Ann. Rev. Pharmacol. Toxicol. 1979. 19:511–30

THE PREDICTIVE VALUE OF RODENT CARCINOGENICITY TESTS IN THE EVALUATION OF HUMAN RISKS

❖6752

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INTRODUCTION

In the last fifteen years various authors have estimated that from about 70% to 90% of all human cancer cases can be attributed to environmental causes (4, 19, 20, 61). These percentages were based on two main considerations: (*a*) a certain number of environmental factors have been identified in the etiology of human cancer, and (*b*) significant variations in the incidence of cancer in different population groups in different countries suggest that environmental risk factors play an important role.

The variation in different countries in the incidence of cancers that occur at the most common target organs fluctuates betweeen fourfold and more than one hundredfold (10, 19). It was therefore proposed that the lowest observed incidence rates could be taken as a baseline and that any increase over this baseline could be attributed to environmental factors, of which only a few so far have been identified. Ignoring, or disregarding, such considerations, it has been simplistically inferred that 90% of all cancer cases could now be prevented; this is certainly not what the above-mentioned authors meant to imply. The euphoria so engendered has not yet been dispelled, despite the words of caution that some authors have tried to interject, in an attempt to define environment and the role of environmental factors (21).

An assessment of the number of cancers that could, in fact, be prevented would obviously be of paramount importance; however, it would be difficult

0362-1642/79/0415-0511$01.00

to quantify what can be achieved today in terms of primary prevention of cancer. This difficulty stems from two sources. The first is that although it is reasonable to assume that a large proportion of cancer cases are of environmental origin, etiological factors have not yet been identified for cancers that occur at some of the most frequent target organs (e.g. prostate and colon in men, breast and colon in women). It has been suggested that dietary factors play a prominent role in some of the most commonly occurring cancers, but the nature of the specific environmental determinants is still to be defined (10). The second source of difficulty is that for a large proportion of cancers that occur at other frequent target organs (in particular, the lung), environmental factors have been identified, such as cigarette smoking, which have been related to individual "lifestyle" (63). This finding may have another simplistic implication—that these cancers can be prevented by individual choice. The term *lifestyle* does not, in fact, distinguish between true personal choice and habitual behavior, like smoking, the drinking of alcohol, and certain dietary habits, which are determined by a variety of causal inputs. Personal choice is just one of those inputs, and it is usually less prominent than social influences.

The danger of imposing such a dichotomy between individual and social responsibilities has been clearly underlined with regard to public health in general (14, 15, 55). The example was given for instance, of nineteenth century health reformers who concentrated their activity not on persuading individuals to boil water but rather on pressing for the construction of safe water supplies and sewage disposal systems (55). To state that primary prevention of cancer depends mainly on personal action, whereby individuals control their own environment and that of their family, therefore implies an unrealistic perception of past and present societies.

It is difficult to discern how much of this attitude is influenced by the biomedical model of disease, which has dominated Western society up to the present and is only now beginning seriously to be questioned. The biomedical model demands, in fact, that on the one hand disease be dealt with "as an entity independent of social behavior" and on the other hand that "behavioral aberrations be explained on the basis of disordered somatic (biomedical or neurophysiological) processes" (11). Those who preach individual safety risk, in fact, being enmeshed, consciously or unconsciously, in the strong net of political and economic interests, whose powers concur formidably to repell any attempts to alter biomedical dogmatism.

Social influences are indeed the most relevant environmental factors to be altered in implementing primary prevention. In the case of tobacco smoking, for example, individual efforts to prevent cancer by avoiding smoking or, to a lesser extent, by stopping smoking are conspicuously dwarfed by industrial (5) and governmental opposition.

Personal choice plays little or no role in occupational or iatrogenic exposures, and the term lifestyle should not be used to describe such exposures, which are, in fact, those in which intervention can today be most direct and effective.

PRIMARY AND SECONDARY PREVENTION

It would seem totally unnecessary to recall that the final goal of cancer control, i.e. reduction of mortality from cancer, can be achieved either by the improvement of diagnostic and therapeutic measures or by decreasing morbidity, if this obvious postulate were not at the center of the present confusion. The private medical profession, as well as the biomedical profession, has been largely in favor of the purely medical approach to cancer control. It is also natural that the public support their view, since what is obviously urgent to patients is to recover from the disease or to be relieved from their suffering.

The effectiveness of the medical approach to cancer control should be easier to verify than the effectiveness of measures aimed at decreasing morbidity, i.e. common primary prevention. The former can be approached by examining cancer survival rates over the last decades and evaluating whether these have improved recently. For the latter, the effectiveness of measures taken will be perceived only 20 or 30 years later; even then, in fact, such effectiveness may be difficult to assess if one does not take into account that while some carcinogenic exposures or cancer-risk factors have been eliminated, others may have entered the environment. Effective prevention can be achieved only if it is applied both to the elimination of recognized or suspected carcinogens already present in our environment and to the prevention of the emission of potential carcinogens into our environment.

