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Quantitative Approaches in Use to Assess Cancer Risk

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Scientists have long used conventional toxicological methods to establish "safe levels of exposure" for chemicals presumed to have threshold health effects or doses below which significant effects are unlikely to occur. These same methods cannot be used to establish safe levels of exposure for non-threshold pollutants, such as carcinogens. Therefore, Federal regulatory agencies in the United States are using risk assessment methods to provide information for public health policy decisions concerning increases in risk associated with increases in exposure to carcinogenic and other non-threshold pollutants. Acceptable exposure/risk levels are decided by policymakers who consider descriptions and estimates of risks together with social and economic benefits from the uses of the chemical. This paper focuses on the development of quantitative risk assessment approaches by Federal regulatory agencies in the United States, and identifies the mathematical models currently being used for risk extrapolation, including their inherent uncertainties. The uncertainties and limitations of these methods have led some scientists to question the utility of quantitative risk extrapolation. The experience of the U.S. Environmental Protection Agency (EPA), as summarized in this paper, can provide a realistic basis for evaluating the pros and cons. Finally, shortcomings in current risk assessment methods and their use in policy decisions are explored, and areas for possible improvement, given current scientific knowledge, are identified.

KEY WORDS: Carcinogens; risk assessment; federal regulation; mathematical modeling; health policy.

1. INTRODUCTION

Conventional toxicological methods, usually the application of safety factors to the "no observed effect level" in animal studies to estimate safe exposure levels for humans, have long been available for agents causing diseases which have identifiable thresholds or levels below which no serious effect is expected.[1] More recently, quantitative risk assessment methods have been developed to provide information about non-threshold agents, most notably for potential carcinogens, where safe levels of exposure cannot be identified by conventional methods.[2, 3, 4] All major Federal regulatory agencies in the United States have used information from quantitative risk assessment methods to implement protective public health policies. Applications include radiation, air pollutants, food contaminants, pesticide exposures, water contaminants, worker protection, consumer protection, hazardous waste disposal, and the cleanup of uncontrolled waste sites. In addition, the National Academy of Sciences, in a recent report, called for the separation of risk assessment and risk management in the Federal regulatory program to protect public health.[5] The report further emphasized the

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[2]The entire Carcinogen Assessment Group within the Office of Health and Environmental Assessment contributed to this paper through their assessment activities from 1976 to 1983. Selected examples of their work, referenced herein, provided the data base for significant parts of the discussion that relate to the U.S. Environmental Protection Agency. Members of the group are: R. E. Albert, Chairman (also Professor and Deputy Director, Institute of Environmental Medicine, New York University Medical Center), R. McGaughy, Director, L. Anderson, S. Bayard, D. Bayliss, C. Chen, M. Chu, H. Gibb, B. Haberman, C. Hiremath, D. Singh, and T. Thorslund.

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importance of a consistent and scientifically sound basis for risk assessment to ensure its integrity.

In the context of carcinogenicity, risk assessment is characterized as a two-step process. The first step involves a qualitative evaluation of all available biomedical data in order to answer the question: How likely is an agent to be a human carcinogen? The answer is expressed in terms of the weight of the biomedical evidence. The second step in the risk assessment process involves fitting some shape to the dose-response curve and coupling it with information about population exposures to answer a second question: On the assumption that the agent is a human carcinogen, what is the magnitude of its health impacts for current and projected exposures? These estimates are generally expressed as increased individual lifetime risks for exposed population subgroups and numbers of annual cancer cases as an index to describe nationwide impacts. Since large uncertainties are associated with this extrapolation process, these risk estimates must be used with caution.

To provide quantitative estimates of risk at the low levels of exposure generally found in the ambient environment, one must most often extrapolate from high doses in the observed range, usually involving animal bioassay studies, to much lower exposures involving human populations. Although a variety of mathematical models for risk extrapolation has been presented in the literature, U.S. regulatory agencies have most often used a linear non-threshold model or a similar model employing a linear non-threshold component in the low-dose region of the dose-response curve, to place an upper bound on risk.[6,7,8] When adequate human data are available, they are used in preference to animal data for quantitative risk extrapolation. For human data, the best fit to the dose-response data is employed to extrapolate from high doses to low doses.[9,10] Negative epidemiologic data are used to place upper bounds on risks.

The U.S. Environmental Protection Agency (EPA) has extensive experience with the use of quantitative risk assessment as a basis for making public health policy decisions. Other Federal agencies in the United States are using similar approaches. The EPA experience is presented in some detail in this paper to illustrate quantitative approaches in use in the United States. The Appendix provides a detailed discussion of the quantitative risk extrapolation models being used by the EPA, as previously published.[9]

2. DEVELOPMENT OF QUANTITATIVE RISK ASSESSMENT APPROACHES FOR CHEMICAL CARCINOGENS BY U.S. REGULATORY AGENCIES

The EPA was organized by executive order in December 1970. Soon afterward, a series of actions commenced which thrust the Agency into the evaluation of carcinogenesis data and the translation of these evaluations into public policy. Controversy about the evaluation of the scientific data as a basis for weighing risks and benefits to regulate possibly carcinogenic pesticides formed the impetus for EPA to adopt risk assessment approaches for the evaluation of these data. A brief history will provide a perspective for the current EPA policy, which involves an internal process for qualitative and quantitative risk assessment of potential carcinogens.

Between December 1970 and mid-1975, the EPA moved to suspend and cancel most uses of three major pesticides: DDT, aldrin/dieldrin, and chlordane/heptachlor. At the time it took these actions, the Agency lacked internal procedures for assessing the risks associated with the use of these pesticides. Instead, much of the information that focused on these potential risks came from sometimes conflicting evaluations that had been conducted by scientists outside the EPA; these evaluations were mostly qualitative in nature. The full scientific evaluation occurred largely during subsequent administrative hearings, and in testimony by expert witnesses called by the EPA and the registrants. In short, much of the scientific information was assimilated as part of the adversarial process and had to be summarized in legal briefs at the conclusion of the hearings.

In summarizing the testimony of their expert witnesses in several litigations, the attorneys for the EPA set forth certain summary statements which, in the legal motion, were referred to as "cancer principles".[11,12] This triggered a widespread perception that these summary statements represented an Agency cancer policy. Because of this perception, these so-called "Cancer Principles" received broad and general criticism by the scientific community, a substantial part of the private sector, and the Congress (e.g., see the 1976 *Lancet* editorial.[13]) The major thrust of the criticism was not so much that these statements were incorrect, as that such a complex field as carcinogen assessment cannot be adequately covered in summary statements.

More specifically, there was a widespread concern that the Agency would simply regard all agents associated with the induction of cancer in animals as equally likely to be potential human carcinogens; treat all such agents as if they had the same potency; and regulate exposures, in the absence of a threshold or information about degree of risk, toward zero risk, so far as possible. To some this meant a zero risk policy, similar to the approach adopted by the U.S. Food, Drug, and Cosmetic Act for food additives, for literally hundreds of environmental agents. Such a policy was perceived even though the Administrator, in his earlier decisions on DDT, aldrin/dieldrin, and chlordane/heptachlor, did not adopt a zero risk position, but rather attempted to qualitatively balance risks and benefits for each use.

