expected in workers exposed to 2,4,5-T, with or without other chemicals. One was a lymphoma (Hodgkin's disease), and none was a soft-tissue sarcoma. Exposure to 2,4,5-T in association with 2,4,5-trichlorophenol and TCDD has been related to the occurrence of a neurogenic sarcoma and a liposarcoma in two further case reports. [See also the summaries of data on 'Phenoxyacetic acid herbicides (occupational exposure to)' and on 'Tetrachlorodibenzo-*para*-dioxin (TCDD)'.]

B. Evidence for carcinogenicity to animals (*inadequate*)

2,4,5-T was tested in mice in three studies by oral and subcutaneous administration. All of these studies had limitations due to the small numbers of animals used. Therefore, although an increased incidence of tumours at various sites was observed in one study in which 2,4,5-T (containing less than 0.05 ppm chlorinated dibenzodioxins) was given orally, no evaluation of the carcinogenicity of this compound could be made on the basis of the available data[12]. In groups of male and female rats fed diets containing 3, 10 or 30 mg/kg bw per day for up to two years, the incidences of all tumour types were comparable in the treated and control groups, with the exception that interfollicular C-cell adenomas of the thyroid were increased significantly in female rats receiving the lowest dose. The increase was not dose-related, however, and was not considered to be related to treatment[13]. Mice of C3Hf and XVII/G strains were given 2,4,5-T containing less than 0.05 ppm dioxins by two different routes. After four subcutaneous injections of 10 mg/kg bw during the neonatal period, there was no significant difference in the frequency of tumours in treated and control mice, although a few tumours appeared earlier in those of the XVII/G strain. A significant increase in the incidence of neoplastic lesions was found in C3Hf mice that received 2,4,5-T by continuous oral administration (80 mg/kg in the diet), but no further information was provided. No significant difference was found for the XVII/G strain; but rare forms [unspecified] of tumour that were not observed in the controls were present in treated C3Hf mice[14]. [The Working Group noted the lack of detail in this report.]

[Phenoxyacetic acid herbicides have been shown to cause peroxisome proliferation in Chinese hamsters[15]. Certain agents known to cause this proliferation are carcinogenic, and the phenomenon has been suggested to have mechanistic significance in the induction of tumours.]

C. Evidence for activity in short-term tests (*inadequate*)

2,4,5-T was not mutagenic to a range of bacterial species and strains after treatment *in vitro* or in host-mediated assay systems[12,16]. Results obtained using *Saccharomyces cerevisiae* are conflicting, but in experiments conducted at low pH 2,4,5-T was a mild mutagen[12,17,18]. The substance was also a mild mutagen for sex-linked recessive lethals in *Drosophila melanogaster* exposed to high dose levels, but was negative for non-disjunction and sex chromosome loss or exchange[12,19-22]. There are few data on the effects of 2,4,5-T on chromosomes of mammalian cells exposed *in vitro*, and studies of bone-marrow cells *in vivo* are inadequate and conflicting[12,23,24]. One study on the induction of dominant lethal mutations in the mouse was negative[12]. Small increases in chromosomal aberration frequencies have been noted in individuals occupationally exposed to mixtures of compounds including 2,4,5-T, but these increases could not be attributed specifically to exposure to 2,4,5-T[25,26]. One large study of workers exposed to 2,4,5-T during its manufacture and studies on soldiers and civilians exposed to 'Agent Orange' reveal no evidence for a chromosome damaging effect of 2,4,5-T in humans[27,28].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		?		
Insects		+	-	
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*			?	DL(-)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

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TETRACHLORODIBENZO-*para*-DIOXIN (TCDD) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

There is no report of human exposure only to TCDD. Three case-control studies[1-3] have shown relative risks of 5.7 (95% confidence limits, 2.9-11.3) and 5.1 (2.5-10.4) for soft-tissue sarcoma and 6.0 (3.7-9.7) for lymphoma in association with exposure to phenoxyacetic acids or chlorophenols, in which TCDD was a likely contaminant. In six[7-13] of seven[4-13] cohort studies, 37 deaths from cancer were observed with 33.3 expected in some 869 men exposed to TCDD during the manufacture or use of 2,4,5-trichlorophenol and/or 2,4,5-T. There was an appreciable deficit of deaths from all causes (135 observed, 157.3 expected). Two of the deaths were from lymphoma (both Hodgkin's disease) and two from

soft-tissue sarcomas. Three additional cases of soft-tissue sarcoma[14,15] (and possibly two more[16]) have been reported in men associated with the manufacture of 2,4,5-trichlorophenol or 2,4,5-T, and therefore possibly exposed to TCDD. Two of the three case-control studies referred to above[2,3] gave evidence of an increased risk of soft-tissue sarcoma or lymphoma in association with exposure to phenoxyacetic acids not usually contaminated with TCDD.

B. Evidence for carcinogenicity to animals (*sufficient*)

TCDD and other chlorinated dibenzodioxins were tested in mice and rats by oral administration and in mice by skin application, but no evaluation of their carcinogenicity could be made on the basis of the available data[17]. Rats were maintained for two years on diets calculated to provide 0.1, 0.01 or 0.001 μg/kg bw per day of TCDD. The level of 0.1 μg caused an increased incidence of hepatocellular carcinomas and squamous-cell carcinomas of the lung, hard palate/nasal turbinates or tongue. With 0.01 μg, signs of toxicity, including hepatocellular nodules, were found[18,19]. When rats were fed diets containing 0.001 μg/kg to 1 mg/kg TCDD for 78 weeks, doses equal to and greater than 50 μg/kg produced acute toxicity in all animals. Increased incidences of tumours in a variety of organs were observed at all dietary levels greater than 0.005 μg/kg; the control rats and those receiving the lowest dose were reported to have no neoplasm at the time of death[20].

Mice were given TCDD intragastrically alone and in various combinations with 2,4,5-trichlorophenoxyethanol (TCPE). A level of 0.7 μg/kg bw significantly enhanced liver tumour incidence, while 0.007 μg/kg bw did not. Spontaneous and induced liver tumours were not histologically different, and the ratios of benign to malignant liver tumours were the same in the control and treated groups[21]. A maximum tolerated dietary level of 70 mg/kg bw TCPE containing 7 ng/kg bw TCDD doubled the incidence of liver tumours in treated mice over that in controls[22].

