Issues and Current Applications of Interspecies Extrapolation of Carcinogenic Potency as a Component of Risk Assessment

by Willard J. Visek*

The Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) is conducting this symposium under contract with the Center for Food Safety and Applied Nutrition (CFSAN) of the Food and Drug Administration (FDA). The FDA has requested information on the strengths and weaknesses of current interspecies extrapolation methods using metabolic and pharmacokinetic data, identity of data for these methods, bases for choice of extrapolation method and selection of data base, validity and uniformity of interspecies extrapolation from target organ data, and nature and completeness of supporting data. Definitions and basic concepts of dose scaling are addressed and questions regarding appropriate units of measurement (e.g., mg/kg body weight, mg/m^3 respired air, mg/m^2 surface area) are raised. The use of DNA damage as a marker or end point upon which to scale carcinogenic potency is considered. Genotoxic mechanisms of carcinogenesis are emphasized because the roles of DNA adducts and DNA repair processes in initiation and promotion are much better defined than the mechanism for nongenotoxic carcinogenesis. The problems encountered in evaluating the human carcinogenicity of trichloroethylene are reviewed. The broad objectives of the symposium are discussed and the development of a structured format for the presentation of invited papers is presented.

Introduction

By mandate of the 96th Congress, the Food and Drug Administration was directed to contract with the National Academy of Sciences for a study on the institutional means of risk assessment. In 1983, a report entitled "Risk Assessment in the Federal Government: Managing the Process" was delivered to FDA by the Commission on Life Sciences of the National Research Council (1). In that report the risk assessment process was characterized by the following four steps: (a) hazard identification, (b) dose-response assessment, (c) exposure assessment, and (d) risk characterization.

In carcinogenic risk assessment, the second step (i.e., dose-response assessment) estimates the dose associated with acceptable levels of risk in humans on the basis of high-dose cancer incidence data from animal experiments. Such estimates are made from intraspecies extrapolation of high-dose incidence to low-dose incidence and by the conversion of dose estimates in animals to equivalent or equipotent estimates of dose in humans. The estimation of low-dose incidence on the basis of high-dose data within the same species is defined as dose-range extrapolation. Various mathematical models are used to make these calculations. Con-

version of animal dose to human dose (i.e., interspecies extrapolation) is defined as dose scaling. Dose scaling may refer to animal-to-animal as well as animal-to-human. We will further define a scaling factor as any characteristic of a test species or in vitro system that is used as a common denominator for dose scaling.

The purpose of this symposium is to examine the biologic bases for developing effective dose-scaling procedures. Dose-range extrapolations and the mathematical and statistical models from which they are derived have been reviewed in a number of other forums and will not be directly addressed in this symposium.

An advisory committee to the Food and Drug Administration, commenting on downward extrapolation from results obtained at some level well above the level of actual use, said, "The basic problem is that extrapolation outside the range of observation must be based on generally unverifiable assumptions about the mathematical nature of the dose-response relationship near zero dosage" (2). It is not certain that the situation has improved in the last 15 years. The FDA has asked the Life Sciences Research Office to investigate the validity and utility of current procedures for interspecies extrapolation of data from animal studies of food chemicals to the estimation of chemical carcinogenesis in humans. Our examination of these topics in the papers and sup-

*University of Illinois, College of Medicine, Urbana, IL 61801.

plemental presentations that follow will be guided by the following questions posed by FDA:

- What are the existing methods for interspecies extrapolation based on qualitative and quantitative differences between test species and man?
- What are the strengths and weaknesses of the data bases supporting these methods?
- What circumstances make one data base or extrapolation method more informative than another?
- Do existing data on target tissues provide a uniform method for extrapolating carcinogenic potency data for all substances and all species to man? If so, what are the nature and extent of these data bases, and what additional data are needed?

It should be emphasized that this symposium, in order to be most effective in providing useful information for the FDA and answering the questions the agency has posed, will focus on biological data and concepts and not on mathematical modeling or statistical approaches to extrapolation of high-dose to low-dose effects.

