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Chemicals and Cancer in Humans: First Evidence in Experimental Animals

by James Huff [1]

Certain human diseases have been traced to exposure to environmental and occupational chemicals. In many instances the first evidence of potential adverse effects came from experimental studies and were subsequently discovered in humans. Associations of human cancers, as a diverse group of diseases, and chemicals have been made since the middle 1700s. Since then, nearly 100 chemicals, mixtures of chemicals, or exposure circumstances are now recognized as being or strongly implicated as being carcinogenic to humans. Of the less than 1000 agents evaluated adequately for carcinogenicity in laboratory animals, a varying spectrum of data from studies on humans are available for only about 20–25%. So far, more than 60 agents are linked unequivocally as causing cancer in humans, and another 50 or so are strongly suspected of being carcinogenic to humans. Not all of these have been or can be evaluated in animals because some are industrial processes or "occupations," some are environmental and cultural risk factors, and some are mixtures of agents. For those that can be studied experimentally, the qualitative concordance between humans and animals approaches unity, and in every case there is at least one common organ site of cancer in both species. The evidence of carcinogenicity in experimental animals preceded that observed in humans for nearly 30 agents and is the subject of this paper.

> A risk can be imagined or it can be real; it can be immediate or distant. There are risks that an individual can control, and those over which he or she has no power. There are risks that have already resulted from past exposures and there are those that are predicted from exposures which have not taken place. Sensitivity to these distinctions is crucial not only for assessing and managing risks, but also for diagnosing and treating disease.
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> [Rall, 1981 (*1*)]*

Chemicals cause cancer. Some cause cancer in experimental animals. Certain chemicals cause cancer in humans. Fortunately, not all chemicals are considered either potentially carcinogenic to humans (*2–4*) or to animals (*5–9*), and the proportion of chemicals eventually identified to cause cancer in experimental animals is forecast to be relatively low (*10*). Occupationally associated cancers will continue to be discovered long into the future (*11,12*). Those chemicals identified as being causally associated with cancers in humans have all been shown to produce cancer in laboratory animals; in every instance at least one site of cancer was common to both mammalian species (*13–15*). This knowledge together with patent similarities in mechanisms of carcinogenesis across species (*16–19*) led to the scientific logic that chemicals shown clearly to be carcinogenic in animals (*13–15,20,21*) should be considered as being likely to present cancer risks to humans (*2,4*).

> . . .experimental evidence. . . [indicates]. . . that there are more physiologic, biochemical, and metabolic similarities between laboratory animals and humans than there are differences. These similarities increase the probability that results observed in a laboratory setting will predict similar results for humans. Clearly the accumulated experience in the field of carcinogenesis supports this concept.
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> [Rall et al., 1987 (21)]

For those chemicals, mixtures of chemicals, or undefined circumstances to which humans are exposed to known or potential health hazards such as carcinogens, the hallmark public health issue centers on what level of exposure, if any, will present no or little carcinogenic risks to the individuals or populations in unprotected or uniform conditions (*22–26*). Obviously, if humans are not exposed to a chemical carcinogen, then the expectation that that chemical will be a carcinogenic hazard to humans must be recognized as not being readily possible. Yet, even this apparent comfort might be short-lived because other laboratory chemical curiosities or industrial intermediates have had or do exhibit widespread human exposure: examples are vinyl chloride (*27–30*), methyl isocyanate (*31*), tetrachlorodibenzo-*p*-dioxin (*32,33*), and 1,3-butadiene (*34,35*). Further, the concept of "safe" exposure levels to carcinogens accepts the erroneous concept of threshold (*36*).

> If thresholds do exist and the regulatory decisions are based on a no-threshold concept, there will be short-term economic losses. If thresholds do not exist and the regulatory decisions are based on thresholds, then there will be fewer short-term economic losses, but we would face a future of damaged somatic and germinal DNA and an increased incidence of neoplastic (and other) diseases.
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> [Rall, 1978 (*37*)]

In this paper, chemicals are identified that were first shown to cause cancer in laboratory animals and were only subsequently found to be associated with cancers in humans. For each, the epidemiological and experimental evidence are given to support this conclusion (*2–4,7,8*).

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*As my paper and this volume of EHP are dedicated to David Rall, I have taken the opportunity to reread many of his papers and have selected quotations from his works to emphasize the breadth and freshness of his vision, as well as to strengthen and complement the theme of my paper.

But the issue is not thresholds or no thresholds; it is one of adding a new carcinogen to a pool of present carcinogens.