The impracticality of aiming toward zero risk on a broad scale for a large number of economically important agents is apparent. Also, when one reviews the authority the EPA inherited in a series of laws passed in the 1970s that deal with the control of environmental pollutants, including carcinogens, it is apparent that some basis for setting priorities is needed. The EPA laws cover eight areas: air pollution (Clean Air Act), pesticides (Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA), pollution of water bodies (Federal Water Pollution Control Act), drinking water (Federal Drinking Water Act), toxic substances (Toxic Substances Control Act), hazardous wastes (Resource Conservation and Recovery Act), uncontrolled waste sites (Comprehensive Environmental Response, Compensation, and Liability Act, usually referred to as "Superfund"), and ionizing radiation (under several legislative authorities). In addition, four other major U.S. regulatory agencies are also charged with regulating carcinogens under different authority designations. These include the Food and Drug Administration (FDA) (under the Food, Drug, and Cosmetic Act), the Consumer Product Safety Commission (CSPC) (under the Consumer Product Safety Act), the Occupational Safety and Health Administration (OSHA) (under the Occupational Safety and Health Act), and the U.S. Department of Agriculture (USDA), which has some responsibilities for regulating food safety. Considering the large number of chemicals to which people are exposed, many of which have shown carcinogenic activity in laboratory animal tests, some approach was called for to determine the magnitude of the risks, as a basis for setting priorities and balancing risks against social and economic factors.

Between 1976 and 1980, in order to provide information regarding the degree of risk associated with different levels of exposure, several U.S. Federal regulatory agencies adopted the use of risk assessment in making health policy decisions. The EPA published guidelines for carcinogen risk assessment and established a senior health committee in the Agency to assess cancer risk.[2,3] The scientific basis for the EPA approach was consistent with recommendations from the advisory group to the National Cancer Institute, which published their report at about the same time.[14]

The FDA likewise used risk assessment approaches in a series of decisions involving food contaminants, drugs, and cosmetics, although the FDA did not adopt guidelines for risk assessment. In one interesting application, the FDA retracted a regulation relying on the log-probit model (see Appendix) to establish contaminant levels for carcinogenic agents in animal foodstuffs, and replaced it with a proposed regulation using the linear non-threshold model.[15,16,17] The FDA also used the linear model as a basis for deciding allowable limits of aflatoxin in peanut products and for permitting the use of the suspected carcinogen, lead acetate, in hair dyes.[18,19] The New York Times carried an editorial entitled "A Carcinogen Passes" to point out the reasonableness of an approach that recognized the insignificance of very low risk levels.[20]

In contrast, OSHA adopted a cancer policy that merely mentioned possible limited use of quantitative risk assessment.[21] Following the Supreme Court decision on the OSHA benzene standard, however, OSHA now seems legally bound to provide at least some quantitative analysis to estimate improvements (i.e., reduced risk) in worker health associated with more stringent standards.[22] A New York Times editorial entitled "So It's A Carcinogen, But How Bad?" endorsed the utility of quantitative measures of risk in deciding the extent of risk associated with potential carcinogens to set public policy.[23] This media coverage, although limited, indicates at least the initiation of public awareness and interest in the extent of cancer risk.

Major uncertainties are inherent in the quantitative risk assessment process (e.g., uncertainties associated with high- to low-dose extrapolation and with extrapolation from animal to man), and only rarely is information available concerning synergistic effects or risks to particularly susceptible groups. These limitations have led some to oppose the use of quantita-

tion in the policy process. For example, an article following the Supreme Court decision on benzene cited limitations in quantitative risk assessment as a reason for opposing the use of quantitative assessment.[24] More recently, Weinhouse[25] voiced similar concerns in his presidential address before the American Association for Cancer Research. Nevertheless, EPA, given its regulatory responsibilities, has felt it imperative to use quantitative assessment despite its admitted problems. The Agency's experience, summarized in this paper, can provide a realistic basis for evaluating the pros and cons of such use.

Seeing the need for a common approach, major U.S. regulatory agencies joined in writing a single document to address the issues involving the identification of carcinogens and the estimation of risk.[4] This document emphasized the importance of carefully evaluating all the positive and negative biomedical evidence for carcinogenicity and presenting the strength of this evidence clearly, whether or not quantitative estimates of risk are also presented. The document also discussed available extrapolation models for estimating cancer risk and suggested the use of the linear non-threshold model when only one model is selected. The Interagency Regulatory Liaison Group (IRLG) was abolished before it could revise the original document to respond to public comments received after its publication in the *Federal Register*. An effort is currently under way, chaired by the President's Office of Science and Technology Policy, to provide an updated federal document on these issues.

3. QUANTITATIVE APPROACHES IN USE WITH SPECIFIC REFERENCE TO APPLICATIONS IN THE U.S. ENVIRONMENTAL PROTECTION AGENCY

3.1. Historical Perspective: Adoption of Risk Assessment Guidelines by the U.S. Environmental Protection Agency

In 1976 the EPA became the first agency to adopt guidelines for scientific evaluation of cancer risks and, further, to state that gains in public health (i.e., reductions in risks) would be balanced against social and economic concerns in making regulatory decisions, to the extent permitted by enabling legislation. Previously, risks and benefits had been explicitly balanced, mostly for decisions involving pesticide uses, as required under FIFRA. The most experience to date in using risk assessment in the regulatory process has been in the area of carcinogenesis, although the EPA has proposed guidelines for applying risk assessment approaches to other health effects, such as mutagenicity. This work for mutagenicity and other health effects is continuing.[26,27]

In 1976 the EPA adopted a two-step approach to risk assessment.[2,3] Risk assessment was defined as a process that would answer two questions: (1) How likely is an agent to be a human carcinogen? and (2) If an agent is a human carcinogen, what is the magnitude of its public health impact given current and projected exposures? Since only rarely do we know for sure that an agent is indeed a human carcinogen, the first step involves an evaluation of all the relevant biomedical data to determine the weight of evidence that an agent might be a human carcinogen. The second step involves the quantification of risk, that is, public health impacts, in terms of rough estimates for current exposures as well as estimated exposures for various regulatory options.

To answer the first question regarding the likely carcinogenic potential, the biomedical evidence is described as ranging from the strongest evidence, based on human data backed up by animal bioassay results, to substantial evidence provided by positive results from animal bioassay tests, to suggestive or supporting evidence provided by positive results from short-term tests. The exact nature and extent of the evidence, however, cannot be simply assigned to broad categories, such as the ones mentioned above, but rather each case must be judged individually by experts. These judgments are based on an evaluation of the relevant biomedical data, including both negative and positive studies, pharmacokinetic parameters, and information from short-term tests to determine likely carcinogenic potential. In the EPA, these evaluations have always been summarized in paragraphs that discuss the weight of evidence for carcinogenicity. In addition, at one time the Agency assigned the weight of evidence for positive evidence to one of three broad categories: (1) strongest evidence—for positive epidemiologic results backed up by animal data, (2) substantial evidence—for the broad range of positive results from animal bioassay tests, and (3) suggestive evidence—for positive short-term test results, or for borderline animal or human results. Because these labels were being applied without a full appreciation for the detailed evaluations, the EPA dropped the labels and since

has relied primarily on summary paragraphs to present the data in terms of the nature of the responses, the quality and extent of the data, an evaluation of both positive and negative responses, and other relevant factors, with the understanding that regulators would take this weight of evidence into account in making regulatory decisions. To date, the Agency has not adopted criteria for stratifying the weight of evidence, although the criteria developed by the International Agency for Research on Cancer (IARC) are often used.[28] The qualitative assessment, that is, the weight of the evidence to indicate potential carcinogenicity for humans, has been factored into the risk management process in a variety of ways depending upon the applicable legal standard and the practical circumstance. In one case, numerical weighting factors were assigned to grade the weight of evidence for carcinogenicity in proposing regulations for reporting hazardous spills.[29] Negative studies are reviewed in the qualitative assessment to see if there are data which detract from the evidence contributed by positive results.

