Scand J Work Environ Health 1992;18 Suppl 1:64—73

Identification of carcinogens within the IARC monograph program

by Harri Vainio, MD, Julian Wilbourn, BSc[1]

VAINIO H, WILBOURN J. Identification of carcinogens within the IARC monograph program. *Scand J Work Environ Health* 1992;18 Suppl 1:64—73. Fewer than 50 chemicals, groups of chemicals, or mixtures have been causally linked with cancer in humans. Some 250 chemicals have, however, been found to be carcinogenic to rodents. Carcinogenic risk factors that have been identified for humans occur in clearly quantifiable exposure situations, but epidemiologic information on cancer in humans is missing or inadequate for the great majority of chemicals. Extrapolation of animal data to humans is complicated because long-term carcinogenicity studies on animals are carried out under simplified conditions, whereas humans are exposed to a multitude of exogenous and endogenous agents. Furthermore, the carcinogenic process includes multistage and multifactorial aspects, and human populations are genetically and physiologically heterogeneous. Although the science of carcinogenesis is making rapid progress in terms of understanding some of these processes and interactions, there is still a need to err on the side of safety and accept animal data as a warning signal for possible human effects.

Key terms: cancer, humans, risk.

The history of chemical carcinogenesis began in 1775 with the classic description of cancers of the scrotum among chimney sweeps by Sir Percivall Pott (1). It moved on, in the late 19th century, to the account of bladder cancer among workers exposed to aromatic amines (2). Experimental production of skin cancer in rats following exposure to coal tar was reported in 1915 (3), and this work culminated with the identification of polycyclic aromatic hydrocarbons such as benzo[a]pyrene in coal tar in 1933 (4) and the induction of bladder cancer by 2-naphthylamine in dogs by Hueper et al in 1938 (5). Thus, over a period of 160 years, two classes of chemical carcinogens (polynuclear aromatic hydrocarbons and aromatic amines) were discovered, and specific environmental carcinogenic agents (benzo[a]pyrene and 2-naphthylamine) were identified. Since that time, the relative roles of epidemiology and of experimental studies in the generation of information relevant to the identification and prevention of environmental causes of cancer have been the object of much debate.

Many of the early epidemiologic successes were based on observations made either in occupational settings or in other situations of high-level exposure (eg, to drugs and cigarette smoke). In contrast, much of today's cancer epidemiology deals with general environmental exposures (eg, to pollutants in ambient air and drinking water) and with personal behavior patterns (eg, dietary habits, sexual behavior, and reproduction). Exposures to carcinogens are more difficult to assess epidemiologically in such situations than in some of the earlier studies, although newly emerging methods for detecting carcinogen-induced changes in human tissues and biological fluids may aid the assessment of human exposures to carcinogens.

Toxicologic approaches using experimental systems can be used to avoid many of the problems of epidemiologic studies, but animal and in vitro tests are individually only imperfect means for evaluating potential hazards. The two approaches have complementary roles in the identification and prevention of environmental cancer risks.

In the present review, aspects of the identification and classification of carcinogens within the IARC monograph program are discussed with respect to the combined evidence from epidemiologic and toxicologic approaches. This policy has been applied by the International Agency for Research on Cancer (IARC) in the systematic program "Evaluation of Carcinogenic Risks to Humans," and the results are published in the series *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* The IARC evaluation process is essentially qualitative, aimed at assessing the strength of evidence of whether an agent is or is not carcinogenic to humans (risk identification), and does not extend to the subsequent stage of risk quantification or risk management. To date, 50 volumes have been published within the program, and another three are in preparation (6—58).

Types of risk factors for cancer

Categories of known risk factors for cancers in humans are listed in table 1. These factors can act individually

[1] International Agency for Research on Cancer, Lyon, France.

Reprint requests to: Dr H Vainio, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cédex 08, France.

or in combination. Persons have some control over their behavior, including tobacco use, diet, alcohol consumption, exposure to sunlight, sexual behavior, and general personal hygiene. In contrast, environmental factors, including occupational exposures to carcinogens, exposures during medical procedures, and naturally occurring or man-made factors which contaminate water, air, and soil are beyond a person's influence. Thus, their effective control requires broad social action. Genetic factors are inherited at conception and their control is not feasible at present.

