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Proposed Guidelines for Carcinogen Risk Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-4]

Proposed Guidelines for Carcinogen Risk Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Carcinogen Risk Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Carcinogen Risk Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of carcinogenicity data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Carcinogen Assessment Group (CAG) as the Agency's senior health committee for carcinogenicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the Chairman of CAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESS: Comments may be mailed or delivered to: Dr. Robert McGaughy, Carcinogen Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: Dr. Robert McGaughy, Telephone: 202-382-5952.

SUPPLEMENTARY INFORMATION: This is the first proposed revision of the 1976 Interim Procedures and Guidelines for the Health Risk Assessment of Suspected Carcinogens (Federal Register 41:21402-21405, 1976). This revision incorporates concepts and approaches to carcinogen assessment that have been developed during the last eight years. These proposed revised Guidelines describe salient principles for evaluating the nature and magnitude of the cancer hazard from suspect carcinogens and general framework to be followed in developing analyses of carcinogenic risk.

These Guidelines were sent to 38 scientists in the field of carcinogenesis from universities, environmental groups, industry, labor, and governmental agencies. We have decided to delay incorporating suggestions from the 26 reviewers who submitted comments into the Guidelines published here until comments submitted during this public comment period are received.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street SW., Washington, DC, between the hours of 8:00 and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

Contents

I. Introduction

This is the first revision of the 1976 Interim Procedures and Guidelines for Health Risk Assessments of Suspected Carcinogens (U.S. EPA, 1976; Albert et al., 1977). The impetus for this revision is the need to incorporate into these Guidelines the concepts and approaches to carcinogen risk assessment that have been developed during the last eight years. The purpose of these Guidelines is to promote quality and consistency of carcinogen risk assessments within the EPA and to inform those outside the EPA about its approach to carcinogen risk assessment. These Guidelines emphasize the broad but essential aspects of risk assessment that are needed by the experts in the various disciplines required (e.g., toxicology, pathology, pharmacology, and statistics) for carcinogen assessment. Guidance is given in general terms since the science of carcinogenesis is in a state of rapid advancement, and overly specific approaches may rapidly become obsolete.

These Guidelines describe the general framework to be followed in developing an analysis of carcinogenic risk and some salient principles to be used in evaluating the quality of data and in formulating judgments concerning the nature and magnitude of the cancer hazard from suspect carcinogens.

A summary of the current state of knowledge in the field of carcinogenesis and a statement of broad scientific principles of carcinogen risk assessment, which was developed by the Office of Science and Technology Policy (OSTP, 1984), forms an important basis for these Guidelines; the format of these Guidelines is similar to that proposed by the National Research Council (NRC) of the National Academy of Sciences in a report entitled "Risk Assessment in the Federal Government" (NRC, 1983).

These Guidelines are to be used within the policy framework already provided by applicable EPA statutes and do not alter such policies. These Guidelines provide general directions for analyzing and organizing available data. They do not imply that one kind of data or another is a prerequisite for regulatory action to control, prohibit, or allow the use of a carcinogen. The analysis of carcinogenic risks will be carried out independently from considerations of the socioeconomic consequences of regulatory action.

Regulatory decisionmaking involves two components: Risk assessment and risk management. Risk assessment defines the adverse health consequences of exposure to toxic agents; risk management combines the risk assessment with the directives of the enabling regulatory legislation, together with socioeconomic, technical, political, and other considerations, to reach a decision as to whether or how much to control future exposure to the suspected toxic agents.

Risk assessment includes one or more of the following components: hazard identification, dose-response

assessment, exposure assessment, and risk characterization (NRC, 1983).

Hazard identification is a qualitative risk assessment, dealing with the process of determining whether exposure to an agent has the potential to increase the incidence of cancer. For purposes of these Guidelines, malignant and benign tumors are used in the evaluation of the carcinogenic hazard. The hazard identification component qualitatively answers the question of how likely an agent is to be a human carcinogen.

Traditionally, quantitative risk assessment has been used as an inclusive term to describe all or parts of dose-response assessment, exposure assessment, and risk characterization. Quantitative risk assessment can be a useful general term in some circumstances, but the more explicit terminology is usually preferred. The dose-response assessment defines the relationship between the dose of an agent and the probability of induction of a carcinogenic effect. This component usually entails an extrapolation from the generally high doses administered to experimental animals or exposures noted in epidemiologic studies to the exposure levels expected from human contact with the agent in the environment; it also includes considerations of the validity of these extrapolations.