In the second step, which is providing quantitative estimates of public health impacts, risks are bracketed between an upper bound and a lower bound approaching zero. The upper-bound risks are expressed both in terms of the individual increased cancer risks in exposed population subgroups (i.e., increased risks of, for example, one chance in a thousand or 1×10^{-3}) and the nationwide impact in terms of annual increased number of cancer cases. This second quantitative step is intended to give the regulators a feel for the potency of the suspect carcinogen, and some quantitative information regarding public health impacts. Uncertainties associated with high- to low-dose risk extrapolation, extrapolation from animal to man, and exposure estimation make it impossible to describe risk more precisely. Nevertheless, since the potency of carcinogens can span 50 millionfold or more, it seems important to make some attempt to take this disparity into account in making public policy decisions. The upper bound is calculated using reasonably conservative exposure estimates and the linear non-threshold model at low doses. Since the dose-response curve at low doses is unlikely to be concave downward, the linear, non-threshold dose-response curve is regarded by scientists working in risk assessment in the United States as usually placing a plausible upper bound on risks (i.e., the risks are not likely to be higher but could be lower). The plausibility of upper-bound estimates derived from the linear non-threshold model is based on the correlation between carcinogenicity and mutagenicity; the non-threshold dose-response curve for mutagenicity, in most cases; the quantal nature of DNA interactions; and the linear nature of the dose-response curves suggested by some epidemiology data (e.g., aflatoxin, radiation, and cigarette smoke, see Appendix). However, the linear model could be unduly conservative if an agent exhibits either a concave curve or a threshold at low doses.[30] In the absence of information to define mechanisms of action at low doses and pharmacokinetic differences between animals and humans, extrapolation from high doses to low doses can define risks only within rough bounds. Generally no attempt is being made to further pinpoint the risks within the broad bounds defined at the upper bound by the linear non-threshold model, and at the lower bound as approaching zero. This recognition that the lower bound may approach zero or be indistinguishable from zero stems from the uncertainties associated with mechanisms of carcinogenesis, including the possibility of detoxification and repair mechanisms, metabolic pathways, and the role of the agent in the cancer process. Most often there is no biological justification to support the choice of any one model to describe actual risk. If data are available at doses equivalent to environmental exposures, the model that best fits the data should be used. In the absence of such data a variety of models can be used to fit the data in the observed range, but these models diverge sharply at low doses. Point estimates of risks derived from these models generally fall within the bounds described above. It should be clear from the preceding discussion that the linear non-threshold model has been used by the EPA to place plausible upper bounds on risk, not to establish actual risk.

Before November 1980, the Carcinogen Assessment Group used the one-hit model to estimate upper-bound cancer risks from responses in animal bioassay studies. In response to public comments on the proposed Water Quality Criteria for suspected carcinogens, the EPA changed from the one-hit model to the linearized multistage model (see Appendix) to estimate the upper bound of cancer risk.[9, 31, 32, 33] Where human data are available, the curve best fitting the data in the observed range is selected and then extrapolated to low doses using the linear non-threshold model. Negative human data may be used to place upper bounds on the risk, provided that the incidence and exposure data are good enough. The

appendix to this paper is adapted from the previously published detailed description of the quantitative risk assessment models used by the EPA.[9] A comparison of estimates using the one-hit model and the linearized multistage model indicates close agreement except in the cases of steeply rising dose-response curves, where the multistage model gives lower slope estimates, but lower by less than a factor of five.[9,31,32,33]

Upper-bound risk estimates have inherent uncertainties and must be used with caution. However imprecise, these quantification approaches represent the best scientific tools currently available to establish the relative magnitude of risk. The alternative to their use is to provide no quantitative risk information to the policy process, which generally means that the level of health protection will be decided by definitions of feasibility, best available technology, etc., all of which have considerable uncertainties and may lead to underprotective health policies or to requirements to reduce trivial risks at incommensurately high costs.

The EPA risk assessment approach was certainly experimental at the time it was adopted. In practice, it has provided a conceptual basis for balancing risks against social and economic concerns and for setting priorities for Agency attention and action. Also, risk assessment has provided an alternative to aiming toward zero risks/exposure, where actual acceptable levels must be defined solely in terms of achievability, for a large number of agents introduced into the environment, and for important social and economic reasons. The following section of this paper presents some of these examples.

3.2. Applications of Quantitative Risk Assessment to Public Policy Decisions

Quantitative risk assessment, together with qualitative assessments of the biomedical evidence, has been used in five distinct situations in the EPA for deciding public policy: (1) to set priorities, (2) to review residual risk after application of best available technology to see if anything more needs to be done, (3) to balance risks against benefits, (4) to set standards and target levels of risk, and (5) to provide information regarding the urgency of situations where population subgroups are inadvertently exposed to toxic agents (e.g., populations near uncontrolled waste sites). Several examples of these applications are discussed below.

3.2.1. Setting Priorities

Under provisions of the Clean Air Act, the EPA must "list" hazardous air pollutants and regulate sources as necessary. In order to set priorities for reviewing hundreds of agents that may be potential air pollutants, the EPA Office of Air Programs identified three groups of potentially toxic chemicals suspected of being present in the ambient air at levels of concern because of their use patterns (Tables I and II). The highest priority for health evaluations was given to Group I, then Group II, and finally Group III. These priorities reflected judgments in the air office regarding those chemical which, based on preliminary information about likely exposure and possible toxicity, might present the greatest hazard to humans from air pollution. The Carcinogen Assessment Group (CAG), one of the health subgroups in the EPA Office of Health and Environmental Assessment, provided a qualitative weight of evidence statement and an index of potency expressed as an upper-bound unit risk estimate (Table III). The unit risk estimate is the increased individual lifetime risk for a 70-kg individual breathing air containing 1 $\mu g/m^3$ of the chemicals for a 70-year life span. Notice that the potency index, expressed as unit risk, ranges a millionfold, and that chemicals having the strongest biomedical evidence for carcinogenicity based on responses in humans may have relatively low potencies (e.g., vinyl chloride with a unit risk of 10^{-6} and benzene with a unit risk of 10^{-6}). Obviously strong evidence of carcinogenicity need not mean high potency as well. In the absence of information regarding potency, regulators are inclined to

Table I. Chemical Proposed by the Environmental Protection Agency Office of Air Programs for Unit Risk Assessment[a]

Group I	Group II
Acrylonitrile	Beryllium
Carbon tetrachloride	Cresols (ortho, meta, and para)
Chloroform	Formaldehyde
Ethylene dibromide	Maleic anhydride
Ethylene dichloride	Manganese
Ethylene oxide	Methyl chloroform
Nitrosamines (4)	Methylene chloride
Perchloroethylene	Nickel
Trichloroethylene	Nitrobenzene
Vinylidene chloride	Toluene
	Xylenes (ortho, meta, and para)

[a]Unit risk is excess lifetime risk associated with breathing 1 $\mu g/m^3$ of the chemical over a 70-year life span for a 70-kg person.

Table II. Chemicals Proposed by the Environmental Protection Agency Office of Air Programs for Unit Risk Assessment[a]

Group III	
Acetaldehyde	Dioxane
Acetylene tetrachloride	Epichlorohydrin
Acrolein	Hexachlorocyclopentadiene
Allyl chloride	Methyl iodine
Benzyl chloride	Naphthylamine (1- and 2-) Bis-
Chloromethyl ether (BCME)	2-Nitropropane
Chlorobenzene	Phenol
Chloromethylmethyl ether	Phosgene
Chloroprene	Polychlorinated biphenyls (PCBs)
Dichlorobenzene (ortho and para)	Propylene oxide

[a]Unit risk is excess lifetime risk associated with breathing 1 $\mu g/m^3$ of the chemical over a 70-year life span for a 70-kg person.

