CANCER RISK ASSESSMENT: PRESENT AND FUTURE

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Abstract
Risk assessment is a process based on available scientific information about properties of a given agent, and its effect on biological processes to evaluate potential adverse consequences of exposure to that particular agent. Occupational cancer risk assessment might be considered as a more specific application of the process aimed at finding out whether a particular workplace exposure would lead to cancer. In 1983, a comprehensive model or paradigm of risk assessment was developed by the US National Academy of Sciences (NAS). The overall risk assessment process comprises the following elements: (a) hazard identification, which involves the qualitative determination of whether a particular agent causes a particular adverse effect in humans; (b) dose-response assessment, which describes how such effects are related to the dose; (c) exposure assessment, which estimates the level of human exposure to the substance with and/or without regulatory controls; (d) risk characterization as summary judgments on the existence and magnitude of the public health problem. In this article the authors discuss all the elements of the risk assessment process and present current approaches to this problem as well as research needs in this area.

Key words:
Cancer risk assessment, Dose-response assessment, Mathematical models

INTRODUCTION
From the 1940s, the growing industrialization and proliferation of synthetic organic chemicals have resulted in a myriad of actual and potential health-endangering exposures. In many industrialized countries, cancer, cardiovascular diseases and other chronic conditions have now replaced infectious diseases as the major causes of mortality. This has led to a new emphasis in public health on risks, particularly cancer risks, posed by exposure to chemical agents. Scientists and regulators initially used a qualitative assessment, based on toxicity testing and invoking a binary “Yes/No” classification of agents as human health hazards. However, the setting of permissible exposure limits for the workplace, systematized by industrial hygienists in the USA in the 1940s, introduced a less absolute concept of “acceptable” levels of exposure to toxic agents. The rudimentary quantitative risk-assessment methods that evolved during the 1940s and 1950s included, for health outcomes other than cancer, the use of dose-response graphs to identify a “no-observed-adverse-effect level” (NOAEL), i.e. a dose below which no adverse effect was apparent. This “no-effect dose” approach to risk assessment sought to identify so called “safe level”. For cancer risk, however, the notion of a “virtually safe dose” soon came to be preferred since any exposure to carcinogens was assumed to cause some increment in cancer risk. More recently, the term “risk-specific dose” has been used in order to avoid implying the
acceptability of specific levels of risk. Radiation standards, which historically have been designed primarily to protect against cancer, illustrate the changing view of “safe” exposure. The standards were first described in terms of a “tolerance dose”, then a “maximum permissible dose”, and now a “dose limit” accompanied by explicit advice to keep exposures as low as reasonably possible [1].

Risk assessment is a process based on available scientific information about properties of a given agent and its effect on biological processes to evaluate the potential for adverse consequences of exposure to that particular agent. Occupational cancer risk assessment might be considered as a more specific application of the process, aimed at finding out whether a particular workplace exposure would lead to cancer [2].

In 1983, a comprehensive model or paradigm of the risk assessment was expressed by the US National Academy of Sciences (NAS). The elements in this comprehensive risk assessment process are as follows: (a) hazard identification, which involves the qualitative determination of whether a particular agent causes a particular adverse effect in humans; (b) dose-response assessment, which describes how such effects are related to the dose; (c) exposure assessment, which estimates the level of human exposure to the substance with and/or without regulatory controls; (d) summary judgments on the existence and magnitude of the public health problem so called risk characterization. Therefore, risk assessment combines hazard identification or dose-response assessment with exposure assessment. Risk assessment also includes characterization of the uncertainties in the risk inferring process.

In the NAS paradigm, risk assessment and risk management were separated because risk assessment is inherently scientific in nature; it should be done in isolation from political influences, which can only distort a true scientific judgment. All risk managements are inherently political. As in most controversies, there is probably an element of truth in each of these conflicting observations. It is possible that the difficulty in understanding the relative role of scientific judgment and value judgment in risk assessment is that the observers have addressed the issue of the risk assessment process as a whole. The problem may be resolved by examining the question for the individual components of this process. The key difficulty in distinguishing scientific judgment from value judgment is the definition of the adjective “scientific”. For risk assessment, the term “value judgment” is synonymous with “selection of the appropriate degree of conservatism” [3].

Over the recent two decades, the approach outlined above has been much discussed and debated, especially the question concerning the extent to which risk assessment and risk management are separate fields of activities and the extent to which policy is interjected in both of them. Regardless of the debate outcomes, the general process has become increasingly accepted. The 1983 NAS report served as a stimulus to the US Environmental Protection Agency (EPA) to complete and issue carcinogen risk assessment guidelines [4,5].

HAZARD IDENTIFICATION

The purpose of hazard assessment (hazard identification) is to review and evaluate data pertinent to two questions:

- whether an agent may pose a carcinogenic hazard to human beings, and
- under what circumstances an identified hazard may be expressed.

Hazard assessment is composed of analyses of a variety of data that may range from observations of tumor responses to an analysis of structure-activity relationships. The purpose of the assessment is not simply to assemble these separate evaluations, but to construct a total case analysis, examining the biological story the data reveal as a whole about the carcinogenic effects, mode of action, and implications of these for human hazard and dose-response evaluation [6].

Carcinogens classification criteria and schemes

Several criteria are used to classify carcinogens, including strength-of-evidence consideration, weight-of-evidence consideration, animal carcinogenicity data, human carcinogenicity data, mechanistic data and type of data being evaluated.

The strength-of-evidence approach considers only the positive evidence of carcinogenicity whereas the weight-
of-evidence approach considers all relevant data, including both the positive and negative results from epidemiological and animal carcinogenicity studies. Biological mechanism and relevance of animal findings to the risk of cancer in humans may also be considered. This may include information on genotoxicity, biotransformation and toxicokinetics. The use of data from malignant tumors only, or data from both malignant and benign tumors can also affect the classification. Most European countries and scientific organizations survey and classify chemicals using the weight-of-evidence approach, consider animal carcinogens as having a carcinogenic risk to humans and allow for the use of mechanistic data. However, some differences do exist [7]. Also the US EPA approach is based on the weight-of-evidence consideration [5].

