

Perspective and overview of the concepts and value of hazard identification as the initial phase of risk assessment for cancer and human health

by James Huff, PhD, David Hoel, PhD¹

HUFF JE, HOEL D. Perspective and overview of the concepts and value of hazard identification as the initial phase of risk assessment for cancer and human health. *Scand J Work Environ Health* 1992;18 Suppl 1:83–9. The identification of potential human health hazards stems from the obvious need to prevent, avoid, reduce, and eliminate exposure to hazardous agents, mixtures of agents, or exposure circumstances. The first step in the risk assessment process centers on determining if a hazard exists. The following strategies are used for this purpose: (i) epidemiologic investigations, (ii) long-term chemical toxicology and carcinogenesis studies on laboratory animals, (iii) shorter-term in vivo and in vitro assays, and (iv) physicochemical structure-activity relationships. Indicator 1 is the most relevant and reliable if adequate data are available; indicator 2 is the most valid and useful alternative for human experience; indicator 3 allows certain toxicologic end points to be identified, but generally needs confirmatory and supportive information; and indicator 4 has made gains in the area of predictivity. The advantages and limitations of each are given. The magnitude of the overall cancer hazard identification effort and a likelihood number of eventual chemical carcinogens have also been estimated.

Key terms: advantages and limitations of hazard identification, animal to human extrapolation, carcinogenesis, chemicals, epidemiologic studies, experimental studies, identifying chemical carcinogens, limitations, long-term chemical carcinogenicity experiments, public health.

The most important and significant phase or step in the risk assessment and risk management process is the initial or first alert of a potential environmental hazard to public health (1–5). The hazard identification stage of the assessment procedure relies almost exclusively on information gained from human and animal studies, in vivo and in vitro toxicology and mutagenesis assays, and, to a lesser extent, on chemical and physical properties, including molecular structure. The subsequent three steps in the formal process are concerned with animal and human dose-response assessment, human exposure assessment, and human risk characterization (table 1).

The major sources of information used to identify potential hazards to human health span the range from actual observations on humans (6, 7) to computerized analyses based on chemical structural fragments. Each type of study has both advantages and limitations (table 2) and, collectively, allow one to rank the sources according to value and reliability in predicting potential adverse health hazards. Since human data are generally unavailable, the primary source of information considered to have the most advantages continues to be long-term chemical carcinogenesis experiments (table 2) (8–19).

The use of mechanistic data to evaluate chemical carcinogenesis hazards to humans has gained in value and recognition during recent years (20–26). However, more knowledge on chemically perturbed biomolecular events is certainly needed to allow better informed forecasts and decisions about whether a particular chemical or exposure circumstance will or will not lead to cancer in humans. Nonetheless, mechanistic data, when available, should contribute markedly to the overall evaluation process.

This paper attempts to illustrate the scientific concepts and procedures used to evaluate chemical carcinogenesis experiments and to set forth general criteria for the qualitative identification of those chemicals that may present the most significant potential public health hazards (9, 10, 18, 19, 27–30). Moreover, the magnitude of the overall cancer hazard identification effort, together with a likelihood number of eventual chemical carcinogens, has been estimated.

Carcinogenesis results and magnitude of hazard

Carcinogenesis results

An evaluation of studies conducted by the National Cancer Institute and by the National Toxicology Program (31) showed that roughly one-half of the chemicals in question induced a positive carcinogenic response in at least one organ in at least one of the several sex-species experiments conducted on a particular

¹ National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, United States.

Reprint requests to: Dr JE Huff, NIEHS, Box 12233, Research Triangle Park, NC 27709, USA.

Table 1. Risk assessment steps and comparative definitions (taken from references 1 and 3).

	National Research Council, National Academy of Sciences 1983 (1)	Task Force on Health Risk Assessment 1985 (3)
Hazard identification	Determination of whether a particular chemical is or is not causally linked to particular (adverse) health effects	Qualitative indication that a substance or condition may adversely affect human health
Hazard characterization (dose-response assessment)	Determination of the relation between the magnitude of exposure and the probability of occurrence of the (adverse) health effects in question	Qualitative and quantitative evaluation of the nature of the adverse effects, including their expression as functions of the amount of exposure (dose)
Exposure assessment	Determination of the extent of human exposure before or after the application of regulatory controls	Qualitative and quantitative evaluation of the degree of human exposure likely to occur
Risk characterization	Description of the nature, and often the magnitude, of human risk, including attendant uncertainty	Integration of these steps into a scientific determination of the level of risk as a basis for policy consideration

Table 2. Sources for identifying potential cancer hazards to humans and their advantages and disadvantages.