Obstacles to the identification of specific causes of human cancers include (i) the long latency period between onset of exposure to causal agents and outward appearance of the disease, (ii) the multistage nature of carcinogenesis, and (iii) the likelihood that most human cancers result from a complex interaction between multiple environmental and endogenous (genetic, host) factors. Although significant progress has been made, several important questions have still not been completely resolved. They include the extent to which human cancers are due to specific causes, such as chemicals, hormones and physical and viral agents, the role of nutritional factors, and the interactions between endogenous and environmental factors.

Identification of risk factors for cancer through laboratory experiments

Carcinogens can be identified in the following two main types of toxicologic laboratory tests: (i) long-term carcinogenicity tests on rodents (mice, rats, hamsters) and (ii) short-term tests for a variety of genetic and related effects. Bioassays of single chemicals or of mixtures of chemicals, usually carried out on mice, rats or hamsters, can identify agents that cause cancer. In addition, some short-term tests for genetic and related effects can identify deoxyribonucleic acid (DNA) reactive or "genotoxic" agents. More recently, in vivo and in vitro experimental systems have been developed that may help identify agents that appear to have primarily promoting activity. Short-term tests are valuable to the extent that they can help to reflect underlying events in the carcinogenic process. Consistently positive results in tests for mutations (point mutations or chromosomal rearrangements) are usually regarded as indicating potential carcinogenicity.

Results from laboratory experiments constitute useful supporting evidence when adequate epidemiologic data for the carcinogenicity of an environmental agent exist (eg, vinyl chloride) but become essential when the epidemiologic evidence is nonexistent or inadequate in quality or quantity. In the latter case, although no universally accepted criteria exist for translating the results of long-term or short-term tests in terms of cancer risk for humans, an evaluation of the risk can be made on the basis of experimental scientific evidence.

Aims and scope of the IARC monograph program

The objective of the IARC monograph program is to prepare, with the help of international working groups of experts, critical reviews and evaluations of the evidence of carcinogenicity for a wide range of human exposures. Each monograph consists of a brief description of the chemical and physical properties of the agent; a description of methods and volumes of production and use patterns and occurrence, in order to indicate possible human exposure; methods for its analysis; summaries of case reports and epidemiologic studies of cancer in humans; summaries of experimental carcinogenicity tests; a brief description of other relevant biological data, such as toxicity and genetic and related effects, that may indicate its possible mechanism of action; and an evaluation of its carcinogenicity. The first part of this general scheme is appropriately adjusted when agents other than chemicals or chemical mixtures are dealt with.

The degrees of evidence for carcinogenicity in humans and in experimental animals are first evaluated separately with the use of several predefined categories. An overall evaluation, taking into account all available data, is then made of the probability that the agent is carcinogenic to humans.

Criteria for evaluating carcinogenicity

The criteria by which evidence of carcinogenicity is evaluated in the IARC monograph series have been submitted to periodic revision. The original criteria were reviewed in 1977, followed by further revisions in 1982, 1987, and 1988. Details of how the adequacy of the information contained in individual studies is judged are given in the preamble to each volume.

Table 1. Risk factors for human cancer.

Risk factor	Example
Endogenous	
Genetic predisposition	Xeroderma pigmentosum
Hormones	Estrogens
Exogenous	
Chemicals	Benzene
Metals	Chromium and nickel compounds
Industrial processes	Iron and steel founding
Hormones	Estrogen replacement therapy
Radiation	Therapeutic X rays, radon, ultraviolet radiation
Viruses	Hepatitis B virus
Cultural habits	Tobacco smoking, betel-quid chewing
Iatrogenic exposures	Cyclophosphamide
Diet	Excessive caloric/high fat intake
Dietary contaminants	Aflatoxins
Socioeconomic conditions	Less-favored occupational class

Categories of degree of evidence[2]

In the first 16 volumes of the monograph series, assessments of evidence for carcinogenicity in humans and in experimental animals were made separately. No attempt was made to estimate risk to humans from animal data, and no presumption was made of the predictive relevance of animal data for human risk. In 1977, an IARC working group met to review and standardize the evaluations for evidence of carcinogenic activity from both human and animal studies, and a scheme for categorizing degrees of evidence for carcinogenicity was developed. They can be summarized as "sufficient," "limited," "inadequate," and, later, "evidence suggesting lack of carcinogenicity." With the use of set criteria for evaluating the degree of evidence for carcinogenicity, agents are assigned to one of these categories.

