WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

# IARC MONOGRAPHS

ON THE

# EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

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

**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

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## 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)

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* 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[a])
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

[a] The compound(s) responsible for the carcinogenic effect in humans cannot be specified.
[b] Procarbazine, nitrogen mustard, vinyldine 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 nitrosoureа (BCNU)
Cadmium and cadmium compounds
Carbon tetrachloride
Chloramphenicol
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosoureа (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 thioureа
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)
Urasil mustard

*Group 3*: The remaining 84 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 nitrosoureas (BCNU) | inadequate | sufficient | sufficient | 2B |
| Bis(chloromethyl)ether and technical-grade chloromethylmethyl ether | sufficient | sufficient | limited | 1 |

* In *IARC Monographs* 1-39, 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 |
| Decarbazine | 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 | X |
| 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 | - | - | 1 |
| 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 | 1 |
| Vinylidene chloride | inadequate | limited | sufficient | 3 |

Fourth Annual Report on

# Carcinogens

Summary
1985

NTP 85-002

U.S DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

# Contents



*Agents in italics are new to this Report.

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**Substances or groups of substances that may reasonably be anticipated to be carcinogens:**





Page

# EXECUTIVE SUMMARY

The *Fourth Annual Report on Carcinogens*, prepared by the National Toxicology Program (NTP), U.S. Public Health Service, is issued by the Secretary of the Department of Health and Human Services (DHHS), pursuant to Public Law 95-622 of November 9, 1978.* This law requires the Secretary to publish an annual report which contains "a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed; . . ." Annual reports should also provide available information on the nature of exposures, the estimated number of persons potentially exposed, and the extent to which the implementation of Federal regulations decreases the risk to public health from exposure to these substances.

For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

Substances in the above categories, for which potential exposure of persons residing in the United States has been demonstrated, are included in the Report. Also included are some substances which have been banned, or the use of which has been restricted, because people previously exposed are potentially at risk, or because some of these substances still remain in the environment. The Fourth Annual Report does not contain all known or reasonably anticipated carcinogens. Additional substances with identified carcinogenic properties as defined above will be included in the subsequent Annual Reports.

Several problems are encountered in developing the information required for the Annual Reports on Carcinogens. Estimating the number of people potentially exposed to a substance and identifying the nature, route, and intensity of this potential exposure are difficult tasks. It is often impossible to obtain accurate production volumes and use patterns for most chemicals. The information that is being collected by the U.S. Environmental Protection Agency under the Toxic Substances Control Act, at least that part which is public record, may assist in obtaining more accurate potential exposure estimates in the future. In addition, the upcoming National Occupational Exposure Survey** will provide new information on the extent and degree of potential exposures for different substances and manufacturing processes.

Perhaps the hardest task in preparing the Report is to evaluate the effectiveness of Federal regulations in decreasing the risk to public health. One

* Section 262, Paragraph (4).

** An update of the National Occupational Hazard Survey conducted from 1972 to 1974 by the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH).

reason is that virtually all Federal laws concerned with reducing risk have been enacted within the last 15 years. Thus, given the relatively long period between exposure to a carcinogen and the onset of disease, the extent to which the regulations implemented during these 15 years have reduced the risk remains unknown. Another reason is that reliable information on past exposures which could be used as a baseline for estimating future risk reduction is generally not available. Nonetheless, decreasing exposure should be considered as reducing carcinogenic risk even if the reduction cannot be quantified at present.

The Fourth Annual Report lists 148 agents. Included are the entries from the Third Annual Report and 31 additional substances or groups of substances. The new entries were chosen from those designated by the Agencies participating in the preparation of the Report,* from those tested within the National Toxicology Program and the National Cancer Institute Carcinogenesis Bioassay Program,** or from those evaluated by the International Agency for Research on Cancer (IARC), a component of the World Health Organization (WHO), located in Lyon, France.

Of the 148 entries, 24 substances or groups of substances and 5 occupational exposures (etiologic agent(s) unknown) associated with a technological process are listed as "known carcinogens"

**Substances**

- 4-Aminobiphenyl
- Analgesic mixtures containing phenacetin
- Arsenic and certain arsenic compounds
- Asbestos
- Azathioprine
- Benzene
- Benzidine
- N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)
- Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
- 1,4-Butanediol dimethylsulfonate (myleran)
- Certain combined chemotherapy for lymphomas
- Chlorambucil
- Chromium and certain chromium compounds
- Coke oven emissions
- Conjugated estrogens
- Cyclophosphamide
- Diethylstilbestrol
- Melphalan
- Methoxsalen with ultra-violet A therapy (PUVA)
- Mustard gas
- 2-Naphthylamine
- Nickel refining
- Thorium dioxide
- Vinyl chloride

**Occupational Exposures**

- Hematite underground mining
- Isopropyl alcohol manufacture (strong-acid process)
- Manufacture of auramine
- Rubber manufacture (certain occupations)
- Soots, tars, and mineral oils

One hundred nineteen substances or groups of substances are included because they "may reasonably be anticipated to be carcinogens." Nickel appears in both lists because occupational exposure associated with nickel refining is known to be carcinogenic although specific substances which may be responsible for the carcinogenesis in humans have not yet been identified; and elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

For each substance or group of substances or occupational exposure associated with a technological process, there is a summary description including a synopsis of the evidence that explains inclusion in this Report. This is followed by a collation of regulatory information received from the participating Agencies.