	Advantages	Disadvantages
Epidemiologic studies	Humans are ultimate indicators of disease Sensitive populations evaluated	Generally retrospective (death certificates, recall biases, etc) Insensitive, costly, lengthy Reliable exposure data not available or difficult to obtain Combined, multiple, and complex exposures, lack of appropriate cohorts Experiments on humans not possible
Long-term studies on animals	Prospective and retrospective (validation) evaluations Excellent correlation with human carcinogens Exposure levels and conditions known Toxicity and carcinogenicity effects identified Results obtained relatively quickly Qualitative comparisons among chemical classes Integrative and interactive biological systems closely related to humans	Rarely replicated Resources intensive (staff, money, facilities) Shortage of adequate facilities, scientific expertise and experience Experiments often conducted at exposure levels in excess of those anticipated for humans Debates regarding relevancy of results (eg, routes of exposure and rodents not being humans) Usually single chemical experiments, do not mimic human exposure circumstances
Mid-term in vivo assays and short-term in vivo and in vitro assays	More rapid and less expensive Easily replicated Valuable end points measured (eg, mutations, preneoplasia) Assays easily manipulated [eg, two-stage models, organ systems (liver, urinary bladder)] Single or multiple chemicals and complex mixtures Screening assays	In vitro, not fully predictive for in vivo Usually organism- or organ-specific Systems generally manipulated towards select and sensitive end points Not generally predictive for carcinogenesis Not reliable surrogates for whole animals, long-term experiments or for humans Potencies not easily comparable to whole animals
Chemical structure-activity associations	Relatively easy, rapid and inexpensive Reliable for certain chemical classes (eg, nitrosamines, anthraquinones, benzidine dyes) Developed using biological data, yet not dependent on animal data Computer adaptable and compatible	Not "biological" Many exceptions to formulated rules Retrospective and rarely (but becoming) prospective

chemical (9, 11, 12, 32, 33). Importantly though, from a hazard identification point of view, only 13.8% of the chemicals studied adequately in male and female rats and in male and female mice caused cancer in each of the four experiments. Another 8.0% produced cancer in one or more organ sites in three of the four experiments. Thus these two categories of outcomes rep-

resent only 71 chemicals out of the 326 evaluated in long-term carcinogenesis experiments that would likely present the most potential for cancer hazard to humans (table 3). This "weight of the evidence" approach is based simply on a qualitative evaluation of the totality of the evidence; yet it does not mean that chemicals causing cancer only in a single organ of a single strain

in a single species should be considered inconsequential or unequivocally safe.

These two-species positive experimental findings generally cause a chemical to be placed in the sufficient evidence of carcinogenicity category of the International Agency for Research on Cancer (IARC) (13, 19, 34) and in the group of substances reasonably anticipated to be carcinogens in the *Annual Report on Carcinogens* of the United States (US) Department of Health and Human Services (35). These results permit the identification of those chemicals considered the most likely to be potentially carcinogenic to humans, and thus epidemiologic investigations having identified adequate cohorts should be initiated. Furthermore, regulatory agencies and others legislatively charged with conducting formal risk assessments can best allocate their resources to those chemicals causing cancers in multiple species, both sexes, in several organs or systems, and so on.

Consequently, we decided to evaluate further the carcinogenesis study results of the National Toxicology Program and to aggregate the chemicals qualitatively by the number of positive experiments (table 3). In this way one begins to differentiate at least qualitatively the 50% of chemicals causing cancer in at least one of the sex-species experimental units. Moreover, epidemiologic studies could be considered for the 45 chemicals causing cancer in each of the four experiments or for the 26 chemicals inducing positive responses in three of the four groups. These two classes comprise 21.8% of the total number of chemicals evaluated in long-term studies. Obviously, this finding must not be construed to mean that other chemicals causing cancers in fewer experiments are not to be viewed with appropriate public health scrutiny. This "strength of the evidence" approach simply allows one to establish some selection criteria for ranking chemicals with respect to potential for cancer hazard to humans. Furthermore, even this relatively low percentage of carcinogenic chemicals may be skewed somewhat disproportionately in the direction of positive effects, since the criteria for selecting many of the chemicals so far evaluated for potential carcinogenicity were based on a preexisting "suspicion" that the chemicals would be carcinogenic. In any event, the use of such criteria showed that fewer than 25% of these chemicals induced carcinogenic effects in both species (12).