Although we are primarily interested in assessment of the carcinogenic risk of food chemicals, we do not want to exclude any pertinent information from experiments in acute and chronic toxicity involving other end points. Frequently, throughout the symposium, examples will be drawn from the general toxicology literature in order to illustrate a particular point; however, the principal concern is human dietary exposure to carcinogens.

Dose Scaling: Test Animals to Humans

This symposium will focus on several aspects of dose scaling between test species and humans. The topics are as follows: definition of scaling and scaling functions; differentiation of dose-range extrapolation and dose scaling; common methods of scaling based on body mass, surface area, and dietary intake; biological bases of current methods and their relationship to mechanisms of carcinogenesis; strengths and weaknesses of current scaling procedures.

In addition, there are also several specific concerns and issues that relate to the discussion of these topics. (a) Does the choice of end point (i.e., carcinogenesis rather than acute toxic effect) have a significant impact on the application of scaling methods? What problems may arise when interspecies extrapolations are attempted in the absence of knowledge of a common mechanism of carcinogenicity among species? (b) Is it appropriate to compare dose-response curves between species when there is a significant difference in the slope function of the curves? Does a difference in slope function necessarily imply differing mechanisms of carcinogenicity that make accurate scaling impractical? (c) Should dose scaling between species be based on administered dose or on a quantitative estimate of cumulative target tissue exposure [e.g., tissue concen-

tration integral (TCI) in micromoles × minutes × liters^{-1}]? (d) Are the statistical procedures currently used for comparisons of carcinogenic potency between species being appropriately applied?

In this context it could be especially useful for FDA to explore dose-scaling methods based upon total exposure of the target tissues rather than on administered dose with the expectation that improved correlations with cancer-causing exposures in humans might be found.

Figure 1 illustrates the problem to be addressed in this symposium by identifying the problems that scientists face in scaling potency data among species. The coordinates in Figure 1 are labeled only in the generic sense, identifying neither independent nor dependent variables. The reason for not specifying these coordinates is that at this time we do not know which of several independent variables is most useful or which of dozens of end points is most valid.

In Figure 1, the solid line (curve 1) represents the response of one species (A) to a range of dosage conditions measured in milligrams/kilograms. This curve represents an unacceptable response for the species because the proportion of the exposed population which has been affected is in excess of a minimal background level. The horizontal dashed line represents the response of a second species (B) to dosages over the same range as depicted in curve 1. Curve 2 of the dashed line illustrates an acceptable response because the response remains near the minimum risk level. If the exposure conditions are extended as shown in curve 3 of the dashed line, we would expect to find a range of dosages that is also unacceptable for this species B.

The fallacy of using curve 1 to try to predict curve 2 in the absence of any knowledge about curve 3 is obvious. Although these curves are totally hypothetical, they are not an unreasonable model for trichloroethylene (TCE) induction of mouse liver cancer and the questionable carcinogenicity of TCE in humans.

If curve 3 represents the population that cannot be exposed, except epidemiologically, and simultaneously is the population that one is trying to protect, how can this dilemma be resolved? This symposium is intended to examine the basic biologic characteristics of different species that affect our ability to identify response end points and scaling factors that either minimize the gap between curves 1 and 3 or at least reduce the variability of their relative positions for a broad range of end points from initial DNA defect to metastatic disease.