One of the first cancer classification schemes to be developed was that of the International Agency for Research on Cancer (IARC). In 1969, IARC established a program for classifying chemicals and occupations as to their carcinogenic hazard that still continues and develops [8]. IARC classifications are widely used as a basis for action by the regulatory authorities around the world. The IARC evaluation process considers four types of data: 1) exposure data, 2) human carcinogenicity data, 3) experimental animal carcinogenicity data, and 4) other data relevant to an evaluation of carcinogenicity and its mechanisms.

Epidemiological studies of three types can contribute to the assessment of human carcinogenicity: cohort studies, case-control studies and correlation or ecological studies. The evaluation process considers the quality of the studies, inferences about the mechanisms of action, and evidence of causality. Since 1991, IARC has introduced the use of mechanistic data in the classification process with special attention given to measurements of biological markers of carcinogen exposure or action, such as DNA or protein adducts as well as markers of early steps in the carcinogenic process like proto-oncogene mutation, when these are incorporated into epidemiological studies [9–11].

The IARC evaluation process gives substantial weight to carcinogenicity data from laboratory animals. All known human carcinogens that have been studied adequately in experimental animals have produced positive results in one or more animal species [12,13]. Supporting evidence includes a range of information, e.g., quantitative structure-activity relationships, toxicokinetic information, genotoxicity and mutagenicity data from laboratory animals and humans as well as from lower levels of biological organization, such as tissues and cells. Finally, all relevant data are integrated and the agent is categorized on the weight of the evidence derived from studies in humans and experimental animals and from other studies.

The US National Toxicology Program (NTP) uses a classification scheme similar to that of IARC for evaluating the studies it conducts in laboratory animals. The NTP scheme serves as a major input into preparation of the Biennial Report on Carcinogens [14]. This report lists chemicals of two groups: (a) human carcinogens and (b) reasonably anticipated to be human carcinogens. This classification is widely used by other agencies as a basis for regulatory actions. The US EPA elaborated guidelines for cancer risk assessment on the basis of cancer classification, which is similar to the IARC classification [4].

A review and comparison of carcinogen classification systems in different countries and organizations have been made by Seeley et al. [7]. It is abstracted with the authors’ modification and supplementation in Table 1.

Recognizing the current rapid increase in the use of new techniques for evaluating molecular and cellular changes that may be linked with carcinogenesis, it can be expected that evidence will be found for many chemicals to have exposure-related increases in various parameters causally associated with cancer. It is likely that future working groups may conceivably use such evidence to upgrade other current chemicals probably carcinogenic to humans (e.g., IARC group 2A) to chemicals carcinogenic to humans (e.g., IARC group 1), despite the lack of sufficient evidence of their carcinogenicity in humans.

**EXPOSURE ASSESSMENT**

Exposure assessment is the determination (qualitative and quantitative) of the magnitude, frequency, and duration
# Table 1. Comparison of classification schemes for carcinogens in selected European countries and organizations (including 7 with the authors’ modification)

<table>
<thead>
<tr>
<th>IARC</th>
<th>European Union</th>
<th>Germany</th>
<th>Netherlands</th>
<th>Norway</th>
<th>Poland</th>
<th>Sweden</th>
<th>US EPA</th>
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<tbody>
<tr>
<td>1: Carcinogenic to humans&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1: Carcinogenic to humans&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1: Genotoxic carcinogens&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I-K1: High potency animal and human carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1: Carcinogenic to humans&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1: Substances known to be carcinogenic to humans&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td>A: Human carcinogen&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>2A: Probably carcinogenic to humans&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2: Carcinogenic in animal studies&lt;sup&gt;g&lt;/sup&gt;</td>
<td>I: Direct acting carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td>I-K2: Medium potency animal and human carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2: Probably carcinogenic to humans&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2: Substances which should be regarded as if they are carcinogenic to humans&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>B: Probable human carcinogen</td>
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<tr>
<td>2B: Possibly carcinogenic to humans&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2: Substances which should be regarded as if they are carcinogenic to humans&lt;sup&gt;e&lt;/sup&gt;</td>
<td>II: Nongenotoxic carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B: Limited evidence of carcinogenicity from epidemiology studies</td>
</tr>
<tr>
<td>3: Not classifiable as to carcinogenicity in humans&lt;sup&gt;h&lt;/sup&gt;</td>
<td>3: Suspected carcinogens that cannot be classified according to mechanism&lt;sup&gt;n&lt;/sup&gt;</td>
<td>III: Suspected carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td>I-K3: Low potency animal and human carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3: Substances which cause concern to humans owing to possible carcinogenic effects, but for which the evidence is not sufficient for category 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4: Probably not carcinogenic&lt;sup&gt;i&lt;/sup&gt;</td>
<td>4: Nongenotoxic carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td>III: Suspected carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a: Well-investigated&lt;sup&gt;k&lt;/sup&gt;</td>
<td>5: Weak potency genotoxic carcinogens&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>3b: Insufficiently investigated&lt;sup&gt;l&lt;/sup&gt;</td>
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<sup>a</sup> Based on sufficient evidence of carcinogenicity in humans, or limited evidence of carcinogenicity in humans, and strong evidence that mechanism is relevant in humans;

<sup>b</sup> Based on epidemiological data;

<sup>c</sup> Shown to induce malignant tumors in humans. Generally potent carcinogens capable of inducing a few cases of rare tumors, or carcinogens with wide exposure potential;

<sup>d</sup> Chronic bioassays and mutagenicity tests both positive;

<sup>e</sup> Carcinogenic in at least one mammalian experiment, TD<sub>x</sub> (the lowest dose, in mg/kg-day, from a chronic animal bioassay, which induces a significant increase in tumors) is 1-15 mg/kg-day;

<sup>f</sup> Based on limited evidence of carcinogenicity in humans, sufficient evidence in animals, and inadequate evidence in human and strong evidence that mechanism is relevant in humans;

<sup>g</sup> Based on limited evidence of carcinogenicity in humans, sufficient evidence in animals, and inadequate evidence in human and strong evidence that mechanism is relevant in humans;

<sup>h</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>i</sup> Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system;

<sup>j</sup> Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system;

<sup>k</sup> Based on limited evidence of carcinogenicity in humans, sufficient evidence in animals, and inadequate evidence in human and strong evidence that mechanism is relevant in humans;