Estimated magnitude of the effort and forecasted number of carcinogens

For some perspective of the meaning of this subset of data from the National Toxicology Program, and of the magnitude of the potential problem of chemical exposures, of the 10 million chemicals so far synthesized, estimates of chemicals in the marketplace range from 50 000 to 100 000. Some individuals place this number closer to 60 000 or 70 000 chemicals. Accord-

Table 3. Chemical carcinogenesis summary results (total number of chemicals = 326, or 1304 experiments) (updated from reference 12).

	Number of positive experiments	Percentage of the total
Carcinogenic in both sexes of two species	45	14
Carcinogenic in three of four sex-species experiments	26	8
Carcinogenic in two of four sex-species experiments	60	18
Carcinogenic in one of four sex-species experiments	39	12
Carcinogenic in at least one sex of one species	170	52
No evidence in any of the four sex-species experiments	156	48
Concordance in cancer responses		
Between rats and mice		74
Between sexes		
Rats		85
Mice		87

ing to the inventory of existing chemicals in the Toxic Substances Control Act of the US Environmental Protection Agency, approximately 23% of the more than 60 000 chemicals are polymers of one sort or another. For almost one-third of the chemicals listed no production was reported in 1977 (the most current year with available data), and for an additional 28% production of less than 10 000 pounds (< 4536 kg) a year was reported. Considering these factors for chemicals produced in excess of 10 000 pounds (> 4536 kg) (and excluding inorganics, polymers, and naturally occurring substances), reports from manufacturers and producers were received on only 8500 substances (personal communication, JA Moore). This value could be taken to "indicate" that the other > 50 000 chemicals in the inventory are "low" volume or within the excluded categories (and of course for agents other than polymers allows no knowledge about their potential toxicity). If however these analyses can be considered reasonable, then one could conclude (with less than full confidence) that the number of chemicals posing the most potential harm of induced cancer to humans would be in the vicinity of 10 000. From these data we estimate further that approximately only 10 to 20% or so of these 10 000 chemicals would eventually be considered likely carcinogens to humans, that is, as defined by IARC (34) and by the US Department of Health and Human Services (35).

Continuing this evaluation, if one begins with the retrospective knowledge that about one-half of the critically selected chemicals so far evaluated has shown evidence of carcinogenicity in at least one organ or tissue of one sex of one species and then uses the qualitative information for determining carcinogenicity to identify the percentage of chemicals that would reasonably be anticipated to be carcinogenic to hu-

mans, then approximately 20% of the universe of available chemicals, if studied adequately, would likely be considered potentially carcinogenic to humans. This estimated percentage would translate into approximately 2500 substances that would be identified eventually in long-term carcinogenesis studies (or epidemiologically) as being human carcinogens. However other information (see the later discussion) indicates that this figure might be on the "high" end of a reasonable range estimate.

Since 1972, IARC has searched rigorously the available literature and in the last 20 years has been able to locate and evaluate carcinogenicity data on only 732 substances. In the monograph series of IARC (volumes 1–53), 55 "agents" have been judged to be carcinogenic to humans, another 45 have been considered probably carcinogenic to humans, 191 have been rated possibly carcinogenic to humans, 440 have not been classifiable as to their individual carcinogenicity to humans, and one (caprolactam) has been considered probably not carcinogenic to humans (27, 29, 30). Thus of the 732 agents evaluated by IARC, only 100 (14%) are either known as carcinogenic to humans or are strongly suspected of being carcinogenic to humans. Of course this percentage of carcinogenic agents cannot be considered an accurate estimate of the total universe of chemicals, given the large number of IARC-evaluated agents that could not as yet be classified and the knowledge (as has already been mentioned) that most chemicals already evaluated were selected and studied because of an *a priori* conjecture of being carcinogenic. Furthermore, the great majority of chemicals in past and present use has not been evaluated for potential adverse or harmful biological and toxicologic effects (36).

