ATSDR - Cancer Policy Framework

Historical Document

January 1993

Note: While the original publication dates on some of ATSDR's documents may not appear to be current, the information in the documents is valid and may still provide relevant information.

Table of Contents

Acknowledgments

The Cancer Policy Framework was developed by a workgroup comprised of the following individuals:

Christopher DeRosa, Ph.D. (Chairman)
Dennis Jones, D.V.M.
Kenneth Orloff, Ph.D.
Fred Rosenberg, D.O.
Robert Spengler, Sc.D.
Yee-Wan Stevens, M.S.
Allan Susten, Ph.D., D.A.B.T.
Steve Von Allmen, M.A.
Charles Xintaras, Sc.D.

The editorial assistance of **Ms. Anne Olin** and the secretarial assistance of **Ms. Markitia Hawley** and **Ms. Sandra Malcom** are gratefully acknowledged.

Foreword

Cancer remains at the forefront of public health concerns in the United States and throughout the world. Over the past 20 years a wide range of federal agencies and other organizations have been involved in developing policy statements, classification strategies, and assessment methods to address

carcinogenesis and health risks. Each of these documents was developed in response to issues confronted by those organizations in pursuing their mission, often as a direct function of legislative mandates.

In pursuing its mandated responsibilities, the Agency for Toxic Substances and Disease Registry (ATSDR) must address public health concerns associated with exposure to carcinogens in the context of all available relevant information. This information includes both technical data as well as science policy positions adopted by the range of organizations with programs germane to the assessment and/or regulation of carcinogens. Because of distinct differences in perspective, practice, and policy dictated by the mandated activities of these organizations and the rapidly evolving understanding of carcinogenesis, apparently divergent positions may be reflected in their conclusions.

The differences outlined above, coupled with requests from the public, other agencies, and the private sector for a statement reflecting the Agency's position on science and science policy issues related to cancer, prompted the development of this policy framework. This document is intended to serve as a framework to guide the Agency in its programs and actions regarding carcinogens and to harmonize such efforts with those of other federal agencies and relevant organizations. This framework reflects an assessment of current practice within the Agency and defines the appropriate roles of conclusions derived by other groups, professional judgment, and emerging scientific principles in ATSDR's public health assessments of exposures to carcinogens.

This Cancer Policy Framework is not intended to encompass the development of operational guidelines per se, although the Agency recognizes the utility of such efforts. A central theme of this Cancer Policy Framework is the use of risk analysis as an organizing construct based on sound biomedical and other scientific judgment to define plausible exposure ranges of concern rather than single numerical conclusions that may convey an artificial sense of precision. The development and use of innovative tools for exposure and dose response assessment (with particular emphasis on molecular epidemiology) are also endorsed.

Barry L. Johnson, Ph.D.
Assistant Surgeon General
Assistant Administrator, ATSDR

Executive Summary

Background

The Agency for Toxic Substances and Disease Registry (ATSDR) pursues a range of legislatively mandated programs that address public health concerns regarding carcinogens. The purpose of the ATSDR Cancer Policy Framework is to define scientifically credible, internally consistent policy positions to guide ATSDR's activities that address the public health implications of exposure to carcinogens. This Cancer Policy Framework is not intended to encompass the development of operational guidelines per se, although ATSDR recognizes the utility of such efforts.

A central theme of ATSDR's Cancer Policy Framework is the use of risk analysis as an organizing construct to promote optimal decisions in the Agency's human health assessment programs. Risk analysis is a multidimensional endeavor encompassing biomedical judgment, peer review, and risk assessment (NRC 1983) as well as risk communication and risk management (CEQ 1989). Accordingly, the Agency's Cancer Policy Framework places emphasis on scientific judgment, peer review, and relevant expertise/knowledge of ATSDR and other federal agencies. As a Public Health Service agency, ATSDR places a preeminent emphasis on disease prevention.