TCDD was a weak tumour initiator in a conventional two-stage assay for skin carcinogenesis in mice: animals were treated topically with a single dose of TCDD (2 μg/mouse) followed by twice-weekly topical applications of the skin tumour promoter 12-*O*-tetradecanoylphorbol-13-acetate[23]. TCDD was also cocarcinogenic with 3-methylcholanthrene as an initiator of subcutaneous tumours[24]. However, it inhibited skin carcinogenesis by polycyclic hydrocarbons, including 7,12-dimethylbenz[*a*]anthracene, benzo[*a*]pyrene, 3-methylcholanthrene and a diol epoxide of tetrahydrobenzo[*a*]pyrene in a time-dependent manner[25].

TCDD also has varying activities as a tumour promoter. In a conventional two-stage mouse skin tumorigenesis assay, there was no detectable promoting activity by twice-weekly topical applications of TCDD (0.1 μg) to female mice initiated by 7,12-dimethylbenz[*a*]anthracene[26]. In a rat liver tumour promotion assay, however, TCDD was highly effective: in female rats that received a single dose of 10 mg/kg bw *N*-nitrosodiethylamine, followed 24 hours later by partial hepatectomy and then by treatments with TCDD (0.14 and 1.4 μg/kg bw subcutaneously once every two weeks for seven months), there was a marked increase in enzyme-altered foci; with the higher dose level, hepatocellular carcinomas were present in five out of seven rats. Neither the nitrosamine treatment alone nor a single dose of TCDD resulted in significant numbers of enzyme-altered foci or liver carcinomas. Thus, it was concluded that TCDD enhances hepatocarcinogenesis[27].

C. Evidence for activity in short-term tests (*inadequate*)

Two early reports that TCDD induced frameshift mutations in *Salmonella typhimurium* in the absence of a metabolizing system[17] have not been confirmed; and a large number of later experimenters concluded that TCDD was not mutagenic in the bacteria studied, whether exposed in the presence or absence of a mixed function oxidase system[28-31]. There is a single positive report of mutagenic effects in yeast[32] and conflicting evidence of chromosomal damage in bone-marrow cells of rats following long-term exposure by gavage to high doses[17,33]. One study on dominant lethal mutation in rats was negative, despite the fact that a toxic effect of TCDD treatment was evident in the testes of exposed animals[34]. Small increases have been reported in aberration frequencies in lymphocytes from workers exposed to herbicides contaminated with small amounts of TCDD, but no aberration was observed in a large population of workers exposed to TCDD and suffering from chloracne[17,35]. Extensive studies on workers and on adults, children and foetuses exposed to TCDD in the Seveso incident have not revealed any increase in chromosomal aberration frequencies[36-38].

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*			?	DL(-)
Humans *(in vivo)*			-	

DL = dominant lethal mutations

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TETRACHLOROETHYLENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

A proportionate mortality study[1] comprising 330 death certificates of former laundry workers, mostly women, revealed 87 deaths from cancer with 67.9 expected; the proportions of cancers of lung, cervix and skin were elevated, and there was also a slight excess of leukaemia and primary liver cancer. Although tetrachloroethylene was the predominant cleaning fluid used, exposure to other solvents such as carbon tetrachloride and benzene must have occurred. [Laundry workers belong to a low socio-economic class, which may explain the increased incidences of lung and cervical cancer.] A retrospective cohort study showed a slight excess of colonic cancer (11 observed, 6.98 expected)[2]. [However, in view of the short follow-up period and the possibility of there having been mixed exposure, the result must be considered inconclusive.] Two studies summarized in connection with trichloroethylene[3,4] also involved some exposure to tetrachloroethylene, but the data do not allow a separation of the effects.

B. Evidence for carcinogenicity to animals (*limited*)

Tetrachloroethylene is carcinogenic to mice, producing malignant liver neoplasms. One experiment in rats by oral administration was considered to be inadequate. Tetrachloroethylene was also inadequately tested by inhalation exposure in rats and by intraperitoneal injection in mice[5].

C. Evidence for activity in short-term tests (*inadequate*)

Tetrachloroethylene was not mutagenic to bacteria[5,6], but at high doses it produced genetic effects in yeast[7]. It did not produce chromosomal anomalies in the bone-marrow cells of mice treated *in vivo* and did not bind to the liver DNA of mice exposed *in vivo*[8]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*	-		-	
Humans *(in vivo)*				

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ortho-TOLUIDINE (Group 2A)

A. Evidence for carcinogenicity to humans (*inadequate*)

There are numerous studies of dyestuffs workers, dating back to the classical cohort studies in 1954. Although an excess of bladder tumours has often been found in workers exposed to varying combinations of dyestuffs and dyestuff intermediates, no population of workers exposed to *ortho*-toluidine alone has been described. Occasional cases of bladder tumour have been noted in workers classified as being exposed primarily to *ortho*-toluidine, but either insufficient data or follow-up time have prevented a clear association being made with the exposure[2]. An excess of bladder tumours was noted in workers exposed to toluene, *ortho*-nitrotoluene, *ortho*-toluidine and 4,4′-methylenebis(2-methylaniline) during the manufacture of Fuchsine and Safranine T[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

ortho-Toluidine (hydrochloride) is carcinogenic to mice and rats after its oral administration, producing a variety of malignant tumours[1].

C. Evidence for activity in short-term tests (*sufficient*)

ortho-Toluidine gave indirect evidence of DNA repair in bacteria and yeast and induced unscheduled DNA synthesis in mammalian cells *in vitro*[1,2]. It gave conflicting results with regard to mutagenicity in bacteria[1,2] and yeast[2]. It induced chromosomal anomalies in yeast and sister chromatid exchanges in mammalian cells *in vitro*[2]. It was negative in the micronucleus test in mice *in vivo*, but it induced cell transformation (in the BHK assay)[2]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	?		
Fungi/Green plants	+	?	+	
Insects				
Mammalian cells *(in vitro)*	+		+	T(+)
Mammals *(in vivo)*			-	
Humans *(in vivo)*				

T = cell transformation

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TREOSULPHAN (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

In one epidemiological study of 553 patients with ovarian cancer treated only with treosulphan and followed for one to eight years after treatment (1159 patient-years), seven patients developed acute non-lymphocytic leukaemia 21-58 (median, 50) months after the start of chemotherapy; the expected number of cases among the patients was 0.04, giving a relative risk of 175. There was a correlation between cumulative dose of treosulphan and risk of leukaemia, although it was not statistically significant[1].