[Rall, 1978 (*37*)]

Background and Data Sources

In 1979, Tomatis reported the first listing of chemicals that initially were found to cause cancer in experimental carcinogenesis studies (*13*) and at some later time [and perhaps clinical or epidemiological investigations were stimulated by these data (*38*)] evidence of carcinogenicity in humans came forth. The collection of chemicals has been expanded since this early disclosure (*3,14,21,38*), and now includes upwards of 30 chemicals that are causally or probably associated with cancer in humans whereby the first implication of carcinogenesis was discovered in experimental animals (Table 1).

The primary collective sources of this information come from the *IARC Monographs Series* (*3*), the *NCI/NTP Technical Report Series* (*7,8*), the *DHHS Reports on Carcinogens* (*4*), the *IARC Supplement* 7 (*2*), Tomatis et al. (*14*), Huff and Rall (*15*), Huff et al. (*39,40*), Vainio et al. (*41*), and the carcinogenesis literature. In a few instances wherefore the evidence from humans has not yet been evaluated by independent groups (e.g., DHHS or IARC), I have taken the opportunity to interpret the available findings on reported associations between exposure and human cancers (*15,26*); and appropriate references are given to allow others to judge the levels of evidence [(*42*) Table 2]. The agents listed in Table 1 are not complete, and others will surely be added in the future. For some, the possibility exists that the evidence of agent-associated carcinogenesis in humans may in fact predate the experimental evidence; I would appreciate learning about any such gaps in awareness, with appropriate reference citations. For some other agents the level of evidence of carcinogenesis in humans may be reflected in case reports (recall vinyl chloride), or in bits of evidence cumulated over time (e.g., TCDD (*43*)]. In any event, these are my opinions, and those readers who wish to suggest additions to or subtractions from the listing are encouraged.

Table 1. Chemicals and cancer in humans: evidence of carcinogenicity first observed in experimental animals and subsequently by epidemiologic evidence.

Chemicals causally or probably associated with cancer in humans	
1. Acrylonitrile	16. Formaldehyde
2. Aflatoxins	17. Gasoline
3. 4-Aminobiphenyl	18. Glass wool
4. Analgesix mixtures with phenacetin	19. Lead and lead compounds
	20. Melphalan
5. Asbestos	21. 8-Methoxysoralen + UV radiation
6. Beryllium	22. 4,4-Methylene *bis*(2-chloroanilene)
7. *bis*(Chloromethyl) ether	23. 4,4-Methylene dianiline diHCl
8. 1,3-Butadiene	24. Mustard gas
9. Cadmium	25. Ochratoxin A
10. Chlorination + by products	26. Phenacetin
11. DDT and related compounds	27. Radon Gas
12. Diethylstillbestrol	28. Silica, crystalline
13. Dibromoethane	29. 2,3,7,8-TCDD
14. Ethyl acrylate	30. Vinyl chloride
15. Ethylene oxide	

Table 2. Human carcinogens and levels of evidence of carcinogenicity.

Level 1	Chemicals shown epidemiologically as causally associated with cancers in humans.
Level 2	Chemicals shown epidemiologically as possibly associated with cancers in humans, and confirmed experimentally as causing cancers in laboratory animals.
Level 3	Chemicals shown experimentally as causing cancers in laboratory animals
Level 4	Chemicals shown to exhibit molecular mechanisms similar to those in levels 1-3

Chemicals = mixtures of chemicals, exposure circumstances, and/or occupations.

. . . positive results in these long-term experiments demonstrate that a chemical is carcinogenic for laboratory animals . . . and indicate that exposure to the chemical has the potential for hazard to humans.

[Rall et al., 1987 (*21*)]

Chemicals and Cancer

Since 1971, the International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), has been evaluating the epidemiological and experimental evidence for carcinogenicity of chemicals, mixtures of chemicals, industrial processes, occupations, life-style and cultural habits, and exposure circumstances ("agents"). This comprehensive information and the consensus scientific evaluations are collected and made available as *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Included in the 57 volumes already published or in press through 1992 are evaluations or reevaluations on almost 750 agents (*2,3,14,41, 44–51*). Of these 750 agents, data on humans were available for only about 20–25% [or approximately 200 agents (*3,14,15,26, 41,46,47,49,50*)].