Have survival rates of cancer patients really improved in the recent past? There does not seem to be a consensus on this issue. In a recent survey, for instance, incidence and mortality rates for most cancers appear to have changed proportionally (12). If, therefore, progress in cancer control is measured by the number of people who get cancer and the number who die from it, survival rates do not seem to indicate that real progress has been made. There may be a better way of measuring the efficacy of the therapeutic approach to cancer control, but certainly the analysis of survival rates is rather discouraging.

Paradoxically, it would appear that morbidity has done slightly better than mortality, at least in adults and in males. This may to a large extent be attributable to the fact that the increase in incidence in males is mostly due to an increase in lung cancer, whose prognosis is almost inevitably poor, and to urinary bladder cancer (8). It has also been reported (*a*) that patients

of higher social classes tend to have a better survival rate than those of lower social classes, since patients in private hospitals survive cancer better than patients in public hospitals and (*b*) that this cannot be attributed solely to the fact that people of lower social classes have access to therapy only when the stage of the disease is most advanced and therefore incurable (12). In addition, if white and nonwhite populations in the United States are taken broadly to indicate higher and lower social classes, respectively, the upward incidence trends among nonwhites, as compared with white males (8), would indicate that people of lower social classes, are less privileged also with regard to incidence. In general, it would appear that whatever can be achieved with improved therapeutic measures costs more than the public can afford (7, 53). Therefore, in spite of some indubitable success in the therapy of childhood cancers (13) and of Hodgkin's disease, a better prognosis for certain other cancers, like the cervix and large bowel, and improvement of diagnostic methods, the progress of cancer control through secondary prevention has been slow and limited.

As has been stressed in a recent historical review of cancer control in the USA (5), very few people paid attention to W. C. Hueper when in the 1930s he tried to convince public health authorities that many workers were exposed by their occupation to carcinogenic factors that were responsible for a much larger number of cancers than was then suggested. Even in 1967 when Doll (9) published his masterly lecture on the prevention of cancer, he was probably addressing a medical and public health audience still incapable of accepting the wide implications of primary prevention.

The situation has now partly changed, and cancer is increasingly being recognized as being, at least in part a man-made disease, a significant part of which can be related to the technological advances made by industry since the beginning of the twentieth century (5).

In opposition to this view, which one would reasonably believe to be unbiased, several authors voiced opinions that were not so different from those that Hueper fought more than 40 years ago. This may be due to the fact that some spokesmen for industry tend to equate any indication of a possible carcinogenic risk of industrial chemicals with a direct attack on industry at large, and to consider anyone who is concerned about health risks related to industrialization as an anti-industry visionary (17).

A comparison of the number of chemicals presently in use with the number for which adequate information on possible toxicity exists gives rise to some perplexity. In fact, 4,039,907 chemicals appear in the computerized registry of the Chemical Abstracts Service (CAS) of the American Chemical Society, of which 3.4 million are organic and inorganic chemicals whose structures are fully defined. Although the number of chemicals in the register is increasing at the rate of 6000 per week, only a minority of these

are actually in everyday use; the CAS has apparently estimated that 63,000 chemicals are in common use (47). The fact that acute and chronic toxicity data are available for only a minority of these can be explained by the rapid development of industry during a period in which health problems related to chemicals did not receive adequate attention. We are therefore faced at present with a backlog accumulated over many decades. Since an increasing effort to investigate the possible toxicity of environmental chemicals has been initiated only in recent years, it is no surprise that an increasing number of reports indicate toxic effects for chemicals. The greater awareness of a relationship between health problems and industrial development is obviously resulting in an increase in the cost of developing new chemicals, which may, in turn, result in a slowdown in their production. No small part of the enthusiasm for short-term carcinogenicity and related tests probably has its roots in the legitimate desire to reduce this cost increase. It is interesting to learn, however, that production and sales of most major chemicals over the last years are reported to be increasing (54).

However, the emphasis on the "moral obligation to preserve one's own health" is still gaining momentum (46), and meanwhile, information is accumulating on the possible role of environmental factors in causing human cancer (3, 22).

EXPERIMENTAL CARCINOGENESIS

The first successful long-term carcinogenicity test was carried out in 1915, when tumors were produced experimentally by painting rabbits' ears with coal tar (64). This result was obtained with a chemical mixture which was associated with a carcinogenic effect in humans; this indicated the possiblility of confirming observations in humans experimentally. Much of the credibility of this confirmation probably lay in the fact that the tumors obtained were comparable with those observed in people exposed to coal tar.

