

Response of experimental animals to human carcinogens: an analysis based upon the IARC Monographs programme

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Only the results of epidemiological studies can be used to establish a causal relationship between an exposure to an agent and human cancer; however, such studies often cannot be carried out due to limitations of population or latent period or to the presence of mixed exposures. It is essential, therefore, that the validity be established of extrapolating to humans the results obtained from long-term carcinogenicity tests in animals. The responses of experimental animals to known and suspected human carcinogens, as evaluated in the *IARC Monographs* series, were analysed as an indication of the sensitivity of animal tests for predicting human carcinogens. Although the response was high – 84% – it would have been even higher had all the compounds been adequately tested experimentally. An additional finding was that for many exposures causally related to human cancer, there is a target organ in common between humans and at least one animal species, despite many inherent physiological differences. These findings show clearly the importance of experimental carcinogenicity studies in the primary prevention of cancer.

Introduction

Extrapolation of the results from long-term carcinogenicity tests in animals to predict carcinogenic risk to humans is in many instances the only means of alerting concerned persons about the hazard of an exposure to an agent. The major reason that this indirect method must be used is that direct human observations are often lacking – because the number of people exposed is too small, because the time since exposure began is too short to detect a carcinogenic effect, because human exposure has not yet occurred, or because the exposure occurs in conjunction with exposure to other hazardous exposures or processes. Although the validity of such extrapolations has been questioned, it is essential that it be established, in the absence of other means of demonstrating human risk.

This paper attempts such validation by analysing the effects of known human carcinogens in long-term carcinogenicity tests in animals. It is based on evaluations of the carcinogenicity of certain exposures to humans and to animals made within the International Agency for Research on Cancer (IARC) programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.

The aim of the IARC programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, begun in 1969, is to identify, through the deliberations of Working Groups of experts

in epidemiology, chemical carcinogenesis and related fields, chemicals, industrial processes, industries and cultural habits associated with cancer in humans. Several interim reviews of this programme (1–6) have been published.

By April 1986, 41 volumes of *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* (7–47) had been published or were in press. Evaluations are based upon published data on epidemiological and experimental carcinogenicity; the degrees of evidence that an exposure is associated with the induction of cancer in humans and in experimental animals are assessed. The definitions of degrees of evidence of carcinogenicity to humans and to experimental animals (see Table I) were evolved by a number of working groups convened by the IARC (26–47).

To date, evaluations of the carcinogenicity to humans and/or experimental animals have been made on 743 exposures. Because of the limitations described above, however, case reports or epidemiological investigations of cancer in humans are available for only 183 chemicals or complex mixtures and for 20 industrial processes, occupations or habits. It is disquieting that of the 540 exposures for which there are no epidemiological data, there is a large number of chemicals (presently 126) for which there is sufficient evidence of carcinogenicity to experimental animals. Of the 139 chemicals for which there is inadequate evidence of carcinogenicity for humans, there is sufficient evidence of carcinogenicity in animals for 90.

Because of the incompleteness of epidemiological information and the increasing number of new chemicals introduced into the environment, decisions relating to public health measures to limit exposure to carcinogenic chemicals must rely heavily upon the results of long-term carcinogenicity studies in animals. Unfortunately, it is not possible to study the mathematical correlation between carcinogenicity in humans and animals on the basis of the evaluations in the *IARC Monographs*, since one of the criteria for selecting chemicals and other exposures for evaluation is that there be some suspicion of carcinogenicity to humans and/or experimental animals. Moreover, very few chemicals have been evaluated as having no evidence of carcinogenicity to humans and to experimental animals. However, one can investigate the effect of human carcinogens in long-term animal experiments. While such analyses do not permit estimation of the correlation of response between animals and humans, they do allow calculation of the sensitivity of animal tests, i.e., the proportion of human carcinogens which also give positive results in animal tests. They also allow a comparison of the target organs that are affected in humans and in animals.

As part of a review of the first 16 volumes of *IARC Monographs* in 1977, Tomatis *et al.* (1) examined the evidence for carcinogenicity to experimental animals of chemicals or processes considered to be carcinogenic to humans or strongly suspected of being so. The aim of the present paper is to expand that work, using data from all 41 volumes of *IARC Monographs* published so far, and from Supplement 4 of the series (3,7–47).