<sup>l</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>m</sup> Carcinogenic in at least one mammalian experiment, TD<sub>x</sub> (the lowest dose, in mg/kg-day, from a chronic animal bioassay, which induces a significant increase in tumors) is 1-15 mg/kg-day;

<sup>n</sup> Based on sufficient evidence of carcinogenicity in humans, or limited evidence of carcinogenicity in humans, and strong evidence that mechanism is relevant in humans;

<sup>o</sup> Based on limited evidence of carcinogenicity in humans, sufficient evidence in animals, and inadequate evidence in human and strong evidence that mechanism is relevant in humans;

<sup>p</sup> Based on limited evidence of carcinogenicity in humans, sufficient evidence in animals, and inadequate evidence in human and strong evidence that mechanism is relevant in humans;

<sup>q</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>r</sup> Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system;

<sup>s</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>t</sup> Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system;

<sup>u</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>v</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>w</sup> Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system;

<sup>x</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>y</sup> Based on epidemiological data, or clear positive evidence of carcinogenicity in a species, or positive evidence in one species along with supporting genotoxicity data, metabolic or biological studies, structure-activity relationships, or suggestive epidemiological data;

<sup>z</sup> Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system;
of exposure. Exposure assessment generally consists of four major steps: (a) defining the assessment questions; (b) selecting or developing the conceptual and mathematical models; (c) collecting data or selecting and evaluating available data, and (d) exposure characterization.

**Defining assessment questions**

To define clearly and explicitly the purpose and scope of exposure assessment, depending on the assessment objectives, it is necessary to:

- determine whether deterministic screening level analyses are adequate or whether full probabilistic exposure characterization is needed;
- identify and include in the assessment all important sources (e.g., pesticide applications), pathways (e.g., food or water), and routes (e.g., ingestion, inhalation, and dermal) of exposure. If a particular source, pathway or route is omitted, a clear and transparent explanation should be provided;
- conduct separate analyses for each definable subgroup of the study population, in particular, subgroups that are believed to be highly exposed or susceptible to a particular health effect, e.g., physiological differences between men and women may lead to important differences in exposure (exposures of pregnant and lactating women may differ from those in the general population; children consume more food per body weight than adults, while consuming fewer types of foods).

**Selecting or developing conceptual and mathematical models**

Carcinogen risk assessment models are generally based on the premise that risk is proportional to total lifetime dose. Therefore, the exposure metric used for carcinogenic risk assessment is the lifetime average daily dose (LADD). It is an estimate of the daily intake of a carcinogenic agent throughout the entire life of an individual for all routes of exposure. Depending on the objectives of the assessment, LADD may be calculated deterministically (using point estimates for each factor to derive a point estimate of the exposure) or stochastically (using probability distributions to represent each factor and such techniques as the Monte Carlo analysis to derive a distribution of the LADD). Stochastic analyses may help to identify certain population segments that are highly exposed and may need to be assessed as a special subgroup.

When inhalation or dermal contact is the route of exposure, derivation of the LADD often requires the “route-to-route extrapolation” approach. Measures of toxicity are typically derived from orally administered doses in animal studies. Therefore, for ingestion exposures in a human population it is not usually necessary to make adjustments to account for route-specific differences in absorption and uptake. However, for inhalation and dermal exposures such adjustments may be necessary.

There may be cases, where the mode of action indicates that dose rates are important in the carcinogenic process. Then short-term, less-than-lifetime exposure estimates may be more appropriate for risk assessment than LADD.

**Collecting data or selecting and evaluating available data**

Having defined the assessment questions and having developed the conceptual and mathematical models, it is necessary to compile and evaluate the existing data or, if necessary, to collect new data. Depending on the exposure scenario under consideration, data on a variety of exposure factors may be needed. When using the existing data, it is important to evaluate their quality and the extent to which they are representative of the population under study. If the existing data fail to provide an adequate surrogate for the needs of a particular assessment, new data must be collected. Once again, the subgroups of concern are an important consideration in any data collection effort.

**Exposure characterization**

Exposure characterization provides the explicit information about the purpose, scope, and approach used in the assessment, identifying the exposure scenarios and coverage of population subgroups. It provides estimates of the magnitude, frequency, duration, and distribution of exposures among members of the exposed population as the data permit. It identifies and compares the contribution of different
sources, pathways, and routes of exposure. In particular, a qualitative discussion on the strengths and limitations (uncertainties) of the data and models is presented. The discussion on uncertainties is a critical component of exposure characterization. Uncertainties may be generated by conceptual or mathematical models. Uncertainties may also arise from poor quality of data and their limited representativeness of the population or scenario in question. All in all, exposure characterization should provide a full description of exposure sources, pathways, and routes. It should also include a full description of the assessed populations. In particular, highly exposed or susceptible subgroups should be discussed [6].

DOSE-RESPONSE ASSESSMENT

The dose-response assessment is aimed at evaluating potential risks posed to humans by a specified adverse effect at a given exposure level. The cancer dose-response relationship(s) for a chemical is considered in a two-step process. First, the determination of the mode of action and dose-response for each tumor type that results in a significant increase in tumor incidence. Second, an analysis of the information bearing on all tumor types that are increased in incidence by the chemical. The overall synthesis includes consideration of the number of sites, their consistency across sexes, strains and species, the strength of the mode of action information for each tumor type, the anticipated relevance of each tumor type to humans, and the consistency of the means of estimating risks across tumor types. Quantitative risk assessment involves the fitting of mathematical functions to some measures of tumor incidence, e.g., tumors observed in long-term carcinogenicity studies. These functions are based on mathematical models, and they are extended or extrapolated to doses far below those used in experiments.

Mode of action and dose-response approach

For each tumor, the mode of action and other information may support one of the following dose-response extrapolations:
- linear
- nonlinear using a margin of exposure (MOE) analysis, or
- both linear and nonlinear using MOE analysis.

In rare cases, detailed information on the mode of action may be available, which allows the formulation of a biologically-based model. Any of the following conclusions leads to the selection of a linear dose-response assessment approach:
- there is lack of sufficient tumor mode of action information;
- the chemical has direct DNA mutagenic activity or other indications of DNA effects that are consistent with linearity;
- the human exposure or body burden is high and near the doses associated with key events in the carcinogenic process;
- the mode of action analysis does not support direct DNA effects, but the dose-response relationship is expected to be linear (e.g., certain receptor-mediated effects).