This policy framework was developed based on an assessment of current practice across programs within ATSDR and as such is multifaceted encompassing aspects of exposure as well as carcinogenicity. Collectively, the elements of the ATSDR Cancer Policy Framework are intended to guide ATSDR's

pursuit of its mandate to assess the relationship between exposure to hazardous substances and the effects of those substances on human health.

Risk analysis typically involves significant uncertainty associated with required assumptions and extrapolation. Accordingly, it is anticipated that as knowledge and understanding of the carcinogenic process matures, the Agency's Cancer Policy Framework will have to be modified. For these reasons, ATSDR's Cancer Policy Framework is best viewed as a dynamic, continuously evolving instrument intended to mirror the scientific community's new insights into and understanding of carcinogenicity.

ATSDR's Cancer Policy Framework Position Statements are listed below. Supporting documentation for these positions is presented.

Exposure

ATSDR recognizes that, at present, no single generally applicable procedure for exposure assessment exists, and, therefore, exposures to carcinogens are best assessed on a case-by-case basis with an emphasis on prevention of exposure.

Analysis of Hazard and Risk

(a) Qualitative Issues

In conveying qualitative conclusions regarding carcinogenicity, the Agency endorses the use of a narrative statement incorporating weight-of-evidence conclusions in lieu of alpha-numeric designations alone. In this regard, ATSDR adopts the findings of the Department of Health and Human Services' most recent Annual Report on Carcinogens, as coordinated by the National Toxicology Program.

Analytical epidemiologic investigations, such as case- control or cohort studies, can provide the basis for testing causal associations and are an invaluable resource in public health decisions. Risk estimates derived from such studies are useful in assessing the potential range of human health risks.

ATSDR believes that although an agent may not have been demonstrated to be a carcinogen in a well-designed and well-conducted epidemiologic study, a potential association between exposure to the agent and human cancer cannot be ruled out.

The Agency considers that a substance which has been shown to cause cancer in animals should be presumed to pose a carcinogenic risk to humans in the absence of compelling data to the contrary. ATSDR evaluates the relevance of the animal data to humans on a case-by-case basis.

(b) Quantitative Issues

In terms of quantitative risk assessment per se, ATSDR does not currently engage in low-dose modeling efforts or in the development of associated cancer potency factors or slope estimates. In some instances, cancer potency factors, developed by the Environmental Protection Agency (EPA), are used by ATSDR to estimate cancer risk levels.

ATSDR recognizes that estimation of lifetime cancer risks is further complicated when available data are derived from less than lifetime exposures and that pharmacokinetic insights from animal models may be of utility in addressing this issue.

ATSDR strongly endorses the development of analytical tools to better define exposures, effects, and risks, including individual risk, in the broad context of risk analysis.

Risk Analysis

Emphasis is placed on the use of risk analysis as a decision-making construct contingent on sound biomedical and other scientific judgment to define plausible exposure ranges of concern.

ATSDR will employ the plausible ranges associated with default exposure, toxicological, and other assumptions and policy positions. These may include ranges of default values such as the range of pulmonary ventilation rates (i.e., 8-20 m3/day), human body weight (i.e., 10-60 or 70 kg), or ranges based on the use of low-dose extrapolation models (i.e., logit, probit, multistage, etc.).

Although ATSDR recognizes the utility of numerical risk estimates, the Agency considers these estimates in the context of the variables and assumptions involved in their derivation and in the broader context of biomedical opinion, host factors, and actual exposure conditions.

I. Preface

A. Background:

The establishment of the Agency for Toxic Substances and Disease Registry (ATSDR), a United States Public Health Service agency, was mandated by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) or Superfund. The mission of ATSDR is to prevent or mitigate the adverse human health effects and diminished quality of life that result from exposure to hazardous substances in the environment (ATSDR 1989).