Table III. Upper-Bound Unit Calculations for Suspected Carcinogenic Air Pollutants[a,b]

Chemical	Upper-bound unit risk estimates
Acrylonitrile	7×10^{-5}
Allyl chloride	5×10^{-8}
Arsenic	4×10^{-3}
Benzene	7×10^{-6}
Beryllium	6×10^{-4}
Diethylnitrosamine (DEN)	2×10^{-2}
Dimethylnitrosamine (DMN)	5×10^{-3}
Dioxin (2,3,7,8-tetrachloro-)[c]	1
Ethylene dibromide	6×10^{-5}
Ethylene dichloride	7×10^{-6}
Ethylene oxide	2×10^{-4}
Formaldehyde	5×10^{-5}
Manganese	4×10^{-4}
Nickel	6×10^{-4}
N-nitroso-N-ethylurea (NEU)	1×10^{-2}
N-nitroso-N-methylurea (NRU)	7×10^{-1}
Perchloroethylene	2×10^{-6}
Trichloroethylene	3×10^{-6}
Vinyl chloride	4×10^{-6}
Vinylidene chloride	4×10^{-5}

[a]From U.S. Environmental Protection Agency, Carcinogen Assessment Group Reports 1976–1983. These calculations are periodically revised as new data become available.

[b]Unit risk is excess lifetime risk associated with breathing 1 $\mu g/m^3$ of the chemical over a 70-year life span for a 70-kg person.

[c]The potency of dioxin is estimated to be about 1600 times greater than that of DEN at low exposure levels; therefore, for lifetime exposure to 1 $\mu g/m^3$, the upper-bound unit risk estimate is 100% chance of cancer occurrence. The upper-bound estimate of the potency (slope) for dioxin is 33 $\mu g/m^3$ or $3.3\times10^{-2}/ng/m^3$.

regulate known human carcinogens more severely than animal carcinogens, even though some human carcinogens appear to be relatively much less potent than some chemicals whose carcinogenic effect has only been demonstrated in animal studies. The weight of evidence for carcinogenicity, the unit risk estimate as a measure of potency, and information concerning exposure levels, have provided a basis for selecting the most hazardous air pollutants for further study and possible regulation.

After an agent has been "listed" as a hazardous air pollutant, the EPA must decide which sources to regulate first, and indeed whether or not regulation is warranted. Table IV presents a comparison of data for different source categories contributing arsenic to the ambient air. The upper-bound risk estimates to population subgroups and the related upper-bound nationwide impacts always rely on estimates of exposures, which also have great uncertainties. Uncertainties associated with exposure estimates must always be included in the exposure assessment and taken into account in using risk assessment information. For example, where estimates of exposure are highly uncertain it may be possible to present a range for the exposure. Risk estimates based on this range can be instructive, particularly in circumstances where either the upper end of the range provides low estimates or, conversely, where the lower end of the range still suggests possible associated high risks.

3.2.2. Residual Risk

Quantitative risk assessment was used to compare residual risk, after application of best available technology to control ambient levels of vinyl chloride monomer, with risk associated with other potentially hazardous air pollutants that had not yet been regulated [see Tables V(a) and V(b)]. The risk assessment information indicated that reductions in risk had been considerable for vinyl chloride, and that the remaining risk was low relative to risks associated with the other air pollutants [see individual risks for arsenic and benzene, Table V(a); and nationwide impacts for arsenic and benzene, Table V(b)]. The Office of Air Quality Programs allocated Agency resources to consider other air pollutants and not to further reduce risks associated with vinyl chloride emissions. To data, vinyl chloride has not been further regulated. The Agency has agreed, however, to periodically review the regulation of vinyl chloride emissions.

Table IV. Upper-Limit Lifetime Cancer Risk for Arsenic Exposures[a,b]

Source	Number exposed in highest two groups[c]	Highest two exposure levels ($\times 10^{-4}$ mg/kg/day)[d]	Associated lifetime upper-bound cancer risk	Upper-bound estimates/cases per year
Copper smelters	43,800	2.7–1.5	$2-1\times10^{-3}$	1.5–0.821
Lead smelters	3,400	0.69–0.27	$6-2\times10^{-4}$	0.029–0.017
Zinc smelters	37,000	0.69–0.27	$6-2\times10^{-4}$	0.32–0.13
Cotton gins	32	15.4–6.9	$13-6\times10^{-3}$	0.0061–0.0027
Pesticide manufacturing	1,480	0.026–0.014	$2-1\times10^{-5}$	0.0004–0.00025
Glass manufacturing	11,580	0.69–0.014	$6-2\times10^{-4}$	0.099–0.040

[a]From Table 6 of the U.S. Environmental Protection Agency, Carcinogen Assessment Group's Risk Assessment on Arsenic, May 2, 1980, National Technical Information Service, PB 81-206013.
[b]The significant figures presented do not indicate precision or accuracy; rather, they are included to make it easier to trace the derivation of these numbers through the various extrapolation and mathematical calculations.
[c]Population exposed to ambient levels of arsenic from the sources listed.
[d]For example, the highest exposure level for copper smelters is 2.7×10^{-4} mg/kg/day.

Table V(a). Comparison of Upper-Bound Risks Associated with Ambient Exposure to Carcinogenic Air Pollutants[a]

Chemical[b]	Upper-bound lifetime probability of cancer death due to maximum exposure near stationary sources[c]	Total number exposed[c,e]	Total number of cancer deaths/year at the upper bound in U.S. due to chemical in air[c]
Arsenic	2×10^{-3}	44,000	1
Benzene	2×10^{-4}	55,000	0.1
Coke ovens	6×10^{-3}	1,800	0.2
Vinyl chloride[d]			
Before regulation	4×10^{-3}	34,000	1.9
After regulation	2×10^{-4}	34,000	0.1

[a]From the U.S. Environmental Protection Agency, Carcinogen Assessment Group Reports 1976–1981. These estimates may change as additional data become available.
[b]All risks are before regulations unless otherwise indicated.
[c]The significant figures presented do not indicate precision or accuracy, but are included to make it easier to trace the derivation of these numbers through the various extrapolation and mathematical calculations.
[d]If risks were based on the incidence of mammary tumors in the animal bioassay studies, the results would be four times higher.
[e]Population exposed to ambient levels of chemical listed. Exposure is from stationary air sources.

3.2.3. Balancing Risk and Benefits

Many decisions involving the balancing of risks and benefits under EPA's pesticide registration authorities have relied on risk assessment. Table VI presents the quantitative risk estimates associated with three examples for which registration decisions have been made. In the case of chlorobenzilate, a pesticide used on citrus fruit, the weight of evidence for carcinogenic potential is based on responses in the liver of both male and female mice; studies in rats were negative. There is considerable disagreement among some scientists regarding the appropriate weight to be given to such responses. Nevertheless, on the assumption that chlorobenzilate is a human carcinogen, quantitative risk estimates indicate that risk associated with exposure to the general population is relatively low, on the order of one chance in a million of increased risk, and the annual cancer rate on a nationwide basis is relatively low. However, the risk to applicators of the pesticide was higher by two orders of magnitude. Since the pesticide act (FIFRA)

Table V(b). Comparison of Upper-Bound Risks Associated with Ambient Exposure to Carcinogenic Air Pollutants[a]

Chemical[b]	Upper-bound lifetime probability of cancer death due to average exposure near stationary sources[c]	Total number exposed[c,e]	Total number of cancer deaths/year at the upper bound in U.S. due to chemical in air[c]
Arsenic	4×10^{-5}	25 million	16
Benzene	3×10^{-5}	220 million	78
Coke ovens	7×10^{-4}	15 million	150
Vinyl chloride[d]			
Before regulation	2×10^{-4}	5 million	20
After regulation	1×10^{-5}	5 million	1

[a]From the U.S. Environmental Protection Agency, Carcinogen Assessment, Group Reports 1976–1981. These estimates may change as additional data become available.
[b]All risks are before regulations unless otherwise indicated.
[c]The significant figures presented do not indicate precision or accuracy, but are included to make it easier to trace the derivation of these numbers through the various extrapolation and mathematical calculations.
[d]If risks were based on the incidence of mammary tumors in the animal bioassay studies, the results would be four times higher.
[e]Population exposed to ambient levels of chemicals listed. Exposure is from stationary air sources.