IARC has thus far identified 59 agents that are recognized and accepted widely as being linked unequivocally to human cancers; these can be collated into five groups (*3,14,48,50,51*): 8 single chemicals; 10 groups (or mixtures) of chemicals; 19 individual or combination pharmaceuticals; 13 industrial processes or occupations; and 9 environmental or cultural–life-style risk factors. Tomatis et al. (*14*) have listed four other environmental risk factors as causally associated with human cancers (yet to be formally reviewed by IARC): hepatitis B virus, human T-cell leukemia virus, ionizing radiation, and ultraviolet radiation (J. Wilbourn, personal communication). Thus, a total of 63 agents evaluated by IARC are known to cause cancer in humans. An equal or greater number of agents are strongly suspected of posing a cancer risk to humans. Thomatis et al. (*14*) have identified another five risk factors for which an association with the occurrence of human cancer has been observed although a casual relation has not been fully established: *Clonorchis sinensis, Schistosomia haematobium, Opisthorchis vivarrini*, Epstein-Barr virus; and papilloma virus (*14*).

All the single-entity chemicals known to cause cancer in humans are also carcinogenic in experimental models; importantly, moreover, in each case there is a concordant target organ for cancer occurrence in both humans and in at least one of the animal species studied (*2,3,14,15,26,41,45–47,50–52*). This correspondence holds likewise for 9 of the 10 groups of chemicals. Available experimental data on talc-containing asbestiform fibers are considered inadequate. However, a nonasbestos form of talc has been studied by the NTP using the inhalation route of exposure: a spectrum of lung toxicity was observed, as were benign and malignant tumors of the lung in

female rats, and benign and malignant pheochromocytomas of the adrenal gland medulla in male and female rats. No talc-associated neoplasms were found in mice (K. Abdo, personal communication). Hence, when comparing chemicals or reasonably identified groups or mixtures of chemicals, the correspondence between animals and humans regarding carcinogenic activity *per se* and target sites in particular nears perfection.

Drugs have full qualitative correspondence and comparative target organ concordance on 16 of the 19: methyl-CCNU (leukemogen in humans) has been evaluated in only one study in rats, wherein lung is a suspected target organ; MOPP (as the combination) and Treosulfan (both induce leukemia in humans) have either inadequate experimental data or no data at all. (The latter alkylating chemical undergoes metabolism to diepoxybutane, known as carcinogenic to animals). However, two of the four components of MOPP do induce cancers in experimental animals: M (mechlorethamine, nitrogen mustard), lung, lymphoma, and skin; O (Oncovin, vincristine); inadequate studies; P (procarbazine), nervous and hematopoietic systems, mammary, hemangio- and osteosarcomas, and lung; P (prednisone), inadequate studies. Many of these carcinogenic drugs are alkylating cancer-chemotherapeutic agents, often if not always resulting in secondary cancers after or during long-term treatment of primary cancers (*53–55*). Although they are immediately useful and life-saving, these cancer chemotherapeutic agents do cause toxicity at the high doses used and all too frequently eventually lead to cancer in other organs.

> Once we have identified a hazard and estimated the risk, we must then determine whether it is socially acceptable, and if so, at what level. But in considering this we are no longer in the realm of the scientist. This is a decision that should be made through our political process. At best, it should be based upon firm scientific data and clearly articulated social and economic values.
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> [Rall, 1981 (*1*)]

Undefined Exposure Circumstances

For the 13 processes or occupations associated with cancer in humans, none have been evaluated properly in whole-animal laboratory experiments (*3,14,15*). Other than using sentinel animals in the offending occupational setting or catching and examining native mammalian or avian stock, the design and conduct of "mimic experiments" on these processes are not logically feasible or logistically possible. One simply has to design more innovative experimental protocols to better evaluate likely correspondence in animals. Environmental sentinels have proven useful for identifying "carcinogenic environs," such as fish with liver tumors in Boston Harbor and elsewhere (*56*).

The eight "life style" agents so far identified as causing carcinogenesis in humans have good complementation among species; however, neither alcoholic beverages nor smokeless tobacco has been studied adequately in laboratory animals. Experimental study of alcoholic beverages presents a unique and perhaps baffling dilemma of not only deciding how to design a "definitive" experiment (since the carcinogenic agent or agents have not been identified), but most importantly to which "cocktail" should the animals be exposed? One theory asserts that ethanol may simply be an "irritant promoter" acting locally (e.g., esophagus) as a cell stimulatory growth factor, thus being an "application-site" carcinogen. Some suggest that ethanol may be a co-carcinogen. Others believe that the causative carcinogen resides in the "nonalcoholic" portion of the *spiritus frumenti*. Perhaps experiments should be designed not using ethyl alcohol alone, but as a potential promoter or cocarcinogen (with what?) or better yet expose animals to the "alcoholic beverages" that humans actually drink. This can be done rather easily, but the mixture selected would somehow have to be a "universal drink." As an example, one could identify the top 10 brands consumed (liquors, beers, or wines, or even a combination of these three) and then concoct an exposure regimen mixture. This may or may not provide the final or definitive answers, but such an experiment would help to evaluate and validate once again the human-surrogate animal model. Until now limited data exist (*57*) to implicate ethyl alcohol alone as being carcinogenic to laboratory animals (*58*). Nonetheless, alcohol beverages have been shown conclusively as being carcinogenic to humans for the oral cavity, pharynx, larynx, esophagus, and liver.