Following these studies, experimental cancer research entered a period during which most efforts were divided almost equally between attempts to identify the pure chemicals responsible for the carcinogenic effect of the coal tar mixture, and attempts to identify carcinogens pertaining to chemical classes other than the polycyclic hydrocarbons. Notable achievements in this period were the identification of 1,2,5,6-dibenzanthracene (44) and of 3,4-benzo(a)pyrene (6) as carcinogenic components of coal tar and the induction of tumors of the liver in rats by ortho-aminoazotoluene (65) and by N,N-dimethyl-4-aminoazobenzene (45). While, in the first case, the research was addressed to a chemical mixture for which there was evidence of a carcinogenic effect in humans in the case of the two azo dyes, experi-

mental results for the first time supplied evidence of the carcinogenicity of chemicals for which an effect in humans had not been observed.

In 1937 and 1938, Hueper et al (23, 24) published their reports of the induction of bladder tumors in dogs by β-naphthylamine. Within the fields of evidence provided by human observation and by experimental results, Hueper's results again confirmed an observation in humans in an experimental model. Further experimentation on β-naphthylamine showed that its target organs varied not only between humans and experimental animals, but also between different experimental animal species.

In this way, long-term tests were introduced (*a*) to prove or disprove that chemicals or chemical mixtures suspected of producing cancer in humans could induce tumors in experimental animals, the induction of tumors in experimental animals being required as confirmation of the suspected carcinogenic activity of the chemical or chemical mixture in humans, and (*b*) to verify, independently from observations in humans, that a chemical could produce cancer in an animal model. The main end point of the tests was therefore of a qualitative nature.

SIGNIFICANCE OF EXPERIMENTAL RESULTS

The difficulties in assessing the significance of experimental results for predicting similar hazards in humans are both qualitative and quantitative and can be summarized in the following questions: 1. Are chemicals that have been shown to be carcinogenic to experimental animals also carcinogenic to humans? 2. Do experimental animals (rodents, in particular) and humans have similar susceptibility to the carcinogenic effect of chemicals, or are rodents incomparably more susceptible than humans? (58).

A partial answer to the first question is usually given by reversing the terms of the question: Most of the chemicals that are carcinogenic to humans are carcinogenic to at least one, and in most cases to more than one, animal species. Another partial answer is that experimental evidence of carcinogenicity has in several cases preceded human observation and could have predicted it.

CORRELATION BETWEEN HUMAN AND EXPERIMENTAL DATA

At least 26 chemicals or industrial processes have proven or strongly suspected associations with cancer in humans (Table 1) (60). Among these are five industrial processes—the manufacture of auramine, the use of cadmium compounds, chromate-producing industries, hematite mining, and nickel refining—for which no direct correlation between human and experimental

animal data can be made because the chemical identity of the agent responsible for the carcinogenic effect in humans is unknown. There is some evidence, however, that, with the exception of hematite, the animal model responds to some of the factors that might be responsible for the effects in humans.

In fact, auramine (of unknown purity) produces liver tumors in rats and mice; many chromate salts produce local sarcomas following repeated intramuscular injections, and cadmium chromate induces lung tumors in rats after intrabronchial implantation; many cadmium compounds (including cadmium powder, chloride, sulfide, phosphate, and oxide) produce sarcomas in rats after repeated subcutaneous or intramuscular injections. Nickel subsulfide induces malignant lung tumors in rats after inhalation; many nickel compounds produce local sarcomas after repeated subcutaneous injections in rats; and inhalation of nickel carbonyl has been reported to produce a few malignant lung tumors in rats. The agent responsible for lung tumors in workers in hematite mining has not been identified, but radon is suspected. Ferric oxide was not carcinogenic in mice, guinea pigs, or hamsters when given by inhalation or intratracheally.

Four other compounds among the 26 listed in Table 1—namely, benzene, chloramphenicol, isopropyl oils, and oxymetholone—have not been adequately tested for carcinogenicity; recent studies of phenacetin, however, indicate that it is carcinogenic to rats (43). For arsenic, alone among the other 16 compounds, results from available carcinogenicity tests are negative, although there is sufficient evidence that arsenic compounds induce skin and lung cancer in humans. Of the remaining 15 compounds two (melphalan and mustard gas) are carcinogenic in one or several animal species, and the others in several.

For these 15 chemicals for which a correlation can be made between human and experimental data, a comparison of organ specificities indicates that they can have the same target organ(s) in humans in at least one of the experimental animal species tested (the similar target organ may be found in only one of the species tested). Although it might appear that the chances of finding similar target organs are greater if similar routes of exposure are used, chemicals that have been found to be carcinogenic in both humans and experimental animals were also carcinogenic in the latter when administered by routes different from the one(s) by which humans are exposed. In addition, multiple target organs are found more often in experimental animals than in humans.