B. Evidence for carcinogenicity to animals

No data were available.

C. Evidence for activity in short-term tests (*inadequate*)

Treosulphan is an alkylating agent. The only available short-term studies showed that it produced chromosomal aberrations in plants[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants			+	
Insects				
Mammalian cells *(in vitro)*				
Mammals *(in vivo)*				
Humans *(in vivo)*				

Reference

[1] *IARC Monographs*, *26*, 341-347, 1981

TRICHLOROETHYLENE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Three studies showed no excess of cancers in workers exposed to trichloroethylene[1-3]. [No conclusion can be drawn because of small sample size, short follow-up or insufficient time since onset of exposure.] Mixed exposure to trichloroethylene, tetrachloroethylene and some other solvents in the electroplating industry resulted in elevated proportions of oesophageal cancer (proportional mortality ratio, 185) and primary liver cancer (278) and slight increases in the incidences of lymphomas and of buccal cavity and pharynx, rectal, pancreatic and laryngeal cancers[4]. [There was no increase in lung cancer, which suggests that chromates or nickel were not the causative agents for the observed excesses. This study is inconclusive because proportional mortality ratios are vulnerable to error, because there was mixed exposure and because the study did not allow analysis of causes of deaths for those leaving work while active.] Another attempt to analyse mortality within the metal electroplating industry by comparing figures from counties in which there were many electroplating factories with those from other counties was uninformative[5].

B. Evidence for carcinogenicity to animals (*limited*)

Trichloroethylene is carcinogenic to mice after its oral administration, producing liver and lung neoplasms. An experiment by oral administration in rats was considered to be inadequate[1]. Administration by inhalation was associated with an increased incidence of lymphomas in female mice, but not in rats or hamsters[6].

C. Evidence for activity in short-term tests (*inadequate*)

Trichloroethylene was weakly mutagenic to bacteria[1,7], but strongly so to yeast[1,8]. In a mouse host-mediated assay, it induced point mutations and gene conversions in yeast recovered from liver and kidneys[1]. It was claimed in an abstract to be mutagenic in spot tests for somatic mutations in mice[1]. It did not induce dominant lethal mutations in mice[9]

or rats[10]. Trichloroethylene bound to macromolecules *in vivo* and *in vitro*[1,11]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		?		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	?			
Mammals *(in vivo)*	?	?		DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

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2,4,5-TRICHLOROPHENOL (Group 3) and 2,4,6-TRICHLOROPHENOL (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate* for 2,4,5- and 2,4,6-trichlorophenols)

Specific mention of trichlorophenols (probably mainly, if not entirely, 2,4,5-trichlorophenol) was made in one case report of retroperitoneal neurogenic sarcoma in a man employed in cartage and maintenance work in a chemical plant where trichlorophenols (isomer unspecified, but probably 2,4,5) and 2,4,5-T were manufactured[1], and in four cohort studies of a total of 460 men involved in the manufacture of 2,4,5-trichlorophenol or of 2,4,5-T from 2,4,5-trichlorophenol[2-5]. The latter studies provide an aggregate of 20 deaths from cancer with 18.4 expected. Each study (except that of Thiess *et al.*[2]) showed a deficit of deaths from all causes - in total, 68 deaths observed and 94 expected. There were two deaths from soft-tissue sarcoma among the 20 deaths from cancer in the follow-up reports. An additional case of soft-tissue sarcoma has since been reported from one of the cohorts[6]. Reference to chlorophenols generically (mainly 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol and pentachlorophenol[7]) is made in three case-control studies, which showed relative risks of 6.6 and 3.3 for soft-tissue sarcomas and 7.6 (heavy exposure) or 2.2 (light exposure) for lymphomas in association with exposure to chlorophenols[8-10]. In none of these studies could exposure to trichlorophenols be distinguished with any certainty from exposure to tetrachlorodibenzo-*para*-dioxin (TCDD). In some, exposure to other related and unrelated chemicals also occurred.

B. Evidence for carcinogenicity to animals (*inadequate* for 2,4,5-trichlorophenol; *sufficient* for 2,4,6-trichlorophenol)

2,4,6-Trichlorophenol was tested in one experiment in two strains of mice by oral administration, and 2,4,5- and 2,4,6-trichlorophenols were tested in one experiment by subcutaneous injection in two strains of mice. 2,4,5-Trichlorophenol was also tested in one experiment for its promoting activity in female mice. All three experiments were considered to be inadequate[11].

Groups of 50 male mice were fed 5000 or 10 000 mg/kg 2,4,6-trichlorophenol (96-97% pure) in the diet for 105 weeks; groups of 50 female mice were given 10 000 or 20 000 mg/kg in the diet for 38 weeks, then 2500 or 5000 mg/kg for 67 weeks. Survival was 80% or more in all groups. Hepatocellular carcinomas or adenomas occurred in statistically significant incidences in both male and female mice. Groups of 50 rats of each sex were

fed 5000 or 10 000 mg/kg 2,4,6-trichlorophenol in the diet for 106-107 weeks. Survival by the end of the experiment was 68% or more in all groups. Statistically significant increased incidences of lymphomas and leukaemias occurred in male rats[12].

C. Evidence for activity in short-term tests

No data were available.

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TRIS(AZIRIDINYL)-*para*-BENZOQUINONE (TRIAZIQUONE) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

The four available case reports were inadequate to evaluate the carcinogenicity to humans of triaziquone[1].

B. Evidence for carcinogenicity to animals (*limited*)

Tris(aziridinyl)-*para*-benzoquinone is carcinogenic to rats after repeated intravenous injections or after repeated intravenous injections followed by repeated intraperitoneal injections, producing a variety of malignant tumours[1].