Any of the following conclusions leads to the selection of a nonlinear (margin of exposure) approach to dose-response assessment:
- a tumor mode of action supporting nonlinearity applies (e.g., some cytotoxic and hormonal agents, such as disruptors of hormone homeostasis), and the chemical does not demonstrate mutagenic effects consistent with linearity;
- a mode of action supporting nonlinearity has been demonstrated, and the chemical has some indication of a mutagenic activity, but it is judged not to play a significant role in tumor causation.

Any of the following conclusions leads to the selection of both linear and nonlinear approaches to dose-response assessment:
- modes of action for a single tumor type support both linear and nonlinear dose response in different parts of the dose-response (e.g., 4,4’ methylene chloride);
- a tumor mode of action supports different approaches at high and low doses; for instance, nonlinearity at a high dose, but linearity at a low dose, (e.g., formaldehyde);
- the agent is not DNA-reactive and all plausible modes of action are consistent with nonlinearity, but not fully established (e.g., arsenic);
modes of action for different tumor types support distinct approaches, for example, nonlinear for one and linear due to the lacking mode of action information for the other (e.g., trichloroethylene).

Relative support for each dose-response assessment method and advice on the use of that information need to be presented. In some cases, evidence for one mode of action is stronger than for the other, allowing emphasis to be placed on that dose-response approach. In other cases, both modes of action are equally possible, and both dose-response approaches should be emphasized [6].

Mathematical models

Mathematical models are categorized loosely on the basis of their underlying statistical assumptions. These categories are termed linear, mechanistic, tolerance distribution, time-to-tumor, and biologically motivated. The division between the models is somewhat arbitrary as there is a considerable overlap. Although these models claim to reflect the underlying biology in their designs, experience has shown that they represent gross oversimplification, with the possible exception of the biologically motivated Moolgavkar-Venzon-Knudson (MVK) model.

Stochastic or mechanistic model

The discussion carried on between researchers on the processes underlying malignant transformations indicates that carcinogenesis is a complex, multistage process modulated by genetic and environmental influences. It is obviously impossible to take explicit account of all the factors involved in carcinogenesis in any model. In fact, since any model is an abstraction that incorporates (in the opinion of the modeller) the most important features of the process, any attempt to take explicit account of the myriad factors involved in carcinogenesis would defeat the whole purpose of modeling.

The models described here acknowledge the multistage nature of carcinogenesis, and the importance of cell proliferation kinetics in the process. Modulating genetic and environmental factors affect carcinogenesis by affecting the rates of mutation and cell proliferation.

The concept of a multistage carcinogenesis was formalized in mathematical models about 50 years ago [15,16]. Originally, these models were proposed to explain the observation that the age-specific incidence curves of many common carcinomas increase roughly with a power of age. The central thesis of the models that a malignant tumor arises from a single cell that has sustained a small number of critical insults to its genetic apparatus is supported by modern laboratory observations.

The one-hit model is based on the theory that a single "hit" (i.e., DNA damage or binding to a receptor) can initiate an irreversible series of events, leading to cancer and the probability of a "hit" is directly proportional to the chemical concentration. The low-dose region of the model approximates a linear relationship. An extension of the one-hit model is the multi-hit model, which assumes that multiple hits are required to initiate cancer. The dose-response function in the multi-hit model has the form:

$$P(d) = \frac{d}{\Gamma(k)} \lambda^k t^{k-1} \exp(-\lambda t) dt$$

where:
- $\Gamma(k)$ denotes the gamma function;
- $\lambda$ is the transition probability;
- $\Gamma(x) = \int_0^x e^{-t} t^{x-1} dt$ if $x > 0$.

The most widely used (by regulatory agencies) and referenced model in the literature is the multi-stage model [17], of which the linearized multi-stage model is a special case [18]:

$$P(d) = 1 - \exp\left\{ - \sum_{i=0}^{k} q_i d^i \right\}, \quad q_i \geq 0$$

or

$$P(d) = \gamma + (1 - \gamma) \left( 1 - \exp\left\{ - \sum_{i=0}^{k} q_i d^i \right\} \right), \quad q_i \geq 0$$

where:
- $d$ is the average lifetime dose,
- $q_0, ..., q_k$ denote parameters whose values are estimated by maximum likelihood method,
- $\gamma$ is a background parameter,
- $P(d)$ is the probability of tumor development.

This model assumes that several random hits or events are required in a specific sequence for the development of
cancer. It is based on the assumptions that the transition rates between successive stages are not necessarily equal, but at least one of these transitions is linearly related to the dose. Linearity at low doses is based on the argument that some level of background tumors is always present and a carcinogenic agent simply enhances or augments this process linearly [19]. Only a small portion of the background needs to be additive for this to be true [20].

The multi-stage model is sometimes considered the most plausible, based on a superficial similarity between this model and multi-stage biological models of cancer. However, the mathematical equation derived from the multi-stage model almost certainly oversimplifies the biological process of carcinogenesis.

To understand the difference between true mechanistic modeling and curve fitting, we must begin by studying the levels of information available to the researcher attempting to model carcinogenesis. Below are shown the examples of the levels of such information.

Biochemical: gene expression, protein levels, receptor binding, adduct formation.

Cell: mitosis, cell death.

Tissue: hyperplasia, hypertrophy, carcinogenicity, chemical distribution/disposition, improper development of the function.

Organism: morbidity, mortality.

True mechanistic modeling of carcinogenesis should involve the application of information from the lowest level (in this case biochemical data) to predict results at a higher level. For example, in true mechanistic modeling of carcinogenesis, we should use cellular and biochemical data to characterize a carcinogenic response and only tissue-specific cancer data to verify whether the model predictions are correct. This has been described by numerous researchers as a bottom-up process of modeling carcinogenesis.

Curve fitting, on the other hand, generally involves information obtained at the level, for which inference is desired. In this case, a certain model that describes an endpoint, say, cancer is needed, and the direct information on that endpoint is required to estimate the parameters in this model [21].