*Abbreviations: IARC, International Agency for Research on Cancer; DES, diethylstilboestrol; Chlornaphazine, *N,N*-bis(2-chloroethyl)-2-naphthylamine; Myleran, 1,4-butanediol dimethanesulphonate.

Table I. Criteria for evaluation used in IARC monographs

Degree of evidence	In humans	In experimental animals
Sufficient evidence	there is a causal relationship between the agent and human cancer	there is an increased incidence of malignant tumours: (a) in multiple species or strains; (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data on dose-response effects
Limited evidence	a causal relationship between the agent and human cancer is credible, but alternative explanations, such as chance, bias or confounding, cannot adequately be excluded	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 adenomas and adenocarcinomas and liver tumours in certain strains of mice)
Inadequate evidence	(a) there are few pertinent data; or (b) the available studies, while showing evidence of an association do not exclude chance, bias or confounding	because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect
No evidence	several adequate studies are available which do not show evidence of carcinogenicity	several adequate studies are available which show that, within the limits of the test used, the chemical is not carcinogenic

Table II. Chemicals and groups of chemicals with sufficient or limited evidence of carcinogenicity to humans – comparison of target organs and main routes of exposures in humans and animals*

Chemical or group of chemicals (degree of evidence of carcinogenicity) ^b	Humans			Animals		
	Main type of exposure ^c	Main route of exposure ^d	Target organ	Species	Route of exposure	Target organ
1. Acrylonitrile (H. limited) (A. sufficient)	occupational	inhalation, oral, skin?	lung*, brain*, stomach*, prostate*, lymphatic and haematopoietic system*	rat	inhalation, oral	Zymbal gland, digestive tract, central nervous system, mammary gland*
2. Aflatoxins (H. limited) (A. sufficient)	environmental	oral	liver*	mouse	s.c. i.p. i.p. to newborns oral	local lung liver inadequate
				rat	i.p. oral intratracheal s.c.	liver liver, kidney, colon liver, trachea local
				duck	oral	liver
				primates	oral, i.p.	liver, gall bladder*, pancreas*, bone*
				fish	oral	liver
				3. 4-Aminobiphenyl (H. sufficient) (A. sufficient)	occupational	inhalation, skin, oral
4. Analgesic mixtures containing phenacetin (H. sufficient) Phenacetin alone or with caffeine Phenacetin, phenazone and caffeine in combinations	medicinal	oral	renal pelvis, bladder*, ureter*	rat	s.c.	mammary gland, intestinal tract
				rabbit	oral	bladder
				dog	oral	bladder
				rat	oral	urinary tract and bladder
rat	oral	liver				

Chemical or group of chemicals (degree of evidence of carcinogenicity) ^b	Humans			Animals		
	Main type of exposure ^c	Main route of exposure ^d	Target organ	Species	Route of exposure	Target organ
(A. limited)						
Phenacetin, aspirin and caffeine				mouse	oral	negative
				rat	oral	negative
5. Arsenic and certain arsenic compounds (H. sufficient) (A. inadequate) ^e	occupational, medicinal, environmental	inhalation, skin oral	skin, lung, liver*, lymphatic and haematopoietic system*	mouse	oral, i.v., inhalation, skin s.c.	inadequate lymphoreticular system*
				rat	oral, s.c., intratracheal	inadequate
				dog	oral	inadequate
				rabbit	intramedullary	inadequate
6. Asbestos (H. sufficient) (A. sufficient)	occupational, environmental	inhalation, oral	lung, pleural cavity, peritoneum, gastrointestinal tract*, larynx*	mouse	inhalation i.p.	inadequate local
				rat	inhalation, intrapleural, i.p.	lung, pleura inadequate
				hamster	intrapleural	pleura
				rabbit	intrapleural	pleura
7. Auramine (technical grade) (H. limited) (A. limited)	occupational	skin	bladder	mouse	oral	liver
				rat	oral s.c.	liver, bile duct local
8. Azathioprine (H. sufficient) (A. limited)	medicinal	oral, injection	lymphoma, leukaemia*, skin*, hepatobiliary system*, bladder*, thyroid*, lung*	mouse	i.p., s.c., i.m.	lymphoreticular system
				rat	oral	ear duct
9. Benzene (H. sufficient) (A. limited) ^f	occupational	inhalation, skin, oral	leukaemia	mouse	s.c., inhalation, skin	inadequate
				rat	inhalation oral	negative Zymbal gland
10. Benzidine (H. sufficient) (A. sufficient)	occupational	inhalation, oral, skin?	bladder	mouse	s.c., oral	liver
				rat	s.c., oral i.p., s.c. oral, i.p. s.c.	liver Zymbal gland mammary gland colon
				hamster	oral	liver
				dog	oral	bladder
11. Beryllium and beryllium compounds (H. limited) (A. sufficient)	occupational	inhalation oral	lung*	mouse	i.v.	bone*
				rat	oral inhalation, intratracheal intramedullary	inadequate lung inadequate
				rabbit	i.v., intramedullary, subperiosteal, inhalation	bone
				hamster	inhalation	inadequate
				monkey	inhalation	lung
12. Betel quid containing tobacco (chewing) (H. sufficient) (A. limited)	cultural habit	oral	oral cavity, oropharynx*, hypopharynx*, larynx*, oesophagus*	mouse	oral skin s.c. (aqueous extracts)	inadequate local local
				hamster	cheek-pouch painting (aqueous extracts) cheek-pouch implantation	forestomach forestomach, local