C. Evidence for activity in short-term tests (*sufficient*)

Triaziquone is an alkylating agent and caused DNA alkylation *in vitro*[1]. It was mutagenic to bacteria[2], yeast[1], *Drosophila melanogaster*[1] and mouse lymphoma cells *in vitro*[3]. It caused chromosomal anomalies in plants[4], *Drosophila*[1], rodent cells and human lymphocytes *in vitro*[1]. It was positive in the micronucleus test in various rodent species and in rhesus monkeys treated *in vivo*[1]. Dominant lethal mutations and heritable translocations were observed in mice[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+	+	
Insects		+	+	
Mammalian cells *(in vitro)*		+	+	
Mammals *(in vivo)*			+	DL(+)
Humans *(in vivo)*				

DL = dominant lethal mutations

References

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TRIS(1-AZIRIDINYL)PHOSPHINE SULPHIDE (THIOTEPA) (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

A number of case reports describe the occurrence of acute nonlymphocytic leukaemia in patients treated with thiotepa, usually in combination with other therapeutic agents, for ovarian and other malignant tumours[1-5]. A study of 5455 ovarian cancer patients, diagnosed between 1935 and 1971, found 13 cases (0.62 expected) of acute nonlymphocytic leukaemia in those who had received therapeutic doses of alkylating agents. Of these, one had received thiotepa for 46 months without other therapies[6]. In a clinical trial of adjuvant thiotepa after radical mastectomy, 90 patients who received the drug for one year were compared with 77 controls. After an average of at least five years of follow up, no increase in the incidence of second primary cancers was observed in the group that received thiotepa, and no case of acute nonlymphocytic leukaemia was observed in either group[7].

B. Evidence for carcinogenicity to animals (*sufficient*)

Tris(1-aziridinyl)phosphine sulphide is carcinogenic to mice after its intraperitoneal injection and to rats after its intraperitoneal or intravenous injection, producing a variety of malignant tumours[1,8,9].

C. Evidence for activity in short-term tests (*sufficient*)

Tris(1-aziridinyl)phosphine sulphide, an alkylating agent, was mutagenic to *Salmonella typhimurium*[10] and to *Drosophila melanogaster*[1] and to mouse lymphoma cells *in vitro*[11]. It induced chromosomal aberrations in rodent[12,13] and human cells *in vitro*[1] and in mice[14] and hamsters[15] *in vivo*, and sister chromatid exchanges in hamster cells *in vitro*[16]. Dominant lethal mutations were observed in mice treated *in vivo*[1,15,17-19] and in rabbits whose sperm were treated *in vitro*[1]; sperm abnormalities were induced in mice[20]. It induced cell transformation (in C3H/10T$\frac{1}{2}$)[21]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants				
Insects		+		
Mammalian cells *(in vitro)*		+	+	T(+)
Mammals *(in vivo)*			+	DL(+) SA(+)
Humans *(in vivo)*				

T = cell transformation; DL = dominant lethal mutations; SA = sperm abnormalities

References

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UNDERGROUND HAEMATITE MINING (WITH EXPOSURE TO RADON) (Group 1) and HAEMATITE (Group 3)

A. Evidence for carcinogenicity to humans (*sufficient* for underground haematite mining (with exposure to radon), *inadequate* for haematite)

Underground haematite miners have a high incidence of lung cancer, whereas surface haematite miners do not. It is not known whether this excess risk is due to radioactivity in the air of the mines (radon is a known lung carcinogen), the inhalation of ferric oxide

or silica, or to a combination of these and other factors[1]. Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer[1,2], but the influence of factors in the workplace other than ferric oxide cannot be discounted. In other studies of metal and chemical workers exposed to ferric oxide, the incidence of lung cancer has generally not been increased[1,3].

B. Evidence for carcinogenicity to animals (*inadequate* for haematite)

No carcinogenic effect was observed in mice, hamsters or guinea-pigs given ferric oxide intratracheally[1]. Repeated intratracheal instillation to hamsters of benzo[*a*]pyrene bound to equal quantities of ferric oxide induced squamous-cell carcinomas that resembled certain human bronchogenic carcinomas[4]. In a similar study, there was no increase in tumour yield in animals administered a constant dose of 3 mg benzo[*a*]pyrene and increasing amounts of ferric oxide (3, 6 and 9 mg per dose), indicating that beyond a certain ratio of benzo[*a*]pyrene to ferric oxide, the latter does not affect tumour yield[5]. In a third study of the same design, administration of ferric oxide particles alone induced nonspecific epithelial alterations, interstitial-cell proliferation and a few granulomatous changes but no respiratory-tract tumours, indicating that ferric oxide particles act as cofactors in this system[6].

C. Evidence for activity in short-term tests (*inadequate* for haematite)

Ferric oxide did not cause cell transformation in Syrian hamster embryos[7]. No data on humans were available.

Haematite

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes				
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*				T(-)
Mammals *(in vivo)*				
Humans *(in vivo)*				

T = cell transformation

References

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URACIL MUSTARD (Group 2B)

A. Evidence for carcinogenicity to humans (*inadequate*)

A study of 5455 ovarian cancer patients diagnosed between 1935 and 1971 showed 13 cases (0.62 expected) of acute nonlymphocytic leukaemia in patients who had received therapeutic doses of alkylating agents. Of these, one had received uracil mustard plus 5-fluorouracil for 19 months[1].

B. Evidence for carcinogenicity to animals (*sufficient*)

Intraperitoneal administration of uracil mustard to mice of two strains induced lung adenomas and adenocarcinomas in a dose-dependent incidence; in one of the strains, liver, ovarian and lymphatic tumours were also observed. In rats, intraperitoneal administration induced peritoneal sarcomas and lymphomas and tumours in the pancreas, ovary and mammary gland[2].

C. Evidence for activity in short-term tests (*sufficient*)

Uracil mustard is an alkylating agent; it induced DNA damage in prokaryotes and in rats *in vivo*[2]. It was mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic activation system[3,4] and produced mutations in yeast[5] and in mouse lymphoma cells *in vitro*[6]. It caused 'minute' chromosomal anomalies in *Drosophila melanogaster*[7]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects			+	
Mammalian cells *(in vitro)*		+		
Mammals *(in vivo)*	+			
Humans *(in vivo)*				

References

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VINBLASTINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Treatment with vinblastine, mainly in combination therapy, has been associated in case reports with the subsequent development of leukaemias. In a small epidemiological study of short duration, no excess of subsequent neoplasms was observed in patients treated with a regimen including vinblastine, adriamycin, bleomycins and dacarbazine[1]. [See also the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'.]

B. Evidence for carcinogenicity to animals (*inadequate*)

No evidence of carcinogenicity was found after intraperitoneal administration of vinblastine to mice and rats or after its intravenous administration to rats, but it has not been adequately tested at high doses[1].