The exposure assessment identifies populations exposed to the agent, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent.

In risk characterization, the outputs of the exposure assessment and the dose-response assessment are combined to estimate quantitatively some measure of the carcinogenic risk. As part of risk characterization, a summary of the strengths and weaknesses in the hazard identification, dose-response assessment, exposure assessment, and the public health risk estimates are presented. Major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties embodied in the assessment are also presented, distinguishing clearly between fact, assumption, and science policy.

II. Hazard Identification (Qualitative Risk Assessment)

A. Overview

The qualitative assessment or hazard identification part of risk assessment contains a review of the relevant biological land chemical information bearing on whether or not an agent may pose a carcinogenic hazard. Since chemical agents seldom occur in a pure state and are often transformed in the body, the review should include information on contaminants, degradation products, and metabolites.

Studies are evaluated according to sound biological and statistical considerations and procedures. These have been described in several publications (Interagency Regulatory Liaison Group, 1979; OSTP, 1984; Peto et al., 1980; Mantel, 1980; Mantel and Haenszel, 1959; Interdisciplinary Panel on Carcinogenicity, 1984; National Center for Toxicological Research, 1981; National Toxicology Program, 1984; U.S. EPA, 1983a; 1983b; 1983c). Results and conclusions concerning the agent, derived from different types of information, whether indicating positive or negative responses, are melded together into a weight-of-evidence determination. The strength of the evidence supporting a potential human carcinogenicity judgment is developed in a weight-of-evidence stratification scheme.

B. Elements of Hazard Identification

1. Physical-Chemical Properties and Routes and Patterns of Exposure

Parameters relevant to carcinogenesis, including physical state, physical-chemical properties, and exposure pathways in the environment should be described.

2. Structure-Activity Relationships

This section should summarize relevant structure-activity correlations that support the prediction of potential carcinogenicity.

3. Metabolic and Pharmacokinetic Properties

This section should summarize relevant metabolic information. Information such as whether the agent is direct-acting or requires conversion to a reactive carcinogenic (e.g., an electrophilic) species, metabolic pathways for such conversions, macromolecular interactions, and transport in, fate in, and excretion from the body as well as species differences in metabolism should be discussed.

4. Toxicologic Effects

Toxicologic effects other than carcinogenicity (e.g., suppression of the immune system, endocrine disturbances, organ damage), which are relevant to the evaluation of carcinogenicity, should be summarized. Prechronic and chronic toxicity evaluations, as well as other test results, may yield information on target organ effects, pathophysiological reactions, and preneoplastic lesions that bear on the evaluation of carcinogenicity. Dose-response and time-to-response analyses of these reactions may also be helpful.

5. Short-Term Tests

Tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and *in vitro* transformation provide supportive evidence of carcinogenicity and may give information on potential carcinogenic mechanisms. A range of tests from each of the above end points helps to characterize an agent's response spectrum.

Short-term *in vivo* and *in vitro* tests that can give indication of initiation and promotion activity may also provide supportive evidence for carcinogenicity.

6. Long-Term Animal Studies

Criteria for the technical adequacy of animal carcinogenicity studies have been published (e.g., U.S. Food and Drug Administration, 1982; Interagency Regulatory Liaison Group, 1979; National Toxicology Program, 1984; OSTP, 1984; U.S. EPA, 1983a; 1983b; 1983c; Feron et al., 1980; Mantel, 1980) and should be used to judge the acceptability of individual studies.

The strength of the evidence that an agent is carcinogenic increases with the increase in number of tissue sites affected by the agent; the increase in number of animal species, strains, and sexes showing a carcinogenic response; the occurrence of clear-cut dose-response relationships as well as a high level of statistical significance of the increased tumor incidence is treated with respect to control groups; the dose-related shortening of the time-to-tumor occurrence or time to death with tumor, and a dose-related increase in the proportion of tumors that are malignant.

Long-term animal studies at or near the maximum tolerated dose level (MTD) are used to ensure an adequate power for the detection of carcinogenic activity. Negative long-term animal studies at exposure levels above the MTD or partial lifetime exposures at the MTD may not be acceptable because of toxicity, or if animal survival is so impaired that the sensitivity of the study is significantly reduced below that of a conventional chronic animal study at the MTD. Positive studies at levels above the MTD should be carefully reviewed to ensure that the responses are not due to factors which do not operate at exposure levels below the MTD. Evidence indicating that high-dose testing produces tumor responses by indirect mechanisms that may be

unrelated to effects at lower does should be dealt with on an individual basis.