Chemical or group of chemicals (degree of evidence of carcinogenicity) ^b	Humans			Animals		
	Main type of exposure ^c	Main route of exposure ^d	Target organ	Species	Route of exposure	Target organ
13. <i>N,N</i> -Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine) (H. sufficient) (A. limited)	medicinal	oral	bladder	mouse	i.p.	lung
				rat	s.c.	local
14. Bis(chloromethyl)ether and technical chloromethyl methyl ether (H. sufficient) (A. sufficient)	occupational	inhalation	lung	mouse	skin inhalation s.c. to newborns	local lung lung
				rat	inhalation s.c.	lung, nasal cavity local
15. 1,4-Butanediol dimethanesulphonate (Myleran) (H. sufficient) (A. limited)	medicinal	oral	leukaemia	mouse	i.p., i.v.	lymphoreticular system*, ovary*
				rat	i.p., i.v., oral	inadequate
16. Cadmium and cadmium compounds (H. limited) (A. sufficient)	occupational	inhalation, oral	nasopharynx*, colon*, rectum*, lung*, prostate*, genito-urinary tract	mouse	s.c.	testis
				rat	i.m. s.c.	local local, testis
					oral	negative
17. Certain combined chemotherapy regimes for lymphomas including MOPP* (H. sufficient) (A. no data)	medicinal	oral, injection	leukaemia, lymphoma*	not tested		
18. Chlorambucil (H. sufficient) (A. sufficient)	medicinal	oral, injection	leukaemia	mouse	i.p. skin (with croton oil)	lung, lympho-haematopoietic system*, ovary* local
				rat	i.p.	lympho-haematopoietic system
19. Chloramphenicol (H. limited) (A. inadequate)	medicinal	oral, skin	leukaemia*	no adequate study		
20. Chromium and certain chromium compounds (H. sufficient) (A. sufficient)	occupational	inhalation	lung, gastrointestinal tract*, nose*	mouse	oral, inhalation, intratracheal, intrapleural i.m. i.p.	negative, inadequate local inadequate
				rat	oral inhalation intratracheal, intra-bronchial, i.v. s.c., i.m. intrapleural i.p.	inadequate inadequate lung local local inadequate
				rabbit	i.v., inhalation	inadequate
				guinea-pig	inhalation	lung*
				mouse	skin, i.m. inhalation	local lung, skin
				rat	skin, inhalation	lung
21. Coal-tars (H. sufficient) ^h (A. sufficient)	occupational, medicinal	skin, inhalation	skin	mouse	skin, i.m. inhalation	local lung, skin
				rat	skin, inhalation	lung
				rabbit	skin	local
22. Coal-tar pitches (H. sufficient) (A. sufficient)	occupational	skin, inhalation	skin, lung*, larynx*, oral cavity*, bladder*	mouse	skin	local