**Tolerance distribution models (statistical models)**

These models assume that a population contains individuals of different susceptibilities, and the susceptibility, as a random variable, has specified probability distribution. The models include the log-probit [22], logit, and Weibull models [23]. The log-probit model utilizes a linear relationship between probits and the logarithm of dose and there is a very rapid decline towards zero response. An upper bound on risk (upper confidence limit) can be calculated. The logit model differs only slightly in the logit transformation factor, which shows linear dependence on the logarithm of the dose. Both models display a sigmoid curve in the experimental range and are similar at the midpoint of the curve.

The Weibull model, which has been used extensively to predict time to failure of electrical and mechanical components is more widely applied. It is capable of representing threshold and concave curves and is sensitive to the shape of the dose-response curve. It has the advantage of being able to incorporate a time-to-tumor function.

A general class of tolerance distribution of models is defined by

\[ G(\tau) = F(\alpha + \beta \log \tau) \]

where:

\[ F \] denotes any cumulative distribution function standardized so as to be free of unknown parameters, \( \alpha \) and \( \beta > 0 \) are unknown parameters to be estimated on the basis of the experimental data. For the probit model, \( F \) corresponds with the standard normal distribution function:

\[ F(x) = (2\pi)^{-1/2} \int_{-\infty}^{x} \exp(-u^2/2) \, du, \]

and event (cancer) probability is:

\[ P(d) = \frac{1}{2\pi} \int_{-\infty}^{\alpha + \beta d} \exp(-u^2/2) \, du. \]

In this case, the distribution of tolerances is log-normal. The logistic model with

\[ F(x) = \left[ 1 + \exp(-x) \right]^{-1} \]

and

\[ P(d) = \frac{1}{1 + \exp\left\{-(\alpha + \beta d)\right\}} , \]
and the Weibull model with

\[ F(x) = 1 - \exp(-\exp(x)), \]

and

\[ P(d) = \gamma + (1 - \gamma)(1 - \exp(-\beta d^a)) \]

where:
- \( \gamma \) is a background parameter,
- \( \alpha, \beta \) are parameters whose values are estimated by the maximum likelihood method,
- \( d \) denotes the average lifetime dose;
are also used to describe quantal-response toxicity data.

Prentice [24] has described a more general parametric family of dose-response models that includes the above models as special cases. These models are used less often than the multi-stage model.

**Time to tumor models**

The stochastic (mechanistic) and tolerance distribution models are quantal; the only information used is the presence or absence of a tumor in an animal by a fixed time. Complications can arise in fitting equations to such binary or dichotomous data if there is a differential survival between the groups.

In a long-term rodent bioassay, the animal's age at death is normally recorded. Tumors can be defined as either fatal (cause of death) or incidental (death occurred from other causes). The animal's age at death can be used as an approximation of the time to the occurrence of a fatal tumor. These data can be used in the statistical analysis outlined by Peto et al. [25] to detect differences in the time-to-tumor incidence as well as differences in overall tumor incidence between the treated and control groups.

These data can also be used in mathematical models in an attempt to improve the accuracy of extrapolation to doses below those used in experiments. The models developed to include data on the time until the tumor was observed (time-to-tumor or time-to-observation) are generalizations of the multi-stage and Weibull equations and are based on the probability of a tumor being observed at a specified age at a given dose. The most widely quoted model is the generalization of the multi-stage model developed by Hartley and Sielken [26]. A major limitation to the use of such models has been the large number of parameters needed, which require more complex experiments than the current standard two-year studies. However, Peto et al. [27,28] and Portier et al. [29] have concluded that the Weibull model is most appropriate to describe the statistical functions of the studies with time-to-tumor data.

Armitage [30] has suggested that the supposed advantage of time-to-tumor models over the quantal models may be overstated because in practice there may be little extra information associated with knowledge of the time-to-tumor over a simple proportion of animals with tumors. Time-to-tumor models have not been widely validated and comparisons with other models are rare. The present evidence is that they generally offer no advantage over the quantal models after the data have been adjusted to account for differences in life-span. An exception may be when the lifetimes of the animals in a bioassay are appreciably different (e.g., when the compound caused very early deaths or in a study, where all of the animals died before the end of the expected dosing period).

**Biologically motivated models**

These models are based on knowledge of tissue growth and cell kinetics. The Moolgavkar-Venzon-Knudson model is the only valuable example of models developed so far. This model assumes that malignant tumors arise from a single malignant cell and that malignant transformation of a stem cell is the result of two specific rate-limiting irreversible events (mutations), which occur during cell division. All such models are dependent on the “birth” and “death” rates of cells in different stages (normal, initiated and transformed) and therefore, rely heavily upon experimental data, which are difficult to obtain. These models represent the most plausible current approach, but the data necessary to validate the models are incomplete [31].

**Pharmacokinetic modeling**

Pharmacokinetics is the study of the absorption, distribution, metabolism and elimination of xenobiotics in biological systems. The studying of the fate of chemicals entering the body makes it possible to obtain information on the
amount of either the parent compound or its metabolites reaching tissues that may be targets for the induction of cancerous lesions. Pharmacokinetics thus affords an opportunity to incorporate information on tissue dose in cancer risk assessment. Pharmacokinetic models permit an evaluation of the relationship between tissue dose and toxic response under different conditions of exposure. The development of physiologically-based pharmacokinetic (PBPK) models has provided a powerful tool for tissue dosimetry. In PBPK modeling, a biological system is envisaged as consisting of a small number of physiologically relevant compartments. The model is characterized by actual physiological parameters, such as body weight, cardiac output, breathing rates, blood flow rates, and tissue volumes. Biochemical parameters are used to describe the partitioning of the parent chemical or its metabolites among target tissues.

A PBPK model is described mathematically by a system of non-linear partial differential equations that consist of a mass balance equation, describing the entry and exit of xenobiotics in each compartment in the model. This system of equations can be solved simultaneously to predict the concentration of metabolites in each compartment as a function of time.

The construction of appropriate PBPK models to describe the kinetic properties of specific chemicals is not a trivial undertaking. Substantial practical experience has now accumulated with PBPK models, and has demonstrated their utility as tools for describing the pharmacokinetic behavior of toxic chemicals and predicting the dose of reactive metabolites reaching target tissues.