Table VI. Upper-Bound Risk Estimates for Population Exposure to Suspected Carcinogenic Pesticides[a]

Pesticide	Population exposed	Upper-bound lifetime probability of cancer death due to exposure[b]	Number of expected cancer deaths/year at the upper bound[b]
Chlorobenzilate	220 million–citrus consumption	2×10^{-6}	7
	-citrus applicators[e]	4×10^{-4} to 1×10^{-3}	...
Amitraz (BAAM)	220 million–apple consumption	3×10^{-6}	8
	220 million–pear consumption	2×10^{-6}	6
	1400 applicators–spraying apples	1×10^{-4}	0.002
	1550 applicators–spraying pears	6×10^{-5}	0.001
	1600 applicators–spraying pears	1×10^{-4}	0.003
Chlordane/heptachlor	220 million	2×10^{-4c}	500[b]
		5×10^{-5d}	150[c]

[a]U.S. Environmental Protection Agency, Carcinogen Assessment Group Reports 1976–1981. These estimates may change as additional data become available.
[b]The significant figures presented do not indicate precision or accuracy, but are included to make it easier to trace the derivation of these numbers through the various extrapolation and mathematical calculations.
[c]Based on total tumors.
[d]Based on large carcinomas.
[e]The total number of applicators was not included in the study.

requires the balancing of risks and benefits, the presence of applicator risk was evaluated in view of the fact that no substitute exists for chlorobenzilate on citrus. The EPA decided that the risks did not outweigh the benefits and therefore retained the registration of chlorobenzilate for use on citrus. The Agency added labeling requirements to further protect applicators.

The next case in Table VI involved the application of risk assessment to the registration of the new pesticide BAAM for use on pears and apples. Only one carcinogenesis bioassay had been performed, and it provided very weak evidence of carcinogenic activity. Since the possibility that this weak signal in one test could be real, a quantitative risk assessment was completed. The calculated

upper-bound risk estimates indicated relatively low projected risk for the U.S. population, on the order of one chance in a million of increased risk. Balancing risks against benefits, the EPA made a decision (1) to permit a 3-year temporary registration of BAAM for use on pears but not on apples, because substitutes were not available in the former case but were available in the latter case; and (2) to require submission of more definitive data before granting a permanent registration for any uses. While the final results of these tests are not yet available, this example demonstrates how time and effort can be put to good use when guided by quantitative risk assessment.

In the final example in Table VI risk assessment was used to balance risks and benefits for registered uses of chlordane/heptachlor. The biomedical evidence for the carcinogenicity of these chemicals is reasonably strong based on liver carcinomas in a series of bioassay studies in the mouse and rat. These chemicals bioaccumulate, and most humans carry a body burden of the chemicals in adipose tissue. Application of quantitative risk assessment indicated risks at least an order of magnitude higher than the previous two cases presented in Table VI; considerable potential nationwide impacts were also projected. The decision in this case was to cancel most uses of chlordane/heptachlor with the exception of underground applications for termite control, for which good substitutes were not available and exposures were estimated to be less.

Table VII presents projected risks associated with the resumed manufacturing of nitrilotriacetic acid (NTA) in the United States. This risk assessment was done because the manufacturer asked EPA for guidance as to whether or not the EPA would regulate NTA if manufacturing was resumed. (The manufacturing of NTA had been voluntarily suspended in the early 1970s because of early indications in animal bioassay studies that NTA might be a carcinogen.) NTA is used in detergents to replace phosphates since phosphates contribute to the eutrophication of water bodies. The risk estimates presented in Table VII are based on monitoring data from Canada, where NTA has been in continuous use for a number of years. With the exception of private wells, where only 21 samples had been monitored, potential cancer risks associated with the Canadian monitoring data indicated low projected U.S. risks calculated at the upper bound. Although questions were raised about the applicability of the Canadian

Table VII. Upper-Bound Projected Lifetime Cancer Risk Based on One-Hit Model from NTA Exposure-Response[a,b]

Type of exposure	Number exposed	Exposure level[c] mg/kg/day	Associated cancer risk at the upper bound	Cancer cases/year at the upper bound
Public drinking				
Water	220 million	8×10^{-5}	4×10^{-7}	1
(Range)		7×10^{-4}	3×10^{-6}	10
(Mean)		4×10^{-5}	2×10^{-7}	1
Private wells	66 million	up to 0.1	4×10^{-4}	370
(Max)		(insufficient data)	(insufficient data)	(insufficient data)[d]
General consumers				
Laundry	125 million	2×10^{-4}	1×10^{-6}	2
Dishwashing	125 million	2×10^{-4}	1×10^{-6}	2
Residue on unrinsed dishes	2 million	0.01	6×10^{-5}	2
Workers/	100	1×10^{-3}	6×10^{-6}	...
Manufacture		7×10^{-3}	3×10^{-5}	...
Formulations	1750	5×10^{-3}	2×10^{-5}	< 0.001
		5×10^{-2}	2×10^{-4}	

[a]From U.S. Environmental Protection Agency, Office of Toxic Substances Draft Report, 1979.
[b]The significant figures presented do not indicate precision or accuracy, but are included to make it easier to trace the derivation of these numbers through the various extrapolation and mathematical calculations.
[c]Projected U.S. exposures based on Canadian monitoring data.
[d]Only 21 well samples were analyzed.

exposure data to project U.S. exposures, the decision not to regulate the resumed manufacture of NTA cited these relatively low risk estimates as the reason.

3.2.4. *Setting Target Levels of Risk*

In this example (Table VIII), the EPA was obligated to recommend nationwide water quality criteria for a large number of chemicals, including suspected carcinogens.[9] The statute under which these criteria were issued, the Federal Water Pollution Control Act, required that water quality criteria be published by the Agency to protect the public health; no provisions are included in this section of the statute to incorporate social and economic factors in setting water quality criteria. Since thresholds could not be established for suspected carcinogens, quantitative risk assessment was used to recommend water quality concentrations associated with lifetime risk in a range from 10^{-7} to 10^{-5} at the upper bound. These concentrations were calculated by assuming an ingestion of two liters of drinking water per day plus the average intake of fish (6.5 g per day edible portion) to factor in bioaccumulation. The slope, presented in the second column of Table VIII, is calculated using the linearized multistage model (see Appendix). In the proposed criteria, the linear model was used to calculate the concentrations associated with increased individual lifetime risk of 10^{-5}. In response to public comment, the Agency reviewed alternative models and decided to adopt the linearized multistage model in order to make full use of all the data points.[9] The slope and the concentrations (in parentheses) in Table VIII were calculated using the one-hit model.[31, 32, 33] These values have been included so that the relative slopes can be compared. From these comparisons it is evident that the slopes derived from the one-hit model and from the multistage model are very close for most cases. Obviously, the weight of the biomedical evidence varies enormously for the chemicals presented in Table VIII, and this information should not be ignored in applying these target concentrations to local situations where the regulatory process of permitting discharges actually takes place.

A fifth example of risks for specific population subgroups inadvertently exposed to suspect carcinogens has not been included because most of these analyses have involved exposure from uncontrolled waste sites. Because legal action may follow, such analyses are generally not discussed until the conclusion of the cases. The approach to estimating risks for these exposed populations has been much the same as already discussed, and the use of the risk assessment information has likewise been employed in a similar way in each health-protective decision.