C. Evidence for activity in short-term tests (*inadequate*)

Vinblastine was not mutagenic to *Salmonella typhimurium*[1,2] or to yeasts[3,4]. It was reported to produce dose- and time-dependent increases in the incidences of various chromatid aberrations in Don Chinese hamster lung cells *in vitro*[1]; however, no mutation was seen in V79 Chinese hamster cells[5]. Vinblastine also produced increases in bone-marrow micronucleus formation and sperm abnormalities in mice[1]; but it is a well-known spindle inhibitor, and these abnormalities have been considered to be related to spindle effects and not to mutagenicity. Vinblastine did not induce dominant lethal mutations in mice; chromosomal translocations were observed in male mice[6]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants		-		
Insects				
Mammalian cells *(in vitro)*			?	
Mammals *(in vivo)*			?	DL(-) SA(?)
Humans *(in vivo)*				

DL = dominant lethal mutations; SA = sperm abnormalities

References

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VINCRISTINE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

Treatment with vincristine, mainly in combination therapy, has been associated in case reports with the subsequent development of leukaemias[1]. [See also the summary of data on 'Certain combined chemotherapy for lymphomas (including MOPP)'.]

B. Evidence for carcinogenicity to animals (*inadequate*)

In limited studies in mice and rats, no evidence of carcinogenicity was found after intraperitoneal administration of vincristine[1].

C. Evidence for activity in short-term tests (*inadequate*)

Vincristine was not mutagenic to *Salmonella typhimurium*[1,2]. It was mutagenic to the mouse lymphoma line L5178Y, at high concentrations[3], although negative results were obtained using the same cell system *in vitro*, and in a host-mediated assay[4] and in Chinese hamster V79 cells *in vitro*[5]. No chromosomal aberration was seen in CHO cells or in Syrian hamster fibroblasts exposed to vincristine *in vitro*[1]. Vincristine increased the incidence of micronuclei in bone-marrow cells of Chinese hamsters[6] and produced a dose-dependent increase in micronuclei of bone-marrow cells of mice[1]; but it is a well-known spindle inhibitor, and these abnormalities have been considered to be related to spindle effects and not to mutagenicity. Although small increases in sister chromatid exchange frequency were reported in a hamster cell line and in human lymphocytes cultured *in vitro*[1], more extensive studies using human lymphocytes showed that vincristine does not affect the yield of sister chromatid exchanges[7]. It did not induce morphological transformations in C3H/10T$\frac{1}{2}$ clone 8 cells, even when added at highly toxic doses[1]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		-		
Fungi/Green plants				
Insects				
Mammalian cells *(in vitro)*		?	?	T(-)
Mammals *(in vivo)*			?	
Humans *(in vivo)*				

T = cell transformation

References

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VINYL CHLORIDE (Group 1)*

A. Evidence for carcinogenicity to humans (*sufficient*)

Vinyl chloride causes angiosarcomas of the liver; it has also been associated with tumours of the brain and lung and of the haematopoietic and lymphatic systems in humans. Reports of increased incidences of tumours of the digestive system, urinary tract and breast (in women) are inadequate to evaluate the carcinogenicity of vinyl chloride for these sites[1].

* Categorized as Group 1 by the previous Working Group, and data on humans and on animals not reevaluated by the present Group.

B. Evidence for carcinogenicity to animals (*sufficient*)

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

C. Evidence for activity in short-term tests (*sufficient*)

Vinyl chloride induced DNA damage in prokaryotes and in mammalian cells *in vitro*[2]. It was mutagenic to *Salmonella typhimurium* in the absence of an exogenous metabolic activation system[3] and to *Escherichia coli*, *Schizosaccharomyces pombe*[3] and *Saccharomyces cerevisiae*[4] but not to *Neurospora crassa*[3]. It was mutagenic to *Drosophila melanogaster*, inducing sex-linked recessive lethal mutations[3] and to hamster cells *in vitro*[5]. It induced chromosomal aberrations and sister chromatid exchanges in Chinese hamsters exposed *in vivo*[6]. It did not induce dominant lethal[3] or somatic mutations in mice[7]. Vinyl chloride alkylated the liver DNA of rats treated *in vivo*[8]. Chromosomal aberrations and sister chromatid exchanges were induced in workers exposed to vinyl chloride[3,10-12]. Most such data were obtained when exposure was to levels of 25 ppm. In follow-up studies, in which workers were exposed to levels that had been reduced to 15 ppm and lower, no aberration or sister chromatid exchange was reported[12,13]. Sister chromatid exchange incidence dropped to a normal level shortly after termination of exposure to higher levels; however, the incidence of chromosomal aberrations returned to normal only after two years[10]. [Thus, although sister chromatid exchanges were not observed in some studies, sampling may have occurred after the level returned to normal.]

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes	+	+		
Fungi/Green plants		+		
Insects		+		
Mammalian cells *(in vitro)*	+	+		
Mammals *(in vivo)*	+	-	+	DL(-)
Humans *(in vivo)*			+	

DL = dominant lethal mutations

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VINYLIDENE CHLORIDE (Group 3)

A. Evidence for carcinogenicity to humans (*inadequate*)

In one epidemiological study of 138 workers exposed to vinylidene chloride (with no concomitant exposure to vinyl chloride), no excess of cancer was found, but follow-up was incomplete and nearly 40% of the workers had less than 15 years' latency since first exposure[1]. A study of 447 German and 182 foreign workers exposed to vinyl chloride,

reported seven deaths from cancer, which was not in excess of expected values. Two cases of bronchial carcinoma were found in workers both of whom were 37 years old, whereas 0.07 were expected for persons aged 35-39 years. [The Working Group noted that this study has severe methodological weaknesses, e.g., no allowance for latency, no information on smoking habits, 76% loss from follow-up for the guest workers, young age structure of the cohort, and a reference category that can be considered valid only for the German workers.]

B. Evidence for carcinogenicity to animals (*limited*)

Vinylidene chloride was tested by oral administration to female rats and mice and to their offspring. In rats, liver and meningeal tumours, and in mice, liver and gastric tumours, were seen more frequently in treated than in control animals, although the differences were not statistically significant[3]. It was also tested in one experiment by inhalation in mice, rats and hamsters, inducing adenocarcinomas of the kidney in male mice and an increased incidence of mammary fibroadenomas and carcinomas in rats (although with no dose-response relationship). In hamsters exposed for 52 weeks, no tumour had occurred by 74 weeks, but the study was still in progress at the time of reporting[1].