Human carcinogenicity data are classified using the aforementioned four categories. The criteria for placing an agent in each category reflect the limitations to epidemiologic research. When studies indicate a positive relationship and bias and confounding and chance can be ruled out with reasonable confidence, there is considered to be *sufficient evidence of carcinogenicity.* If a positive relationship is found, but such effects cannot be ruled out, the evidence is considered to be *limited.* Several adequate studies which provide mutually consistent results showing no positive association at relevant exposure levels provide *evidence suggesting lack of carcinogenicity.* Last, if the available studies are of insufficient quality, consistency, or statistical power, there is considered to be *inadequate evidence of carcinogenicity.*

The degrees of evidence for carcinogenicity derived from animal studies can vary from strongly positive to ostensibly negative. *Sufficient evidence of carcinogenicity* in animals is provided by positive results for at least two species or in two or more independent studies for one species. An exceptionally high incidence and/or early onset of rare neoplasms in one species in a single study can also suffice. *Limited evidence of carcinogenicity* exists when positive results are observed in only a single experiment, if only benign neoplasms are involved, or if unresolved questions about the data remain. There is considered to be *inadequate evidence* when the results cannot be interpreted because of serious limitations in the study design or reporting. The final category is one of *evidence suggesting lack of carcinogenicity.* To be classified in this way, an agent must show evidence of no carcinogenic effect for at least two species. This category provides, in a sense, an operational definition of "noncarcinogenic." However, in using the term lack of carcinogenicity, IARC implicitly recognizes the difficulties in establishing a negative outcome.

[2] For an exact description of the criteria for different categories of evidence, see the preamble of a recent volume of the monograph series.

Overall evaluations of carcinogenicity to humans

When an overall evaluation of the carcinogenicity of an agent, mixture, or exposure circumstance to humans is made, all the available evidence is considered. Assignment of an agent to a given group is a matter of scientific judgement reflecting the strength of the evidence derived from studies on humans and experimental animals and from other relevant data. It should be emphasized that the categorization scheme used refers to the strength of the evidence that an agent is carcinogenic and not to its carcinogenic strength or potency. There are four main groups.

Group 1. In group 1 the agent (mixture) is carcinogenic to humans, or the exposure circumstance entails exposures that are carcinogenic to humans. This category is used only when there is sufficient evidence of carcinogenicity in humans.

Group 2. Group 2 includes agents, mixtures, and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is sufficient evidence of carcinogenicity in experimental animals. Agents, mixtures, and exposure circumstances are assigned to either group 2A (probably carcinogenic) or group 2B (possibly carcinogenic) on the basis of epidemiologic, experimental, and other relevant data.

In group 2A the agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Exceptionally, an agent, mixture, or exposure circumstance can be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

In group 2B the agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans. This category is generally used for agents, mixtures, and exposure circumstances for which there is limited evidence of carcinogenicity in humans in the absence of sufficient evidence of carcinogenicity in experimental animals. It can also be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent or mixture for which there is inadequate evidence of or no data on carcinogenicity in humans but limited evidence of carcinogenicity in experimental animals, together with supporting evidence from other relevant data, can be placed in this group.

Group 3. Included in group 3 are agents (mixtures, exposure circumstances) not classifiable as to their carcinogenicity to humans. Agents, mixtures, and exposure circumstances are placed in this category when they do not fall into any other group.

Group 4. If the agent (mixture, exposure circumstance) is probably not carcinogenic to humans, it is placed in group 4. This category is used for agents, mixtures, and exposure circumstances for which there is evidence suggesting a lack of carcinogenicity in humans, together with evidence suggesting a lack of carcinogenicity in experimental animals. In some instances, agents or mixtures for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting a lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, can be classified into this group.

Carcinogens identified thus far

The goal of the assessments reported in the monograph series is to evaluate carcinogenicity to humans. Agents in group 1 are definitely carcinogenic to humans according to evidence from epidemiologic studies. Agents in group 2 are likely to be carcinogenic to humans, agents assigned to group 2A having a greater probability of being carcinogenic than those assigned to group 2B, according to evidence from epidemiologic, experimental carcinogenicity, and other relevant biological studies. For public health purposes, it is prudent, as well as biologically plausible, to regard those agents for which there is sufficient evidence of carcinogenicity in experimental animals but inconclusive epidemiologic data as if they presented a carcinogenic risk to humans. The distribution, by group, of all the agents and exposures (N = 738) that have been evaluated up to the end of 1991 (volumes 1—53) is given in table 2. In order for an agent to be classified into group 1, the evidence of carcinogenicity in humans must be judged to be sufficient for at least one target organ (see table 3), although the evaluations are related to exposure and not to target organ. Similarly, judgements of sufficient evidence of carcinogenicity in experimental animals are normally based on evidence from one or more species. For many exposures that are causally related to human cancers, target organs can differ from one species to another. However, there is nearly always at least one common target organ in humans, and in one or more animal species, despite the inherent physiological differences (59).