Of the many classic examples that can be used to illustrate the problems of milligram per kilogram scaling between species, one was reviewed in some detail by Calabrese (3) based on a quotation from Schmidt-Nielsen's 1972 book, *How Animals Work (4)*. In reference to an article published in *Science* about dosing an elephant with LSD to produce a rage reaction, Schmidt-Nielsen said, "The authors had calculated the dose based on the amount that puts a cat into a rage, and had multiplied it up by weight until they arrived at 297 mg of LSD to be given to the elephant. After the injection
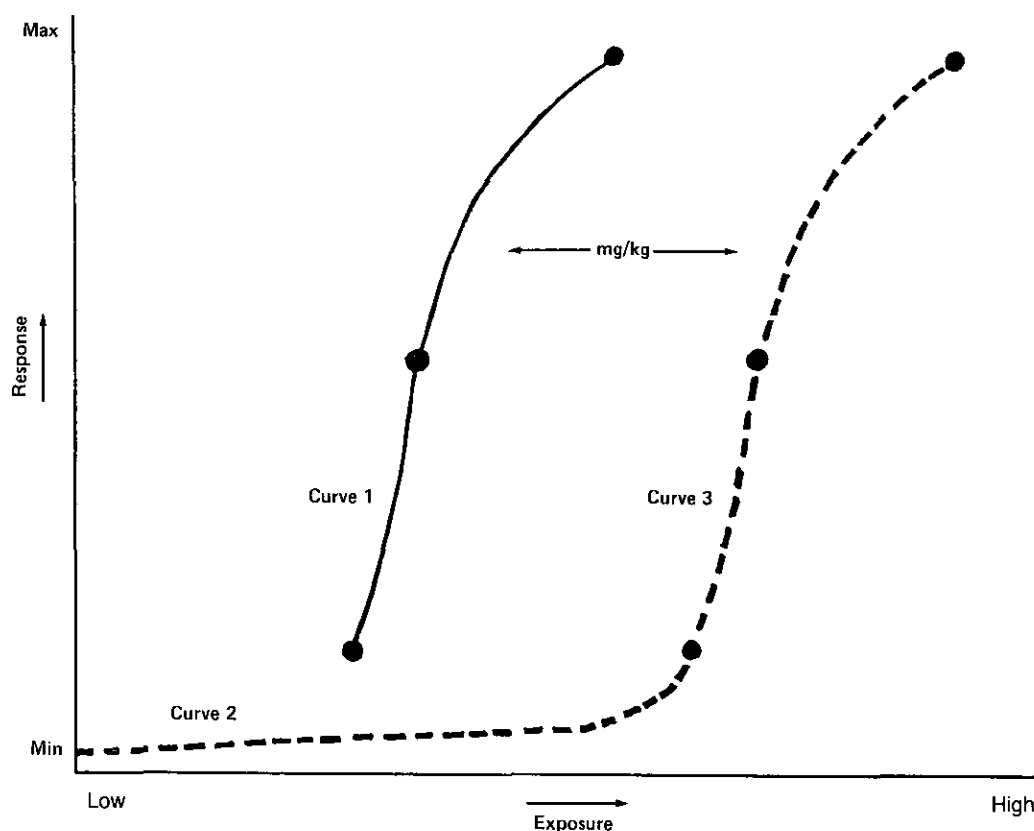
FIGURE 1. Comparison of a hypothetical dose-response curve for Species A(—) and Species B (---).

of 297 mg the elephant immediately started trumpeting and running around, then he stopped and swayed; five minutes after the injection he collapsed, went into convulsions, defecated and died." There is no evidence that this experiment has been or is likely to be replicated at lower doses, so we will probably never know if the alternate scaling factors computed by Calabrese would have ensured a more satisfactory outcome (Table 1).

Experiences such as those with the elephant and cat strongly suggest that the relationship between curves 1 and 3 in Figure 1 is not likely to be constant on a milligram per kilogram basis between any two test species nor between test species and man. Such relation-

Table 1. Projected dose of LSD required to induce rage in an elephant.[a]

Dose, mg	Basis for calculation
0.4	Brain size ratio (elephant:human) and effective dose (human)
3.0	Metabolic rate ratio (human:elephant) and effective dose (human)
8.0	Body weight ratio (elephant:human) and effective dose (human)
80.0	Metabolic rate ratio (cat:elephant) and effective dose (cat)
297.0	Body weight ratio (elephant:cat) and effective dose (cat)

[a] Modified from Calabrese (3).

ships are not expected to hold for different chemicals, nor for all routes of administration of a single chemical, and usually not even for the same chemical by the same route of administration. For some classes of compounds the gap between the curves has been reduced or eliminated by using other scaling functions, such as dose per unit body surface area or dose as a constant percentage of diet. However, there is no scaling factor that is consistently reliable. The objective of this study is to identify the factors and conditions responsible for the gap between the dose-response curves for different species and to explore potential solutions to the problem of identifying valid and useful scaling factors.