Among the 148 entries, two are natural substances which are not used or produced commercially: aflatoxins and cycasin. Two are food or cosmetic additives: saccharin and safrole. Safrole has been banned for most uses. The use of saccharin has been continued by Congressional mandate.

Thirteen pesticides are listed: amitrole; Aramite®; arsenical pesticides; 1,2-dibromo-3-chloropropane; hexachlorobenzene, Kepone®, lindane and other hexachlorocyclohexane isomers, mirex, nitrofen; sulfallate; toxaphene, 2,4,6-trichlorophenol; and DDT. Most of these substances have been banned or limited in use.

There are 31 therapeutic substances. Twelve of these are anticancer agents: adriamycin, bischloroethyl nitrosourea, 1,4-butanediol dimethylsulfonate (myleran), certain combined chemotherapy for lymphomas, chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), cyclophosphamide, dacarbazine, melphalan, nitrogen mustard, procarbazine, and tris(1-aziridinyl)phosphine sulfide. Six are hormonal: conjugated estrogens, diethylstilbestrol, estrogens (not conjugated:estradiol-17$\beta$, estrone, ethinylestradiol, mestranol), norethisterone, oxymetholone, and progesterone. The remaining 13 are used in other therapeutic applications: analgesic mixtures containing phenacetin, azathioprine, N,N-bis(2-chloroethyl)-2-naphthylamine, iron dextran complex, methoxsalen with ultra-violet A therapy (PUVA), metronidazole, phenacetin, phenazopyridine hydrochloride, phenytoin, propylthiouracil, reserpine, selenium sulfide, and streptozotocin.

Two of these other therapeutics are no longer produced or used in the United States: N,N-bis-(2-chloroethyl)-2-naphthylamine and streptozotocin. Five of the anticancer agents also are no longer produced but are imported into the U.S.: adriamycin, chlorambucil, cyclophosphamide, dacarbazine, and melphalan. Six of the anticancer agents are imported and produced in limited quantities by one U.S. manufacturer: bischloroethyl nitrosourea, 1, 4-butanediol dimethyl sulfonate, 1-(2-chloroethyl) 3-

* Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH), Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Institutes of Health/National Cancer Institute (NIH/NCI), National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS), National Institutes of Health/National Library of Medicine (NIH/NLM), and U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA)

** Now part of NTP/NIEHS

cyclohexyl-1-nitrosourea, nitrogen mustard, procarbazine, and tris (1-aziridinyl) phosphine sulfide.

The remaining 95 substances may be classified as various industrial chemicals and byproducts (33); dyes, dye intermediates, and pigments (20); combustion products (14); solvents (7); metals and metal compounds occurring in mining, extraction, and refining processes (6); analytical and research chemicals (6); and chemicals used for miscellaneous purposes (9).

The five occupational exposures (etiological agents(s) unknown) associated with a technological process known to be carcinogenic are those associated with hematite underground mining, isopropyl alcohol manufacture (strong-acid process), manufacture of auramine, rubber manufacture (certain occupations), and soots, tars and mineral oils.

Scientific knowledge and judgment play important roles in grading the available evidence of carcinogenicity as sufficient, limited, or inadequate. Similarly, in all but one category of substances, regulatory action is an interpretation by the regulators of their Congressional mandates. The only mandated exception is the deliberate addition of additives and colors to foods. The Delaney Clause in the Food Additives Amendment of 1958 to the Federal Food, Drug, and Cosmetic Act requires that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals; . . ."*

Corrections or suggestions, as well as any additional information that the reader may have should be sent to the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Summaries of this Report may be obtained from the Public Information Office, National Toxicology Program, B2-04, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Copies of the complete Report are available for a fee from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161. Request number PB 85-134633 should be indicated.

* So far only two substances have been banned on the basis of the Delaney Clause: Flectol H in 1967 and chloroanilne in 1969. According to the FDA, both substances were used to make adhesives for food packaging material.



# INTRODUCTION

Cancer is the second most common cause of death in the United States. One in every four Americans will suffer from cancer sometime during their lifetime; one in every five will die from cancer. In 1983, more than 440,000 Americans died of cancer.[1] In addition to the physical and emotional suffering caused by cancer, this disease may cost the Nation as much as $39 billion each year in lost production and income, medical expenses, and research resources. For these reasons, the American public is concerned about cancer and cancer hazards, especially about ways to prevent the occurrence or decrease the incidence of cancers.