In pursuing its legislatively mandated responsibilities, ATSDR engages in activities in the following general program areas:

- Public health assessment of hazardous waste sites
- Health consultations regarding specific hazardous waste sites and substances
- Health investigations, including the development of exposure and disease registries
- Emergency response to releases of hazardous substances
- Applied research to enhance its health assessment capabilities
- Identification, prioritization, and critical assessment of hazardous substances
- Education and training of health care providers and communities potentially exposed to hazardous wastes

Public health concerns arising from past, ongoing, and/or potential exposures to carcinogens are attendant to each program area pursued by ATSDR.

B. Purpose:

Although ATSDR uses all relevant and available information on the health effects of carcinogens, the Agency has no formal statement or policy regarding:

- Current cancer assessment practice within ATSDR programs
- Human exposure to carcinogens
- Reliance on or use of existing programs and institutional experience germane to cancer policy principles and guidance in cancer health assessment
- Criteria/principles to be used in resolving divergent conclusions derived from cancer assessments conducted by other organizations
- Definition of environmental levels of concern for purposes of screening human exposures to carcinogens
- ATSDR's appropriate role as a practitioner/client of risk assessments for carcinogens
- The appropriate role of peer review and use of emerging scientific principles, methods, and techniques in cancer health assessment
- Its long-term involvement/responsibility in harmonizing cancer policy issues across federal agencies

The purpose of this Cancer Policy Framework is to set forth scientifically credible, and internally consistent, policy positions to guide ATSDR's activities that address the public health implications of

exposure to carcinogens and to harmonize those activities with related activities of other federal agencies and relevant organizations.

C. Scope:

As described above, ATSDR's Cancer Policy Framework is intended to define a general structure to facilitate technical and administrative decisions within programs, all of which have developed and implemented relevant guideline-like efforts or are in the process of so doing. This policy framework is not intended to encompass the development of prescriptive guidelines for the purpose of public health or risk assessment, although the merit and value of such endeavors are recognized. ATSDR also recognizes the existence of a wealth of experience accrued by its programs, other groups, and institutions with significant programs in the area of health and risk assessment. ATSDR intends to reference and build on such experience where applicable.

Collectively, the elements of this Cancer Policy Framework are intended to guide ATSDR's pursuit of its mandate to assess the relationship between exposure to hazardous substances and the effects of those substances on human health, in this case, cancer. Emphasis is placed on the use of risk analysis as an organizing construct contingent on sound biomedical and other scientific judgment to define plausible exposure ranges of concern rather than single numeric conclusions that may convey an artificial sense of precision. The development and utilization of innovative tools for exposure and dose-response assessment are also endorsed.

II. Current Practice within ATSDR

A. Qualitative Practice:

ATSDR's qualitative conclusions regarding carcinogenicity are presented in the Agency's toxicological profiles in which a weight-of-evidence approach is used. This approach relies upon the Department of Health and Human Services' most recent Annual Report on Carcinogens (NTP 1991). Conclusions of the International Agency for Research on Cancer (IARC 1987), the U.S. Environmental Protection Agency (EPA 1986a), and the Occupational Safety and Health Administration (OSHA 1980) are also considered and presented as appropriate (see Appendix A). Discrepancies are resolved based on ATSDR's evaluation of data used by different organizations and scientific peer review. In the absence of toxicological profiles, relevant peer-reviewed literature, EPA documents, and on-line data bases, such as TOXNET and TOXLINE, are consulted.

B. Quantitative Practice:

In terms of quantitative risk assessment per se, ATSDR does not currently engage in low-dose modeling efforts or in the development of cancer potency factors. In some instances, cancer potency factors, derived by EPA, are employed to estimate cancer risk levels. These, in turn, are used by ATSDR internally in combination with broader professional judgment to define exposure levels of concern (i.e., those presenting a potentially significant human health hazard).

All dose/exposure levels reported in studies of carcinogenic effects of hazardous substances are presented in the toxicological profiles irrespective of whether a carcinogenic response was observed. The lowest dose levels associated with carcinogenic effects are identified as cancer effect levels (CELs), with the stipulation that such a designation should not be construed to imply the existence of a threshold for carcinogenesis. Also, exposures associated with upper- bound excess risk estimates over a lifetime of exposure (i.e., one case of cancer in 10,000 to one case of cancer in 10,000,000) as developed by EPA are presented.