The mechanism of the carcinogenic responses under conditions of the experiment should be reviewed carefully as it relates to the relevance of the evidence to human carcinogenic risks (e.g., the occurrence of bladder tumors in the presence of bladder stones and injection site sarcomas). Interpretation of animal studies is aided by the review of target organ toxicity and other effects (e.g., changes in the immune and endocrine systems) that may be noted in prechronic or other toxicological studies. Time and dose-related changes in the incidence of preneoplastic lesions may also be helpful in interpreting animal studies.

Historical control data are often valuable and could be used along with concurrent control data in the evaluation of carcinogenic responses. For the evaluation of rare tumors, even small tumor responses may be significant compared to historical data. In the case of tumors with relatively high spontaneous rates, a response that is significant with respect to the experimental control group becomes questionable if the historical control data indicate that the experimental control group had an unusually low background incidence.

Agents that are positive in long-term animal experiments and also show evidence of promoting or cocarcingenic activity in specialized tests should be considered as complete carcinogens unless there is evidence to the contrary. Agents that show positive results in special tests for initiation, promotion, or cocarcingenicity and no indication of tumor response in well-conducted and well-designed long-term animal studies should be dealt with on an individual basis.

There are widely diverging scientific views (OSTP, 1984; Ward et al. 1979a; 1979b; Tomatis, 1977; Nutrition Foundation, 1983) about the validity of mouse liver tumors when such tumors occur in strains with high spontaneous background incidence and when they constitute the only tumor response to an agent. These Guidelines take the position that the mouse-liver-only tumor response, when other conditions for a classification of "sufficient" evidence in animal studies are met, should be considered as "sufficient" evidence of carcinogenicity with the understanding that this classification could be changed to "limited" if warranted when a number of factors such as the following are observed: The occurrence of tumors only in the highest dose group and/or only at the end of the study; no substantial dose-related increase in the proportion of tumors that are malignant; the occurrence of tumors that are predominately benign, showing no evidence of metastases or invasion; no dose-related shortening of the time to the appearance of tumors; negative or inconclusive results from a spectrum of short-term tests for mutagenic activity; the occurrence of excess tumors only in a single sex.

Positive carcinogenic responses in one species/strain/sex are not generally negated by negative results in other species/strain/sex. Replicate negative studies that are essentially identical in all other respects to a positive study may indicate that the positive results are spurious.

Evidence for carcinogenic action should be based on the observation of statistically significant tumor responses in specific organs or tissues. Appropriate statistical analysis should be performed on data from long-term studies to help determine whether the effects are treatment-related or possibly due to chance. These should at least include a statistical test for trend, including appropriate correction for differences in survival. The weight to be given to the level of statistical significance (the p-value) and to other available pieces of information is a matter of overall scientific judgment. A statistically significant excess of tumors of all types in the aggregate, in the absence of a statistically significant increase of any individual tumor type should be regarded as minimal evidence of carcinogenic action unless there are persuasive reasons to the contrary.

7. Human Studies

Epidemiologic studies provide unique information about the response of humans who have been exposed to suspect carcinogens. Descriptive epidemiologic studies are useful in generating hypotheses and providing supporting data, but can rarely be used to make a causal inference. Analytical epidemiologic studies of the case-control or cohort variety, on the other hand, are especially useful in assessing risks to exposed humans.

Criteria for the adequacy of epidemiologic studies are well recognized and include factors such as the proper selection and characterization of exposed and control groups, the adequacy of duration and quality of follow-up, the proper identification and characterization of confounding factors and bias, the appropriate consideration of latency effects, and the valid ascertainment of the causes of morbidity and death.

The strength of the epidemiologica evidence for carcinogenicity depends on the magnitude, specificity, and statistical significance of the response and increases rapidly with the number of adequate studies which show the same results on populations exposed to the same agent under different conditions.

It should be recognized that epidemiologic studies are inherently capable of detecting only comparatively large increases in the relative risk of cancer. Negative results from such studies cannot prove the absence of carcinogenic action; however, negative results from a well-designed and conducted epidemiologic study that contains usable exposure data can serve to define upper limits of risk which are useful if animal evidence indicates that the agent is potentially carcinogenic.