Table 2. Agents and exposures evaluated within the IARC monograph program (6—57).

Group	Number
Carcinogenic to humans (group 1)	55
Probably carcinogenic to humans (group 2A)	45
Possibly carcinogenic to humans (group 2B)	191
Cannot be classified as to its carcinogenicity to humans (group 3)	440
Probably not carcinogenic to humans (group 4)	1
Total	732

Recognized human carcinogens (group 1)

More than 50 agents have been shown to be causally related to human cancer (table 3). The majority are environmental chemicals to which humans have been exposed only relatively recently (60). Most are either chemicals to which people are exposed occupationally or pharmaceutical products or naturally occurring compounds to which specific groups of people have been exposed at high concentrations for periods of time long enough for an increased risk to be detected by the methods used in human epidemiology. Table 3 also gives the organs in which cancers have been observed. Those involved the most frequently are the lung, urinary bladder, hematopoietic tissue, and skin.

Probable human carcinogens (group 2A)

The 45 agents, complex mixtures, and exposure circumstances for which there is less than conclusive evidence from epidemiologic studies and experimental evidence of carcinogenicity are as follows:

Agents
Acrylonitrile
Adriamycin
Androgenic (anabolic) steroids
Azacitidine
Benz[a]anthracene
Benzidine-based dyes
Benzo[a]pyrene
Beryllium and beryllium compounds
Bischloroethyl nitrosourea (BCNU)
Cadmium and cadmium compounds
Captafol
Chloramphenicol
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)
para-Chloro-*ortho*-toluidine and its strong acid salts
Chlorozotocin
Cisplatin
Dibenz[a,h]anthracene
Diethyl sulfate
Dimethylcarbamoyl chloride
Dimethyl sulfate
Epichlorohydrin
Ethylene dibromide
Ethylene oxide
Formaldehyde
5-Methoxypsoralen
4,4'-Methylene bis(2-chloroaniline) (MOCA)
N-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)
Nitrogen mustard
N-nitrosodiethylamine
N-nitrosodimethylamine
N-nitroso-*N*-ethylurea
N-nitroso-*N*-methylurea
Phenacetin
Procarbazine hydrochloride
Propylene oxide
Silica, crystalline

Styrene oxide
Tris(2,3-dibromopropyl)phosphate
Vinyl bromide

Mixtures
Creosotes
Diesel engine exhaust
Hot mate
Polychlorinated biphenyls

Exposure circumstances
Occupational exposures in petroleum refining
Occupational exposures in spraying and application of non-arsenical insecticides

Table 3. Established human carcinogens and their target organs.