C. Exposure Assessment:

Statements regarding the significance of exposures to carcinogens are based on EPA-derived risk levels (e.g., one case of cancer in 1,000,000 in ATSDR public health assessments), investigations of cancer occurrence, and biological markers of exposure to carcinogens. The linkage of exposures to cancer occurrence is qualitative rather than quantitative. Thus, the Agency's current use of dose-response relationships in risk characterization is limited.

III. ATSDR Policy Statement on Exposure to Carcinogens

Both exposure and toxicity information are necessary to fully characterize the potential hazard of an agent. ATSDR considers exposure to an agent to be "an event consisting of contact at a boundary between a human and the environment at a specific environmental contaminant concentration for a specified interval of time; the units to express exposure are concentration multiplied by time" (NAS 1991). Furthermore, dose is defined as "the amount of contaminant that is absorbed or deposited in the body of an exposed individual over a specified time. Therefore, dose is different from, and occurs as a result of, an exposure" (NAS 1991).

In assessing exposure to hazardous substances, ATSDR considers all parameters with potential impact on human health outcomes including the following:

A. Exposure Duration and Frequency:

A single high-dose exposure to an agent may result in toxic effects different from those following repeated lower dose exposures. Therefore, consideration is given to the duration [acute (ó14 days), intermediate (15-364 days), and chronic (ò 365 days)], the intensity (dose rate vs. total dose), and the frequency (continuous or intermittent) of exposure in evaluating carcinogenic risk, along with relevant pharmacokinetic parameters for constituents of concern. With regard to doses and exposure duration employed in the National Toxicology Program (NTP) bioassays, ATSDR believes that caution should be exercised in interpreting the significance of tumors that are induced only at the maximum tolerated dose (MTD) of an agent. In such cases, the Agency will weigh all information relevant to the particular exposure scenario in developing its public health assessment.

B. Exposure Routes:

Exposure to hazardous substances is often complex, entailing exposures via more than one route and/or media; it may also be "indirect," in which case an agent is released into one medium (e.g., air) and subsequently partitioned to other media such as water, soil, or food. For these reasons, ATSDR considers all such possible exposure routes in assessing the carcinogenic risk posed by an agent.

C. Monitoring Studies:

The Agency uses information obtained from assessment of direct exposure (e.g., drinking contaminated water in the vicinity of a hazardous waste site) and/or indirect exposure (e.g., accumulation of contaminants via the food chain). Ideally, assessment will include monitored levels of the agent in contaminated environmental media, and in human tissues and fluids, and in particular, an estimate of the dose at a biologic target tissue(s) where an effect(s) may occur. Such information is necessary to accurately evaluate the potential health risk of exposed populations.

D. Exposure Modeling:

In the absence of complete monitoring information, mathematical exposure assessment models may be employed. These models provide a methodology through which various factors, such as the temporal/spatial distribution of an agent emitted from a source, can be combined to predict levels of human exposure. ATSDR does not view modeling as a fully satisfactory substitute for adequate data but rather as a surrogate to be employed when confronted by compelling needs and inadequate data. Uncertainty associated with these and all methods must be articulated to the extent feasible.

E. Default Assumptions:

In estimating total exposure it is necessary to have information on inhalation rate, water consumption, food consumption, life span or body weight, and other factors depending on the route of exposure. In the absence of actual values for these parameters, ATSDR will use default estimates including those described by EPA (EPA 1986b), recognizing that significant uncertainty is associated with the use of default values.

F. Host Factors:

ATSDR considers the influence of behavior, such as the amount of time spent indoors compared with that spent outdoors, and its underlying variability in assessing potential human health effects. Furthermore, ATSDR recognizes that factors such as nutritional status and lifestyle variables (e.g., tobacco, alcohol, and occupation) may all affect health risk(s) associated with exposure.