In addition to physical parameters such as body mass and surface area, time has also been identified as a significant variable for consideration in scaling. Rall (5) noted that the lifespan of a human is approximately 35 times that of a mouse and that one man may represent between 160 to 3000 mice in terms of the number of cells susceptible to carcinogens. In a summary of testimony on interspecies extrapolation, the lifetime chance of a single cell being hit by a carcinogen was estimated to be approximately 100,000 times as great for a human as for a mouse based on the product of 35 × 3000 (6). Although assumptions of this nature are not used directly as scaling factors, they do imply a significant difference in sensitivity as a function of body size (number of cells) and longevity.

Schwartz and Moore (7) reported *in vitro* experiments modeling the earliest stages of carcinogenesis, as we currently understand them, and suggested a diametrically opposed probability of risk as a function of cell mass and longevity. They studied the capacity of cultured mammalian fibroblasts to metabolize dimethylbenz[a]anthracene (DMBA) to yield a mutagenic metabolite. Figure 2 demonstrates substantial differences between species in the proportion of mutants formed by fibroblast cultures as a function of carcinogen concentration or dosage. At first glance the inverse correlation of response and physical size of the intact animal is remarkable; however, the comparison of human fibroblast susceptibility with that for the elephant suggests that body size is probably not the most appropriate correlate. The relationship between the horse, human, and elephant data shown in the graph corresponds much more closely with species lifespan and metabolic rate. However, the response of human fibroblasts is so nearly zero that there is a built-in bias against demonstrating a difference between them and fibroblasts of an elephant. Shank and Barrows (8) propose that mammalian cell-mediated mutagenesis is a simplified method of rapidly obtaining a quantitative measure of the relative potency for initiating carcinogenesis. Langenbach et al. (9) and Jones et al. (10), using V79 cells with hamster or rat hepatocytes, respectively, were able to correlate the mutagenicity of many compounds with their carcinogenic potency. For compounds requiring activation by endogenous metabolic processes, dosage computation as some function of lifespan may be useful.

Another factor that contributes to the present uncertainty of scaling potency data between animals and humans is the duration of the animal experiments and the latency of tumors as a function of dose. Jones and Grendon (11) have proposed a simple inverse cube root function relating dose to latency. For example, a 1000-fold increase in dose results in a 90% decrease in latency. The question therefore arises when one attempts to scale potency data based on lifespan. What impact does the change in absolute dose between species have on the latency of tumor appearance?

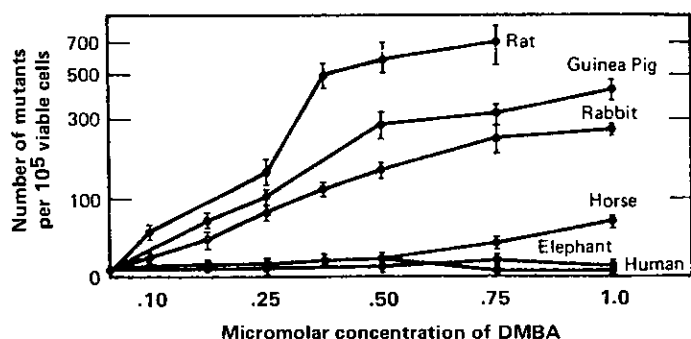Scaling may be further complicated by differential responses to total dose versus dose rate. For example, if a daily dose rate of 2 mg/kg/day is used over a lifespan, the total dose administered will vary with longevity. If the experiment is designed to deliver a fixed total dose, the number of fractional doses and their size are variables that may have a significant impact on the result (12). It should be noted that the cumulative dose over time is not, by itself, a reliable method for scaling carcinogenic potency. Yanysheva and Antomonov in 1976 observed increasing latency of tumor development with decreasing total dose, but also saw an increased incidence of tumors as the number of fractional administrations approached a predetermined total dose. Similarly, when Pike (13) compared lung cancer rates in 60-year-old cigarette smokers who had smoked 30 cigarettes/day from age 20 to 40 years with those who had smoked 15 cigarettes/day from age 20 to 60 years, the longer exposure to a comparable total dose was associated with a 10-fold higher rate than the shorter, more intense exposure. The results led to much debate but little concurrence on the reliability of extrapolations of biochemical or epidemiological data except as components of multidisciplinary studies (14).