C. Evidence for activity in short-term tests (*sufficient*)

Vinylidene chloride was mutagenic to bacteria in the presence of an exogenous metabolic activation system[1] and to yeast[1,4], but it was not mutagenic to V79 Chinese hamster cells *in vitro*[5]. It alkylated DNA in mammalian cells *in vitro*[6], and, at tumorigenic doses in mice, it produced minimal amounts of DNA alkylation and repair but massive amounts of tissue damage[6]. It did not induce dominant lethal mutations in mice[4]. No data on humans were available.

	DNA damage	Mutation	Chromosomal anomalies	Other
Prokaryotes		+		
Fungi/Green plants		+		
Insects				
Mammalian cells *(in vitro)*	+	-		
Mammals *(in vivo)*				DL(-)
Humans *(in vivo)*				

DL = dominant lethal mutations

References

[1] *IARC Monographs*, *19*, 439-459, 1979

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[3] Ponomarkov, V. & Tomatis, L. (1980) Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. *Oncology, 37*, 136-141

[4] Bronzetti, G., Bauer, C., Corsi, C., Leporini, C., Nieri, R. & del Carratore, R. (1981) Genetic activity of vinylidene chloride in yeast. *Mutat. Res., 89*, 179-185

[5] Drevon, C. & Kuroki, T. (1979) Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. *Mutat. Res., 67*, 173-182

[6] Reitz, R.H., Watanabe, P.G., McKenna, M.J., Quast, J.F. & Gehring, P.J. (1980) Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine. *Toxicol. appl. Pharmacol., 52*, 357-370

APPENDIX 1

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines N-Nitroso Compounds, and Natural Products	Volume 1, 1972; 184 pages (out of print)
Some Inorganic and Organometallic Compounds	Volume 2, 1973; 181 pages
Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds	Volume 3, 1973; 271 pages
Some Aromatic Amines, Hydrazine and Related Substances, N-Nitroso Compounds and Miscellaneous Alkylating Agents	Volume 4, 1974; 286 pages
Some Organochlorine Pesticides	Volume 5, 1974; 241 pages
Sex Hormones	Volume 6, 1974; 243 pages
Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals	Volume 7, 1974; 326 pages
Some Aromatic Azo Compounds	Volume 8, 1975; 357 pages
Some Aziridines, N-, S- and O-Mustards and Selenium	Volume 9, 1975; 268 pages
Some Naturally Occurring Substances	Volume 10, 1976; 353 pages
Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics	Volume 11, 1976; 306 pages
Some Carbamates, Thiocarbamates and Carbazides	Volume 12, 1976; 282 pages
Some Miscellaneous Pharmaceutical Substances	Volume 13, 1977; 255 pages
Asbestos	Volume 14, 1977; 106 pages
Some Fumigants, the Herbicides 2,4-D and 2,4,5-T Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals	Volume 15, 1977; 254 pages

Some Aromatic Amines and Related Nitro Compounds — Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals	Volume 16, 1978; 400 pages
Some N-Nitroso Compounds	Volume 17, 1978; 365 pages
Polychlorinated Biphenyls and Polybrominated Biphenyls	Volume 18, 1978; 140 pages
Some Monomers, Plastics and Synthetic Elastomers, and Acrolein	Volume 19, 1979; 513 pages
Some Halogenated Hydrocarbons	Volume 20, 1979; 609 pages
Chemicals and Industrial Processes Associated with Cancer in Humans	Supplement 1, 1979; 71 pages
Sex Hormones (II)	Volume 21, 1979; 583 pages
Some Non-nutritive Sweetening Agents	Volume 22, 1980; 208 pages
Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal	Supplement 2, 1980; 426 pages
Some Metals and Metallic Compounds	Volume 23, 1980; 438 pages
Some Pharmaceutical Drugs	Volume 24, 1980; 337 pages
Wood, Leather and Some Associated Industries	Volume 25, 1980; 412 pages
Some Anticancer and Immunosuppressive Drugs	Volume 26, 1981; 411 pages
Some Aromatic Amines, Anthraquinones, Nitroso Compounds and Inorganic Fluorides Used in Drinking-Water and Dental Preparations	Volume 27, 1982; 341 pages
The Rubber Industry	Volume 28, 1982; 486 pages
Some Industrial Chemicals and Dyestuffs	Volume 29, 1982; 416 pages

APPENDIX 2

CHEMICALS EVALUATED IN *IARC MONOGRAPHS*, VOLUMES 1-29, FOR WHICH THERE IS CONSIDERED TO BE *SUFFICIENT EVIDENCE* OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS[a]

Acrylonitrile
Adriamycin
Aflatoxins
ortho-Aminoazotoluene
4-Aminobiphenyl
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole
Amitrole
ortho-Anisidine
Aramite[R]
Asbestos
Azaserine
Benz[*a*]anthracene
Benzidine
Benzo[*b*]fluoranthene
Benzo[a]pyrene
Benzotrichloride
Benzyl violet 4B
Beryllium metal
Beryllium oxide
Beryllium sulphate
Bischloroethyl nitrosourea (BCNU)
Bis(chloromethyl)ether and technical-grade chloromethyl methyl ether
β-Butyrolactone
Cadmium chloride
Cadmium oxide
Cadmium sulphate
Cadmium sulphide
Calcium chromate
Carbon tetrachloride
Chlorambucil
Chlordecone (Kepone)
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)
Chloroform
4-Chloro-*ortho*-phenylenediamine
Citrus Red No. 2
para-Cresidine
Cycasin
Cyclophosphamide
Dacarbazine

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[a] Chemicals for which data on cancer in humans are available are shown in italics

Daunomycin
DDT
N,N′-Diacetylbenzidine
2,4-Diaminoanisole sulphate
4,4′-Diaminodiphenyl ether
2,4-Diaminotoluene
Dibenz[*a,h*]acridine
Dibenz[*a,j*]acridine
Dibenz[*a,h*]anthracene
7*H*-Dibenzo[*c,g*]carbazole
Dibenzo[*a,e*]pyrene
Dibenzo[*a,h*]pyrene
Dibenzo[*a,i*]pyrene
1,2-Dibromo-3-chloropropane
3,3′-Dichlorobenzidine
3,3′-Dichloro-4,4′-diaminodiphenyl ether
1,2-Dichloroethane
Diepoxybutane
Di(2-ethylhexyl)phthalate
1,2-Diethylhydrazine
Diethylstilboestrol
Diethyl sulphate
Dihydrosafrole
*3,3′-Dimethoxybenzidine (*ortho-*Dianisidine)*
para-Dimethylaminoazobenzene
trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole
3,3′-Dimethylbenzidine (*ortho*-Tolidine)
Dimethylcarbamoyl chloride
1,1-Dimethylhydrazine
1,2-Dimethylhydrazine
Dimethyl sulphate
1,4-Dioxane
Direct Black 38 (technical-grade)
Direct Blue 6 (technical-grade)
Epichlorohydrin
Ethinyloestradiol
Ethylene dibromide
Ethylene thiourea
Ethyl methanesulphonate
Formaldehyde gas
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole
Glycidaldehyde
Hexachlorobenzene
Hexamethylphosphoramide
Hydrazine
Indeno[1,2-*cd*]pyrene
Iron dextran complex
Isosafrole
Lasiocarpine
Lead acetate
Lead chromate
Lead phosphate