G. Current, Past, and Potential Exposure:

Carcinogenic effects may occur in populations not only as a result of current exposure to agents but also from past exposures. Furthermore, based on current knowledge of the agents, these adverse health effects might be predicted from potential exposures. Therefore, ATSDR considers past, current, and potential exposure to hazardous substances to be of public health concern.

With respect to ongoing and/or potential exposure, ATSDR places emphasis on identifying and implementing strategies to interdict exposures, mitigate toxicity, and institute other necessary preventive actions.

H. Summary:

ATSDR recognizes that, at present, no single generally applicable procedure for exposure assessment exists, and, therefore, exposures to carcinogens must be assessed on a case-by-case or context-specific basis. While the need for, and reliance on, models and default assumptions is acknowledged, ATSDR strongly encourages the use of applicable empirical data (including ranges) in exposure assessment.

IV. ATSDR Policy Statement on Health Assessment of Carcinogens

A. Analysis of Hazard and Risk:

ATSDR recognizes the utility and relevance of the Office of Science and Technology Policy (OSTP) for assessing risks from chemicals (OSTP 1985), the Occupational Safety and Health Administration's (OSHA) Generic Carcinogen Policy (OSHA 1980), the Department of Health and Human Services' most recent Annual Report on Carcinogens (NTP 1991), and the Report of the Department of Health and Human Services (DHHS) Committee to Coordinate Environmental Health and Related Programs (CCEHRP) on Risk Assessment and Risk Management of Toxic Substances (CCEHRP 1985). The Agency embraces these principles along with emerging insights regarding carcinogenic processes to guide its evaluation of carcinogenic risks in its public health assessment efforts. In particular they provide valuable insights related to the relevance of animal data to human carcinogenesis, the significance of nonpositive study results, and the potential correlation between benign and malignant tumors.

Cancer assessment by necessity involves a number of assumptions, all of which reflect scientific and policy judgments. ATSDR places a premium on such informed professional judgment and peer review. The Agency considers that a substance which has been shown to cause cancer in animals should be presumed to pose a potential carcinogenic risk to humans in the absence of data to the contrary. As more knowledge on particular agents and the oncogenic process in general is obtained, the Agency's position on these issues may be subject to change.

ATSDR's positions with regard to these principles are described below.

1. Qualitative Issues:

a) Weight of Evidence:

ATSDR adopts a weight-of-evidence approach in evaluating all relevant data, following the approach used by the National Toxicology Program (NTP 1991), the International Agency for Research on Cancer (IARC 1987), the Environmental Protection Agency (EPA 1986a), and the Occupational Safety and Health Administration (OSHA 1980) (see Appendix A). Types of evidence that may be used for qualitatively identifying carcinogens include case studies, epidemiologic studies, long-term animal bioassays, short-term tests, and structure-activity relationships.

Factors to be evaluated in determining if a substance poses a carcinogenic risk to humans include, but are not limited to, the quality of the toxicity studies (choice of appropriate control groups, sufficient number of animals, administration route, dose selection, tumor types) and the relevance of animal data to humans. ATSDR places great importance on quality of studies in evaluating health risks and, therefore, will rely exclusively on peer- reviewed studies in its assessment of the potential carcinogenic risk. The Agency endorses the use of a narrative statement incorporating weight-of-evidence conclusions in lieu of alphanumeric designations alone in conveying qualitative conclusions regarding carcinogenicity.

b) Mechanistic Inference and Species Concordance:

Carcinogenesis is generally viewed as a multistage process, proceeding from initiation, through promotion, and progression. Carcinogens may work through mechanisms that directly alter the genome (genotoxic), or through mechanisms that indirectly involve the genome (epigenetic). Currently, it is assumed that many or most carcinogens are characterized by the absence of a threshold in eliciting a tumorigenic response. However, the presence or absence of a threshold for one step in the multistage process of carcinogenesis does not necessarily imply the presence or absence of a threshold for other steps or the entire process. For example, carcinogenic effects of some agents may result from nonphysiologic responses to the agents, such as extensive organ damage or formation of calculi in the urinary tract. Under such circumstances, ATSDR evaluates the relevance of the animal data to humans on a case-by-case basis with a view towards extending its assessment effort beyond the dominant paradigm of carcinogenesis (i.e., initiation, promotion, and progression).