Chemical or group of chemicals (degree of evidence of carcinogenicity) ^b	Humans			Animals		
	Main type of exposure ^c	Main route of exposure ^d	Target organ	Species	Route of exposure	Target organ
23. Conjugated oestrogens (H. sufficient) (A. inadequate)	medicinal	oral, skin	endometrium, breast*, ovary*, testis*	rat	oral	inadequate
24. Creosotes (coal-tar derived) (H. limited) (A. sufficient)	occupational	skin, inhalation	skin*	mouse	skin	local, lung
25. Cyclophosphamide (H. sufficient) (A. sufficient)	medicinal	oral, parenteral	bladder, lymphatic and haematopoietic system*, skin*	mouse	s.c. s.c., i.p.	haematopoietic system lung, mammary gland, local, various sites
				rat	i.p., oral oral i.p.	bladder haematopoietic system, neurogenic mammary gland
26. Dienoestrol (H. limited) (A. inadequate)	medicinal	oral	endometrium*	mouse	i.v.	inadequate
				guinea-pig	s.c.	inadequate
27. Diethylstilboestrol (H. sufficient) (A. sufficient)	medicinal	prenatal	cervix and vagina in daughters of treated mothers endometrium*, breast*	mouse	oral s.c.	mammary gland, uterus, cervix, vagina*, bone* mammary gland, haematopoietic system, ovary, testis
					intravaginal prenatal	cervix, vagina endometrium, cervix, vagina, lung, ovary
		rat	s.c. oral	mammary gland, pituitary gland, bladder* pituitary gland, mammary gland		
		hamster	s.c. prenatal	kidney uterus, cervix, vagina, testis*		
		dog	s.c.	ovary		
		frog	s.c.	liver, haematopoietic system		
28. Diethyl sulphate (H. limited) (A. sufficient)	occupational	inhalation	larynx*	rat	oral s.c. prenatal	forestomach* local nervous system
29. Melphalan (H. sufficient) (A. sufficient)	medicinal	injection, oral	leukaemia	mouse	i.p.	lung, lymphoreticular system
				rat	i.p.	local, mammary gland
30. Methoxsalen with u.v. A (PUVA) (H. sufficient) (A. sufficient)	medicinal	oral, skin	skin	mouse	oral, i.p., skin	skin
31. Mineral oils (containing various additives and impurities) (H. sufficient) ⁱ (A. sufficient) ^j	occupational	skin, inhalation,	skin (scrotum), bladder*, respiratory tract*, alimentary tract*	mouse	skin	local
		oral				
32. Mustard gas (H. sufficient) (A. limited)	occupational	inhalation	lung, larynx*, pharynx*	mouse	i.v., inhalation s.c.	lung local
33. 2-Naphthylamine (H. sufficient) (A. sufficient)	occupational	inhalation, oral, skin?	bladder	mouse	s.c., oral s.c. to newborns s.c.	liver lung local
				rat	oral	inadequate
				dog	oral	bladder

Chemical or group of chemicals (degree of evidence of carcinogenicity) ^b	Humans			Animals		
	Main type of exposure ^c	Main route of exposure ^d	Target organ	Species	Route of exposure	Target organ
34. Nickel and certain nickel compounds (H. limited) (A. sufficient)	occupational	inhalation, oral	respiratory tract* (nose, larynx, lung)	hamster	oral	bladder
				monkey	oral	bladder
				rabbit	oral	inadequate
				mouse	i.m. implants into various tissues	local
					i.p.	lung
				rat	inhalation	lung
					i.m., implants into various tissues	local
					i.v.	various sites
				hamster	i.m.	local
				rabbit	i.v. intramedullary	inadequate
	i.m.	local				
			guinea-pig	inhalation	inadequate	
35. Oral contraceptives Combined ^k (H. limited)	medicinal	oral	liver*,breast*, cervix*			
Sequential (H. limited)	medicinal	oral	endometrium*			
Some oestrogen/progestin combinations (A. limited)				mouse	oral	pituitary, mammary gland, cervix, uterus
					s.c.	mammary gland, cervix
				rat	oral	liver, mammary gland, pituitary
					s.c.	mammary gland
				monkey	oral	no effect (study in progress)
				dog	oral	mammary nodules
36. Oxymetholone (H. limited) (A. no data)	medicinal	oral	liver*	not tested		
37. Phenacetin (H. limited) (A. sufficient)	medicinal	oral	renal pelvis*, bladder*	rat	oral	urinary tract, nasal cavity
38. Phenytoin (H. limited) (A. limited)	medicinal	oral, i.v., i.m.	Nervous system*, lympho-haematopoietic system*	mouse	oral, i.p.	lympho-haematopoietic system
				rat	oral	inadequate
39. Shale-oils (H. sufficient) (A. sufficient)	occupational	skin, inhalation	skin (scrotum), colon*	mouse	skin	local
					intratracheal	lung
					i.m.	local
			rabbit	skin	local	
40. Smokeless tobacco products (H. sufficient) (A. inadequate)	cultural habit	oral	oral cavity, pharynx*, oesophagus*	mouse	oral, skin, s.c. (extracts), inhalation, intravesicular and intravaginal implantation	inadequate
				rat	topical to oral mucosa (extracts)	inadequate
				hamster	topical to oral mucosa (extracts), cheek pouch	inadequate