Nonetheless, considering the information of the US Environmental Protection Agency, the IARC information, and our data, one could make a reasonable and logical estimate that approximately 10–20% (at most) of those chemicals considered the most likely to represent significant exposures would eventually be shown to be convincingly carcinogenic in long-term experiments with animals. These chemicals then should be considered likely to be carcinogenic to humans (34, 35). Others of course may wish to propose equally acceptable ranges, and ours are given largely because no one else has apparently taken the opportunity to do so, and, furthermore, ours is a personal-opinion estimate for others to use and compare. In any event, this estimate does allow us a reasonable and working hypothesis, with some scientific support and conjecture, with which to probe and plan for the magnitude of the dynamic task that must be dealt with in the future.

However, worldwide capacity for conducting these essential carcinogenesis evaluations is limited, and it is becoming more expensive to undertake the necessary experiments needed to identify confidently those chemicals or exposures that are potential carcinogenic hazards to humans. An international survey (37)

reports that 80 organizations located in 20 countries are conducting long-term chemical carcinogenesis studies on a total of about 900 to 1000 chemicals — that is, a maximum of 300 additional chemical studies can be started each year since one study takes five or more years to design and conduct the experiments; gather, evaluate, and interpret the results; peer review the evaluations in public forum; and prepare a report or manuscript for publication. Currently 10 of the 20 countries [ie, Germany (195 studies), France (14 studies), Hungary (27 studies), India (18 studies), Italy (11 studies), Japan (174 studies), The Netherlands (37 studies), Norway (11 studies), the United Kingdom (67 studies), and the United States (609 studies)] do more than 95% of these studies, and four conduct more than 85% of the 95% (38).

We suspect that the total capacity and interest would certainly increase if there were more money made available for these experiments. However money alone will not automatically increase the number of chemicals studied. Other factors must be considered. For example, knowledgeable staff and adequate facilities are today in very limited supply. Not everyone can or even wants to do these "semiroutine" studies. In some cases those individuals or laboratories actively seeking to do these time-consuming, meticulous, and laborious investigations are not considered qualified or adequate. Thus the search continues for shorter-term, less complicated, easily performed, and more reasonably priced *in vitro* or *in vivo* assays (and perhaps some day eventually computer-simulated model experiments). However, as most scientists in these fields of research believe, the day for replacing, or even reducing, current efforts or for duplicating the value of long-term *in vivo* carcinogenesis studies will be far into the future.

Concepts and perspectives

The most readily available, reliable, and historical means for identifying potential human health hazards necessarily involves undertaking long-term studies with laboratory animals. These chemical carcinogenesis experiments are designed and conducted principally to identify those chemicals, mixtures of chemicals, or environmental and occupational exposures that have a potential to induce diseases and untoward toxic effects, especially cancer, in humans. Besides human experience and epidemiologic investigations, long-term studies with laboratory animals are the most universally accepted and extensively validated means with which to determine carcinogenic hazards to public health.

The data and information engendered in the hazard identification step, together with the available information from the later three steps in the risk assessment process (table 1), form the bases for what has been termed the "weight of the evidence" approach to risk assessment. These scientifically based estimations of risks to human health are then weighed against

Table 4. Some examples of "super chemical carcinogens."^a

Chemical	Exposure concentrations	Route	Tumor sites
Benzene	25–200 mg · kg ⁻¹ ^b	Gavage	9
1,3-Butadiene	6.25–1250 ppm	Inhalation	12 ^c
Dibromochloropropane (DBCP)	0.6–3.0 ppm	Inhalation	5
1,2-Dibromoethane (EDB)	10–40 ppm	Inhalation	6
Dimethoxybenzidine	80–330 ppm	Drinking water	11 ^d
Dimethylbenzidine	30–150 ppm	Drinking water	12 ^d
Dimethylvinylchloride (DMVC)	100–200 mg · kg ⁻¹	Gavage	8
Ethylene oxide	50–100 ppm	Inhalation	5 ^e
Glycidol	37.5–75 mg · kg ⁻¹	Gavage	16
Ochratoxin A	70–210 mg · kg ⁻¹ ^f	Gavage	2 ^g , ^h
Pentachlorophenol	100–600 ppm	Feed	3
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	0.001–0.29 mg · kg ⁻¹	Gavage	4 ⁱ
Tetranitromethane (TNM)	0.5–5.0 ppm	Inhalation	1 ^h
1,2,3-Trichloropropane	3.0–60 mg · kg ⁻¹	Gavage	10

^a These chemicals have been selected on a comparative basis from the 400 chemicals listed in the data base of the National Toxicology Program, largely on the low-exposure levels used, the number of organs showing induced cancers, and the uniqueness and consistency of the carcinogenic responses (ie, carcinogenic in all sex-species experiments at all exposure levels).