Lead subacetate
Melphalan
Merphalan
Mestranol
Methoxsalen with ultra-violet A therapy (PUVA)
2-Methylaziridine
Methylazoxymethanol and its acetate
4,4′-Methylene bis(2-chloroaniline)
4,4′-Methylene bis(2-methylaniline)
Methyl iodide
Methyl methanesulphonate
2-Methyl-1-nitroanthraquinone (of uncertain purity)
N-Methyl-*N*′-nitro-*N*-nitrosoguanidine
Methylthiouracil
Metronidazole
Mirex
Mitomycin C
Monocrotaline
5-(Morpholinomethyl)-3[(5-nitrofurfurylidene)amino]-2-oxazolidinone
Nafenopin
2-Naphthylamine
Nickel subsulphide
Niridazole
5-Nitroacenaphthene
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide
Nitrogen mustard
Nitrogen mustard *N*-oxide
2-Nitropropane
N-Nitrosodi-*n*-butylamine
N-Nitrosodiethanolamine
N-Nitrosodiethylamine
N-Nitrosodimethylamine
N-Nitrosodi-*n*-propylamine
N-Nitroso-*N*-ethylurea
N-Nitrosomethylethylamine
N-Nitroso-*N*-methylurea
N-Nitroso-*N*-methylurethane
N-Nitrosomethylvinylamine
N-Nitrosomorpholine
N′-Nitrosonornicotine
N-Nitrosopiperidine
N-Nitrosopyrrolidine
N-Nitrososarcosine
Norethisterone
*Oestradiol-17*β
Oestrone
Oil orange SS
Panfuran S (Dihydroxymethylfuratrizine)
Phenacetin
Phenazopyridine
Phenoxybenzamine and its hydrochloride

Polychlorinated biphenyls
Ponceau MX
Ponceau 3R
Procarbazine
Progesterone
1,3-Propane sultone
β-Propiolactone
Propylthiouracil
Safrole
Sintered calcium chromate
Sintered chromium trioxide
Sodium saccharin
Soots, tars and oils
Sterigmatocystin
Streptozotocin
Strontium chromate
Testosterone and its esters
Tetrachlorodibenzo-para-*dioxin (TCDD)*
Thioacetamide
4,4′-Thiodianiline
Thiourea
ortho-*Toluidine*
Toxaphene (polychlorinated camphenes)
2,4,6-Trichlorophenol
Tris(1-aziridinyl)phosphine sulphate (Thiotepa)
Tris(2,3-dibromopropyl)phosphate
Trypan blue (commercial grade)
Uracil mustard
Urethane
Vinyl chloride
Zinc beryllium silicate
Zinc chromate

Summary table of results from short-term tests

	DNA damage					Mutation						Chromosomal anomalies					Other				
	Prokaryotes	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Prokaryotes	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Humans *(in vivo)*	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Humans *(in vivo)*	Petite mutation	Domin.lethal (insect)	Cell transformation	Domin.lethal (mamm.)	Sperm anomalies
Acrylonitrile				+		+								+	?	-			+		
Actinomycin D						-	+	+						+							
Adriamycin	+					+			+					+	+	+			+		
Aflatoxins	+			+		+	+	+	+					+	+				+		
Aldrin	-			-		-	-	-						?	-						
4-Aminobiphenyl				+		+	+														
Amitrole	-					-	+	-				+		-					+		
Anaesthetics, volatile						-	+	?				?		-	-					-	
Halothane																					
Cyclopropane						-															
Methoxyflurane						-								-							
Isoflurane						-								-							
Nitrous oxide						-	+	+	-					-							
Enflurane						-			-					-							
Fluroxene						+								+							
Divinyl ether						+								+							
Diethyl ether								-						-							
Analgesic mixtures containing phenacetin																					
Phenacetin						+		-						+	?						
Aniline	-			-		?	-	-	+					-	-				-		
Arsenic and certain arsenic compounds	+					-			-				+	+	?	+				-	
Asbestos						-			-					?							
Auramine (technical-grade)	+			+		?	+							+	-				+		
Azathioprine						+	+	+						?	+	-		+		?	+

Benzene				-	-	-	-	-				+	+	+			-				
Benzidine	+		?	+	+	?	+			+		+	?				+		?		
Benzidine-based dyes				+																	
Beryllium and certain beryllium compounds			-	-			?					?					+				
N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)				+		+															
Bischloroethyl nitrosourea (BCNU)	+			+		+	+						+								
Bis(chloromethyl)ether	+			+																	
Technical-grade chloromethyl methyl ether				+																	
Bleomycins	+		+	-	+	+						+	+	+			+				
1,4-Butanediol dimethanesulphonate (Myleran)	+			+	+	+	+			+		+	+	+			+	+			
Cadmium and certain cadmium compounds	?			?	?	-						+		?			+	-	-		
Carbon tetrachloride			-	-	?							-									
Chlorambucil			+	+	+							+	+	?							
Chloramphenicol	-			-								?	-					-			
Chlordane/Heptachlor																					
Chlordane	-		-	-			-											-			
Heptachlor	-		-	-		-	-					?						-			
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)	+			+			+					,		+							
Chlorinated toluenes																					
Benzyl chloride	+		+	+	+	?	+					+	-				+	-			
Benzoyl chloride	-			-																	
Benzal chloride	+			+																	
Benzotrichloride	+			+																	
Chloroform	-			-	-	-						-	-				?				
Chloroprene				+		+	-						?	+			+	?			
Chromium and certain chromium compounds																					
Hexavalent chromium	+			+	+		+	+				+	+	+			+	+			
Trivalent chromium				?	?		?					?					?				
Cisplatin	+			+		+	+					+	+				+	-			
Clofibrate				-																	