Chemical or group of chemicals (degree of evidence of carcinogenicity) ^b	Humans			Animals		
	Main type of exposure ^c	Main route of exposure ^d	Target organ	Species	Route of exposure	Target organ
41. Soots (H. sufficient) (A. sufficient) ^l	occupational, environmental	inhalation, skin	skin, lung	mouse	skin	local
42. Tobacco smoke (H. sufficient) (A. sufficient)	Cultural habit	inhalation	lung, bladder, renal pelvis, oral cavity, larynx, pancreas, stomach*	mouse rat hamster rabbit dog	inhalation inhalation inhalation inhalation inhalation	lung lung, oral cavity larynx inadequate inadequate
43. Treosulphan (H. sufficient) (A. no data)	medicinal	oral	leukaemia	not tested		
44. Vinyl chloride (H. sufficient) (A. sufficient)	occupational	inhalation, skin	liver (angiosarcoma), respiratory tract*, brain*, lymphatic and haematopoietic system*, gastrointestinal tract*	mouse rat hamster rabbit	inhalation inhalation, oral inhalation inhalation	liver (angiosarcoma), mammary gland, lung liver (angiosarcoma), Zymbal gland, various sites liver (angiosarcoma), skin, forestomach lung, skin

^aFrom *IARC Monographs* Volumes 1–41. This list does not include certain occupational exposures in boot and shoe manufacture and repair, coal gasification, coke production, furniture manufacturing and the rubber industry for which sufficient evidence or a causal association with human cancer exists; nor does it include known carcinogenic exposures such as auramine manufacture, isopropyl alcohol manufacture (strong-acid process), nickel refining and underground mining of haematite or certain exposures in aluminium production and iron and steel founding or the manufacture of magenta, which are probably associated with cancer in humans.

^bH, humans; A, animals.

^cThe main types of exposure listed are those with which the association with or the suspicion of cancer has been demonstrated.

^dThe main routes of exposure given may not be the only ones by which such effects occur.

^eNew data would provide limited evidence.

^fNew data would provide sufficient evidence.

^gMechlorethamine (nitrogen mustard), oncovine (vincristine), procarbazine, prednisone.

^hExposures occurring during the destructive distillation of coal.

ⁱFor oils used in occupations such as mulespinning, metal machining and jute spinning.

^jFor vacuum distillates, acid-treated oils, mildly solvent-refined oils, mildly hydrotreated oils, aromatic oils.

^kSufficient evidence for liver adenomas.

^lFor coal-soot and oil-shale soot extracts.

*Suspected association.

Materials and methods

The data base used for this paper comprises 30 chemicals, groups of chemicals and complex mixtures for which there has been established to be sufficient evidence for carcinogenicity to humans, and 14 for which there has been considered to be limited evidence for carcinogenicity to humans. Since industrial processes and occupational exposures cannot be adequately studied in experimental models, they are not considered in this paper. For the 44 exposures chosen, we have compiled information on the route of exposure and affected target organs for humans and experimental animals. Recently published data that change the original evaluations substantially are also considered.

The epidemiological data on chemicals and exposures considered in Supplement 4 to the *IARC Monographs* (3) were re-evaluated in a recent article (48) with the aim of identifying the target organs involved, to complement the evaluations of the evidence for association between the exposure and cancer in humans made by the relevant IARC Working Group. The conclusions of that review have been used in this paper; for chemicals and complex mixtures evaluated by Working Groups that met subsequent to the meeting to formulate Supplement 4, we have attempted to identify the main target organs on the basis of the published evaluations.

The routes of administration and corresponding target organs in animals were identified from the summaries of published data as reported in the *IARC Monographs*.