Carcinogen	Target organ (suspected target organ)
Agents	
Aflatoxins	Liver (lung)
4-Aminobiphenyl	Bladder
Arsenic and arsenic compounds[a]	Lung, skin
Asbestos	Lung, pleura, peritoneum (gastrointestinal tract, larynx)
Azathioprine	Lymphatic system, mesenchyma, hepatobiliary system, skin
Benzene	Hematopoietic system
Benzidine	Bladder
N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	Bladder
Bis(chloromethyl)ether chloromethyl methyl ether (technical grade)	Lung
1,4-Butanediol dimethanesulfonate (Myleran)	Hematopoietic system
Chlorambucil	Hematopoietic system
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU)	Hematopoietic system
Chromium [VI] compounds	Lung (nasal cavity)
Ciclosporin	Lymphatic system
Cyclophosphamide	Bladder, hematopoietic system
Diethylstilbestrol	Cervix/vagina, breast, testis (uterus)
Erionite	Pleura, peritoneum
Melphalan	Hematopoietic system
8-Methoxypsoralen (Methoxsalen) plus ultraviolet radiation	Skin
MOPP and other combined chemotherapy including alkylating agents	Hematopoietic system
Mustard gas (Sulfur mustard)	Pharynx, larynx, lung
2-Naphthylamine	Bladder (liver)
Nickel compounds	Nasal cavity, lung
Estrogen replacement therapy	Uterus, breast
Estrogens, nonsteroidal[a]	Cervix/vagina, breast, testis (uterus)
Estrogens, steroidal[a]	Uterus, breast
Oral contraceptives, combined[b]	Liver
Oral contraceptives, sequential	Uterus
Radon and its decay products	Lung
Talc containing asbestiform fibers	Lung
Thiotepa	Hematopoietic system
Treosulfan	Hematopoietic system
Vinyl chloride	Liver, blood vessels (brain, lung, lymphatic system)
Mixtures	
Alcoholic beverages	Pharynx, esophagus, liver, larynx, oral cavity (breast)
Analgesic mixtures containing phenacetin	Bladder, kidney
Betel quid with tobacco	Oral cavity, pharynx, larynx, esophagus
Coal-tar pitches	Skin, lung, bladder (larynx, oral cavity)
Coal tars	Skin, lung (bladder)
Mineral oils, untreated and mildly treated	Skin (lung, bladder, gastrointestinal tract)
Shale oils	Skin (gastrointestinal tract)
Soots	Skin, lung
Tobacco products, smokeless	Oral cavity, pharynx, esophagus
Tobacco smoke	Lung, bladder, oral cavity, pharynx, larynx, esophagus, pancreas, kidney
Exposure circumstances	
Aluminum production	Lung, bladder (lymphatic system)
Auramine, manufacture of	Bladder (prostate)
Boot and shoe manufacture and repair	Nasal cavity, hematopoietic system (pharynx, lung, liver, gastrointestinal tract, bladder)
Coal gasification	Skin, lung, bladder
Coke production	Skin, lung, kidney
Furniture and cabinet making	Nasal cavity
Iron and steel founding	Lung (gastrointestinal tract, genitourinary system, hematopoietic system)
Isopropyl alcohol manufacture (strong-acid process)	Nasal cavity (larynx)
Magenta, manufacture of	Bladder
Painter (occupational exposure as a)	Lung
Rubber industry	Bladder, hematopoietic system (lung, gastrointestinal tract, skin, lymphatic system)
Underground hematite mining with exposure to radon	Lung

[a] This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.
[b] There is also conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium.

Many of the agents in this group (24 of the 45) were classified on the basis of inadequate evidence or no data on humans, together with sufficient evidence of carcinogenicity in experimental animals. They are adriamycin, benz[a]anthracene, benzidine-based dyes, benzo[a]pyrene, captafol, 1-(2-choroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), cisplatin, dibenz[a,h]anthracene, dimethylcarbamoyl chloride, dimethyl sulfate, epichlorohydrin, ethylene dibromide, 5-methoxypsoralen, 4,4'-methylene bis(2-chloroaniline) (MOCA), *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, *N*-nitrosodiethylamine, *N*-nitrosodimethylamine, *N*-nitroso-*N*-ethylurea, *N*-nitroso-*N*-methylurea, procarbazine hydrochloride, propylene oxide, styrene oxide, tris-(2,3-dibromopropyl)phosphate, vinyl bromide. In accordance with the aforementioned criteria, this combination would normally have resulted in a classification of 2B. The 24 agents were upgraded from group 2B to group 2A on the basis of other relevant data. Thus, in most cases, it could be concluded that (i) the agent produces genetic or related effects (ie, DNA or chromosomal damage) in exposed humans and also gives positive results in a range of other in vitro and in vivo assays or (ii) the agent is active in a broad spectrum of assays for genetic and related effects, including those involving mammalian cells, and there is evidence from structure activity and/or metabolic studies that the agent itself reacts covalently with DNA or is likely to be converted to a reactive form in humans.

Possible human carcinogens (group 2B)

For most of the 191 agents classified into group 2B, there is sufficient evidence of carcinogenicity in animals but no supporting evidence from epidemiologic studies or from other relevant data. The paucity of epidemiologic data is due in some cases to a lack of adequate studies, because no large cohort had been identified that was exposed to the agent in question or no case-referent study had been carried out. For the majority of exposures indicated by animal studies to be a carcinogenic hazard, no human data at all are available. The following agents, mixtures, and exposure circumstances belong to group 2B:

Agents

A-α-C (2-Amino-9*H*-pyrido[2,3-*b*]indole)
Acetaldehyde
Acetamide
Acrylamide
AF-2 [2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide]
para-Aminoazobenzene
ortho-Aminoazotoluene
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole
Amitrole
ortho-Anisidine
Antimony trioxide
Aramite®
Atrazine
Auramine (technical grade)
Azaserine
Benzo[b]fluoranthene
Benzo[j]fluoranthene
Benzo[k]fluoranthene
Benzyl violet 4B
Bleomycins
Bracken fern
Bromodichloromethane
1,3-Butadiene
Butylated hydroxyanisole (BHA)
β-Butyrolactone
Carbon-black extracts
Carbon tetrachloride
Ceramic fibers
Chlordane and heptachlor
Chlordecone (kepone)
Chlorendic acid
α-Chlorinated toluenes
Chloroform
Chlorophenols
Chlorophenoxy herbicides
4-Chloro-*ortho*-phenylenediamine
Citrus red no 2
Cobalt and cobalt compounds
  Cobalt metal powder
  Cobalt[II] oxide
  Cobalt[II] chloride
  Cobalt[II] sulfide
  Cobalt/chromium/molybdenum alloy
  Cobalt[III] acetate
  Cobalt naphthenate
  Cobalt[II,III] oxide
  Cobalt/aluminum/chromium spinel
para-Cresidine
Cycasin
Dacarbazine
Dantron (Chrysazin; 1,8-Dihydroxyanthraquinone)
Daunomycin
N,N'-Diacetylbenzidine
2,4-Diaminoanisole
4,4'-Diaminodiphenyl ether
2,4-Diaminotoluene
Dibenz[a,h]acridine
Dibenz[a,j]acridine
7*H*-Dibenzo[c,g]carbazole
Dibenzo[a,e]pyrene
Dibenzo[a,h]pyrene
Dibenzo[a,i]pyrene
Dibenzo[a,l]pyrene
1,2-Dibromo-3-chloropropane
para-Dichlorobenzene
3,3'-Dichlorobenzidine
3,3'-Dichloro-4,4'-diaminodiphenyl ether
Dichlorodiphenyltrichloroethane (DDT)
1,2-Dichloroethane
Dichloromethane
1,3-Dichloropropene (technical grade)
Dichlorvos
Diepoxybutane
Di(2-ethylhexyl)phthalate
1,2-Diethylhydrazine
Diglycidyl resorcinol ether
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)
Dimethylformamide
1,1-Dimethylhydrazine
1,6-Dinitropyrene
1,8-Dinitropyrene
1,4-Dioxane
Disperse Blue 1
Ethyl acrylate
Ethylene thiourea
Ethyl methanesulfonate

2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole
Glass wool
Glu-P-1 (2-Amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole)
Glu-P-2 (2-Aminodipyrido[1,2-*a*:3',2'-*d*]imidazole)
Glycidaldehyde
Griseofulvin
Hexachlorobenzene
Hexachlorocyclohexanes (HCH)
Hexamethylphosphoramide
Hydrazine
Indeno[1,2,3-*cd*]pyrene
IQ (2-Amino-3-methylimidazo[4,5-*f*]quinoline)
Iron-dextran complex
Lasiocarpine
Lead and lead compounds, inorganic
MeA-α-C (2-Amino-3-methyl-9*H*-pyrido[2,3-*b*]indole)
Medroxyprogesterone acetate
Merphalan
2-Methylaziridine
Methylazoxymethanol and its acetate
5-Methylchrysene
4,4'-Methylene bis(2-methylaniline)
4,4'-Methylenedianiline
Methyl methanesulfonate
2-Methyl-1-nitroanthraquinone (uncertain purity)
N-Methyl-*N*-nitrosourethane
Methylthiouracil
Metronidazole
Mirex
Mitomycin C
Monocrotaline
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone
Nafenopin
Nickel, metallic
Niridazole
Nitrilotriacetic acid and its salts
5-Nitroacenaphthene
6-Nitrochrysene
Nitrofen, technical grade
2-Nitrofluorene
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide
Nitrogen mustard *N*-oxide
2-Nitropropane
1-Nitropyrene
4-Nitropyrene
N-Nitrosodi-*n*-butylamine
N-Nitrosodiethanolamine
N-Nitrosodi-*n*-propylamine
3-(*N*-Nitrosomethylamino)propionitrile
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)
N-Nitrosomethylethylamine
N-Nitrosomethylvinylamine
N-Nitrosomorpholine
N'-Nitrosonornicotine
N-Nitrosopiperidine
N-Nitrosopyrrolidine
N-Nitrososarcosine
Oil orange SS
Panfuran S (containing dihydroxymethylfuratrizine)
Pentachlorophenol
Phenazopyridine hydrochloride
Phenobarbital
Phenoxybenzamine hydrochloride
Phenyl glycidyl ether
Phenytoin
Ponceau MX
Ponceau 3R
Potassium bromate
Progestins
1,3-Propane sultone
β-Propiolactone
Propylthiouracil
Rock wool
Saccharin
Safrole
Slag wool
Sodium *ortho*-phenylphenate
Sterigmatocystin
Streptozotocin
Styrene
Sulfallate
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)
Tetrachloroethylene
Thioacetamide
4,4'-Thiodianiline
Thiourea
Toluene diisocyanates
ortho-Toluidine
Trichlormethine (Trimustine hydrochloride)
Trp-P-1 (3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole)
Trp-P-2 (3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]indole)
Trypan blue
Uracil mustard
Urethane