A notable exception with regard to similar organ specificity is N,N-bis-(2-chloroethyl)-2-naphthylamine, which produces bladder tumors in humans and lung and local tumors in mice and rats respectively. Cyclophosphamide induces bladder tumors in humans and tumors at various sites in mice and

Table 1 Chemical or industrial processes associated or strongly suspected of being associated with cancer induction in humans, and comparison of target organs and main routes of exposure in animals and humans[a, b]

Chemical or industrial process	Main type of exposure[c]	Target organs—humans (main route of exposure)[d]		Target organs—animals (route of exposure)	
1. Aflatoxins	Environmental, occupational[e]	Liver	(Oral, inhalation)[e]	Rat	Liver, stomach, colon, kidney (oral)
				Fish, duck, marmoset, tree shrew, monkey	*Liver (oral)*
				Rat	Liver, trachea (intratracheal), liver (i.p. injection)
				Mouse, rat	Local (s.c. injection)
				Mouse	Lung (i.p. injection)
2. 4-Aminobiphenyl	Occupational	Bladder	(Inhalation, skin, oral)	Mouse, rabbit, dog	Bladder (oral)
				Newborn mouse	Liver (s.c. injection)
				Rat	Mammary gland, intestine (s.c. injection)
3. Arsenic compounds	Occupational, medicinal, environmental	Skin, lung, liver[e]	(Inhalation, oral, skin)	Mouse, rat, dog	Inadequate, negative (oral)
				Mouse	Inadequate, negative (skin, s.c., i.v. injection)
4. Asbestos	Occupational	Lung, pleural cavity, gastrointestinal *tract*	(Inhalation, oral)	Mouse, rat, hamster, rabbit	Lung, pleura (inhalation and intratracheal)
				Rat, hamster	*Local (intrapleural)*
				Rat	Local (i.p., s.c. injection)
					Various sites[e] (oral)
5. *Auramine (manufacture of)*	*Occupational*	*Bladder*	*(Inhalation, skin, oral)*	*Mouse, rat*	*Liver (oral)*
				Rabbit, dog	Negative (oral)
				Rat	Local, liver, intestine (s.c. injection)
6. Benzene	Occupational	Hemopoietic system	(Inhalation, skin)	Mouse	Inadequate (skin, s.c. injection)
7. *Benzidine*	*Occupational*	*Bladder*	*(Inhalation, skin, oral)*	Mouse	*Liver (s.c. injection)*
				Rat	Liver (oral), Zymbal gland, liver, colon (s.c. injection)
				Hamster	Liver (oral)
				Dog	Bladder (oral)
8. Bis (chloromethyl) ether	Occupational	Lung	(Inhalation)	Mouse, rat	Respiratory tract (inhalation)
				Mouse	Skin (skin), local, lung (s.c. injection)
				Rat	Local (s.c. injection)
9. Cadmium-using industries (possibly cadmium oxide)	Occupational	Prostate, lung[e]	(Inhalation, oral)	Rat	Local, testis (s.c. or i.m. injection)
10. Chloramphenicol	Medicinal	Hemopoietic system	(Oral, injection)	No adequate tests	
11. Chloromethyl methyl ether [possibly associated with bis (chloromethyl) ether]	Occupational	Lung	(Inhalation)	Mouse	Initiator (skin), lung[e] (inhalation), local, lung (s.c. injection)
				Rat	Local[e] (s.c. injection)
12. Chromium (chromate-producing industries)	Occupational	Lung, nasal cavities[e]	(Inhalation)	Mouse, rat	Local (s.c., i.m. injection)
				Rat	Lung (intrabronchial implantation)
13. Cyclophosphamide	Medicinal	Bladder	(Oral, injection)	Mouse	Hemopoietic system, lung (i.p., s.c. injection), various sites (oral), bladder[e] *(i.p. injection)*

Table 1 *(continued)*

Chemical or industrial process	Main type of exposure[c]	Target organs—humans (main route of exposure)[d]		Target organs—animals (route of exposure)	
				Rat	Mammary gland (i.p. injection), various sites (i.v. injection)
14. Diethylstilbestrol	Medicinal	Uterus, vagina	(Oral)	Mouse	Mammary (oral)
				Mouse	Mammary, lymphoreticular, testis (s.c. injection, s.c. implantation), vagina (local)
				Rat	Mammary, hypophysis[e], bladder (s.c. implantation)
				Hamster	Kidney (s.c. injection, s.c. implantation)
				Squirrel, monkey	Uterine serosa (s.c. implantation)
15. Hematite mining (? radon)	Occupational	Lung	(Inhalation)	Mouse, hamster, guinea pig	Negative (inhalation, intratracheal)
				Rat	Negative (s.c. injection)
16. Isopropyl oils	Occupational	Nasal cavity, larynx	(Inhalation)	No adequate tests	
17. Melphalan	Medicinal	Hemopoietic system	(Oral, injection)	Mouse	Initiator (skin), lung, lymphosarcomas (i.p. injection)
				Rat	Local, mammary (i.p. injection)
18. Mustard gas	Occupational	Lung, larynx	(Inhalation)	Mouse	Lung (inhalation, i.v. injection), local (s.c. injection)
19. 2-Naphthylamine	Occupational	Bladder	(Inhalation, skin, oral)	Hamster, dog, monkey	Bladder (oral)
				Mouse	Liver, lung (s.c. injection)
				Rat, rabbit	Inadequate (oral)
20. Nickel (nickel refining)	Occupational	Nasal cavity, lung	(Inhalation)	Rat	Lung (inhalation)
				Mouse, rat, hamster	Local (s.c., i.m. injection)
				Mouse, rat	Local (i.m. implantation)
21. N, N-Bis (2-chloroethyl)-2-naphthylamine	Medicinal	Bladder	(Oral)	Mouse	Lung (i.p. injection)
				Rat	Local (s.c. injection)
22. Oxymetholone	Medicinal	Liver	(Oral)	No adequate tests	
23. Phenacetin	Medicinal	Kidney	(Oral)	No adequate tests[f]	
24. Phenytoin	Medicinal	Lymphoreticular tissues	(Oral, injection)	Mouse	Lymphoreticular tissues (oral, i.p. injection)
25. Soot, tars, oils	Occupational, environmental	Lung, skin (scrotum)	(Inhalation, skin)	Mouse, rabbit	Skin (skin)
26. Vinyl chloride	Occupational	Liver, brain,[e] lung[e]	(Inhalation, skin)	Mouse, rat	Lung, liver, blood vessels, mammary, Zymbal gland, kidney (inhalation)