Contrary to popular belief, cancer is not one but many diseases which may have different causes. Most scientists now consider that about one-third to two-thirds of all cancers are associated with the environment in which we live and work. In this context, the environment is understood as "anything that interacts with humans, including substances eaten, drunk, and smoked, natural and medical radiation, workplace exposures, drugs, aspects of sexual behavior, and substances in air, water, and soil."[2] Some cultural and behavioral patterns, apart from defined habits of smoking and alcohol consumption, may significantly influence the development of tumors in the gastrointestinal tract, breast, uterus, and prostate. These aspects of social environment, personal behavior, and habits are sometimes called "lifestyle." Although we rarely know the environmental factors and conditions which are responsible for the development of specific cancers, in some cases we are beginning to have some understanding. Most cancers that are associated with the environment should be avoidable, at least potentially.

Development of cancer also depends on "host factors." Host factors are attributes of human organisms associated with individual differences in the risk of developing a specified cancer. A host factor may be associated with reduced risk of a cancer, not only with increased risk.[3] Examples of host factors are immunological and endocrine functions, nutritional status, genetic constitution, age, and sex.[4]

As Americans have become more and more concerned about the environment and cancer, they have repeatedly asked the Federal Government to clarify what is known about cancer-causing substances. The public wants to know and should know which substances are regarded as cancer hazards in the work place and in the general environment and how well we are protected from exposure to these substances.

Section 262 of Public Law 95-622 of November 9, 1978* reflects the requests for this information. Paragraph (4) of this section stipulates that the "Secretary shall publish an annual report which contains—

> "(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;

* Community Mental Health Centers Act Amendments

"(B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;

"(C) a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency; and (ii) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance. . . ."

Annual Reports on Carcinogens are issued in response to these requirements. These Reports discuss individual substances, mixtures of chemicals or exposures associated with technological processes which are known to be carcinogens or which may reasonably be anticipated to be carcinogens; they contain information received from Federal agencies participating in the preparation of the Reports.

### Participants

Within the Department of Health and Human Services, the responsibility for preparing these Annual Reports has been given to the National Toxicology Program.* Other agencies participating in this effort are:

Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH)

Consumer Product Safety Commission (CPSC)

U.S. Environmental Protection Agency (EPA)

Food and Drug Administration (FDA)

National Institutes of Health/National Cancer Institute (NIH/NCI)

National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS)

National Institutes of Health/National Library of Medicine (NIH/NLM)

U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA)

Four of these agencies—CPSC, EPA, FDA, and OSHA—are responsible for regulating hazardous substances and limiting the exposure to and use of such substances.

### Identifying Carcinogens

For many years Government research agencies, industries, universities, and other research organizations have studied various substances to ascertain those which might cause cancer. Other Federal agencies have been developing information on possible exposure and potential hazards and making rules and regulations to control substances which have been identified as carcinogens.

The largest single national testing effort, the National Cancer Institute's Carcinogenesis Testing Program, has now become a part of NTP/NIEHS. The NCI Clearinghouse on Environmental Carcinogens, consisting of a panel of experts from governmental and nongovernmental institutions, was reviewing the NCI testing results, and an analysis of results of NCI carcinogenesis bioassays of 190 chemicals was published.[5] The Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors, augmented by an ad hoc panel of experts in chemical carcinogenesis, has replaced the NCI Clearinghouse as the body of nongovernment experts conducting peer reviews of the NTP carcinogenesis bioassay results.

Many of the substances, mixtures of chemicals, and occupational exposures associated with some technological processes listed in the *Fourth Annual Report on Carcinogens* have been chosen from the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" published by the International Agency for Research on Cancer (IARC) in Lyon, France.* Each monograph is the product of an individual working group of experts in chemical carcinogenesis and related fields. The experts evaluate the data for each substance included in a monograph. The evaluation is based on the published information available at the time the working group was convened. A joint IARC/WHO ad hoc working group met in October 1977 to review and revise the criteria for judging the adequacy of available data. The terms 'sufficient evidence' and 'limited evidence' of carcinogenicity used in these criteria refer only to the amount and adequacy of the available evidence and not to the potency of carcinogenic effect or the mechanisms involved. An updated version of these criteria is included in each IARC Monograph Volume. The IARC Monograph Supplement 4 contains reevaluations by an ad hoc working group of all chemicals, industrial processes and occupational exposures for which some data on carcinogenicity in humans are available either in the first 29 volumes of monographs or in other subsequent publications.[6] For the most part human data are discussed only for those in this Report that have been re-evaluated in IARC Monograph Supplement 4.

A direct comparison of the IARC evaluations[6] and the evaluation of NCI/NTP bioassay results[5] cannot be made because different criteria were used to assess the evidence, but these criteria can be related.[7] All such evaluations involve a component of personal judgment. In some cases the available evidence may be assessed differently depending on the criteria used and the composition of the group of experts. Thus according to an OTA correlative interpretation to their IARC equivalents, classes 1 and 2 in the NCI classification may be regarded as sufficient evidence animal carcinogens.[2,8]

Clause (i) in subparagraph (A)(4) of Section 262 requires "a list of all substances which are either known to be carcinogens or may reasonably be anticipated to be carcinogens." For the purpose of this Report, the two categories in the law—those substances known to be

* DHHS agencies participating in NTP are NIH/NCI; NIH/NIEHS, FDA/National Center for Toxicological Research (FDA/NCTR); and CDC/NIOSH.