C. Weight of Evidence

Evidence of possible carcinogenicity in humans comes primarily from two sources: Long-term animal tests and epidemiologic investigations. Results from these studies are supplemented with information from short-term tests, pharmacokinetic studies, comparative metabolism studies, structure-activity relationships, and other relevant toxicologic studies. The question of how likely an agent is to be a human carcinogen should be answered in the framework of a weight-of-evidence judgment. Judgments about the weight of evidence involve considerations of the quality and adequacy of the data and the kinds of responses induced by a suspect carcinogen. There are three major steps to characterizing the weight of evidence for carcinogenicity: (1) Characterization of the evidence from human studies and from animal studies individually, (2) combination of the characterizations of these two types of data into a final indication of the overall weight of evidence for human carcinogenicity, and (3) evaluation of all supportive information to determine if the overall weight of evidence should be modified.

A system for stratifying the weight of evidence is recommended, and EPA has developed a scheme (see the Appendix). The EPA scheme is modeled after the classification system developed by the International Agency for Research on Cancer (IARC, 1982). In the IARC classification method, the evidence that an agent produces cancer in humans is divided into three categories: Sufficient, limited, and inadequate. A similar characterization of evidence is provided for animal data.

The EPA classification system is, in general, an adaptation of the IARC approach for classifying the weight of

evidence for human data and animal data. The EPA classification system for the characterization of the overall weight of evidence for carcinogenicity (animal, human, and other supportive data) includes: Group A—Carcinogenic to Humans; Group B—Probably Carcinogenic to Humans; C—Possibly Carcinogenic to Humans; Group D—Not Classifiable as to Human Carcinogenicity; and Group E—No Evidence of Carcinogenicity for Humans.

In addition, the following modifications of the IARC approach have been made for classifying human and animal studies. For human studies: (1) The observation of a statistically significant association between an agent and life-threatening benign tumors in humans is included in the evaluation of risks to humans. (2) A "no evidence" category is added. This category indicates that no association was found between exposure and increased risk of cancer in well-conducted, well-designed, independent analytical epidemiologic studies. For animal studies: (1) An increased incidence of combined benign and malignant tumors will be considered to provide sufficient evidence of carcinogenicity if the other criteria defining the "sufficient" category of evidence are met. Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type. (2) An increased incidence of benign tumors alone as "limited" evidence of carcinogenicity is added. (3) Under specific circumstances, such as the production of neoplasms that occur with high spontaneous background incidence, the evidence may be decreased to "limited" if warranted (e.g., there are widely diverging scientific views regarding the validity of the mouse liver tumors as an indicator of potential human carcinogenicity when this is the only response observed, even in replicated experiments, in the absence of other short-term evidence). (4) A "no evidence" category is also added. This operational category would include substances for which there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies of adequate power and dose in different species.

D. Guidance For Quantitative Assessment

The qualitative evidence for carcinogenesis should be discussed for purposes of guiding the dose-response assessment. The guidance should be given in terms of the appropriateness and limitation of specific studies as well as pharmacokinetic considerations that should be factored into the dose-response assessment. The appropriate method of extrapolation should be factored in when the experimental route of exposure differs from that occurring in humans.

Agents that are judged to be in the EPA weight-of-evidence stratification Groups A and B would be regarded as suitable for quantitative risk assessments. The appropriateness of quantifying the risks from agents in Group C, specifically those agents that are at the boundary of Groups C and D, would be judged on a case-by-case basis. Agents that are judged to be in Groups D and E would generally not have quantitative risk assessments.

E. Summary and Conclusion

The summary should present all of the key findings in all of the sections of the qualitative assessment and the interpretive rationale that forms the basis for the conclusion. Uncertainties in the evidence as well as factors that may affect the relevance of the chronic animal study to humans should be discussed. The conclusion should present both the weight-of-evidence rankng and a description that brings out the more subtle aspects of the evidence that may not be evident from the ranking alone.

III. Dose-Response Assessment, Exposure Assessment, and Risk Characterization

After data concerning the carcinogenic properties of a substance have been collected, evaluated, and categorized, it is frequently desirable to estimate the likely range of excess cancer risk associated with given levels and conditions of human exposure. The first step of the analysis needed to make such estimations is the development of the likely relationship between dose and response (cancer incidence) in the region of human exposure. This information on dose-response relationships is coupled with information on the nature and magnitude of human exposure to yield an estimate of human risk. The risk-characterization step also includes an interpretation of these estimates in light of the biological, statistical, and exposure assumptions and uncertainities that have arisen throughout the process of assessing risk.