These examples illustrate the applications of quantitative risk assessment in a variety of practical circumstances to provide information regarding risk as a basis for making public health policy decisions in the United States. Between 1976 and 1983, the linear non-threshold model at the lower end of the dose-response curve was applied in hundreds of cases, such as those presented above, to assist policymakers who have to decide how much cost, in social and economic terms, should be expended to reduce risks to some reasonably low level. These policy decisions did not hinge on any "acceptable level" of risk; each decision reflected achievability in some measure. Nevertheless, most decisions reduced risks to near 10^{-5} increased individual lifetime cancer risk at the upper bound. There were some circumstances in which this level of risk was not achievable (e.g., in setting haloform standards for drinking water.[35] Such decisions, in which risks higher than 10^{-5} were accepted, generally were justified on grounds of social and economic tradeoffs, such as the protective value of chlorination of the drinking water supply to prevent infection. Risks lower than 10^{-5} generally were unregulated, as exemplified by the NTA decision, current acceptance of the residual vinyl chloride risk, and the acceptance of risk in the chlorobenzilate decision. Exceptions include the voluntary cancellation of safrole as a dog repellent (risk 10^{-7}) because of low benefits; required reduction of nitrosamine contamination in treflan (risk 10^{-7})[36]; and recommendation of water quality criteria associated with risks ranging from 10^{-7} to 10^{-5}.[9] In a large number of risk assessments on different chemicals performed during this period, the upper-bound risks fell into a relatively low risk range of $<10^{-5}$ for 80% to 90% of the cases studied. Uncertainties in exposure estimates, and other uncertainties inherent in the extrapolation process, need to be taken into account on a case-by-case basis. Despite these deficiencies, the use of upper-bound estimates to identify those cases where the risks may be so low, even at the upper bound, as to fall into a low-priority category for regulatory consideration, has helped regulators to

Table VIII. Guidance for Water Quality Criteria. Upper-Bound Calculations with a Lower Bound Approaching Zero[a]

Chemical	Upper-bound slope B_H (mg/kg/day)$^{-1}$[b]	Water concentrations corresponding to a risk level of 10^{-5} (μg/L) at the upper bound[b,c]
Acrylonitrile	0.6 (2.0)	0.6 (0.08)
Aldrin	11.4 (6.3)	7.4×10^{-4} (5×10^{-5})
Arsenic[d]	14.0	0.02
Asbestos	...	300,000 (fibers/L) (0.05)
Benzene[d]	0.1	7
Benzidine[d]	234.1	1×10^{-3}
Beryllium	4.9 (3.4)	0.1 (0.1)
Carbon tetrachloride	0.1 (0.1)	4 (3)
Chloroform	0.2 (0.2)	2 (2)
Chlordane	1.6 (5.4)	5×10^{-3} (1×10^{-3})
Chloroalkyl ethers		
BCME	9300 (13,600)	4×10^{-5} (2×10^{-5})
BCEE	1.1 (0.7)	0.3 (0.4)
Chlorinated benzenes		
HCB	1.7 (2.5)	7×10^{-3} (1×10^{-3})
Chlorinated ethanes		
1,2-di-	0.04 (0.05)	9 (7)
1,1,2-tri-	0.1 (0.1)	6 (3)
1,1,2,2-tetra-	0.2 (0.2)	2 (2)
Hexa-	0.01 (0.02)	19 (6)
Dichlorobenzine	2 (2)	0.1 (0.02)
DDT	8 (18)	2×10^{-4} (5×10^{-4})
Dichloroethylenes		
1,1-dichloroethylene	1 (0.3)	0.3 (1)
Dieldrin	30 (180)	7×10^{-4} (4×10^{-5})
Dinitrotoluene	0.3 (0.4)	1 (0.1)
Dioxins		
2,3,7,8-tetrachlorodioxin	4×10^{5} (1×10^{4})	2×10^{-9} (5×10^{-7})
Diphenylhydrazine	0.8 (0.7)	0.4 (0.4)
Halomethanes	Same as Chloroform	
Heptachlor	3 (30)	3×10^{-3} (2×10^{-4})
Hexachlorobutadiene	0.08 (0.05)	5 (1)
Hexachlorocyclohexane		
technical grade	5(2)	0.1 (0.02)
alpha isomer	11 (3)	0.02 (0.02)
beta isomer	2 (2)	0.1 (0.03)
gamma isomer	1 (1)	0.2 (0.05)
Nitrosamines		
DMNA	26 (13)	1×10^{-2} (3×10^{-2})
DENA	44 (38)	8×10^{-3} (9×10^{-3})
DBNA	5 (27)	0.1 (0.01)
N-N-P	2 (4)	0.2 (0.1)
PAH	12 (28)	3×10^{-2} (10×10^{-3})
PCBs	4 (3)	8×10^{-4} (3×10^{-4})
Tetrachloroethylene	0.04 (0.1)	8 (2.0)
Trichloroethylene	0.01 (0.01)	27 (21)
Toxaphene	1 (4)	7×10^{-3} (5×10^{-4})
Vinyl chloride[d]	0.02	20

[a] Federal Register 45:79318-79379 (November 28, 1980). This Water Quality Criteria guidance may be revised as new data become available.

[b] The parenthetical values, originally proposed, were calculated using the one-hit model. In response to public comment, these final calculations are derived from the linearized multistage model (34).

[c] Assuming a lifetime daily consumption of 2 liters of water and 6.5 g fish. (Note that a daily consumption of 18.7 g fish was assumed in the original calculation, and some of the bioconcentration factors used in the new calculations are different from original calculations as proposed.)

[d] Slope determined from epidemiological data.

focus attention on more compelling public health problems.

4. REFINING RISK ASSESSMENT APPROACHES: FUTURE TRENDS

Carcinogen risk assessment has provided the scientific basis for a range of policy decisions by Federal agencies responsible for the protection of public health in the United States. Quantitative risk estimates, generally expressed as upper-bound estimates using a linear non-threshold model, coupled with the qualitative evaluation of the weight of the biomedical evidence, have provided policymakers with rough estimates of risk which have served well as a basis for setting priorities and balancing risks and benefits. Protective public health standards for suspected carcinogens may be unduly conservative if agents have a concave dose-response curve or a threshold at low doses, or if some of the other assumptions relating animal to human data are unduly conservative (e.g., the use of surface area versus body weight conversion approaches to relate animal metabolism to human metabolism). Hence, quantitative risk assessment methods are under review to see what can be done to improve quantitative guidance for standard-setting purposes.

In addition, the experience of the EPA over the past decade includes misunderstandings when carcinogen risk assessments have been applied in policy considerations. First, where quantitative estimates have been provided, there has been a tendency to use these risk estimates and ignore the weight of the biomedical evidence, and to treat all suspected carcinogens as if they were known to be human carcinogens. Furthermore, upper-bound estimates in some cases have been treated as actual estimates of risk, and important statements regarding uncertainties have been neglected. Such misunderstandings can lead to errors in policy judgments.

Finally, as more information becomes available as a basis for establishing mutagenic potential for suspected carcinogens, there is an increasing interest in finding the best way to incorporate this information into guidance for establishing protective policies on these substances.

Because of these and related issues, thinking in the EPA is currently focused on (1) methods for stratifying the weight of the biomedical evidence (in qualitative assessment) to make it easier to use this information together with quantitative risk estimates; (2) criteria for judging the weight of evidence for mutagenicity so that mutagenic potential can be more clearly expressed; (3) possible approaches for making greater use of information on reversibility, pharmacokinetics, etc., in the risk assessment process; and (4) possible approaches for establishing quantitative guidance for chemicals where the upper-bound estimate may not be plausible, including a detailed review of various assumptions used in quantitative risk estimation. While the outcomes of this effort are uncertain, most likely the risk evaluation approaches that have been used to date will continue to be used, but with some refinements. These refinements will most likely involve: (1) the stratification of the evidence for carcinogenicity, (2) greater use of information about mutagenic potential and other relevant information about mechanisms of action and target tissue doses, and (3) clearer expressions of the uncertainty that results from the assumptions inherent in quantitative risk assessment.