* The IARC address is: 150, cours Albert Thomas, 69372 Lyon Cedex 2, France. WHO/IARC publications may be obtained from WHO Publications Centre USA, 49 Sheridan Avenue, Albany, New York 12210

...listed to be carcinogens—relate to the IARC criteria for the degree of evidence[8] as follows:

1. Known to be carcinogens:
   There is "sufficient evidence of carcinogenicity" from studies in humans "which indicates a causal relationship between the agent and human cancer."
2. Reasonably anticipated to be carcinogens:
   A. There is "limited evidence of carcinogenicity" from studies in humans, "which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded," or
   B. There is "sufficient evidence of carcinogenicity" from studies in experimental animals "which indicates that there is an increased incidence of malignant tumors: (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 tumor, or age at onset. Additional evidence may be provided by data concerning dose response effects, as well as information on mutagenicity or chemical structure."

Most of the substances contained in the Annual Report can be identified chemically. Some carcinogens occur naturally, some are produced when materials are burned, and others are present in raw materials, or in intermediate and final products of industries. In some cases only the exposure associated with a specific technological or manufacturing process, occupation or industry, or a therapeutic treatment can be related to an increased incidence of cancer in humans, but the substance(s) specifically responsible cannot be identified. Some examples of such technological processes are the underground mining of hematite and the strong-acid process for the manufacture of isopropyl alcohol.

The reader is reminded that the *Fourth Annual Report on Carcinogens* (and all previous editions) is a condensation of large amounts of data and conclusions made by bodies which peer review the data submitted as evidence about cancer and its relation to specific exposures. As such, the *Fourth Annual Report on Carcinogens* must be less detailed about the actual tests and their drawbacks. The original monographs on each listing are given in the footnoted references and the reader is advised to turn to these for specific arguments, both pro and con, which went into the listing decision.

### Human and Animal Studies

Some understanding of the human and animal studies used for identifying carcinogens is necessary to clarify what is meant by the words "known" and "reasonably anticipated." The strongest evidence for a relationship between exposure to a suspected substance and cancer in humans comes from epidemiological studies. Although we have adequate epidemiological evidence only for a few carcinogens, we think the patterns seen in these studies show how other animal carcinogens might affect humans. Epidemiological investigations give the best information on cancer-causing agents, but such studies of groups of individuals do have shortcomings. They may require observations over a long time because the latent period between initial exposure and cancer occurrence may be up to 20-30 years. Intentional, long term exposures of human groups are, of course, unacceptable. As an alternative, qualified scientists make educated predictions about the effects in humans, based on the effects observed in studies with experimental animals.

Although test animals may respond differently from humans, experience has shown that most known human carcinogens also cause cancer in experimental animals if adequately tested.* This finding is understandable since cancer begins in individual cells and all mammalian cells are comparable in structure and function. The basic premise of experimental carcinogenesis research is that substances which produce cancer in rodents and other experimental animals effect human cells in a similar way.

Relatively large doses of chemicals are used in animal studies to compensate for the small number of experimental animals exposed as compared to the size of human populations and also to optimize the potential response. Animal tests are costly, take years to complete, and are often difficult to interpret in terms of human cancer risk. They are, nevertheless, the best testing tool we have for detecting potential hazards.[9,11] Animal tests do not prove beyond doubt that a substance will or will not cause cancer in humans. Even "sufficient evidence" of carcinogenicity in experimental animals may prove not to be definitive. But if we are to prevent cancer, we cannot wait 20 to 30 years to obtain definitive evidence of harm to human health. Therefore, substances which show "sufficient evidence" of cancer causation in experimental animals are considered for practical purposes as reasonably anticipated human carcinogens.

### Inclusion of Substances

The Fourth Annual Report contains substances, groups of substances and exposures associated with technological processes which were listed in the Third Annual Report. Where necessary, the information has been updated. The Fourth Annual Report presents information on 31 additional substances. Each has been chosen either from substances tested by the NCI Carcinogenesis Testing Program or the National Toxicology Program (NTP), from designations of the participating agencies, or from substances evaluated by the IARC working groups. Other substances from the same sources will be added to subsequent Annual Reports.