[a] From Tomatis et al 1978. *Cancer Res.* 38:877–85.

[b] The chemicals or industrial processes listed in this table should not be taken as a thorough compilation of known human chemical carcinogens. They reflect only those chemicals which have been evaluated by the IARC Monograph Programme until now.

[c] The main types of exposure mentioned are those by which the association with cancer has been demonstrated. Exposure via the general environment may also occur.

[d] The main routes of exposure given may not be the only ones by which such effects could occur.

[e] Denotes indicative evidence.

[f] The induction of tumors of the nasal cavities in rats administered phenacetin has recently been reported.

rats, but there is only indicative evidence that bladder tumors are produced in mice. Similarly, chloromethyl methyl ether, possibly associated with bis(chloromethyl)ether, induces lung tumors in humans and local tumors in mice with only indicative evidence of the induction of lung tumors.

As mentioned above, the experimental evidence for the carcinogenicity of aflatoxin, 4-aminobiphenyl, bis(chloromethyl)ether, diethylstilbestrol, melphalan, mustard gas, and vinyl chloride, preceded evidence in humans; the cases of diethylstilbestrol, 4-aminobiphenyl, vinyl chloride, and bis-(chloromethyl)ether have been discussed at length elsewhere (58). It is worth mentioning that with some of these chemicals the first observations of tumor induction in experimental animals did not indicate that tumors occurred at the same organs which later appeared to be the target(s) in humans.

CRITICISMS OF LONG-TERM CARCINOGENICITY TESTS

Experimental procedures have been widely criticized, notably, because in many instances the route of administration used does not correspond to the route by which humans are exposed, because the doses given are high and sometimes exceed considerably the possible level of human exposure, and, in more general terms, because the experimental model used is considered too sensitive. The importance of the route of exposure has been mentioned briefly above.

Although it would seem reasonable to recommend that, whenever possible, experimental animals be exposed by the same routes by which humans are exposed, this is neither always possible nor a strict requirement for all chemicals under test. It is certainly to be recommended that food additives be tested by the oral route, or at least, also by the oral route. Similarly, volatile chemicals, for which human exposure presumably occurs mainly or only through inhalation, should be tested also by inhalation. However, inhalation facilities are presently limited, and to make testing by inhalation a strict requirement would limit very considerably the number of chemicals that could be tested. In addition, the carcinogenicity of some volatile chemicals has been demonstrated when they were given by routes other than inhalation.

The subcutaneous route, which is among those used most frequently, is often said to be unreliable. However, of the 15 chemicals described above that are associated with the induction of tumors in humans and for which a direct correlation between human and experimental data is possible, 11 [aflatoxin, 4-aminobiphenyl, asbestos, benzidine, bis(chloromethyl)ether, chloromethyl methyl ether, cyclophosphamide, diethylstilbestrol, mustard

gas, 2-naphthylamine, and N,N-bis(2-chloroethyl)-2-naphthylamine] were also tested with positive results by the subcutaneous route. As was mentioned above with regard to experimental evidence of the carcinogenic effect of a volatile chemical bis(chloromethyl)ether was carcinogenic when it was given topically and subcutaneously to mice and subcutaneously to rats, and later results confirmed its carcinogenicity by inhalation. Thus, although some good arguments have been advanced to show that the induction of local sarcomas following repeated subcutaneous injections in rats is an unreliable index of the carcinogenicity of a compound (16, 18), a recent survey of the literature has indicated that the subcutaneous route is as reliable as any other in predicting that a chemical would be carcinogenic when given by other routes (58, 59).