Out of the 63 agents considered to cause cancer in humans, 44 have or could be studied in long-term experiments using laboratory rodents; the 13 processes cannot. All 39 human carcino-gens that have undergone adequate experimental studies have been shown to cause cancer in animals, and exhibit concordance for tumor sites (*14,26,45,47*). For the five that may appear to show a lack of agreement, three are considered to have been studied inadequately (methyl-CCNU, MOPP, talc with asbestiform fibers) and two have yet to be evaluated in animals (alcoholic beverages and treosulfan).

Further, IARC has identified an additional 41 chemicals, groups of chemicals, or industrial processes that are probably carcinogenic to humans and sufficient evidence in animals, 8 have limited evidence in humans and no or inadequate data in animals (*2,3,14*), 16 have limited evidence of carcinogenicity in humans, whereas the other 28 were placed in this category based largely on sufficient evidence from studies in laboratory animals. Another 205 agents have been designated as possibly carcinogenic to humans; 9 of these had limited evidence of carcinogenicity in humans. Therefore the available human and animal data that have been evaluated show that at least 96 agents (i.e., 59 + 16 + 8 + 9 + 4) are considered to have sufficient or limited evidence of carcinogenicity in humans. Perhaps these should collectively be considered as causing cancer in humans, especially since appropriately sized human cohorts for confirmatory evidence are most frequently unavailable.

Complementary to the IARC effort and in response to the U.S. Congress, the National Toxicology Program (established in 1978), part of the Public Health Service within the Department of Health and Human Services, publishes an Annual Report on Carcinogens (*4*). These reports contain a series of monographs on substances defined under U.S. Public Law that "are known to be carcinogenic to humans or that may reasonably be anticipated to be carcinogenic" (to humans) (*4*). Selection of candidate entries are based typically on scientific criteria similar to those developed and adopted by IARC. These DHHS monographs summarize the available evidence of carcinogenicity in both humans (where available) and in experimental animals and review any regulatory action taken on a particular substance or mixture of substances. In the Sixth Annual Report (*4*), for example, there are 25 substances, groups of substances, or technological processes designated as being carcinogenic to humans,

and another 148 that may reasonably be anticipated as being carcinogenic to humans (*4*).

Possible differences between the 110 agents listed by IARC and the 180 substances rendered by the DHHS center largely on three reasons: *a)* chemicals not yet evaluated by one group may have been considered and added by the other, *b)* DHHS does not usually prepare individual monographs on processes or occupations (these are often mentioned in the introductory section to the Reports), and *c)* the "may reasonably be anticipated" substances as defined by DHHS may contain some of the 205 agents that IARC has classified as 2B (*possibly carcinogenic to humans*). By-and-large there is considerable consistency among the two listings. Other important sources of lists of agents believed to be associated with human cancers are the European Communities (*59*) and the California Department of Health (*60*), both of whom have published independent, consensus analyses of the available data.

> The question of species-to-species differences in response to chemical carcinogenesis is fundamental to attempts to reduce the incidence of cancer in man by insuring that those chemicals to which man is or will be exposed are not carcinogens.
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> [Rall, 1977 (*61*)]

Chemical Carcinogenesis

Clearly, the accumulated experience in the field of carcinogenesis supports the concept that cancer development is a multistep process and that multiple genetic changes are often considered to be required before a normal cell becomes fully neoplastic (*62–64*). Bannasch et al. (*65*) define carcinogenesis "(as being) characterized by sequential molecular, metabolic, and morphological changes that result in a deficiency of cellular differentiation and a loss of normal growth control." This has been endorsed by Lijinsky (*66*), who insists that "Chemical carcinogenesis is a process driven by the reactivity of the chemical, and. . .the interaction of the carcinogen with critical molecules in certain cells, some of which go on. . .to self-perpetuating cancer cells." Likewise, studies of human tumors suggest the involvement of a multistep paradigm together with similar genetic events as often occur in the development of cancer in animals. In any event, an increasing number of individuals question the dogma surrounding differentiation of chemical carcinogens into discrete genotoxic-nongenotoxic mechanisms of carcinogenesis (*67*), in that "It is difficult to consider. . .that the critical molecule has to be DNA, which (can be) adducted similarly whether tumors arise or not" (*66,67*). And "that more attention to the remaining wondrous structure of cells, and the changes produced in it by carcinogens, will lead to a (better) understanding of the genesis of cancer and its progression" (*66*). Given the expanding numbers of nongenotoxic carcinogens being discovered leads one to support the notion that perturbations of DNA may not be the singular initiating event in chemical carcinogenesis. Obviously more effort is needed.