The Summary of the Fourth Annual Report lists all the substances and technological processes included. The list is divided into two subsets. One contains substances, groups of substances, or technological processes known to be

* The evidence for carcinogenicity in experimental animals of arsenic compounds should now be regarded as limited, and the evidence for benzene is at present limited.† More recent data would make benzene a sufficient evidence animal carcinogen (see benzene, p. 34). Both of these compounds are known sufficient evidence human carcinogens.

carcinogens (29 entries). The other list of 119 entries includes substances or groups of substances which may reasonably be anticipated to be carcinogenic. Nickel appears in both sublists because the nickel refining process is known to be carcinogenic, whereas elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

A substance not listed in this Annual Report may still be a known carcinogen or a reasonably anticipated carcinogen. More substances than those included may potentially present a carcinogenic risk to persons living in the United States. These substances will be incorporated into subsequent Annual Reports as resources permit. Some chemicals will be included as a result of testing performed by industry in response to EPA's requests under the Toxic Substances Control Act. The National Toxicology Program will also provide new information for these reports as further test results become available.

Ionizing radiation, ultraviolet radiation (including sunlight), tobacco, alcoholic beverages, and some viruses are known or suspected to be carcinogens. They have not been included in this Report (unless acting in conjunction with a chemical) because ionizing radiation is discussed thoroughly in a General Accounting Office report[9] and a recent Surgeon General's report[8] reviews the overwhelming relationship between tobacco and cancer. Several publications issued by the National Cancer Institute[10] explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer.

Certain manufacturing processes have also been considered by the International Agency for Research on Cancer (IARC) and have been classified by this Agency as sources of exposure which are associated with increased incidences of cancer in workers in these settings. Among these are Boot and Shoe Manufacture and Repair, and Furniture Manufacture. The IARC reports dealing with these processes are given in the references at the end of this Introduction,[11] and the interested reader is referred to these documents for details. These processes were believed by IARC to constitute exposures which caused cancer in some humans and in some settings.[11] The National Toxicology Program does not disagree with these judgments. However, these processes are not listed separately in this Report, since neither the specific causes of the cancers nor the specific steps in the processes have been identified. Further, IARC has recognized that these two manufacturing processes vary significantly from one country to another, and that the likelihood is great of variation in exposures to whatever causes the cancers that are seen. These manufacturing processes have also changed significantly in several countries over the last few years, particularly with regard to the mix of chemicals, etc. (used in the various steps of the process) which could be the putative carcinogens.[11]

**Estimating Exposure**

According to clause (ii) of subparagraph (4)(A), this Report is required to include those substances "to which a significant number of people residing in the United States are exposed." Substances to which only a few people are exposed are not included for the most part. Yet some substances which have been banned or restricted in use are contained in the Report (e.g., safrole, arsenical pesticides, mirex) either because people who were previously exposed remain potentially at risk, or because these substances are still present in the environment.

Subparagraph (4)(B) requires that the Annual Reports provide "information concerning the nature of such exposure and the estimated number of persons exposed to such substances." The determination of the number of people potentially exposed and the route, intensity, and duration of such exposure for each substance remains a formidable task. This Report attempts to respond to these questions, and wherever adequate answers could be obtained, they are included in Sections IIIB and IIIC. Exposure to carcinogens can occur anywhere. Some carcinogens have always been present in the environment, and their amount varies, depending on geographical location and other environmental conditions. Every year human activities may add more carcinogens to the ambient air, water, food, soil, and occupational environment. Although scientists attempt to estimate the amount of carcinogens present in and added to the environment, there is no reliable way to predict who is exposed to what carcinogen and when exposure occurs. Also, since human populations are always exposed to many chemicals at the same time, this may modify the effects of a specific exposure either by multiplying (synergism) or reducing its action (antagonism).

If exposure is linked to a specific habit such as smoking, a specific use such as medical diagnosis or treatment, or a restricted environment such as the work place, our ability to estimate exposure improves, and in some cases the size of population segments involved can be estimated. Production and use data may also help estimate possible exposure, but this information may not be publicly available for many substances, and where it is, it may be outdated or even contradictory.

The National Occupational Hazard Survey (NOHS), conducted by CDC/NIOSH from 1972 to 1974, gave information on the number of workers potentially exposed and on some broader aspects of potential occupational exposure. The forthcoming National Occupational Exposure Survey (a repeat of NOHS) should yield valuable information with respect to more recent possible exposures. Subsequent Annual Reports on Carcinogens will explore this and other available data bases, and their strengths and limitations.

**Regulatory Status**

Subparagraph (4)(C) of Section 262 also requires "a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency." The Fourth Annual Report responds to this requirement by appending to the description of each substance a summary of Federal regulations as submitted by the participating agencies. Some of these standards and regulations have been enacted for reasons other than the carcinogenicity of the substance, for instance, to prevent other adverse health effects or to improve the quality of the environment or food. Solid or liquid wastes or wastes discharged into the air may contain carcinogens, yet these may

be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. But if these regulations reduce exposure to carcinogens, then the cancer risk posed by such substances will also decrease.

### Estimating Risk Reduction

Clause (ii) in subparagraph (4)(C) requires a statement identifying "for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decrease the risk to public health from exposure to the substance;". This requires quantified information on the amount of protection from cancer the public receives from established Federal standards.