The argument that experimental models are exaggeratedly sensitive has certain obvious weaknesses. The induction of liver tumors in mice is often cited as an example of this exaggerated sensitivity; however, in a survey of a number of chemicals to ascertain the correlation between their capacity to induce parenchymal liver tumors in mice and their capacity to induce tumors at any site in rats or hamsters, it was shown (*a*) that there was a positive correlation, and (*b*) that the induction of liver tumors in mice did not necessarily indicate that the liver would be the target organ in the other two rodent species (56).

If it is true that it is relatively easy to obtain a high incidence of tumors in rodents, it is also true that the incidence of cancer in humans can be as high as that in experimental animals if the exposure is high enough. The incidence of bladder tumors in workers exposed to 4-aminobiphenyl was over 18%. Most of the workers in whom the tumors were found were in their thirties or forties, and for several of them the length of exposure had been less than two years (48). In workers exposed to benzidine and to 2-naphthylamine, the incidence of bladder cancer was up to 90% when exposure lasted for more than five years (62). Although these may be exceptional cases, the fact remains that whenever a chemical was found to be causally associated with the occurrence of cancer in humans, it was because the incidence was exaggeratedly high or the type of tumor induced so rare, that the event assumed macroscopic dimensions. The working environment, as well as certain therapeutic situations, had in these cases maximized the hazard to such gigantic proportions that epidemiologists or alert physicians could not help detect it.

Evidence of carcinogenicity in humans is therefore obtained in situations that are not so very dissimilar from experimental situations in which the sensitivity of the experimental model is maximized. Insofar as industrial chemicals are concerned, workers involved in a particular manufacturing process are at greatest risk; however, this risk may extend far beyond the

boundaries of the factories. Under these circumstances, it is to be expected that even if the incidence of a cancer related to a given chemical were numerically important (since a large proportion of the population would be exposed) the effect would be diluted to such an extent, and negative factors could play such a prevailing role, that a causal relationship would be very difficult to establish. A slight increase in the incidence of tumors at one of the most frequent sites would, in fact, go unnoticed, since the sensitivity of the epidemiological methods used may only indicate risks that are substantially above the conventional limits of variation set primarily for excluding false-positive results. A general trend that can be seen in certain sectors of the scientific literature is to emphasize the fallacy of considering that carcinogenicity data obtained in experimental animals automatically indicate a danger to humans. While there is certainly some justification for this attitude, particularly in view of the undue upgrading of inadequate data which has occurred in some instances, too little attention is paid to the mistakes that can be made by ignoring adequate experimental results as indicators of a possible danger to humans. Similarly, very little emphasis is put on the mistakes that can be made by ignoring human observations of borderline statistical significance, which may still have biological significance. The specific causative agents of a large proportion of human cancers, in particular, those occurring at some of the most frequent target organs (e.g. prostate, colon, breast) have not yet been identified. This objective statement has been taken to mean that their cause(s) cannot be traced to exposure to one, or more, of the chemicals for which there is human and/or experimental evidence of carcinogenic activity. This conclusion may eventually be shown to be partly unjustified.

QUANTITATIVE VALIDITY OF EXPERIMENTAL RESULTS

Chemicals for which a causal association with the occurrence of cancer in humans has been proved or is strongly suspected comprise a clear case, since everybody (or almost everybody) agrees that exposure of humans to carcinogens must be avoided, even if there is disagreement as to how, to what extent, and how quickly this should be done (50). A difficult and major problem is the evaluation of the possible carcinogenic effect of chemicals on humans in the absence of epidemiological studies or case reports; it is in this context that the question of the quantitative validity of the experimental results is the most difficult to answer, since there are no adequate data presently available to interpret experimental carcinogenicity results directly in terms of carcinogenic potential for humans.

The IARC, following a request in 1968 to draft information on environmental carcinogens, initiated in 1971 a program for the evaluation of the carcinogenic risk of chemicals to humans (1, 2, 57, 58, 60). Within this

program, which is focused on the preparation of monographs about individual compounds or groups of compounds, 17 volumes have been published (25–41), and a total of 380 chemicals have been evaluated. Of these, the 26 chemicals or industrial processes described above and listed in Table 1 were found to be associated with the occurrence of cancer in humans. For an additional 124 chemicals, no data on humans existed, and the available experimental data were inadequate to make an evaluation of the presence or absence of a carcinogenic effect in experimental animals. For the remaining 230 chemicals, the available data indicated some degree of experimental evidence of carcinogenicity; human beings are or can be exposed to a majority of these chemicals, but no evaluation of the carcinogenic risk to humans was made in the monographs, either because no epidemiological studies or case reports were available (213 compounds) or because the results were inconclusive (17 compounds).