Results

Table II is a summary of the evaluations of carcinogenicity, the routes of exposure and the target organs affected in humans and in experimental animals for the 44 chemicals, groups of chemicals

Table III. Degrees of evidence for carcinogenicity to humans and to animals of 44 exposures

Humans	Animals			Total
	Sufficient	Limited	Inadequate/ no data	
Sufficient	19	7	4	30
Limited	8	3	3	14
Total	27	10	7	44

and complex mixtures for which there is sufficient or limited evidence for carcinogenicity to humans. Of the 30 exposures for which there is sufficient evidence of carcinogenicity to humans, the animal data provide sufficient evidence for 19 (4-amino-biphenyl, asbestos, benzene, benzidine, bis(chloromethyl)ether and technical chloromethyl methyl ether, chlorambucil, chromium and certain chromium compounds, coal-tars, coal-tar pitches, cyclophosphamide, diethylstilboestrol (DES), melphalan, methoxsalen with u.v. A (PUVA), mineral oils (containing various additives and impurities), 2-naphthylamine, shale oils, soots, tobacco smoke, vinyl chloride), limited evidence for seven [analgesic mixtures containing phenacetin, arsenic and certain arsenic compounds, azathioprine, betel quid (containing tobac-

co), *N,N*-bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine), 1,4-butanediol dimethanesulphonate (Myleran), mustard gas] and inadequate evidence or no data for four (certain combined chemotherapy regimens for lymphomas including MOPP, conjugated oestrogens, smokeless tobacco products, treosulphan). Of the 14 exposures for which there is limited evidence of carcinogenicity to humans, the experimental data provide sufficient evidence for eight (acrylonitrile, aflatoxins, beryllium and beryllium compounds, cadmium and cadmium compounds, creosotes (coal-tar derived), diethyl sulphate, nickel and certain nickel compounds, phenacetin), limited evidence for three [auramine (technical grade), oral contraceptives, phenytoin] and inadequate evidence or no data for three (chloramphenicol, dienestrol, oxymetholone). These comparisons are shown in Table III.

Although at the time the evaluations were made there was considered to be limited evidence for the carcinogenicity of benzene to experimental animals, recent studies in mice and rats (49,50) indicate a clear carcinogenic effect in several organs in both species. Similarly, since arsenic and certain arsenic compounds were considered in 1982, studies on hamsters with arsenic trioxide (51,52) show induction of a low incidence of respiratory-tract tumours following intratracheal instillation. The four exposures for which there is sufficient evidence of carcinogenicity to humans that have not been adequately tested in experimental animals are: certain combined chemotherapy regimens for lymphomas including MOPP, conjugated oestrogens, smokeless tobacco products and treosulphan. However, for some individual components of MOPP – nitrogen mustard and procarbazine – there is sufficient evidence of carcinogenicity in experimental animals (32). Further, it is reasonable to believe that conjugated oestrogens would react similarly to other oestrogens in experimental animals (27); for some oestrogens there is sufficient evidence of carcinogenicity to animals.

Thus, for 37/44, or 84%, of the human exposures considered there are findings of carcinogenicity in experimental animals. The seven remaining chemicals and complex mixtures have simply not been adequately tested in experimental animals and no statement can be made regarding their carcinogenicity in animal models.

For the 19 chemicals, groups of chemicals and complex mixtures for which there is sufficient evidence of carcinogenicity to both humans and experimental animals, there is a good consistency between the target organ(s) in humans and those in various animal species, when there were similar routes of exposure. Occupational exposure to 4-aminobiphenyl, probably by inhalation, skin absorption and ingestion, is associated with the induction of bladder cancer in humans; oral exposures of mice, rabbits and dogs also lead to the production of bladder cancer. Occupational exposure to asbestos fibres by inhalation leads to the development of lung carcinomas and pleural mesotheliomas in humans; similar findings have been obtained in rats after inhalation exposure, and intrapleural administration to rats, hamsters and rabbits results in pleural mesotheliomas. Inhalation of benzene by humans is associated with leukaemia; recent inhalation studies in rats (49) show that benzene induces Zymbal-gland tumours and to a lesser extent myelogenous leukaemia, although stronger evidence for the induction of Zymbal-gland tumours, leukaemia and malignant lymphoma comes from recent studies in which benzene was administered to rats and mice by oral gavage (50). Occupational exposure to benzidine, probably by inhalation and ingestion, leads to bladder cancer in humans, as does oral exposure in dogs. Exposure to bis(chloromethyl)ether and chloromethyl methyl ether in air produces lung cancer in humans;