Flamm and Lorentzen (15), in their introduction to *Mechanisms and Toxicity of Chemical Carcinogens and Mutagens*, suggest that many kinds of carcinogens share a common mechanism. This involves biochemical or enzymatic conversion of the original chemical to active electrophiles that form adducts at the nucleophilic centers of proteins and nucleic acids. DNA adducts often damage DNA, and, if unrepaired, there can be replication of the altered DNA leading to transformed cells that are forerunners of cancer. Hoel et al. (16) described a nonlinear pharmacokinetic model of this process including covalent binding of the activated species and mechanisms of DNA repair. Van Ryzin (17) incorporated elements of the activated electrophile mechanism into a model of nonlinear kinetics for estimating the effective dose at the target site and derived a transformed or calculated dose for extrapolating virtually safe doses for vinyl chloride and saccharin. This model is consistent with a one-hit mechanism at the target site relative to a calculated TCI, rather than administered dose and with nonlinear metabolic activation of vinyl chloride or nonlinear, saturable bladder clearance of saccharin.

Other classes of chemicals, which are not converted to electrophiles and are not genotoxic, nevertheless can cause cancer. These compounds, which have not been shown to bind extensively to DNA, are called nongenotoxic carcinogens. They appear to be effective only after prolonged exposures at doses sufficient to produce either significant long-term depression of cellular growth rate or cell death.

Purchase (18), reviewing the research of Elcombe (19) and Green and Prout (20), notes that pure trichloroethylene is only marginally mutagenic or nonmutagenic and binding of metabolites to DNA occurs only at insignificant levels. Mice given 1000 mg/kg/day by gavage developed hepatocellular carcinomas, but these doses

FIGURE 2.   Mutations in cultured fibroblasts induced by metabolites of 7,12-dimethylbenz[a]anthracene (DMBA) (7).

caused no hepatocarcinogenicity in two strains of rats. Both species metabolize TCE to trichloroacetic acid (TCA). However, in rats the metabolism reaches saturation at 500 mg/kg, whereas in mice the limit exceeds 2000 mg/kg TCE. Consequently, in mice given 1000 mg/kg, the blood level of TCA is 7 times greater than in rats similarly dosed. Doses of TCA above 50 mg/kg produce peroxisomal proliferation in the livers of both species, but because of the metabolic differences only mice develop peroxisomal proliferation following TCE. *In vitro*, mouse hepatocytes produce 30 times more TCA from TCE than do rat hepatocytes, and the latter are 3 times more active than human hepatocytes. Those observations suggest that TCE is carcinogenic via a nongenetic (i.e., no chromosomal damage) mechanism that involves stimulated production of hepatic peroxisomes. Humans convert TCE to TCA at only 1/90 of the rate of mice and peroxisomes do not proliferate in humans with known TCE exposure. These metabolic data suggest that humans may not be susceptible to TCE carcinogenicity. The evidence also suggests that there is a threshold dose for carcinogenicity even in susceptible species.

Although it is now fairly well accepted that there are both frank genotoxic and apparent nongenotoxic mechanisms for the induction of neoplasms, scientists have focused on genotoxic pathways for several reasons: the mechanisms are generally better defined; the materials of concern include food chemicals, which are more likely to act by this mechanism; the pathways are more amenable to biochemical, pharmacological, and physiological definition; and there is also a reasonable body of evidence for a multistage process that begins with normal somatic cells and eventually results in one or more altered clones of individual transformed cells.

The array of variables affecting each stage of this process introduces great difficulty in identifying a simple relationship between administered dose and ultimate tumor incidence. The myriad of mechanisms proposed for the development of neoplasms makes reliable scaling difficult.

If there is to be significant progress in scaling equipotent exposures between test species and humans, emphasis will have to be placed on isolating critical elements of the process for definitive study. It will be necessary to advance our knowledge beyond the ability of treating intact animals with chemicals and then dismembering them as black boxes to see what has happened. There is a need to develop and enhance our ability to understand the processes that take place and to apply this understanding in the solution of scaling problems.

Papers Commissioned for This Symposium

The commissioned papers presented at this symposium provide a review of available information and approach to extrapolation and dose scaling. In the first paper, Dr. Calabrese discusses the influence of differing degrees of heterogeneity in exposed populations on the effectiveness of scaling techniques. An overview of the capacity of animal models to predict the responses of humans to carcinogenic agents is described. The focus of this presentation is on the comparative biology of significant test species and humans with regard to biochemical characteristics that affect the response to carcinogens.