^b Converting to equivalent inhalation exposures: 19 to 234 ppm.

^c Mice only; a study with rats has been reported by others showing four other tumor sites.

^d Rats only.

^e Mice only; studies with rats showed four other tumor sites.

^f A 21 µg · kg⁻¹ exposure group did not develop tumors; for the other chemicals in this table, a carcinogenic response was induced at all exposure levels for each of the sex-species groups.

^g Rats only; studies in mice have been reported by others showing cancer of the liver as well as of the kidney.

^h These one or two organ site carcinogens are included because the exposures were very low and the magnitude of the responses was overwhelming.

ⁱ Other studies have been reported showing four additional tumor sites.

and with the benefits of the identified risk to society and lead to risk management decisions and promulgated policies (1–5). Most people rely on this collective effort to evaluate risks and hence to protect public health, and yet at the same time this philosophy has been misused by some to delay or circumvent policy decisions. However, certain circumstances demand flexibility. For instance, a strong data set that forecasts an obvious potential health hazard need not be subjected to the entire process before remedial actions are initiated to reduce the recognized risk. Examples might include those chemicals that, because of the extraordinary responses observed in long-term carcinogenesis studies, could be considered "super carcinogens" (table 4) and should signal cause for immediate protective action. Obviously, this approach stems from the fact that chemicals considered to be carcinogens differ with regard to the overall strength of the induced carcinogenic response and for practical purposes can be divided into qualitative groupings based on empirical indicators of "potency."

The factors considered most important for judging experiments with laboratory animals are (11, 12) (not in any particular priority order): (i) exposure conditions and concentrations, (ii) number of positive experiments (eg, species and sexes), (iii) magnitude of induced tumor incidence rates, (iv) dose-response patterns, (v) multiplicity of tumor sites (organs, tissues), (vi) numbers of tumors per site, (vii) commonly versus uncommonly occurring tumors, (viii) correspondence of tumor types and sites among species and sexes, (ix) latency, metastases, preneoplastic lesions, and (x) results from short-term tests and structure-activity

evaluations. In our judgment, the data and results from these long-term chemical carcinogenesis studies, together with experience over the years, should permit necessary key public health decisions to be made or recommended. For illustrative purposes we believe the chemicals such as those given in table 4 certainly qualify for quick action — that is, each of these chemicals caused multiple-site cancers (except tetranitromethane) in all sex-species experiments at all exposure concentrations. None of these chemicals (except perhaps ochratoxin A) have yet been shown to have an exposure concentration that did not cause cancer. For several chemicals, of course, regulatory measures have been enforced (eg, for benzene and 1,2-dibromoethane) or are underway (1,3-butadiene).

Thus we believe that carcinogenicity findings from experiments with laboratory animals are logical and scientifically reasonable for identifying and predicting potential carcinogenic risks to humans. We have suggested that a large number of the chemicals so far evaluated are not considered to be potentially carcinogenic to humans, and, furthermore, from the universe of available chemicals, we estimate that most will not present real carcinogenic hazards to humans. Of course due caution must be exercised since the toxicologic data on most chemicals are incomplete or absent (36) and few chemicals are thought to be "safe" when adverse effects other than cancer are considered.

The major and unifying conclusion we have come to endorse after doing chemical carcinogenesis experiments with animals for two decades, and from evaluating the resultant findings singularly at the time and collectively now, centers on the value and overwhelm-

ing proof to support the intuitive notion that results from these experiments have undeniable relevance to likely responses in humans. As a further point of historical interest, of the 55 chemicals or exposures considered to be carcinogenic to humans (with 45 others judged to be probably carcinogenic to humans), only one-half (27 agents) are single "chemicals." Of these, nearly one-third were first identified as carcinogens in animals, and the finding was subsequently confirmed epidemiologically in humans (10, 27, 34, 39). Thus these studies should continue to be done, and the use of quality results from toxicology (and in particular long-term carcinogenesis) experiments with animals as alerts to hazard identification should be further endorsed and expanded.