such cancers are also induced in mice and rats following inhalation exposure. Chlorambucil, which is given orally or *i.v.* during chemotherapy, produces leukaemia in humans and lympho-haematopoietic tumours in rats following its *i.p.* injection. Occupational exposures to chromates in air have been associated with lung cancer in humans; intrabronchial administration of calcium chromate produces lung cancers in rats. Skin contact to coal-tars and coal-tar pitches produce skin cancer in humans and in mice and rabbits. Oral exposure of either humans or rats to cyclophosphamide produces bladder and haematopoietic tumours. DES induces clear-cell adenocarcinomas of the vagina and cervix in the offspring of pregnant women treated with this drug; various tumours of the reproductive tract are produced in female offspring of mice and hamsters administered DES by *s.c.* injection or oral administration during pregnancy. Melphalan, which is given orally or by injection, produces leukaemia in humans and lymphoreticular tumours following *i.p.* injection in mice. Oral administration of methoxsalen with *u.v.* A exposure produces skin carcinomas in both humans and mice. Topical exposure to mineral oils (containing various additives and impurities) is associated with skin cancer in both humans and mice. Occupational exposures to 2-naphthylamine, usually by inhalation and ingestion, are associated with bladder cancer in humans; bladder cancer was also observed in hamsters, dogs and monkeys administered 2-naphthylamine by oral administration, and a recent study (53) shows that the rat bladder is also sensitive to this aromatic amine. Shale-oils produce skin cancer in humans, mice and rabbits following local contact with the materials. Occupational exposures to soots by inhalation and skin contact have been associated with lung and skin cancer in humans; in mice, skin application and *s.c.* injection of soots cause local tumours. Tobacco smoke has been associated with cancers of the oral cavity, larynx, lung, bladder, pancreas and renal pelvis in humans; after exposure to whole or mainstream smoke from cigarettes, cancers of the lung have been observed in mice, of the lung and oral cavity in rats and of the larynx in hamsters. Inhalation of vinyl chloride produces liver angiosarcoma in humans and in mice, rats and hamsters.

For the seven chemicals or complex mixtures for which there is sufficient evidence of carcinogenicity to humans but limited evidence in experimental animals, the findings in experimental animals are in many cases similar to the biological effects seen in humans. Although analgesic mixtures containing phenacetin, which are causally associated with the induction of cancer of the renal pelvis following long-term oral ingestion by humans, have produced only liver tumours in rats after oral administration, phenacetin itself also produces urinary-tract tumours in rats. Certain arsenic compounds are causally associated with lung and skin cancer in humans. Recent studies on arsenic trioxide have shown some increase in the incidence of lung carcinomas in hamsters following intratracheal administration of the compound (51,52); however, no experimental model has yet demonstrated the induction of skin cancer in animals as seen in humans. Azathioprine, which is causally associated with the induction of non-Hodgkins' lymphoma in humans, can produce lymphomas in mice following parenteral injection. The use of betel quid with tobacco is associated with oral cancer in humans; experimental models of this habit are difficult to design, but implantation of wax pellets containing the betel-quid components has produced local tumours in the hamster cheek pouch. Myleran, a cancer chemotherapeutic agent associated with the production of leukaemia in humans, has produced lymphomas following *i.p.* or *i.v.* injection in mice. Mustard gas, which is associated with

the production of lung cancer in humans exposed occupationally, has also produced lung tumours in mice, although the degree of malignancy was not specified. In the case of Chlornaphazine, which is associated with the production of bladder tumours in humans following its therapeutic use, limited studies by s.c. injection in rats and by i.p. injection in mice showed the production of local tumours in rats and an increased incidence of lung tumours in mice. This chemical is no longer produced and will probably never be adequately tested in experimental animals.

For the 14 chemicals, groups of chemicals and complex mixtures for which there is only limited evidence of carcinogenicity to humans, some similarities between target organ(s) in humans and those affected in experimental animals have also been demonstrated. For instance, oral exposure to aflatoxins is associated with liver cancer in humans, mice, rats, ducks, primates and fish. However, no systematic attempt to make such comparisons for all these compounds has been made, since the target organs in humans have not yet been firmly established.

Discussion

Analysis of the available carcinogenicity data on experimental animals indicates that 84% of the 44 exposures with sufficient or limited evidence of carcinogenicity to humans also have some carcinogenic activity in animals. The remaining chemicals and complex mixtures have not been adequately tested for carcinogenicity in experimental animals. In no case was there 'no evidence of carcinogenicity'. The sample size of 44 may be slightly overstated since some of the complex mixtures (e.g. certain mineral oils, shale-oils and soots) may contain common components such as polycyclic aromatic compounds which produce or contribute to the similar effects seen in the species tested and humans. For all those exposures for which there is sufficient evidence of carcinogenicity in both humans and experimental animals, there is a target organ in common between humans and at least one animal species.