The following three presentations deal with interspecies comparability at progressive stages of the overall process of carcinogenesis. The first, presented by Dr. Standaert, addresses basic pharmacokinetics and physiological modeling. He discusses several examples of cumulative target tissue exposure as a quantitative expression of dose as opposed to administered quantity or inhaled concentration. The significance of common biochemical and biophysical mechanisms in the kinetics of chemical interactions with test species and humans is also described.

Intranuclear events involving DNA damage and repair and replication of altered genetic material to begin a new cell line of transformed genotype are discussed by Dr. Slaga. He also reviews the cytoplasmic and nuclear genetic mechanisms in test species and humans which have a significant impact on variation in carcinogenic response at equivalent target tissue exposure levels.

Dr. Scarpelli reviews mechanisms of posttransformation promotion and progression leading to manifestation of neoplasms. Comparisons between organs and between species of the histopathologic changes following various exposures to carcinogenic substances are presented with discussion of the biological bases for similar and differing responses.

The qualitative and quantitative considerations in interspecies extrapolation as they relate to current practices of risk assessment are reviewed by Dr. Clayson. His paper describes interspecies susceptibility to carcinogens, the impact of high background levels of tumorigenesis in untreated animals on assessment of the response, and the significance of maximum tolerated dose in the extrapolation of animal data to humans.

Drs. Gibson and Starr present an overview of potential applications of pharmacokinetic and cellular level mechanisms for more effective interspecies scaling of carcinogenic potency. This paper explores some of the emerging methods and opportunities to improve the state-of-the-art in extrapolating animal carcinogenicity data to the prediction of cancer in humans. This presentation considers the role of metabolic, pharmacokinetic, and genetic information from target tissues in various species in the identification of mechanisms which can improve risk assessment models.

The present day policies and procedures of the Food and Drug Administration for controlling deliberate or incidental food additives are still derived directly from the Food and Drug Act of 1906 as construed by the Supreme Court in 1914. The Court held that the FDA must only find a reasonable possibility of injury to

health, because a small amount of an otherwise dele-
terious ingredient may not be harmful (21). This concept
of "reasonable possibility of injury" is being interpreted
by the Agency and the courts to permit carcinogenic
contaminants at a "generally recognized level of insig-
nificant risk to human health." Experience in the courts
suggests that food contaminants posing a lifetime cancer
risk of less than one in a million for an individual are
acceptable provided the supporting data are of good
quality. Taylor (22) points out that it is the consistency
of current methods to overestimate risk that makes the
procedures acceptable. The acceptability of extrapola-
tion procedures depends on several factors.

When available, consideration should be given to such
matters as the strength of the evidence underlying the
basic finding of carcinogenicity; the human relevance of
the animal results; comparative metabolism; the mech-
anism of action; the dose-response relationship; the pos-
sibility of a threshold; and the true nature of human
exposure as affected, for example, by man's metabolic
handling of the substance.

The ultimate task for the FDA is making decisions
on the safety of trace amounts of potentially cancer-
causing chemicals in our diets. The usefulness of the
scientific information which contributes to those deci-
sions rests with the individual scientists who generate
it. We have a common responsibility to make that in-
formation as practically useful and accurate as possible.

REFERENCES

1. National Research Council, Commission on Life Sciences. Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC, 1983.
2. Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation. Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides. Toxicol. Appl. Pharmacol. 20: 419–438 (1971).
3. Calabrese, E. J. Principles of Animal Extrapolation. John Wiley and Sons, New York, 1983.
4. Schmidt-Nielsen, K. How Animals Work. Cambridge University Press, London, 1972.
5. Rall, D. P. Species differences in carcinogenesis testing. In: Origins of Human Cancer, Book C, Human Risk Assessment (H. H. Hiatt, J. D. Watson, and J. A. Winsten, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1977, pp. 1383–1390.
6. Occupational Safety and Health Administration. Identification, classification and regulation of potential occupational carcinogens. Final rule. Federal Register 45: 5002–5296 (1980).
7. Schwartz, A. G., and Moore, C. J. Inverse correlation between species life span and capacity of cultured fibroblasts to metabolize polycyclic hydrocarbon carcinogens. Fed. Proc. Fed. Am. Soc. Exp. Biol. 38: 1989–1992 (1979).
8. Shank, R. C., and Barrows, L. R. Toxicological effects of carcin-