The elements of dose-response assessment are described in section III.A. Guidance on human exposure assessment is provided in another EPA document (U.S. EPA, 1984); however, section III.B. of these Guidelines includes a brief description of the specific type of exposure information that is necessary for use in carcinogenic risk assessment. Finally, in section III.C. there is a description of the type of information and its interpretation necessary for accurately characterizing risk and the degree to which it can be known.

It should be emphasized that calculation of quantitative estimates of cancer risk does not require that an agent be a human carcinogen. The likelihood that an agent is a human carcinogen is a function of the weight of evidence, as this has been described in the hazard identification section of these Guidelines. It is nevertheless important to present quantitative estimates, appropriately qualified and interpreted, in those circumstances in which there is likelihood that the agent is a human carcinogen. Appropriately qualified quantitative estimates of risk, together with estimates of their uncertainty, are useful in cost-benefit analyses, in setting regulatory priorities, and for evaluating residual risks associated with the application of regulatory controls.

It should be emphasized in every quantitative risk estimation that the results are uncertain. The uncertainties due to experimental and epidemiologic variability as well as uncertainty in the exposure assessment can be important. There are major uncertainties in extrapolating both from animals to humans and from high to low doses. There are important species differnces in uptake, metabolism, and organ distribution of carcinogens, as well as species and strain differences in target site susceptibilty. Human populations are variable with respect to genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors. Risk estimates should be presented together with the associated hazard assessment (section III.C.3.) to ensure that there is an appreciation of the weight of evidence for carcinogenicity that underlies the quantitative risk estimates.

A. Dose-Response Assessment

1. Selection of Data

As indicated in section II.D. guidance needs to be given by the individuals doing the qualitative assessment (toxicologists, pathologists, pharmacologists, etc.) to the statisticans doing the quantitative assessment as to the appropriate data to be used in the dose-response assessment. This is determined by the quality of the data, its relevance to human modes of exposure, and other technical details.

If available, estimates based upon human epidemiologic data are preferred. If adequate exposure data exist in a well-designed and conducted negative epidemiologic study, an upper-bound estimate of risk should be used in preference to higher risks estimated from animal data. In the absence of human data, data from a species that responds most like humans should be used, if information to this effect exists. Where, for a given agent, several studies are available which may involve different animal species, strains, and sexes, at several doses and by different routes of exposure, the following approach to selecting the data sets is used. The tumor incidence data are separated according to organ site and tumor type. All biologically and statistically acceptable data sets are presented. The range of the risk estimates is identified with due regard to biological relevance (particularly in the case of animal studies) and appropriateness of route of exposure. Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical considerations.

When the exposure route in the species from which the dose-response information is obtained differs from the route occurring in environmental exposures, uncertainties about the dose delivered to the target organs from different exposure media should be explicitly considered, and the assumptions should be carefully stated.

Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation; if the tumor sites or types are occurring idependently, this procedure is the same as summing the risks from the several kinds of statistically significant tumors. The pooled estimates will generally be used in preference to risk estimates based on single sites or types.

Benign tumors should generally be combined with malignant tumors for risk estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type. However, the contribution of the benign tumors to the total risk should be indicated.

2. Choice of Mathematical Extrapolation Model

Since risks at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low dose. However, different extrapolation models may fit the observed data reasonably well but may lead to large differences in the projected risk at low doses.

No single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action exists, the models or procedures employed should be consistent with the evidence. However, when data and information are limited, as is the usual case given the high degree of uncertainty associated with the selection of a low-dose extrapolation model, specific guidance on model selection is necessary to provide a desirable degree of consistency in risk assessments. The choice of low-dose extrapolation models should be consistent with current understanding of the mechanisms of carcinogenesis and not solely on goodness of fit to the observed tumor data. Although mechanisms of the carcinogenesis process are largely unknown, at least some elements of the process have been elucidated, e.g., linearity of tumor initiation. In further support of a linear model, it has been shown that, if a carcinogenic agent acts by accelerating the same stages of the carcinogenic process that lead to the background occurrence of cancer, the added effect of the carcinogen at low dose is virtually linear. Thus, a model that is linear at low dose is plausible.