This observation is impressive since there are a number of *a priori* reasons for not expecting target organs to be the same in humans and animals and, indeed, in all animal species. Firstly, the capacity of carcinogens to induce tumours in various organs could differ between species due, for example, to differences in toxicokinetics, carcinogen metabolism, DNA repair and other variables. Secondly, it is sometimes not possible to reproduce the exact exposure conditions in experimental animals that occur for humans. This has been the case for cigarette smoke, owing to the peculiar anatomy and physiology of the rodent respiratory system. In addition, carcinogens may be deposited on the complex nasal surfaces of rodents whereas in humans, who breathe oro-nasally, deposition may be less. Certain arsenic compounds that produce skin cancer in humans do not appear to do so in experimental animals; this may be due to the synergistic effect on humans of u.v. light, from which most laboratory rodents are protected.

In order to evaluate the value of animal bioassays, the parameters sensitivity and specificity are generally used. The first measures the proportion of true positives detected as positive by the assay, while the latter measures the proportion of true negatives that are declared to be negative. In this paper, the proportion of human carcinogenic exposures that produce a positive result in at least one animal species and the proportion that have an effect at the same target organ were calculated. These are both measures of the sensitivity of the animal cancer tests in detecting human carcinogens. Without a series of proven human

non-carcinogens, however, it is not possible to estimate the specificity of the animal experiments in the same manner.

From the practical point of view of human hazard prediction, sensitivity and specificity are not the key parameters of interest. Rather, it is the false-positive and false-negative rates that are of concern. These are, respectively, the probability that a chemical positive in an animal bioassay is not a human carcinogen, and the probability that a chemical not carcinogenic in animal experiments is a human carcinogen. Using a simple probability theory, these parameters may be expressed in terms of sensitivity and specificity, and the *a priori* probabilities that a chemical is a human or animal carcinogen.

Defining H and A as carcinogenicity to humans and carcinogenicity to animals, \bar{H} and \bar{A} as the respective non-carcinogenicities, P as the 'probability of', and $(X|Y)$ as X conditional on Y , we have

$$\begin{aligned} \text{Sensitivity of animal bioassays} &= P(A|H) = 1 - P(\bar{A}|H) \\ \text{Specificity of animal bioassays} &= P(\bar{A}|\bar{H}) = 1 - P(A|\bar{H}) \\ \text{False-positive rate} &= P(H|\bar{A}) = 1 - P(\bar{H}|\bar{A}) \\ \text{False-negative rate} &= P(\bar{H}|A) = 1 - P(H|A) \end{aligned}$$

Then, by the simple probability rule known as Bayes' theorem,

$$P(H|A) = P(A|H) \times P(H)/P(A)$$

From the present study, we find that $P(A|H)$ is close to 1: most human carcinogens seem to be animal carcinogens. If we further suppose that $P(H)$ is roughly equal to $P(A)$ over the ensemble of potential chemical exposures, then $P(H|A)$ is also close to 1, and the false-positive rate, $P(\bar{H}|A)$, is close to zero. Thus, animal carcinogenicity tests provide valid qualitative predictions for human hazard. Of course, if $P(H)$ is considerably smaller than $P(A)$, indicating that overall there are fewer human than animal carcinogens, this reasoning breaks down. In addition the sensitivity of animal cancer tests could be overestimated by the results of this paper since many human carcinogens have been tested more extensively than is usual for compounds whose carcinogenic effect in humans is unknown. Modern cancer bioassays, however, now include two species and larger numbers of animals.

Although no data are available to quantify the parameters $P(H)$ and $P(A)$, the conclusion from the present survey is that there is a strong correspondence between the carcinogenicity of chemicals in humans and their effect in animals. If the overall percentages of human and animal carcinogens are roughly equal, this translates into a very low false-positive rate for animal bioassays.

A further reason for strongly believing in the relevance to humans of predictions from experimental data is that there are a number of human carcinogens which were first demonstrated to be carcinogens in experimental animals. These include 4-aminobiphenyl, DES, melphalan, methoxsalen with u.v. A, mustard gas and vinyl chloride.

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