Mixtures
Bitumens, extracts of steam-refined and air-refined
Carrageenan, degraded
Chlorinated paraffins of average carbon chain length C_{12} and average degree of chlorination approximately 60%
Coffee (urinary bladder)
Diesel fuel, marine
Engine exhaust, gasoline
Fuel oils, residual (heavy)
Gasoline
Polybrominated biphenyls
Toxaphene (polychlorinated camphenes)
Welding fumes

Exposure circumstances
Carpentry and joinery
Work in the textile manufacturing industry

Positive animal studies and lack of human response

Epidemiologic research has, over the past four decades, been able to identify carcinogenic effects of many exposures (especially occupational) in humans. For some agents, however, the available epidemiologic data do not seem to corroborate the results of animal studies. Epidemiologic studies can fail to identify the presence of health risks for several reasons. In all such studies there are varying degrees of exposure misclassification that result in bias in the estimation of risk, and this misclassification entails errors of exposure assignment and inaccuracies in dose estimation, which may lead to the examination of exposures at points in time that are inappropriate to disease occurrence (61, 62). Therefore, any "negative" epidemiologic study should include consideration of the magnitude of risk that may have been overlooked on the basis of plausible estimates of the imprecision of the exposure measurements. In many instances, this contradiction would be neutralized, since "negative" results from human

studies are readily attributable to dilution of very modest associations which may really be present. Moreover, epidemiologic studies have practical limitations in their ability to identify minimal (although real) elevations of risk or risks due to agents that entail minimal or no "pure" exposure. Many exposures of concern to contemporary society entail risks that are below the threshold of detection by conventional epidemiology (63).

Animal studies can, of course, result in an overestimate of risks, often by design. When the most sensitive animal species is selected and the highest tolerated dose is used, there is a potential danger of obtaining false-positive results. The increased incidence of tumors under the highest tolerated dose condition could be due to an indirect effect related to the high dose used, more than to the intrinsic carcinogenicity of the chemical under consideration. However, the number of chemical carcinogens that can be identified as possibly acting through an indirect or secondary mechanism is small according to an analysis of the chemical carcinogenesis data base of the National Toxicology Program (64). Results thus obtained are not necessarily "wrong," however, since the issue is not the validity of findings for that animal species under those exposure circumstances, but rather their inaccuracy if applied directly to humans.

Extrapolation of the results of animal studies across species and exposure conditions could produce errors of inference regarding human risk, but for the purposes of prudent public health policy and in the absence of valid human data, animal data should still be regarded as indicative of a potential risk. For this reason, agents and exposures for which there is sufficient evidence of carcinogenicity in animals but for which no human data or only "nonpositive" human data exist are usually classified into group 2B, "possible" human carcinogens.

Concluding remarks

The risk for cancer in humans is increased by a variety of factors, ranging from exposure to an identified agent to exposures through culturally determined behavior, such as smoking, or socioeconomic conditions. Prophylactic intervention is possible for some of these factors, whereas the effects of other factors are as yet undetermined. Since carcinogenesis is a multisequential process, reductions of exposures to carcinogens in the occupational and general environment can be complemented by reductions of exposures that are under the control of the individual in order to maximize the potential for cancer prevention. Furthermore, exciting developments in epidemiologic and experimental research are providing leads to factors that may reduce cancer risk, and the potential for more general approaches to cancer prevention is being heightened, for example, increasing knowledge on diet and energy intake.

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