The impact of the identification of chemical carcinogens on public health remains difficult to determine, largely because "if we do anticipate hazards and thereby prevent future disease, we will never know that we are right . . . precisely because we are not willing to allow the evidence of disease to accumulate. In short, the price we pay for being right is that we cannot prove that doing nothing was wrong [p 141—142]" (40). Sorely needed are new ideas which will lead to the better identification of specific causes of the major cancers (41) and of the increasing trends (7) in humans. Likewise, expanded efforts to define molecular mechanisms of carcinogenesis will lead eventually to more direct treatments of existing diseases and, as importantly, will allow more informed decisions about preventive measures.

Acknowledgments

We appreciate the useful and critical comments and suggestions made by Dr J Haseman, Dr L Hart, and Dr D Bristol. Ms D Mayer helped with the reference citations and proofreading.

References

1. National Research Council/National Academy of Sciences. Risk assessment in the Federal Government: managing the process. Washington, DC: National Academy Press, 1983.
2. DHHS Task Force on Health Risk Assessment, Department of Health and Human Services. Determining risks to health: federal policy & practice. Dover, MS: Auburn House Publishing Co, 1986.
3. Office of Science and Technology, Interagency Staff Group on Chemical Carcinogenesis, Executive Office of the President. Chemical carcinogens: a review of the science & its associated principles. Fed Regist 1985;50:10371—442. Also published in Environ Health Perspect 1986;67:201—82.
4. Johnson BL, Turturro A, Freni SC, Hogan MD, Huff JE, Kimbrough RD, et al. Risk assessment and risk management of toxic substances. In: Determining risks to health: federal policy & practice. Dover, MS: Auburn House Publishing Co, 1986:336—86.
5. Cohrssen JJ, Covello VT. Risk analysis: a guide to principles & methods for analyzing health & environmental risks. Washington, DC: US Council on Environmental Quality, Executive Office of The President, 1989.
6. Muir C. Epidemiology, basic science, and the prevention of cancer: implications for the future. Cancer Res 1990;50:6441—8.
7. Davis DL, Hoel D, ed. Trends in cancer mortality in industrial countries. Ann NY Acad Sci 1990;609:1—347.
8. Gart JJ, Krewski D, Lee PN, Tarone RE, Wahrendorf J. Statistical methods in cancer research; vol III (The design and analysis of long-term animal experiments). Lyon: International Agency for Research on Cancer, 1986. (IARC scientific publications; no 79.)
9. Huff JE, Haseman JK, Rall DP. Scientific concepts, value, & significance of chemical carcinogenesis studies. Annu Rev Pharmacol Toxicol 1991;31:621—52.
10. Huff JE, Rall DP. Relevance to humans of carcinogenesis results from laboratory animal toxicology studies. In: Last JM, Wallace RB, ed. Maxcy-Rosenau-Last's public health & preventive medicine. 13th ed. Norwalk, CT: Appleton-Century-Crofts, 1992:433—40&453—7.
11. Huff JE. Design strategies, results and evaluations of long-term chemical carcinogenesis studies. Scand J Work Environ Health 1992;18 Suppl 1:31—7.
12. Huff JE, Haseman JK. Long-term chemical carcinogenesis experiments for identifying potential human cancer hazards: collective data base of the National Cancer Institute & National Toxicology Program (1976 — 1991). Environ Health Perspect. 1991;96:23—31.
13. International Agency for Research on Cancer (IARC). Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon: IARC, 1987. (IARC monographs on the evaluation of carcinogenic risks to humans; suppl 7.)
14. Montesano R, Bartsch H, Vainio H, Wilbourn J, Yamasaki H. Long-term & short-term assays for carcinogens: a critical appraisal. Lyon: International Agency for Research on Cancer, 1986. (IARC scientific publications; no 83.)
15. Occupational Safety and Health Administration. Identification, classification & regulation of potential occupational carcinogens. Fed Regist 1980;45:5001—296.
16. Office of Technology Assessment (OTA), Congress of the United States. Assessment of technologies for determining cancer risks from the environment. Washington DC: OTA, 1981.
17. Office of Technology Assessment (OTA), Congress of the United States. Identifying and regulating carcinogens. Washington, DC: OTA, 1987.
18. Rall DP, Hogan MD, Huff JE, Schwetz BA, Tennant RW. Alternatives to using human experience in assessing health risks. Annu Rev Public Health 1987;8:355—85.
19. International Agency for Research on Cancer (IARC). IARC Monographs on the evaluation of carcinogenic risks to humans; vol 1 — 53. Lyon: IARC, 1972—1991.
20. Hoel DG, Kaplan NL, Anderson MW. Implication of non-linear kinetics on risk estimation in carcinogenesis. Science 1983;219:1032—7.
21. International Agency for Research on Cancer (IARC). Approaches to classifying chemical carcinogens according to mechanism of action. Lyon: IARC, 1983. (IARC internal technical report; no 83/001.)
22. Hoel DG, Haseman JK, Hogan MD, Huff JE, McConnell EE. The impact of toxicity on carcinogenicity studies: implications for risk assessment. Carcinogenesis 1988;9:2045—52.
23. Vainio H, Magee P, McGregor D, McMichael AJ, ed. Mechanisms of carcinogenesis in risk evaluation. Lyon: International Agency for Research on Cancer. In press. (IARC scientific publications; no 116.)
24. Barrett JC. Mechanisms of action of known human carcinogens. In: Vainio H, Magee P, McGregor D, McMichael AJ, ed. Mechanisms of carcinogenesis in risk evaluation.