> Properly conducted animal studies have been shown to be predictive for carcinogenicity and toxicologic responses in human populations.
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> [Rall, 1979 (*68*)]

Animals to Humans

From the information currently available, the array and multiplicity of carcinogenic processes are virtually common among mammals, for instance between laboratory rodents and humans. Zbinden (*69*), for example, believes that "the more we know about the similarities of structure and function of higher organisms at the molecular level, the more we are convinced that mechanisms of chemical toxicity are, to a large extent, identical in animals and man." Centering on the carcinogenesis paradigm, Bertram et al. (*17*) state "There is overwhelming evidence that, at the cellular level, humans. . .do not differ qualitatively from experimental animals in their response to carcinogens. Furthermore, processes operative in humans that lead to cancer induction are also operative in rodent systems." Most scientists agree.

The foregoing plus the knowledge that all chemicals known to induce cancer in humans, that have been studied under adequate experimental protocols, also cause cancer in laboratory animals lead most prudent investigators to the persuasive speculation that the obverse would similarly hold true: chemicals shown to unequivocally induce cancer in laboratory animals should be considered capable of causing cancer in humans. The International Agency for Research on Cancer adopted this widely accepted scientific view: "In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans."

Nonetheless, this biologic conundrum of scientific debate regarding the predictability of experimental findings will surely continue. One difficulty of course resides in our individual definitions of "carcinogen," and this led Yamasaki (*70*) to admonish us that "Terminology itself does not advance science; however, the misuse of terminology sometimes hinders the progress of science." Of course others have urged clarity much earlier on. In the second century for example Galen wrote "The chief merit of language is clearness, and we know that nothing detracts so much from this as do unfamiliar terms." As we some times appear driven to define and re-define terms and concepts, Zwickey and Davis (*71*) gave us a "pre-mechanistic" succinct definition of chemical carcinogenicity that still serves well: "Carcinogens are those substances which produce a significant increase in tumor (cancer) incidence when administered at any dosage level by any route of administration in any species of animal as compared to (concurrent) conrols." One of course must be careful to compare carcinogens on the collective strength of the response, since all chemical carcinogens can not be considered equal (*25,38*).

Further there are political motives that some seem to use as a means to discredit experimental carcinogenesis results. Some misleadingly state that everything is carcinogenic (*72*), and label as carcinogenic chemicals (e.g., allyl isothiocyanate or *d*-limonene) those that do not fit the internationally accepted definitions (*2–4,73*), and thereby hindering our understanding of the science and the protection of human health. Naturally this leads to confusion among the administrators who must cope with these dichotomous scientific views; yet this seeming predicament can be easily overcome if one would concenrate on the listings of chemicals identified as presenting most likely cancer hazards to humans by organizations that have the appropriate expertise and who involve groups of experts in carcinogenesis and related disciplines (e.g., IARC and NTP/DHHS), rather than on those *a*) who have never participated in the consensus evaluation

process wherein all the available data and information are critically evaluated before making an interpretation; *b*) who have never designed or conducted such large-scale and intricate long-term experiments; *c*) who never evaluated the totality of the extensive experimental data; *d*) who may comment-for-gain; or *e*) who have only individual opinion. More at issue of course are the eventual social, political, and regulatory uses of these experimental findings of carcinogenesis. Some continue to exhibit confusion in separating the scientific and biologic results from the nonscientific applications and from the mathematically oriented risk assessment models, all of which struggle with assigning numerical (and often esoteric) values of probability. Dodgson (*74*) dealt effectively with this by explaining, "Contrariwise, if it was so, it might be; and if it were so, it would be; but as it isn't, it ain't. That's logic." Thus, one does better to rely more on experience, objectivity, and consensus rather than on individuals who may have a conflict-of-interest or a misunderstanding on the particular agent being evaluated.