Estimating the amount of health protection is perhaps the most difficult task in preparing the Annual Reports. One reason is that most Federal laws concerned with reducing cancer risk have been enacted within the last 15 years. Given the long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate how much Federal standards and other regulations have decreased the human cancer risk. Another reason is that information on past exposure levels, which could serve as a baseline for estimating future risk reduction, often is not available or accurate.

The risk — the probability of developing cancer — depends on the intensity, route, and duration of exposure to a carcinogen. Individuals may respond differently to similar exposures, depending on host factors such as age, sex, nutritional status, overall health, and inherited characteristics. Only in a few instances, where studies of long-term human exposures and cancer incidence in restricted environments are available, can risk be estimated with confidence.

The regulation of asbestos in the work place provides a good example. In 1969, under the Walsh-Healey Act, which then regulated only the firms with Government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter ($cm^3$) of air. Under the Occupational Safety and Health Act, this standard was reduced to 5 fibers/$cm^3$ in 1972 and to 2 fibers/$cm^3$ in 1976. On April 17, 1980, a joint NIOSH-OSHA Working Group recommended the elimination of all nonessential uses of asbestos and the implementation of a public health program to reduce human exposures. On April 10, 1984, OSHA proposed a rule lowering the permissible exposure to 0.2 or 0.5 fibers/$cm^3$ (5 micrometers in length) and requiring other provisions for employee protection. The high risk in workers exposed prior to 1969 is well known. The actual data on exposure levels in the '40s, '50s, and '60s are fragmentary, although exposure levels were undoubtedly unacceptably high by today's standards. Mesothelioma (primarily an asbestos-induced cancer) and lung and other cancers, the incidence of which is increased by exposure to asbestos, generally take 20-40 years or more to develop and become apparent. For these reasons, we will not know until early in the next century to what extent the series of exposure reductions in the '70s and '80s have reduced the cancer risk in persons exposed to asbestos.

One possible way to provide quantitative estimates of risk reduction might be to assume that the cancer risk is directly proportional to exposure. This approach also supposes that data on past and present exposure levels are available, or that conditions in all work places are in compliance with regulations. However, information supporting these assumptions is only rarely obtainable. Nevertheless, it is reasonable and prudent to accept that the reduction of exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer.

This is the basis of current regulatory policies which aim to lower human exposure to cancer-causing substances and thereby improve public health. For a more detailed discussion of the issues involved, see the previously cited report to Congress on the assessment of technologies for determining cancer risks from the environment.[8]

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# 2-ACETYLAMINO-FLUORENE

## CARCINOGENICITY

Incorporation of this compound into the feed caused increased incidences of malignant tumors in a variety of organs in the rat.[1] Long-term studies in which mice were given 2-acetyl-aminofluorene (AAF) in the diet showed increased incidences of liver and urinary bladder cancers.[2]

## PROPERTIES

AAF occurs in the form of crystalline needles. It is insoluble in water.

## USE

AAF is used as a positive control by toxicologists to study the carcinogenicity and mutagenicity of aromatic amines. AAF was intended for use as a pesticide, but was never marketed because it was carcinogenic in experimental animals.

## PRODUCTION

AAF is imported from Europe and distributed by several specialty chemical companies. A typical distributor stocks about 10 pounds of AAF and usually sells it in 1-, 5-, or 25-gram quantities. Total estimated U.S. usage is less than 20 pounds per year.

[1]Wilson, R.H., F. DeEds, and A.J. Cox. The Toxicity and Carcinogenic Activity of 2-Acetylaminofluorene. Cancer Res. Vol. 1, 1941, pp. 595-608.
[2]Stelle, J.A., and M.A. Mehlman, eds. Innovations in Cancer Risk Assessment (ED_ Study): Proceedings of a Symposium. J. Environ Pathol. and Toxicol. Vol. 3, 1980, pp. 1-248.

The 1979 TSCA Inventory reports one producer but no production volume.[3]

## EXPOSURE

Human exposure to AAF may occur through inhalation and skin absorption. People who face the greatest risk to AAF exposure are chemists, chemical stockroom workers, and biomedical researchers. Although neither NIOSH nor OSHA estimated the number of U.S. workers exposed to this animal carcinogen, it may be fewer than 1,000 in 200 laboratories that are possibly exposed.

## REGULATIONS

EPA regulates AAF under the Resource Conservation and Recovery Act and the Comprehensive Environmental Response Compensation and Liability Act. Because AAF is carcinogenic in animals, OSHA promulgated a standard for the chemical on February 11, 1974 designating protective clothing, hygiene procedures for workers, and special engineering requirements for the manufacture or processing of AAF.

# ACRYLONITRILE

## CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of acrylonitrile in experimental animals.[4] Acrylonitrile was carcinogenic in rats when administered

[3]Toxic Substances Control Act, Chemical Substance Inventory, 1979 public record.
[4]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. 292 pp. Lyon, France: IARC. 1982. pp. 25-29.