- ation. Lyon: International Agency for Research on Cancer. In press. (IARC scientific publications; no 116.)
25. Huff JE. Chemical toxicity & chemical carcinogenesis: is there a causal connection? In: Vainio H, Magee P, McGregor D, McMichael AJ, ed. Mechanisms of carcinogenesis in risk evaluation. Lyon: International Agency for Research on Cancer. In press. (IARC scientific publications; no 116.)
26. Lucier, G. Receptor-mediated carcinogenesis. In: Vainio H, Magee P, McGregor D, McMichael AJ, ed. Mechanisms of carcinogenesis in risk evaluation. Lyon: International Agency for Research on Cancer. In press. (IARC scientific publications; no 116.)
27. Tomatis L, Aitio A, Wilbourn J, Shuker L. Human carcinogens so far identified. *Jpn J Cancer Res* 1989;80: 795—807.
28. Tomatis L, Aitio A, Day NE, Heseltine E, Kaldor J, Miller AB, et al. Cancer: causes, occurrence and control. Lyon: International Agency for Research on Cancer, 1990. (IARC scientific publications; no 100.)
29. Vainio H, Wilbourn J. Identification of carcinogens within the IARC monograph program. *Scand J Work Environ Health* 1992;18 Suppl 1:64—73.
30. Vainio H, Coleman M, Wilbourn J. Carcinogenicity evaluations and on-going studies: the IARC databases. *Environ Health Perspect.* 1991;96:5—9.
31. Huff JE. A historical perspective on the classification developed and used for chemical carcinogens by the National Toxicology Program during 1983—1992. *Scand J Work Environ Health* 1992;18 Suppl 1:74—82.
32. Huff JE, Eustis SL, Haseman JK. Occurrence & relevance of chemically induced benign neoplasms in long-term carcinogenicity studies. *Cancer Metast Rev* 1989; 8:1—21.
33. Ashby J, Tennant RW. Definitive relationships among chemical structure, carcinogenicity & mutagenicity for 301 chemicals tested by the US NTP. *Mutat Res* 1991; 257:229—306.
34. International Agency for Research on Cancer (IARC). Preamble. In: Coffee, tea, mate, methylxanthines, and methylglyoxal. Lyon: IARC, 1991:13—33. (IARC monographs on the evaluation of carcinogenic risks to humans; vol 51.)
35. Department of Health and Human Services, National Toxicology Program (NTP). Sixth annual report on carcinogens. Research Triangle Park, NC: NTP, 1991.
36. National Research Council/National Academy of Sciences. Toxicity testing: strategies to determine needs & priorities: identification of toxic & potentially toxic chemicals for consideration by the National Toxicology Program. Washington, DC: National Academy Press, 1984.
37. International Agency for Research on Cancer (IARC). Directory of agents being tested for carcinogenicity: no 14. Lyon: IARC, 1990.
38. International Agency for Research on Cancer (IARC). Information bulletin on the survey of chemicals being tested for carcinogenicity; no 13. Lyon: IARC, 1988.
39. Tomatis L. The predictive value of rodent carcinogenicity tests in the evaluation of human risks. *Annu Rev Pharmacol Toxicol* 1979;19:511—30.
40. Rall DP. Issues in the determination of acceptable risk. *Ann NY Acad Sci* 1981;363:139—44.
41. Schmahl D, Preussmann R, Berger MR. Causes of cancer — an alternative view to Doll and Peto (1981). *Klin Wochenschr* 1989;67:1169—73.