Following a recent revision of the criteria used within the IARC monograph program to evaluate the carcinogenic risk of chemicals to humans, which appear in the preamble to Volume 17 of the monograph series (41), an IARC ad hoc working group was convened to examine critically the available data on these 230 chemicals (42). According to the revised criteria, in the presence of adequate experimental carcinogenicity data and in the absence of adequate human data, chemicals for which there is "sufficient evidence" of carcinogenicity in test animals should be regarded for practical purposes as if they were carcinogenic to humans. Chemicals for which there is "limited evidence" of carcinogenicity will, in general, require more experimental and epidemiological investigations. "Sufficient evidence" of carcinogenicity is indicated by the unquestionable production of malignant tumors, while "limited evidence" reflects the qualitative and/or quantitative limitations of the experimental models, one particular case of which could be, for instance, the induction of solely benign tumors in mice.

"Sufficient evidence" of carcinogenicity and "limited evidence" of carcinogenicity do not represent categories of chemicals, but, as the terms imply, they indicate varying degrees of experimental evidence, which may change if and when new data on the chemicals become available. The main drawback to any rigid classification of chemicals with regard to carcinogenic capacity is our as yet incomplete knowledge of the mechanism(s) of carcinogenesis (49). Of the 230 chemicals considered, 111 were judged by the Working Group to have sufficient evidence of carcinogenicity in experimental animals (Table 2).

CONCLUSION

Although a considerable proportion of cancer research is devoted to the identification of possible human carcinogens by the use of experimental

Table 2 Chemicals evaluated in the first 17 volumes of the IARC Monographs for which *sufficient evidence* of carcinogenicity exists in experimental animals[a]

Compound	IARC Monograph volume and page number[b]
Actinomycins	10, *29*
ortho-Aminoazotoluene	8, *61*
2-Amino-5-(5-nitro-2-furyl)-1, 3, 4-thiadiazole	7, *143*
Amitrole	7, *31*
Aramite	5, *39*
Azaserine	10, *73*
Benz (*a*) anthracene	3, *45*
Benzo (*b*) fluoranthene	3, *69*
Benzo (*a*) pyrene	3, *91*
Benzyl violet 4B	16, *153*
Beryllium and certain beryllium compounds[c]	1, *17*
BHC (technical grades)	5, *47*
β-Butyrolactone	11, *225*
Cadmium and certain cadmium compounds[c]	2, *74*
	11, *39*
Calcium chromate	2, *100*
Carbon tetrachloride	1, *53*
Chlorambucil	9, *125*
Citrus Red No. 2	8, *101*
Cycasin	1, *157*
	10, *121*
Daunomycin	10, *145*
N, N'-Diacetylbenzidine	16, *293*
4, 4'-Diaminodiphenyl ether	16, *301*
2, 4-Diaminotoluene	16, *83*
Dibenz (*a, h*) acridine	3, *247*
Dibenz (*a, j*) acridine	3, *254*
Dibenz (*a, h*) anthracene	3, *178*
7H-Dibenzo (*c, g*) carbazole	3, *260*
Dibenzo (*a, e*) pyrene	3, *201*
Dibenzo (*a, h*) pyrene	3, *207*
Dibenzo (*a, i*) pyrene	3, *215*
1, 2-Dibromo-3-chloropropane	15, *139*
3, 3'-Dichlorobenzidine	4, *49*
3, 3'-Dichloro-4, 4'-diaminodiphenyl ether	16, *309*
Diepoxybutane	11, *115*
1, 2-Diethylhydrazine	4, *153*
Diethyl sulfate	4, *277*
Dihydrosafrole	1, *170*
	10, *233*
3, 3'-Dimethoxybenzidine (*o*-Dianisidine)	4, *41*
para-Dimethylaminoazobenzene	8, *125*
trans-2[(Dimethylamino) methylimino]-5-[2-(5-nitro-2-furyl) vinyl]-1, 3, 4-oxadiazole	7, *147*

Table 2 *(continued)*

Compound	IARC Monograph volume and page number[b]
3, 3'-Dimethylbenzidine (*o*-Tolidine)	1, *87*
Dimethylcarbamoyl chloride	12, *77*
1, 1-Dimethylhydrazine	4, *137*
1, 2-Dimethylhydrazine	4, *145*
Dimethyl sulfate	4, *271*
1, 4-Dioxane	11, *247*
Estradiol-17β	6, *99*
Estrone	6, *123*
Ethinylestradiol	6, *77*
Ethylene dibromide	15, *195*
Ethylenethiourea	7, *45*
Ethyl methanesulfonate	7, *245*
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl) thiazole	7, *151*
Glycidaldehyde	11, *175*
Hexamethylphosphoramide	15, *211*
Hydrazine	4, *127*
Indeno [1, 2, 3-*cd*] pyrene	3, *229*
Isosafrole	1, *169*
	10, *232*
Lasiocarpine	10, *281*
Lead acetate	1, *40*
Lead phosphate	1, *40*
Lead subacetate	1, *40*
Merphalan	9, *167*
2-Methylaziridine	9, *61*
Methylazoxymethanol acetate	1, *164*
	10, *131*
4, 4'-Methylene bis(2-chloroaniline)	4, *65*
4, 4'-Methylene bis(2-methylaniline)	4, *73*
Methyl iodide	15, *245*
Methyl methanesulfonate	7, *253*
N-Methyl-*N'*-nitro-*N*-nitrosoguanidine	4, *183*
Methylthiouracil	7, *53*
Mitomycin C	10, *171*
Monocrotaline	10, *291*
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)-amino]-2-oxazolidinone	7, *161*
Nickel and certain nickel compounds[c]	2, *126*
	11, *75*
Niridazole	13, *123*
5-Nitroacenaphthene	16, *319*
1-[(5-Nitrofurfurylidene) amino]-2-imidazolidinone	7, *181*
N-[4-(5-Nitro-2-furyl)-2-thiazolyl] acetamide	1, *181*
	7, *185*
Nitrogen mustard and its hydrochloride	9, *193*