### PRODUCTION

According to NCI, the U.S. production of decabromobiphenyl reported to the U.S. International Trade Commission was greater than 10,000 pounds for 1980. The 1979 TSCA Inventory identifies one company producing an unstated amount of hexabromobiphenyl.[440] Earlier, EPA also reported one U.S. producer of PBBs.[440] Production of some PBBs ceased in the late 1970's. CPSC reported that the sole U.S. manufacturer of hexabromobiphenyl ceased production in 1974 and held the remaining stock of the product until the supply was exhausted in April, 1976. From 1970 to 1974, about 11 million pounds of hexabromobiphenyl were manufactured by a single U.S. company and marketed under the trade names Firemaster BP-6 and Firemaster FF-1. Commercial production of PBBs began in 1970.

### EXPOSURE

FDA stated that potential human exposure to PBBs is through ingestion of foods containing PBB residues. Present sources of PBBs seem to be residues remaining in and around plants that formerly manufactured, processed, or produced products using PBBs. In 1974, the National Occupational Hazard Survey estimated that 4,900 workers were possibly exposed to PBBs. For example, workers in one company that manufactured PBBs were possibly exposed directly to PBBs by skin contact, inhalation, and unintentional ingestion; investigators detected 1.1 to 1,729 ppb of hexabromobiphenyl in the workers' sera and 0.51 to 581 ppm in their adipose tissue.

### REGULATIONS

The category of PBBs, potentially containing up to 200-300 individual chemicals, is subject to a special TSCA 8(a) reporting rule. EPA has proposed handling and report/recordkeeping requirements for PBBs under the Resource Conservation and Recovery Act. Under section 406 of the Food, Drug, and Cosmetic Act, FDA regulates PBB compounds as unavoidable environmental contaminants. In cooperation with the Centers for Disease Control and the Public Health Department of the State of Michigan, FDA monitors the long-term human health effects from acute exposure to PBBs.

## POLYCHLORINATED BIPHENYLS

### CARCINOGENICITY

The evidence for carcinogenicity of polychlorinated biphenyls (PCBs) in experimental animals is sufficient.[441] Certain mixtures of PCBs (e.g., Kanechlor 500, Aroclor 1254 and 1260) were carcinogenic in mice and rats after administration in the diet, producing liver tumors.[442,443] PCB (1260) was carcinogenic in the female rat, also producing liver tumors.[442]

The evidence for the carcinogenicity of PCBs in humans is inadequate.[441] A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Aroclor 1254, a mixture of PCBs.[441]

### PROPERTIES

PCBs vary in appearance from mobile, oily liquids to white crystalline solids to hard, noncrystalline resins. All forms are insoluble in water.

### USE

Since 1974, all uses of PCBs in the United States have been confined to closed systems. Before 1972, PCBs were used in transformer cooling liquids, heat-transfer and hydraulic fluids, vacuum pump fluids, lubricants, plasticizers, fillers in investment casting waxes, surface coatings and sealants, pesticide extenders, and copy paper.

### PRODUCTION

The 1979 TSCA Inventory identifies one company producing 35,555,500 pounds of PCBs.[444] PCBs are no longer produced in the United States, except for limited research and development applications; import and export of the compounds has not been permitted since July, 1979. Prior to 1977, annual domestic production of PCBs was about 35 million pounds. Domestic production reached a peak volume of 86 million pounds in 1970 and decreased to about 41 million pounds by 1974. PCBs first were produced in the United States in 1929.

### EXPOSURE

The release of PCBs from prior industrial uses and the persistence of the compounds in the environment have resulted in widespread contamination of water and soil, with subsequent potential exposure of the general population. Routes of exposure include skin absorption and ingestion; a major source of exposure is through the diet. A 1974 report indicated that fish, cheese, eggs, and contaminated animal feed were the major U.S. commodities in which PCBs were found. The percentage of food samples contaminated with PCBs decreased between 1973 and 1975. Residues of PCBs have been detected in human milk and fat samples collected from the general U.S. population. EPA reports that about 12 million persons within 12 miles of three existing and ten projected commercial incinerators may possibly be exposed to releases of PCBs.

### REGULATIONS

In 1970, EPA banned PCBs as a pesticide ingredient and canceled registration of products containing PCBs. EPA promulgated toxic pollutant effluent standards in 1977 and modified the marking and disposal rule in 1979, which was effective in identifying and eliminating some PCB sources. In 1979 EPA issued a ban on manufacturing

[440] Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record

[441] International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 4, 292 pp. Lyon, France: IARC, 1982, pp. 217-219.

[442] International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 18, 140 pp. Lyon, France: IARC, 1978, pp. 43-103

[443] International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, 326 pp. Lyon, France: IARC, 1974, pp. 261-299

[444] Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record

processing, and distributing PCBs in commerce; most manufacturing ceased voluntarily before these rules were issued. EPA proposed a water quality criteria document that will protect freshwater, saltwater, and aquatic organisms, as well as human health. PCBs are regulated as hazardous wastes under the Resource Conservation and Recovery Act and the Comprehensive Environmental Response Compensation and Liability Act. EPA recently assessed air pollution sources of PCBs and is considering the need for regulation of emissions from incinerators, the only source for which controls may be essential. Under the Safe Drinking Water Act, EPA is preparing a report to Congress on the nature and extent of PCB contamination, as well as recommendations for further regulatory action, if necessary.