APPENDIX. DESCRIPTION OF THE QUANTITATIVE RISK EXTRAPOLATION MODELS USED BY THE U.S. ENVIRONMENTAL PROTECTION AGENCY[3]

1. INTRODUCTION: CHOICE OF MODEL

There is no really solid scientific basis for any mathematical extrapolation model relating carcinogen exposure to cancer risks at the extremely low levels of concentration that must be dealt with in evaluating environmental hazards. For practical reasons, such low levels of risk cannot be measured directly using either animal experiments or epidemiologic studies. We must, therefore, depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which risk model to use. At the present time, the dominant view of the carcinogenic process involves the concept that most agents that cause cancer also cause irreversible damage to DNA. This position is reflected by the fact that a

[3]Adapted from "Water Quality Criteria Documents: Availability," *Federal Register*, Vol. 45, No. 231, Friday, November 28, 1980, pp. 79350–79353.

very large proportion of agents that cause cancer are also mutagenic. There is reason to expect that the quantal type of biological response characteristic of mutagenesis is associated with a linear non-threshold dose-response relationship. Indeed, there is substantial evidence (from mutagenesis studies with both ionizing radiation and a wide variety of chemicals) that this type of dose-response model is the appropriate one to use. This is particularly true at the lower end of the dose-response curve; at higher doses, there can be an upward curvature, probably reflecting the effects of multistage processes on the mutagenic response. The linear non-threshold dose-response relationship is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation-induced leukemia, breast and thyroid cancer[37, 38, 39, 40]; skin cancer induced by arsenic in drinking water[41]; and liver cancer induced by aflatoxin in the diet[42]). There is also some evidence from animal experiments that is consistent with the linear non-threshold hypothesis (e.g., the initiation stage of the two-stage carcinogenesis model in rat liver and mouse skin).

Because its scientific basis, although limited, is the best of any of the current mathematical extrapolation models, the linear non-threshold model has been adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. The risk assessments made with this model should be regarded as conservative, representing the most plausible upper limit for the risk (i.e., the true risk is not likely to be higher than the estimate, but it could be smaller).

2. THE MULTISTAGE MODEL

The mathematical formulation chosen to describe the linear non-threshold dose-response relationship at low doses is the modified multistage model developed by Crump.[43] This model employs enough arbitrary constants to be able to fit almost any monotonically increasing dose-response data, and it incorporates a procedure for estimating the largest possible linear slope (in the 95% confidence limit sense) at low extrapolated doses that is consistent with the data at all dose levels of the experiment. For this reason it may be called a "linearized" multistage model.

2.1. Procedure for Low-Dose Extrapolation Based on Animal Carcinogenicity Data

2.1.1. Description of the Extrapolation Model

Let $P(d)$ represent the lifetime risk (probability) of cancer at dose d. The multistage model has the form

$$P(d) = 1 - \exp\left[-\left(q_0 + q_1 d + q_2 d^2 + \cdots + q_k d^k\right)\right]$$

where

$$q_i > 0, \quad \text{and} \quad i = 0, 1, 2, \ldots, k$$

Equivalently,

$$A(d) = 1 - \exp\left[-\left(q_1 d + q_2 d^2 + \cdots + q_k d^k\right)\right]$$

where

$$A(d) = \frac{P(d) - P(0)}{1 - P(0)}$$

is the extra risk over background rate at dose d.

The point estimate of the coefficients q_i; $i = 0, 1, 2, \ldots, k$; and consequently the extra risk function $A(d)$; at any given dose d is calculated by maximizing the likelihood function of the data.

The point estimate and the 95% upper confidence limit of the extra risk $A(d)$ are calculated by using the computer program GLOBAL79 developed by Crump and Watson.[44] Upper 95% confidence limits on the extra risk and lower 95% confidence limits on the dose producing a given risk are determined from a 95% upper confidence limit q_1^* on a parameter q_1. Whenever $q_1 \neq 0$, at low doses the extra risk $A(d)$ has approximately the form $A(d) = q_1^* \times d$. Therefore, $q_1^* \times d$ is a 95% upper confidence limit on the extra risk and R/q_1^* is an approximate 95% lower confidence limit on the dose producing an extra risk of R. Let L_0 be the maximum value of the log-likelihood function. The upper limit q_1^* is calculated by increasing q_1 to a value q_1^*, such that when the log-likelihood is remaximized, subject to this fixed value q^* for the linear coefficient, the resulting maximum value of the log-likelihood L_1 satisfies the equation

$$2(L_0 - L_1) = 2.70554$$

where 2.70554 is the cumulative 90% point of the chi-square distribution with one degree of freedom, which corresponds to a 95% upper limit (one-sided). This approach of computing the upper confidence limit for the extra risk $A(d)$ is a modification of the Crump *et al.*[45] model. The upper confidence limit for the extra risk calculated at low doses is always linear. This is conceptually consistent with the linear non-threshold concept discussed earlier. The slope q_1^* is taken as an upper bound of the potency of the chemical in inducing cancer at low doses.

In fitting the dose-response model, the number of terms in the polynomial $g(d)$ is chosen equal to $(h-1)$, where h is the number of dose groups in the experiment including the control group.

Whenever the multistage model does not fit the data sufficiently, data at the highest dose are deleted and the model is refitted to the rest of the data. This is continued until an acceptable fit to the data is obtained. To determine whether or not a fit is acceptable, the chi-square

$$x^2 = \sum_{i=1}^{h} \frac{(X_i - N_i P_i)^2}{N_i P_i (1 - P_i)}$$

is calculated, where N_i is the number of animals in the i^{th} dose group, x_i is the number of animals in the i^{th} dose group with a tumor response, P_i is the probability of a response in the i^{th} dose group estimated by fitting the multistage model to the data, and h is the number of remaining groups. The fit is determined to be unacceptable whenever chi-square (X^2) is larger than the cumulative 99% point of the chi-square distribution with f degrees of freedom, where f equals the number of dose groups minus the number of non-zero multistage coefficients.

2.1.2. Selection and Form of Data used to Estimate Parameters in the Extrapolation Model

For some chemicals several studies in different animal species, strains, and sexes, each conducted at several doses and different routes of exposure, are available. A choice must be made as to which of the data sets from several studies are to be used in the model. It is also necessary to correct for metabolism differences between species and for differences in absorption via different routes of administration. The procedures listed below, used in evaluating these data, are consistent with the estimate of a maximum likely risk.

(a) The tumor incidence data are separated according to organ sites or tumor types. The set of data (i.e., dose and tumor incidence) used in the model is the set where the incidence is statistically significantly higher than the control for at least one test dose level and/or where the tumor incidence rate shows a statistically significant trend with respect to dose level. The data set that gives the highest estimate of lifetime cancer risk, q_1^*, is selected in most cases. However, efforts are made to exclude data sets that produce spuriously high risk estimates because of a small number of animals; that is, if two sets of data show a similar dose-response relationship and one has a very small sample size, the set of data which has the larger sample size is selected for calculating the carcinogenic potency.

(b) If there are two or more data sets of comparable size that are identical with respect to species, strain, sex, and tumor sites, the geometric mean of q_1^*, estimated from each of these data sets, is used for risk assessment. The geometric mean of numbers $A_1, A_2, \cdots, A_m$ is defined as $(A_1 \times A_2 \times \cdots \times A_m)^{1/m}$.

(c) If sufficient data exist for two or more significant tumor sites in the same study, the number of animals with at least one of the specific tumor sites under consideration is used as incidence data in the model.