ogenesis. In: Toxicological Risk Assessment, Vol. 1, Biological and Statistical Criteria (D. B. Clayson, D. Krewski, and I. Munro, Eds.), CRC Press, Boca Raton, FL, 1985, pp. 91–104.
9. Langenbach, R., Gingell, R., Kuszynski, C., Walker, B., Nagel, D., and Pour, P. Mutagenic activities of oxidized derivatives of N-nitrosodipropylamine in the liver cell-mediated and Salmonella typhimurium assays. Cancer Res. 40: 3463–3467 (1980).
10. Jones, C. A., Marlino, P. J., Lijinsky, W., and Huberman, E. The relationship between the carcinogenicity and mutagenicity of nitrosamines in a hepatocyte-mediated mutagenicity assay. Carcinogenesis 2: 1075–1077 (1981).
11. Jones, H. B., and Grenden, A. Environmental factors in the origin of cancer and estimation of the possible hazard to man. Food Cosmet. Toxicol. 13: 251–268 (1975).
12. Yanysheva, N. Ya., and Antomonov, Yu. G. Predicting the risk of tumor occurrence under the effect of small doses of carcinogens. Environ. Health Perspect. 13: 95–99 (1976).
13. Pike, M. C. Epidemiology and risk assessment: Estimation of GI cancer risk from asbestos in drinking water and lung cancer risk from PAHs in air. In: Risk Quantitation and Regulatory Policy, Banbury Report No. 19 (D. G. Hoel, R. A. Merrill, and F. P. Perera, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985, pp. 55–64.
14. Hoel, D. G. The impact of occupational exposure patterns on quantitative risk estimation. In: Risk Quantitation and Regulatory Policy, Banbury Report No. 19 (D. G. Hoel, R. A. Merrill, and F. P. Perera, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985, pp. 105–118.
15. Flamm, W. G., and Lorentzen, R. J., Eds. Mechanisms and Toxicity of Chemical Carcinogens and Mutagens. Advances in Modern Environmental Toxicology, Vol. 12. Princeton Scientific Publishing Co., Princeton, NJ, 1985.
16. Hoel, D. G., Kaplan, N. L., and Anderson, M. W. Implication of nonlinear kinetics on risk estimation in carcinogenesis. Science 219: 1032–1037 (1983).
17. Van Ryzin, J. Consequences of nonlinear kinetic dose-response models on carcinogenic risk assessment. In: Risk Quantitation and Regulatory Policy, Banbury Report No. 19 (D. G. Hoel, R. A. Merrill, and F. P. Perera, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985, pp. 119–132.
18. Purchase, I. F. H. Carcinogenic risk assessment: A toxicologist's view. In: Risk Quantitation and Regulatory Policy, Banbury Report No. 19 (D. G. Hoel, R. A. Merrill, and F. P. Perera, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985, pp. 175–186.
19. Elcombe, C. R. Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene: A biochemical human hazard assessment. Arch. Toxicol. 8(suppl.): 6–17 (1985).
20. Green, T., and Prout, M. S. Species differences in response to trichloroethylene. II. Biotransformation in rats and mice. Toxicol. Appl. Pharmacol. 79: 401–411 (1985).
21. Hutt, P. B. Use of quantitative risk assessment in regulatory decisionmaking under federal health and safety statutes. In: Risk Quantitation and Regulatory Policy, Banbury Report No. 19 (D. G. Hoel, R. A. Merrill, and F. P. Perera, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985, pp. 15–29.
22. Taylor, M. R. The inevitability of risk quantitation and its potential contribution to food safety regulation. In: Risk Quantitation and Regulatory Policy, Banbury Report No. 19 (D. G. Hoel, R. A. Merrill, and F. P. Perera, Eds.), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1985, pp. 31–40.