Thus, we need to concentrate on rising above the fray to do what is right for society and not on some vague notions about how many deaths can we accommodate or tolerate at each incremental exposure scenario. Until the quantitation exercises being promoted become a real science, one might do well to consider (or actually return to) the qualitative concept of simply not exposing people to hazardous chemicals or insidious exposure circumstances. One would think this would be easy. As one example, EPA reports (*75*) that 734 U.S.corporations have pledged to reduce emissions of 17 high-priority toxic chemicals by 304 million pounds; actually this is miniscule when one considers the total released pollution burden, but even this amount equals 10,000 fully loaded 52-foot tanker trucks that end-to-end would stretch for 100 miles! Nonetheless, consider that a single chemical used in the rubber industry is pumped into the atmospheric environment at the astonishing rate (in the United States alone) of nearly 10 million pounds per year (*34,35*). Moreover, in 1989 the EPA's toxic release inventory (based on only 328 chemicals) reported that a total of 18 billion pounds of these toxic pollutants were emitted by 19,000 industrial facilities (or 75 pounds for every person in the United States) (I. Cote, personal communication) Massive pollution will likely continue indefinitely and will increase as well, especially because developing countries are being used more and more frequently as geographic areas in which much chemical production takes place, often with less stringent safeguards or safety precautions. Considerable effort should be mounted to quell this unfortunate and environmentally unhealthy rend.

> It is our job as scientists to attempt, as best we can, to look into the future, see the changes ahead, and anticipate the side effects of these changes. But we know from past experiences that there are few important and useful discoveries that do not have some unanticipated, undesirable side effects. It is our responsibility to alert leaders in public policy and suggest to them how we might prevent or minimize any negative health consequences.
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> [Rall, 1990 (*76*)]

Discussion and Further Commentary

Social and political debate begins when chemicals are shown unequivocally to induce cancer in laboratory animals and no relevant or reliable human data exist to confirm or to counter any association. Differences in scientific opinion, where they occur, generally rest not on the actual experimental findings but *a*) on the interpretation of the data, *b*) on the system or model used to generate the data, *c*) on the person or organization conducting the investigations or reporting the findings, *d*) the forecast economic or employment aspects, and the eventual impact these findings will have on our personal and occupational environments. As long as these data are used to stimulate the regulatory process, the political, social, public, and scientific debates will continue (at times almost regardless of the actual facts). Nonetheless, this array of opinionated thought usually benefits all sides of a particular issue, and often results in scientifically based compromise and a more scientifically objective consensus. Ideally, one would hope that no personal interest in the benefits or economics of chemicals would come into play when considering the scientific evidence of carcinogenicity. Public, individual, and environmental health are too important.

The clear understanding and universal awareness that all chemicals known to induce cancer in humans, that have been studied under adequate experimental protocols also cause cancer in laboratory animals convince most prudent investigators and reasonably thinling scientists and regulators to the persuasive speculation that the obverse would similarly hold true: chemicals shown to unequivocally induce cancer in laboratory animals should be considered capable of and likely to cause cancer in humans. This public health position has served well and should continue. Nonetheless, the scientific debates will surely continue.

As more and more advancements are made in molecular carcinogenesis, our understanding of the mechanisms of cancer induction within the mammalian domain will allow us to shed more light on the value of using animals as predictive surrogates for humans (*16–19, 67,77*). This will predictably further permit us to more closely approach the public health objective of preventing, substantially reducing, or virtually eliminating the burden of chemically induced and chemically enhanced cancers in humans (*36,78,79*).

> If an experiment yields a clear-cut negative result, there is little discussion about the meaning or the meaninglessness of animal studies. When a clear-cut and strong positive result occurs, there is also little discussion. When the result is a slightly positive experiment, interpretation becomes difficult and discussion becomes lengthy. Biology, unfortunately, does not come only in black or white, but in many shades of gray, and in these gray areas disagreement is particularly evident.
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> [Rall, 1988 (*52*)]

Experimental Chemical Carcinogenesis: First Evidence

Because epidemiological data are often absent or past exposure data are unavailable, public health decisions must continue to be based largely on animal data. Historically, this logical concept has served the public well as preventive medicine. Thus, while we hope that subsequent epidemiologic studies on the recognized animal chemical carcinogens do not identify additional causal associations with human cancer, these chemical carcinogenesis results in laboratory animals frequently if not almost always constitute the primary basis for identifying and predicting potential human health hazards (*17,20,21,24,36, 78–80*). Several chemicals identified first as causing cancer in laboratory animals show associations with human cancers. For instance, 1,3-butadiene, the potent rodent carcinogen (*81–84*),

Table 3. Chemicals that are candidates for further evaluation as human carcinogens[a].