(d) Following the suggestion of Mantel and Schneiderman,[46] we assume that mg/surface area/day is an equivalent dose between species. Since, to a close approximation, the surface area is proportional to the 2/3 power of the weight, as would be the case for a perfect sphere, the exposure in mg/2/3 power of the body weight/day is similarly considered to be an equivalent exposure. In an animal experiment this equivalent dose is computed in the following manner. Let:

L_e = duration of experiment
1_e = duration of exposure
m = average dose per day in mg during administration of the agent (i.e., during 1_e)
W = average weight of the experimental animal.

Then, the lifetime average exposure is

$$d = \frac{1_e \times m}{L_e \times W^{2/3}}$$

Often exposures are not given in units of mg/day, and it becomes necessary to convert the given exposures into mg/day. For example, in most feeding studies exposure is expressed as ppm in the diet. In this case the exposure (mg/day) is derived by

$$m = \text{ppm} \times F \times r$$

where ppm is parts per million of the carcinogenic agent in the diet, F is the weight of the food consumed per day in kg, and r is the absorption fraction.

In the absence of any data to the contrary, r is assumed to be one. For a uniform diet, the weight of the food consumed is proportional to the calories required, which in turn is proportional to the surface area of the 2/3 power of the weight, so that

$$m \propto \text{ppm} \times W^{2/3} \times r$$

or

$$\frac{m}{rW^{2/3}} \propto \text{ppm}$$

As a result, ppm in the diet is often assumed to be an equivalent exposure between species. However, we feel that this is not justified, since the calories/kg of food are significantly different in the diet of man as contrasted with that of laboratory animals, primarily due to differences in the moisture content of the foods eaten. Instead, we use an empirically derived food factor, $f = F/W$, which is the fraction of a species' body weight that is consumed per day as food. We use the rates given as follows:

Species	W	f
Man	70	0.028
Rat	0.35	0.05
Mouse	0.03	0.13

Thus, when the exposure is given as a certain dietary concentration in ppm, the exposure in mg/$W^{2/3}$ is

$$\frac{m}{r \times W^{2/3}} = \frac{\text{ppm} \times F}{W^{2/3}} = \frac{\text{ppm} \times f \times W}{W^{2/3}}$$

$$= \text{ppm} \times f \times W^{1/3}$$

When exposure is given in terms of mg/kg/day $= m/Wr = s$, the conversion is simply

$$\frac{m}{rW^{2/3}} = s \times W^{1/3}$$

When exposure is via inhalation, the calculation of dose can be considered for two cases where (1) the carcinogenic agent is either a completely water-soluble gas or an aerosol and is absorbed proportionally to the amount of air breathed in, and (2) the carcinogen is a poorly water-soluble gas which reaches an equilibrium between the air breathed and the body compartments. After equilibrium is reached, the rate of absorption of these agents is expected to be proportional to metabolic rate, which in turn is proportional to the rate of oxygen consumption, which in turn is a function of surface area.

Case 1. Agents that are in the form of particulate matter or virtually completely absorbed gases, such as SO_2, can reasonably be expected to be absorbed proportionally to the breathing rate. In this case the exposure in mg/day may be expressed as

$$m = I \times v \times r$$

where I is inhalation rate per day in m^3, v is mg/m^3 of the agent in air, and r is the absorption fraction.

The inhalation rates I for various species can be calculated from the observation that 25g mice breathe 34.5 liters/day and 113g rats breathe 105 liters/day.[47] For mice and rats of other weights W (expressed in kg), the surface area proportionality can be used to determine breathing rates (in m^3/day) as follows:

$$\text{For mice, } I = 0.0345\ (W/0.025)^{2/3}\ \text{m}^3/\text{day}$$

$$\text{For rats, } I = 0.105\ (W/0.113)^{2/3}\ \text{m}^3/\text{day}$$

For humans, the value of 20 m^3/day is adopted as a standard breathing rate.[48]

The equivalent exposure in mg/$W^{2/3}$ for these agents can be derived from the air intake data in a way analogous to the food intake data. The empirical factors for the air intake per kg per day, $i = I/W$, based upon the previously stated relationships, are as follows.

Species	W	$i = I/W$
Man	70	0.29
Rat	0.35	0.64
Mouse	0.03	1.3

Therefore, for particulates or completely absorbed gases, the equivalent exposure in $mg/W^{2/3}$ is

$$\frac{m}{W^{2/3}} = \frac{Ivr}{W^{2/3}} = \frac{iWvr}{W^{2/3}} = iW^{1/3}vr$$

In the absence of experimental information or a sound theoretical argument to the contrary, the fraction absorbed r is assumed to be the same for all species.

Case 2. The dose in mg/day of partially soluble vapors is proportional to O_2 consumption, which in turn is proportional to $W^{2/3}$ and to the solubility of gas in body fluids, which can be expressed as an absorption coefficient r for the gas. Therefore, when expressing O_2 consumption as $O_2 = kW^{2/3}$, where k is a constant independent of species, it follows that

$$m = kW^{2/3} \times v \times r$$

$$d = \frac{m}{W^{2/3}} = kvr$$

As with *Case 1*, in the absence of experimental information or a sound theoretical argument to the contrary, the absorption fraction r is assumed to be the same for all species. Therefore, for these substances a certain concentration in ppm or $\mu g/m^3$ in experimental animals is equivalent to the same concentration in humans. This is supported by the observation that the minimum alveolar concentration necessary to produce a given stage of anesthesia is similar in man and animals.[49] When the animals were exposed via the oral route, and human exposure is via inhalation (or vice versa), the assumption is made, unless there is pharmacokinetic evidence to the contrary, that absorption is equal by either exposure route.

(e) If the duration of the experiment L_e is less than the natural life-span of the test animal L the slope q_1^* or more generally the exponent $g(d)$ is increased by multiplying a factor $(L/L_e)^3$. We assume that if the average dose d is continued, the age-specific rate of cancer will continue to increase as a constant function of the background rate. The age-specific rates for humans increase at least by the 2nd power of the age and often by a considerably higher power, as demonstrated by Doll.[50] Thus, we would expect the cumulative tumor rate to increase by at least the 3rd power of age. Using this fact, we assume that the slope q_1^* or more generally the exponent $g(d)$ would also increase by at least the 3rd power of age. As a result, if the slope q_1^* [or $g(d)$] is calculated at age L_e, we would expect that if the experiment had been continued for the full life span L at the given average exposure, the slope q_1^* [or $g(d)$] would have been increased by at least $(L/L_e)^3$.

This adjustment is conceptually consistent with the proportional hazard model proposed by Cox[51] and the time-to-tumor model considered by Crump and Watson,[44] in which the probability of cancer by age t and at dose d is given by

$$P(d,t) = 1 - \exp[-f(t) \times g(d)]$$

3. CALCULATION OF CARCINOGENIC POTENCY BASED ON HUMAN DATA

If human epidemiologic studies and sufficiently valid exposure information are available for the compound, they are always used in some way. If they show a carcinogenic effect, the data are analyzed to give an estimate of the linear dependence of cancer rates on lifetime average dose, which is equivalent to the factor q_1^*. If they show no carcinogenic effect when positive animal evidence is available, then it is assumed that a risk does exist, but it is smaller than could have been observed in the epidemiologic study; and an upper limit of cancer incidence is calculated assuming hypothetically that the true incidence is just below the level of detection in the cohort studied, which is determined largely by the cohort size. Whenever possible, human data are used in preference to animal bioassay data.

In human studies, the response is measured in terms of the relative risk of the exposed cohort of individuals compared to the control group. In the analysis of this data, it is assumed that the excess risk, or relative risk minus one $R(X)-1$ is proportional to the lifetime average exposure X, and that it is the same for all ages. It follows that the carcinogenic potency is equal to $[R(X)-1]/X$ multiplied by the lifetime risk at that site in the general population. Except for an unusually well-documented human study, the confidence limit for the excess risk is not calculated, due to the difficulty in accounting for the uncertainty inherent in the data (exposure and cancer response).

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