In 1973, FDA established tolerances for PCBs in several foods and in feeds for food-producing animals. In 1979, four of those tolerances were reduced. The tolerances now are 1.5 ppm (fat basis) in milk and manufactured dairy products, 3 ppm (fat basis) in poultry, 0.3 ppm in eggs, 0.2 ppm in finished animal feed, 2 ppm in animal feed components of animal origin, 5 ppm in fish and shellfish (edible portion), and 0.2 ppm in infant and junior foods. FDA has lowered the PCB standard in fish and shellfish from 5 ppm to 2 ppm and has established action levels of 3 ppm (fat basis) in red meat and 10 ppm in paper food-packaging material. OSHA adopted a standard of 1 mg/m$^3$ (an 8-hour time-weighted average) for PCBs containing 42 percent chlorine, and 0.5 mg/m$^3$ for PCBs containing 54 percent chlorine; OSHA adopted these standards for toxic effects other than cancer.

# PROCARBAZINE AND PROCARBAZINE HYDROCHLORIDE

## CARCINOGENICITY

There is sufficient evidence for carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vinca alkaloids, procarbazine hydrochloride, and prednisone. There is inadequate evidence for carcinogenicity of procarbazine hydrochloride alone in humans.

There is sufficient evidence for the carcinogenicity of procarbazine in experimental animals.[445-447] Laboratory exposure of animals to procarbazine was studied by intraperitoneal injection. In rats, lymph system cancers and cancers of the mammary gland and olfactory nerve were induced in statistically significant numbers. In mice, cancers of the lymph system or leukemia, cancers of the olfactory nerve, pulmonary neoplasms, and cancers of the uterus were induced in statistically significant numbers.[446]

Evidence of carcinogenicity was also found in mice and rats following administration by gavage; in rats following intravenous administration and in one instance following transplacental exposure. Two studies in two species of nonhuman primates suggest that procarbazine hydrochloride may also produce leukemia when administered by multiple routes to the same animal.[445]

[445]International Agency for Research on Cancer IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol 26 411 pp. Lyon, France IARC, 1981, pp. 311-339
[446]National Cancer Institute Bioassay of Procarbazine for Possible Carcinogenicity Technical Report Series No. 19 DHHS Publication No. (NIH) 78-819 124 pp. Bethesda, Maryland, 1978
[447]International Agency for Research on Cancer IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Supplement 4 392 pp. Lyon, France IARC, 1982, pp 220 221.

## PROPERTIES

Procarbazine is a white to pale yellow crystalline powder that is soluble but unstable in water and aqueous solutions.

## USE

Procarbazine hydrochloride is used mainly as an antineoplastic agent to treat Hodgkin's disease and oat-cell carcinoma of the lung. FDA approved its use in 1969, indicating that the drug should be used as an adjunct to standard therapy.

## PRODUCTION

The 1979 TSCA Inventory reports no production data for procarbazine and its hydrochloride.[448]

## EXPOSURE

Possible exposure to procarbazine and its hydrochloride occurs during manufacture of the drug; direct exposure occurs during administration of procarbazine hydrochloride to patients. In 1980, the National Prescription Audit reported 1.5 million prescriptions dispensed for the drug. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

[448]Toxic Substances Control Act, Chemical Substance Inventory, 1979 public record

## REGULATIONS

There is no indication that procarbazine and procarbazine hydrochloride pose a waste or pollution problem and therefore, EPA has little interest in their regulation. Procarbazine hydrochloride is subject to FDA prescription drug labeling requirements.

# PROGESTERONE

## CARCINOGENICITY

There is sufficient evidence that progesterone is carcinogenic in experimental animals.[449] Progesterone was tested by subcutaneous and intramuscular injection in mice, rats, rabbits, and dogs and by subcutaneous implantation in mice and rats. In mice and dogs, progesterone was tested alone; in rats and rabbits, it was given in combination with other chemicals. When given alone progesterone increased the incidence of ovarian, uterine, and mammary tumors in mice. In female mice, treatment of newborn animals with progesterone enhanced the occurrence of precancerous and cancerous lesions of the genital tract and increased mammary tumorigenesis.[449] Dogs treated with progesterone for four years developed a dose-related incidence of mammary gland neoplasms.[449 450]

Administration of progesterone in combination with known carcinogens in mice, rats, and rabbits affected the

[449]International Agency for Research on Cancer IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Supplement 4, 392 pp. Lyon, France IARC, 1982, pp 202-203
[450]International Agency for Research on Cancer IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol 583 pp. Lyon, France IARC, 1979, pp 481-5