	DNA damage					Mutation						Chromosomal anomalies					Other				
	Prokaryotes	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Prokaryotes	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Humans *(in vivo)*	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Humans *(in vivo)*	Petite mutation	Domin.lethal (insect)	Cell transformation	Domin.lethal (mamm.)	Sperm anomalies
Cyclamates						-								+	-				-	-	-
Cyclophosphamide	+			+		+	+	+	+	+		+		+	+	+		-	+	+	
2,4-D and esters				?		-	?	?	+			?		?	?					-	
Dacarbazine						?		+	+												
Dapsone						-															
DDT	-			-		-	-	-	-	-				-				-		-	
ortho-Dichlorobenzene						-	?														
para-Dichlorobenzene						-	?					+									
3,3′-Dichlorobenzidine	+			+		+													+		
Dichloromethane				-		+		+	-					-	-						
Dieldrin	-			-		-	-	-	?					?	?				-	-	
Diethyl sulphate	+			+		+	+	+	+	+					?					+	
3,3′-Dimethoxybenzidine (*ortho*-Dianisidine)	-			+		+													+		
Dimethylcarbamoyl chloride	+	+		-		+	+	-	+			+		+	+	-			+		
Dimethyl sulphate	+			+	+	+	+	+	+			+		+						-	
1,4-Dioxane				-	-	-															
Epichlorohydrin	+	+		+		+	+	+	+			+		+	+	?			+	-	+
Ethylene dibromide	+			+	+	+	+	+	+					+							
Ethylene oxide				+	+	+	+	+	+	+			+		+	+				+	
Ethylene thiourea	?	?		?	-	?	?	-	-			+		-	-				+	-	
5-Fluorouracil	-					-				?				?	+	?	+		+	-	
Formaldehyde (gas)	+	+		+		+	+	+						+	-				?	?	
Hexachlorocyclohexane	-			-		-	-	-				?		?	?						
Hydralazine	+			+	-	+								+	+						
Hydrazine	+	+		?		+	+		-			+		?	-				+		
Iron dextran complex														-							

Isonicotinic acid hydrazide	+			-	?	+	+			+					-	-				-		
Lead and certain lead compounds	?					-	?						?		?	?	?			+	-	-
Magenta	+			+	-				?											-		
Melphalan	+					+			+	+					+	+	+					
6-Mercaptopurine	+					+			+						+	+	+			-	?	
Methotrexate	-					?	+		+						+	+	+			+	+	
Methoxsalen with ultra-violet A therapy (PUVA)	+			+		+	+		+		+				+	+	?			+		
Metronidazole	+					+	+	-							-	?	-		-			
Mustard gas	+			+	+		+	+	+						+	+					+	
1-Naphthylamine	+	+		+		+	+	-	+						+	-				-	-	
2-Naphthylamine	+	+		+		+	+	+	+						+	?				+	-	
Nickel and certain nickel compounds	-					-			?				?		?	-	-			+	-	
Nitrogen mustard	+	+		+	+	+	+	+	+				+		+	+	+				+	+
Oestrogens and progestins:																						
Combined oral contraceptives																	-					
Conjugated oestrogens						-									-							
						-									?							
Oestrogens: Dienoestrol																						
Diethylstilboestrol				-		-	?		-				?		?	?				+	+	+
Ethinyloestradiol						-		-		-					-		-					
Mestranol								-		-					-		-				+	
Oestradiol-17β									-						-	-						
Oestrone																+						
Chlormadinone acetate															-							
Progestins: Dimethisterone															-							
Ethynodiol diacetate																-	-					
Lynoestrenol																	-				+	
Medroxyprogesterone acetate																-	-					
Megestrol acetate															-		-					
Norethisterone															-	-	-				?	
Norethynodrel						-			-	-							+					
Progesterone															?	+						
Pentachlorophenol						-	+	-		?							-					

	DNA damage					Mutation						Chromosomal anomalies					Other				
	Prokaryotes	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Prokaryotes	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Humans *(in vivo)*	Fungi and plants	Insects	Mammalian cells *(in vitro)*	Mammals *(in vivo)*	Humans *(in vivo)*	Petite mutation	Domin lethal (insect)	Cell transformation	Domin lethal (mamm.)	Sperm anomalies
Phenelzine	+				-	+															
Phenobarbital				-		-		?											-		
Phenylbutazone						-						-		?	-	?				-	
N-Phenyl-2-naphthylamine						-													-		
Phenytoin														-	-	-				-	
Polychlorinated biphenyls				-		?		-						-	-					-	
Prednisone						-									-	-					
Procarbazine	+					+	+	+	+	+			+		+	+		+		+	+
Reserpine	-			-		-								-	-						
Saccharin	-				-	-	+	-	?	?				?	-				-	?	-
Soots, tars and oils and benzo[*a*]pyrene																					
Benzo[a]pyrene	+			+	+	+	+	+	+	+				+	+				+		+
Styrene and styrene oxide																					
Styrene				-		+	?	+	-			+		+	?	+					
Styrene oxide				+		+	+	+	+			+		+	?					?	
Sulfamethoxazole														-		-					
2,4,5-T and esters						-	?	+					-	?	?	-				-	
Tetrachlorodibenzo-*para*-dioxin (TCDD)						-	+								?	-				-	
Tetrachloroethylene					-	-	+								-						
ortho-Toluidine	+	+		+		?	?					+		+	-				+		
Treosulphan												+									
Trichloroethylene				?	?	?	+			?										-	
Tris(aziridinyl)-*para*-benzoquinone (Triaziquone)	+					+	+	+	+			+	+	+	+					+	

Tris(1-aziridinyl)phosphine sulphide (Thiotepa)					+			+	+					+	+				+	+	+	
Underground haematite mining *Haematite*																			-			
Uracil mustard	+			+	+	+			+				+									
Vinblastine					-	-								?	?					-	?	
Vincristine					-				?					?	?				-			
Vinyl chloride	+			+	+	+		+	+	-					+	+				-		
Vinylidene chloride				+	+	+			-											-		

CUMULATIVE INDEX TO IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Numbers in bold indicate volume, and other numbers 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 carcinogenicity were not available.

Composition, impression et façonnage
Groupe MCP-Mame
Dépôt légal : janvier 1985