Chemical	Cancer	References
1,3-Butadiene	Leukemia	(*85–87*)
Hair dye	Leukemia/lymphoma	(*88–90*)
Chlorinated drinking water	Urinary bladder	(*91,92*)
Sulfuric acid/acid mists	Lung	(*93,94*)
Dimethylformamide	Testicular	(*95–98*)
Ethylene oxide	Leukemia	(*99–102*)
Ethylene dibromide	Lymphoma	(*103,104*)
Formaldehyde	Lung	(*105–113*)
Acrylonitrile	Lung	(*114–118*)
Methylene chloride	Liver	(*119–121*)
4-Chloro-*o*-toluidine	Urinary bladder	(*122*)
2,4-D	Non-Hodgkins lymphoma	(*123–127*)
Ethyl acrylate	Colon, rectum	(*128*)
Aviation gasoline	Kidney	(*129,131*)
DDT and related products	Pancreatic	(*132,133*)

[a]Some of these chemicals have been placed into Table 1 as associated with human cancers. See also references (*2–4*).

has been causally associated with the development of lymphatic and hematopoietic cancers in humans (*85,86*). In a nested case-control study of the styrene-butadiene rubber industry [note: the rubber industry as a whole is considered a human carcinogen (*2,3*)], Matanoski et al. (*87*) found that leukemia cases were associated with exposure to butadiene (odds ratio = 9.4; 95% confidence interval = 2.1–23).

Certain other chemicals with strong animal data and in my view adequate human evidence seem to be prime candidates for further evaluation as human carcinogens (Table 3).

As stated by Doll (*11,12*), the final number of proven occupational (and environmental) carcinogens may eventually be quite large. Thus we must continue in our scientific and public health efforts to identify potential carcinogenic hazards to humans, and for those agents that are considered to inflict undue harm these should no longer be permitted unregulated exposures.

Regarding causes of cancer in humans, Doll and Peto (*136*) argued that the causes of 97% of human cancers can be explainable, with a large proportion (10–70%; best estimate,35%) due to diet. Using the most relevant and common sites of human cancer, Schmahl et al. (*135*) estimate only one-third of the cancers (in the Federal Republic of Germany) can be assigned ecologically to exogenous carcinogenic agents or lifestyle. These latter authors stress that indirect primary prevention, based on the probable summaration of subcarcinogenic effects of single carcinogens identified from animal experiments, may lead to a reduction of carcinogen-induced cancers even if the effects of a particular carcinogenic compound cannot be determined precisely. Regarding the influence of diet on the incidence and mortality of cancer, Schmahl et al. (*135*) agree with Byers and Graham (*136*) who indicate that the relationship between dietary factors and cancer increases has not revealed a single unequivocal conclusion of causality.

Most followers of the diet-causality theme appear to simply default this notion without unequivocal supporting evidence, often driven by the different cancers types occurring in different continental locations (*137–140*). If one examines the incidence or mortality maps of the United States for example, clustering or pockets of cancers are perhaps the most striking observations. Do these distributions impugn diet as causal? Or must we investigate these "local outbreaks" rather than ascribing diet as the ultimate de facto carcinogen. As Boyland (*141*) so cogently stated, "Cancer, like other natural phenomena, has causes. When a tumor is described as being spontaneous (or ascribed to dietary influences) it means that the causes are unknown, like those of most events which occur in living things." Also the contradictory dichotomy of epidemiologic results (e.g., fats protect against or cause cancer) simply adds to the confusion.

All agents identified as causing cancer in humans have likewise been shown to cause cancer in laboratory animals. A key biological and public health question that seems to dominate the interactions of research, regulatory, and industrial communities around the issue of cross-species extrapolation of chemcal carcinogenesis findings. In my view, and one shared by most, the preponderance of evidence supports the logic that chemical-induced toxicity [e.g., Zbinden (*69*)] and carcinogenesis [e.g., Bertram et al. (*17*)] are sufficiently and (un)remarkably similar among mammalian species, although one (toxicity) does not forecast the other (carcinogenesis) (*142,143*). Thus one would remain scientifically sound to continue to predict carcinogenic hazards for humans by using results obtained from long-term chemical carcinogenesis experiments.