The linearized multistage model procedure for low-dose extrapolation (U.S. EPA, 1980) is therefore recommended in most cases unless there is evidence on carcinogenesis mechanisms or other biological evidence that indicates the greater suitability of an alternative extrapolation model, or there is statistical or biological evidence that excludes the use of the linearized multistage model.

It should be emphasized that the linearized multistage model leads to a plausible upper limit to the risk which is consistent with some mechanisms of carcinogenesis. However, such an estimate does not necessarily give a realistic prediction of the risk. In certain cases, the linearized multistage model cannot be used successfully with the observed data as, for example, when the data are nonmonotonic or flatten out at high doses. In these cases it may be necessary to make adjustments to the procedure to achieve low-dose linearity.

When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a different low-dose extrapolation model might be considered more appropriate on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and strength of the evidence that lead to the choice. In most cases, considerable uncertainty will remain concerning response at low doses; therefore, an upper-limit risk estimate using the linearized multistage model should also be presented.

3. Equivalent Exposure Units Among Species

Low-dose risk estimates derived from laboratory animal data extrapolated to humans are complicated by a variety of factors that differ among species and potentially affect the response to carcinogens. Included among these factors are differences between humans and experimental test animals with respect to life span, body size, genetic variability, population homogeneity, existence of concurrent disease, pharmacokinetic effects such as metabolism and excretion patterns, and the exposure regimen.

The usual approach for making interspecies comparisons has been to use standardized scaling factors. Commonly employed standardized dosage scales include mg per kg body weight per day, ppm in the diet or water, mg per m^2 body surface area per day, and mg per kg body weight per lifetime. In the absence of comparative toxicological, physiological, metabolic, and pharmacokinetic data for a given suspect carcinogen, the extrapolation of body weight to the 0.67 power is considered to be appropriate.

B. Exposure Assessment

In order to obtain a quantitative estimate of the risk, the results of the dose-response assessment must be combined with an estimate of the exposures to which the populations of interest are likely to be subject. While the reader is referred to the Proposed Guidelines for Exposure Assessment (U.S. EPA, 1984) for specific details, it is important that the cancer risk assessor and the decision-maker have an appreciation of the impact of the

strengths and weaknesses of exposure assessment on the overall cancer risk assessment process.

At present there is no single approach to exposure assessment that is appropriate for all cases. On a case-by-case basis, appropriate methods are selected to match the data on hand and the level of sophistication required (e.g., preliminary assessment using crude data and worst case assumptions versus a final assessment using extensive monitoring data). The assumptions, approximations, and uncertainties need to be clearly stated because, in some instances, these will have a major effect on the risk assessment.

In general, the magnitude, duration, and frequency of exposure provide fundamental information for estimating the concentration of the carcinogen to which the organism is exposed. These data are generated from monitoring information, modeling results, and/or reasoned estimates. An appropriate treatment of exposure should consider the potential for exposure via ingestion, inhalation, and dermal penetration from relevant sources of exposures. Where feasible, an attempt should be made to assess the dose to the target organ, either through experimental evidence or reasonable assumptions and modeling.

Special problems arise when the human exposure situation of concern suggests exposure regimens, e.g., route and dosing schedule, which are substantially different from those used in the relevant animal studies. Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is recommended as the appropriate measure of exposure to a carcinogen. That is, the assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a coresponding low dose spread over a lifetime. This approach becomes more problematical as the exposures in question become more intense but less frequent, especially when there is evidence that the agent has shown dose-rate effects.

An attempt should be made to assess the level of uncertainty associated with the exposure assessment which is to be used in a cancer risk assessment. This measure of uncertainty should be included in the risk characterization (section III.C.) in order to provide the decision-maker with a clear understanding of the impact of this uncertainty on any final quantitative risk estimate.

C. Risk Charcterization

1. Options for Numerical Risk Estimates

Depending on the needs of the individual program offices, numerical estimates can be presented in one or more of the following three ways.

a. Unit Risk—Under an assumption of low-dose linearity, the unit cancer risk is the excess lifetime risk due to a continuous constant lifetime exposure of one unit of carcinogen concentration. Typical exposure units include ppm or ppb in food or water, mg/kg/day by ingestion, or ppm or ug/m ^{3} in air.

b. The Dose Corresponding to a Given Level of Risk—This approach can be useful, particularly when using nonlinear extrapolation models where the unit risk would differ at different dose levels.

c. Individual and Population Risks—Risk may be characterized either in terms of the excess individual lifetime risks or the excess number of cancers produced per year in the exposed population or both.