For their application in risk assessment, it is important to establish a clear linkage between the tissue doses predicted by the PBPK model and pharmacodynamic effects associated with tumor indication. Linkage of pharmacokinetic and pharmacodynamic effects provides a more complete description of the process of chemical carcinogenesis, and offers the promise of improved estimates of cancer risk. While the use of tissue dose rather than external measures of exposure may lead to more accurate estimates of risk, the uncertainty associated with the PBPK model-based predictions of tissue dose must not be overlooked. This uncertainty can be evaluated by considering the precision associated with each of the model parameters, and by identifying those parameters to which predictions of tissue dose are most sensitive [1].

**Benchmark dose: An alternative approach to basic mathematical modeling in risk assessment**

The concept of a benchmark dose (BMD) has been investigated in other than cancer risk assessment areas. The BMD approach provides a more quantitative alternative to the first step in the dose-response assessment than the current no-observed adverse effect level/the lowest observed adverse effect level (NOAEL/LOAEL) process for non-cancer health effects. The basis of this approach is a mathematical model fitted to the experimental data within the observable range to estimate a dose corresponding with a defined level of effect, such as 1, 5 or 10% increase in the incidence of a specified effect (ED01, ED05, or ED10). As a 10% increase is about the smallest change that is statistically significant in a standard cancer bioassay, ED10 is appropriate for cancer data. Using a BMD that is within (or at worst, very close to) the observable range of the experiment, reduces the problems associated with dose extrapolation. Estimates of the benchmark dose (e.g., ED10, or its lower confidence limit, LED10) should reflect the doses at which changes in tumor incidence occur, and are quite insensitive to the mathematical model used. It must be recognized that the benchmark model suffers from the same data limitations as the other models in current use. Thus under normal circumstances only one, or at best two, doses are available for the model development. This may be the reason for various models to produce similar results rather than an inherent robust property of the BMD, and the use of this model may still lead to over-conservative evaluations. Nevertheless, where appropriate data exist, the benchmark dose may find use in risk assessment as an apparently robust measure of tumor potency and could be combined with appropriate assessment factors to set acceptable levels for human exposure. The model should encourage the generation of additional data points to improve extrapolation and may therefore remain applicable only to shorter-term studies with a smaller group size [32].
Use of mathematical models
An accurate estimation of the probability of developing cancer when exposed to a specific chemical carcinogen would be a great benefit. However, it is apparent that the many uncertainties surrounding the current use of mathematical models severely limit the value of the calculated estimates to a point where their worth must be questioned.

All mathematical models essentially assume linearity at low doses as a feature of their calculation. This assumption overestimates the risk if the true response below the experimental range of the response is sublinear. Zeise et al. [33] support this assumption on the basis of the dose-response relationship for the formation of DNA adducts which is linear or very nearly linear over a wide range of doses, including those possibly relevant to human exposure. Examples include benzo(a)pyrene in the stomach and aflatoxin in the liver. Caution is required in the interpretation of such data since there may be non-linear dose-response relationships hidden in the overall linear observation of adduct formation, and DNA adduct formation may not be the only mechanism of carcinogenesis.

Nevertheless, these observations suggest that at least for some compounds linearity at low doses may be a reasonable approximation.

A large bioassay (on 4080 rats) of chronic ingestion of N-nitrosodiethylamine and N-nitrosodimethylamine, reported by Peto et al. [27,28], provides some support for the assumption of linear response at low doses. Nonetheless, this remains a contentious issue in the application of current mathematical models and may be a source of serious errors in risk estimates, particularly when the positive results are confined to the high dose.

By contrast, Bailat et al. [34] have argued that for 308 chemicals tested by the National Cancer Institute or National Toxicology Program (NCI/NTP), the one-hit model underestimates lifetime cancer risk in the observable range of the bioassay for a significant fraction of chemicals, suggesting that the low dose responses are supra-linear. However Hoel and Portier [21], in a more comprehensive analysis of the NCI/NTP database, revealed a stronger tendency towards sub-linearity, indicating that a linear assumption can overestimate the risk.

More recently, Sielken et al. [35] have suggested that for many compounds capable of including specific metabolic pathways, low dose levels may produce a hormetic effect, i.e. the risk is actually reduced at low doses compared to the control. This theory is an extension of the “invaders” and “defenders” theory of Sielken [36] and provides an alternative mathematical model for low dose extrapolations. The phenomenon had previously been suggested to hold good for many situations, including ionising radiation [37] and there is some experimental evidence in protozoa [38] to support this position. The model should impose an effective threshold even for genotoxic carcinogens. Thus there is no firm evidence that could provide a base for shaping the dose-response curve below the observable range in animal studies. In the absence of data to the contrary, it has been considered reasonable to assume a linear response at low doses [31].

RISK CHARACTERIZATION
The risk characterization process first summarizes findings on hazard, dose-response, and exposure characterization, then develops an integrative analysis of the whole risk case. The nature of the risk characterization will depend on the available information, the regulatory application of the risk information, and the available resources (including time).

In all cases, however, the assessment should identify and discuss all the major issues associated with determining the nature and extent of the risk and provide commentary on any constraints limiting a fuller exploitation. Risk characterization should be clear, transparent and reasonable.

A summary of the risk characterization should be comprehensible because it will be presented to risk managers who may or may not be familiar with the scientific details of cancer assessment. It should also provide information to other interested readers.

In general, risk characterization routinely includes capturing the important items covered in hazard, dose-response, and the following exposure characterization:

- primary conclusions about hazard, dose-response, and exposure, including equally plausible alternatives;
- nature of key supporting information and analytic methods;
risk estimates and their attendant uncertainties, including key uses of default assumptions when data are missing or uncertain;
- statement of the extent of extrapolation of risk estimates from observed data to exposure levels of interest (i.e., margin of exposure) and its implications for certainty or uncertainty in quantifying risk;
- significant strengths and limitations of the data and analyses, including any major peer reviewers’ issues;
- comparison with assessment of the same problem by another organizations (6).