Table 2 *(continued)*

Compound	IARC Monograph volume and page number[b]
Nitrogen mustard *N*-oxide and its hydrochloride	9, *209*
N-Nitrosodi-*n*-butylamine	4, *197*
	17, *51*
N-Nitrosodiethanolamine	17, *77*
N-Nitrosodiethylamine	1, *107*
	17, *83*
N-Nitrosodimethylamine	1, *95*
	17, *125*
N-Nitrosodi-*n*-propylamine	17, *177*
N-Nitroso-*N*-ethylurea	1, *135*
	17, *191*
N-Nitrosomethylethylamine	17, *221*
N-Nitroso-*N*-methylurea	1, *125*
	17, *227*
N-Nitroso-*N*-methylurethane	4, *211*
N-Nitrosomethylvinylamine	17, *257*
N-Nitrosomorpholine	17, *263*
N-Nitrosonornicotine	17, *281*
N-Nitrosopiperidine	17, *287*
N-Nitrosopyrrolidine	17, *313*
N-Nitrososarcosine	17, *327*
Oil Orange SS	8, *165*
Polychlorinated biphenyls (PCBs)[c]	7, *261*
Ponceau MX	8, *189*
Ponceau 3R	8, *199*
1, 3-Propane sulfone	4, *253*
β-Propiolactone	4, *259*
Propylthiouracil	7, *67*
Safrole	1, *169*
	10, *231*
Sterigmatocystin	1, *175*
	10, *245*
Streptozotocin	4, *221*
	17, *337*
Thioacetamide	7, *77*
Thiourea	7, *95*
Trypan blue (commercial grade)	8, *267*
Uracil mustard	9, *235*
Urethane	7, *111*

[a] Not including chemicals associated with cancer induction in humans (see Table 1).

[b] Numbers in roman type indicate the volume, and numbers in italic type indicate the first page of the monograph.

[c] Beryllium and certain beryllium compounds, cadmium and certain cadmium compounds, nickel and certain nickel compounds, and polychlorinated biphenyls have each been counted as one compound but of course include several chemicals.

systems, past and present experience has shown that once such evidence has been acquired the data are not necessarily used for the implementation of primary prevention of cancer. In fact, a recent survey of legislation related to protection against occupational carcinogens in 14 industrial countries has revealed a large number of inadequacies and inconsistencies, even with regard to chemicals that are indisputably carcinogenic in humans (50). We believe that, even in the absence of epidemiological data, a clearer distinction between those chemicals for which there is and those for which there is not adequate evidence of a possible carcinogenic effect in humans can be made by applying the revised criteria for evaluating the carcinogenicity of chemicals (41), and by using further carcinogenicity and related data on chemicals, together with new knowledge about the mechanism(s) of carcinogenesis as it becomes available. At present, there are no acceptable methods for measuring possible errors in an approximate quantitative evaluation of human risk for a given level of exposure to a chemical made on the basis of data that provide "sufficient evidence" of carcinogenicity in experimental animals. The limited data available suggest, however, that such a relationship might exist (42, 51, 52), at least for certain classes of carcinogenic chemicals, provided that one takes into account the nature of the chemical concerned and the possible physiological, pharmacological, and toxicological differences between the test animals and humans.

The experience of the past has also shown that for several environmental chemicals, experimental evidence of carcinogenicity preceded evidence in humans and would have predicted similar effects in humans. It is therefore hoped that the provision of adequate, critically analyzed experimental data will serve the purpose of better assisting national and international authorities in formulating decisions concerning preventive measures, at least with regard to occupational and iatrogenic exposures, in which intervention can be the most direct and effective.

ACKNOWLEDGMENTS

Part of the work discussed in this paper has been supported by NCI Contract No. N01 CP 45608. The author would like to thank M. J. Ghess for the typing of the manuscript and E. Ward for its editing.

NOTE ADDED IN PROOF H. Isaka has presented the results of his study on phenacetin (see 43) at the XII International Cancer Congress, Buenos Aires, in October 1978. A summary of his presentation is available in Volume 1 of the Abstracts (p. 40, no. 24) of the XII International Cancer Congress. An excess of urinary tract and nasal cavity tumors was observed in phenacetin-treated rats.

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