Irrespective of the options chosen, the degree of precision and accuracy in the numerical risk estimates currently do not permit more than one significant figure to be presented.

2. Concurrent Exposure

In characterizing the risk due to concurrent exposure to several carcinogens, the risks are combined on the basis of additivity unless there is specific information to the contrary. Interactions of cocarcinogens, promoters, and inititators with known carcinogens should be considered on a case-by-case basis.

3. Summary of Risk Characterization

Whichever method of presentation is chosen, it is critical that the numerical estimates not be allowed to stand alone, separated from the various assumptions and uncertainties upon which they are based. The risk characterization should contain a discussion and interpretation of the numerical estimates that affords the risk manager some insight into the degree to which the quantitative estimates are likely to reflect the true magnitude of human risk, which generally cannot be known with the degree of quantitative accuracy reflected in the numerical estimates. The final risk estimate will be generally rounded to one significant figure and will be coupled with the EPA classification of the qualitative weight of evidence. For example, a lifetime individual risk of 2×10^{-4} resulting from exposure to a "possible human carcinogen" (Group C) should be designated as:

$2 \cdot 10^{-4}$ [C]

This bracketed designation of the qualitative evidence should be included with all numerical risk estimates (i.e., unit risks, which are risks at a specified concentration, or concentrations corresponding to a given risk). Agency statements, such as Federal Register notices, briefings, and action memoranda, frequently include numerical estimates of carcinogenic risk. It is recommended that whenever these numerical estimates are used, the qualitative weight-of-evidence classification should also be included.

IV. Appendix—EPA Classification System for Evidence of Carcinogenicity From Human Studies and From Animal Studies (Adapted From IARC)

A. Assessment of Evidence for Carcinogenicity From Studies in Humans

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the agent(s).

2. Descriptive epidemiologic studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agent(s).

3. Analytical epidemiologic (case-control and cohort) studies in which individual exposure to the agent(s) was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.

2. The possibility of confounding has been considered and ruled out as explaining the association.

3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity* from studies in humans are categorized as:

1. Sufficient evidence of

*For purpose of public health protection, agents associated with life-threatening benign tumors in humans are included in the evaluation.

carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. Inadequate evidence, which indicates that one of two conditions prevailed: (a) There were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding.

4. No evidence, which indicates that no association was found between exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiologic studies.

5. No data, which indicates that data are not available.

B. Assessment of Evidence for Carcinogenicity From Studies in Experimental Animals

These assessments are classified into five groups:

1. Sufficient evidence* of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors§: (a) In multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) The studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only.

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

4. No evidence, which indicates that there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies in different species.

5. No data, which indicates that data are not available.

The categories "sufficient evidence" and "limited evidence" refer only to the strength of the experimental evidence that these agents(s) are carcinogenic and not to the power of their carcinogenic action.

C. Categorization of Overall Evidence

Group A—Human Carcinogen

This category is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agent(s) and cancer.

Group B—Probable Human Carcinogen

This category includes agents for which the evidence of human carcinogenicity from epidemiologic studies ranges from almost "sufficient" to "inadequate." To reflect this range, the category is divided into higher (Group B1) and lower (Group B2) degrees of evidence. Usually, category B1 is reserved for agents for which there is at least limited evidence of carcinogenicity to humans from epidemiologic studies. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard agents for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. Therefore, agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies would usually result in a classification of B2.

In some cases, the known chemical or physical properties of an agent and the results from short-term tests allow its transfer from Group B2 to B1.

Group C—Possible Human Carcinogen

This category is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence: (a) Definitive malignant tumor response in a single well-conducted experiment, (b) marginal tumor response in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) marginal responses in a tissue known to have a high and variable background rate.

In some cases, the known physical or chemical properties of an agent and results from short-term tests allow a transfer from Group C to B2 or from Group D to C.

Group D—Not Classified

This category is used for agent(s) with inadequate animal evidence of carcinogenicity.

Group E—No Evidence of Carcinogenicity for Humans

This category is used for agent(s) that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies.

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*Under specific circumstances, such as the production of neoplasms that occur with high spontaneous background incidence, the evidence may be decreased to "limited" if warranted (e.g., there are widely diverging scientific views regarding the validity of the mouse liver tumor as an indicator of potential human carcinogenicity when this is the only response observed, even in replicated experiments in the absence of short-term or other evidence).

§Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type.

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