Uncertainty
There are three types of uncertainties that can be found in the risk assessment process. First, in the realization of the harm that may result from exposure to a hazard (the cause) due to variability in the system response to such exposures. Second, the converse to the first, namely the uncertainty in the cause (i.e., uncertainty about the precise causal hazard among several different possible hazards, any of which could have resulted in the harm). Third, the hazard-harm relationship itself (i.e., the uncertainty in the degree of correlation between exposure to a particular hazard and realization of a particular harm). This uncertainty arises because we do not have sufficient scientific knowledge of a postulated risk scenario or a hazard-harm pair. Consequently, it is termed epistemic uncertainty and it is of particular concern to the regulators [39].

CURRENT APPROACHES TO RISK ASSESSMENT
Case by case judgment
In most European countries scientific experts make a judgment on a case by case basis, considering all the available evidence, to derive an exposure level unlikely to lead to an increased cancer incidence in man. This can lead to overconservative decisions based on relatively inadequate information. Regulations then seek to reduce exposures to levels as low as reasonably practicable or eliminate it completely. This approach does not allow the estimation of an “acceptable risk” and thus can be overzealous in regulation. Risk communication may also be difficult as the specific risk is not definable in recognizable terms. However, this system does provide an incentive to accumulate additional data, which improves the accuracy of the risk assessment.

The use of mathematical models to calculate potency figures
Another approach commonly used, e.g., in the USA and the Netherlands, seeks to estimate a lower limit for the dose associated with a specified, increased lifetime risk of inducing cancer by using mathematical models to calculate potency figures. The limitations of this process are formally recognized and the figure obtained is officially termed “a plausible upper limit to the risk” [4]. Nevertheless, a single figure risk estimate gives a spurious sense of accuracy and the qualifications tend to be forgotten. However, the process may facilitate risk communication as the risk can be quantified in recognizable terms. For many chemicals, the calculated extreme upper limit of the risk does not present any practical problem.

The use of non-tumor data in cancer risk assessment
The estimation and characterization of cancer risk is grounded in the observations of tumors in humans and/or experimental animals. Increasingly, however, other kinds of data (non-tumor data) are finding application in cancer risk assessment. Metabolism and kinetics, adduct formation, genetic damage, mode of action, and biomarkers of exposure, susceptibility, end effects are the examples. While these and other parameters have been studied for many important chemicals over the past 30–40 years, their use for risk assessment is more recent, and new insights and opportunities continue to unfold [40].

Utilizing data from multiple studies (meta-analysis)
In acute and short-term studies, specific doses such as the NOAEL, benchmark dose (a 95% lower confidence bound on ED01, ED05, or ED10, the dose associated with 1, 5, or 10% response, respectively) and ED50 (dose associated with a 50% response—particularly for lethality, usually called LD50), are of special interest. These and other toxicity markers vary not only in the dose, but also in the duration of dosing. In practice, a single study
is typically used to estimate a toxicity marker. For example, a critical study and endpoint are used to determine the NOAEL, generally the highest experimental dose at which the critical effect(s) is not demonstrated, with the outcomes dependent on the characteristics of the study design, such as dose placement and the number of animals at risk. Small sample sizes at each dose are typical in acute and short-term studies, which means that no effect may be observed even when the probability of occurrence is substantial, e.g., if the sample size is 10, zero occurrence of the critical health endpoint is consistent with an expected occurrence in up to 26% of the animals (the probability of occurrence in a single animal drawn at random from the population sampled is 0.26). This is an argument for considering meta-analysis of toxicity markers (using data from multiple studies, subject to tests for homogeneity of the data) if possible [41].

A PERSPECTIVE ON CARCINOGEN RISK ASSESSMENT

Integration of animal and human studies
A better integration of animal and human studies might be particularly important for the occupational cancer risk assessment process. Ever too often the animal and human studies are not formally or effectively linked to address the unknown factors in occupational cancer. Animal and human studies should be better coordinated using the results of each to inform the other. At present, the most important need, paradoxically, is to explore the markers and mechanisms of the agents for which human carcinogenicity is well established. The relationship between laboratory indices and human effects will help establish a paradigm for future hazards identified in experimental conditions. The ability to identify similar biological pathways, or modes of action, in different species will be critical to this process. For example, the markers of intermediate cancer-related endpoints, metabolism, or non cancer-related toxicity can be examined interactively in animal and human studies rather than confirmed in large-scale human studies. Approaches should also be developed to foster collaboration between scientists who study cancer in humans and those who carry out cancer studies in animals. When exposure-response data are available from human studies, they should be used in the risk assessment process [42].

A comprehensive approach to integration of toxicity and cancer risk assessment
Experimental findings and theoretical considerations indicate a dose threshold for most chemically induced noncancer toxic effects below which the increased risk of toxicity is zero. On the contrary, for radiation- and chemically-induced cancer, it has been assumed that all agents operate by a genotoxic mode of action and that some risk can be assigned to even vanishingly small doses. Accordingly, risk assessments for carcinogens have commonly been based on the assumption that the tumor dose-response curve at low doses is linear and passes through the origin. Mode of action is defined as a fundamental obligatory step in the induction of toxicity or cancer. It is now clear that tumor induction can arise in a variety of ways, including not only DNA-reactive genotoxic mode of action, but also non-DNA-reactive nongenotoxic-cytotoxic and nongenotoxic-mitogenic modes of action. Initial risk assessment approaches that recognized this distinction identified a chemical carcinogen as either genotoxic or nongenotoxic, with no middle ground. The realization that there is a continuum whereby different chemicals can act by a combination of the mode of action as well as the recent explosion of outcomes of research into molecular mechanisms of carcinogenesis indicate that all relevant information should be integrated into the risk assessment process based on a case by case judgment. A comprehensive approach to risk assessment demands that default assumptions be replaced by an integrated understanding of the rate-limiting steps in the induction of toxicity or cancer, along with quantitative measures of the shapes of those dose-response curves [43,44].

Using cell replication data
Endogenous DNA damage from normal oxidation is enormous. Extensive evidence suggests that oxidative damage is a major factor, not only in aging, but also in degenerative diseases related to aging such as cancer. The steady-
state level of oxidative damage in DNA is over one million oxidative lesions per rat cell. Thus the cell division rate must be a decisive factor in converting lesions to mutations and further to cancer [45]. Raising the level of either DNA lesions or cell division rate increases the probability of cancer. Just as DNA repair protects against lesions, p53 guards the cell cycle and protects against cell division if the lesion level gets too high, however neither defense is perfect. Cell division is also a major factor in the loss of heterozygocity through non-disjunction and other mechanisms. The critical factor is a chronic cell division in stem cells, not in the cells that are discarded.