Nonetheless, because chemicals inducing carcinogenic responses in animals should not be considered empirically equal, one would be ill-advised to simply divide all chemicals into two motley groups: carcinogens or noncarcinogens. One needs to evaluate and compare *a*) the available published carcinogenesis data (e.g., the IARC Monographs process) or *b*) the actual experimental data and interpretations (e.g., the public peer review system of the NTP) and thereby establish a consistent and consensus evaluation process. In this manner one begins to gather and develop a storehouse of carcinogenesis data that permits placing chemicals into generic groups based largely on qualitative potencies. Appropriate levels of qualitative evidence for determining chemically or environmentally associated carcinogenesis in humans can be divided into at least four general, and at times overlapping, classes (Table 2). Added to these simplified groupings one must consider other relevant data as well; that is, using a "weight-of-evidence" approach (*21,42*) that, for example, takes into account the strength of the carcinogenic response in experimental animals (*6*). In addition, all carcinogens are not equal in their carcinogenicity (e.g., Table 4) or in their potential to pose a cancer hazard to humans. Conversely, in my opinion, one cannot make a carcinogen out of an innately noncarcinogen (or carcinogen into a noncarcinogen) simply by manipulating the experimental conditions or further, or by altering the protocol designs (e.g., using so-called high doses). Likewise, one should not attempt to label a carcinogen as a noncarcinogen because humans may be exposed to levels below or

Table 4. Distribution of carcinogenic responses for 326 chemical studies (male rats, female rats, male mice and female mice).

Positive in sex–species	+/Total	%
+,+,+,+ (4 of 4)	45/326	14
+,+,+,− (3 of 4)	26/326	8
+,+,−,− (2 of 4)	60/326	18
+,−,−,− (1 of 4)	39/326	12
−,−,−,− (0 of 4)	156/326	48

Table 5. Major public health issue.

Fact:	All exposures identified as being carcinogenic to humans that have been studied adequately have been shown to cause cancer in experimental animals at minimally toxic exposures.
Question:	Will all identified animal carcinogens cause cancer in humans?
Answer:	Probably not, but the answer remains to be discovered. For some (too many), we must say yes.

even considerably below those concentrations which induced carcinogenesis in animals. Importantly, we need to remember that these long-term experiments are conducted under somewhat artificial conditions: single chemical exposures (whereas humans receive myriad carcinogens from multiple and varied sources); only two species of rodents, relatively few animals; most often exposure begins in adulthood (and not preconceptionally or prenatally); the tests are for identifying weak or cocarcinogens or promoters, and the duration is typically less than optimum for discovering late-acting carcinogens. Nonetheless, because most chemicals are not or will not be "real" carcinogens (*2–4,9,10*), those that are must receive due cautionary attention (Table 5).

The decades-old question remains: how confident should we be that consensus experimental carcinogens will predict cancers in populations exposed to the same chemical or exposure circumstance? History, biology, and the theme of this paper certainly support the concept of extrapolating carcinogenesis findings from animals to humans. Even more basic, will chemicals shown conclusively to cause cancers in laboratory animals also eventually be found to cause cancer in humans (Table 5)? Ignoring for the moment the important and controversial issue of exposure, the answer is yes. The object correctness and prudency of this response come not only from the obvious cross-mammalian consistency but from knowing that nearly one-third of those agents considered carcinogenic to humans were discovered first in animals.

> . . . a commitment to deal with this problem (of chemical-hazards) buys us into a highly imprecise world of inadequate data and conflicting values. Not only is the information incomplete, but if we do anticipate hazards and thereby prevent future disease, we will never know that we are right. In fact the naysayers will tell us that we cannot demonstrate that we were right, precisely because we are not willing to allow the evidence to accumulate. In short, the price we pay for being right is that we cannot prove that doing nothing was wrong.
>
> [Rall, 1981 (*2*)]

Data reported herein show that nearly 25–30% of those agents, substances, or chemicals that have been causally or strongly associated with cancer in humans were first identified as being carcinogenic in experimental animals. If more attention would have been given to these findings, perhaps some undue suffering and death could have been avoided. Likewise for those chemicals shown to cause cancer in laboratory animals that have not as yet had undergone epidemiological investigations, one should reduce or eliminate all unnecessary exposures. Meanwhile cohorts being exposed to these agents should be identified and evaluated. To continue to ignore experimental data for reasons of uncertainty must no longer be tolerated or condoned.

NOTE ADDED IN PROOF: Suppressed experimental information now exists that asbestos was first shown to cause cancer in laboratory animals (*144,145*) approximately 12 years before the epidemiological evidence was made known and published (*146*). Interim report noted that 81.8 percent of animals [mice] exposed to asbestos had developed lung tumors, an overly high rate.

Here is to David Rall, a scientist and physician dedicated to the public health of the individual, of the nation, and of the world.

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