Chronic cell division is plausibly the major reason for the fact that more than half of the chemicals are classified as carcinogens when tested at the maximum tolerated dose (MTD) in standard rodent cancer bioassays. What is the explanation for the high positivity rate in high-dose animal cancer tests? For a number of reasons, one have to reject bias in picking more suspicious chemicals as the major explanation of the results. One explanation of the high positivity rate that is supported by an ever increasing array of papers is that the MTD for a given chemical can cause chronic cell killing and cell replacement in the target tissue, a risk factor for cancer that can be limited to the high dose. Thus it seems likely that a high proportion of chemicals in the world may be “carcinogens” if run through the standard rodent bioassay at the MTD, but this will be primarily due to the effects of high doses for the non-mutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens.

Taking cell division into account makes the priority setting in cancer prevention more effective. For example, the regulatory policy aimed at reducing tiny exposures to synthetic rodent carcinogens has confused the public about what factors are important for preventing cancer, and has diverted resources from more important health risks [46].

The role of diet and nutrition in carcinogenesis
A new appreciation of the impact that dietary intake and nutrition can exert on toxicity assessment, has given rise to questions about the appropriateness of our present methods for estimating cancer risk in humans from exposure to chemicals shown to be positive in chronic animal bioassays. The majority of low dose extrapolation methodologies assume that cancer induction occurs through a non-threshold mechanism. Dietary intake is a model non-monotonic agent. If the total intake is too low, the animal dies from protein-calorie malnutrition prior to cancer induction. As caloric intake increases above an optimum level the risk of cancer increases, consistent with elevated body weights. Using dietary intake as a “model non-monotonic compound” (i.e. one which does not have a monotonic dose-response relationship) allows investigators to address a number of important issues.

One of the problems that almost always arises when low-dose modeling is discussed is whether or not the agent of concern exhibits a threshold. A number of arguments assume that: (a) the only time in which the test subject is exposed is during the study; and (b) the agent under evaluation acts independently of all other agents. These assumptions need to be reconsidered in the light of new findings. The concept of zero exposure is thus untenable for many agents, and should be replaced, as has been done in an analytical context, by the concept of the level too low to measure. Thus, theoretical concerns about the efficacy of a single molecule of an agent to induce cancer in an individual have become a moot point. Like calories, chemical exposure appears to be unavoidable.

Relative to the latter assumption, if carcinogens and anti-carcinogens are ubiquitous then the concept that an agent can induce toxicity in isolation becomes untenable. Another aspect in the debate on the appropriateness of the present risk assessment paradigm, which should be re-evaluated in the light of the findings in diet and nutrition is the role played by hormesis, i.e. where a low-dose of certain toxicants may have a salutary effect, while higher doses are toxic [47]. This phenomenon is not simple to evaluate. A number of mechanisms have been suggested for hormetic effects.

Is a new cancer risk assessment paradigm needed? Perhaps, but prior to doing so, the present risk assessment paradigm needs to be modified to incorporate new scientific findings, especially the new appreciation of the impact of dietary intake on the modulation of the agent’s toxicity.
Suggested changes in the paradigm require more information than presently used. Placing the threshold within the context of specified conditions, and the definition of rational safety factors under those conditions, are not trivial exercises, and when data are not available the default procedure must be conservative enough to provide safety for the general public. Suggestions for lower or higher safety factors should be based on data, and it is anticipated that deriving data relevant to certain classes of compounds should allow refinement of the safety factors used, and should also stimulate the acquisition of more information on compounds of critical concern. Fortunately, risk assessment appears to be flexible enough to accommodate these changes [48].

**Incorporating hormesis in the routine testing of hazards**

Bailer and Oris [49] have defined hormesis as a dose-response relationship that is stimulatory at low doses, but is inhibitory at higher doses. Sielken and Stevenson [50] believe that there are strong theoretical reasons that support the existence of hormesis as well as data sets that support the existence of the phenomenon. The fields of micronutrients and pharmacology provide many examples of beneficial effects at low doses, but toxicity at higher doses. The implications for risk assessment is that the current methodologies do not reflect richness or complexity of biological processes. Furthermore, hormesis may be exhibited in a parameter such as life-span that is not described in the current potency estimates. The current regulatory caveat that the risk is unlikely to be higher than the upper bound estimates and may be as low as zero requires revision. If hormesis exists, then revision needs to be accompanied by several others, including changes in dose-response models, experimental designs, dose scales, uncertainty characterizations, and the definition of the response of concern. The inclusion of hormesis should impact quantitative risk assessment in at least seven fundamental ways.

1) The dose-response models for bioassay and epidemiological data should be more flexible to fit the observed shape of the dose-response data and no longer be forced to always be linearly increasing at low doses.
2) Experimental designs should be altered to provide greater opportunity to identify the hormetic component of a dose-response relationship.
3) Rather than a lifetime average daily dose or its analogue for shorter time periods, dose scales or metrics should be used to reflect the age- or time-dependence of the dose level.
4) Low-dose risk characterization should include the likelihood of beneficial effects and the likelihood that a dose level has reasonable certainty of no appreciable adverse health effects.
5) Exposure assessments should make greater efforts to characterize the distribution of actual doses from exposure rather than just upper bounds.
6) Uncertainty characterizations should be expanded to include both upper and lower bounds, and there should be an increased explicit use of expert judgement and weight-of-evidence based distributional analyses reflecting more of the available relevant dose-response information and alternative risk characterizations.
7) Risk should be characterized in terms of the net effect of a dose on health rather than a dose’s effect on a single factor affecting health, for example, risk would be better expressed in terms of mortality from all causes combined rather than a specific type of fatal disease [50].

**CONCLUSION**

Just as new cancer models need to be developed and validated, regulatory agencies need to develop guidelines for their application consistent with the regulatory policies and authority. Ultimately, the utility of risk assessments will be judged on how well they lead to effective risk management and cancer prevention decisions. More research is needed to find out how this type of information is communicated to managers, decision makers, and the public, how it is used, and how it can be improved [2].

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