c) Route Specificity:

In the analysis of potential carcinogenic risk of agents to humans, it is important to address the issue of exposure route specificity. For some agents, exposure results in adverse health effects via one route only. For example, while chronic oral exposures to an agent may not result in cancer in animals and/or humans, the same agent may be carcinogenic via inhalation in the same species. Accordingly, ATSDR evaluates the potential health risk of toxic substances taking into account the relevant route(s) of exposure. In the absence of data to the contrary, an agent that is carcinogenic via one route will be considered to be a potential carcinogen via alternate routes.

d) Role of Epidemiologic Data:

Epidemiologic studies provide direct information on the carcinogenic risk of environmental agents to humans. For this reason, ATSDR assigns a higher weight to well-designed and well-executed epidemiologic studies than to animal studies of comparable quality in evaluating the potential human cancer risks. However, the observational nature of such studies, as well as the use of indirect measures of exposure, sometimes constrains interpretation of the data.

Descriptive epidemiologic studies may be useful in generating/refining hypotheses that suggest further in-depth studies. These studies also provide limited information on causal relationships. Alternatively, analytical epidemiologic investigations such as case- control or cohort studies can

provide the basis for testing causal associations and are an invaluable resource in public health decisions. The causal association of toxic chemical exposure and cancer is greatly enhanced when studies show: relationships without significant bias, a temporal sequence of exposure and response, consistency with other studies, strength of association, a dose-response relationship, and biologic plausibility.

ATSDR believes that although an agent may not have been shown to be a carcinogen in a well-designed epidemiologic study, a potential association between exposure to the agent and human cancer cannot be ruled out. The potential for an association will remain, particularly if relevant animal data suggest that a carcinogenic effect exists. This premise would also apply in the case of health effects other than cancer.

e) Susceptible Populations:

Certain populations may be at high risk of developing cancer because of several factors, including exposure to unusually high levels of carcinogens, genetic predisposition, age, and other host factors such as physiological and nutritional status. ATSDR places great importance on identifying these susceptible populations and addressing associated public health concerns.

f) Structure-Activity Relationships:

Information on the physical, chemical, and toxicological characteristics as well as the environmental fate of many hazardous substances is available. Thus, some correlations can be made between the structures of some hazardous substances and the properties they exhibit. ATSDR endorses the use of structure-activity relationships to derive preliminary estimates of both the environmental and toxicological characteristics of hazardous substances for which little or no information is available. However, ATSDR recognizes that a great deal of scientific judgment is required in interpreting these results since these methods need to be refined and validated. Further, the Agency recognizes that conclusions derived by such approaches are, at present, inadequate as surrogates for human or other bioassay data.

g) Chemical Interactions:

Health evaluations are often complicated by the fact that multiple hazardous substances may be of concern at specific waste sites. The Agency believes that no single approach is appropriate for all risk assessments of multiple chemical exposures. Furthermore, at present, the scientific community has not reached consensus on the appropriate use of a particular multiplicative model. Given the paucity of empirical data and the complexity of this issue, ATSDR assumes that, in the absence of information regarding the interaction of these substances, their effects are additive. Such assessments should also be accompanied by a qualitative weight-of- evidence-like statement on the potential for interactive effects, be they potentiating, additive, antagonistic, and/or synergistic. Ideally, these conclusions are based on insights regarding mechanism of action of individual components as the insights relate to the potential for interaction among components of the mixture.

2. Quantitative Issues:

a) Dose Scaling:

Conversion of exposure levels derived from experimental animal studies to humans is an equivocal process because of recognized differences among species, e.g., life span and body size, and pharmacokinetic and genetic factors, among others. Although a number of default scaling factors have been proposed, no single scaling approach may be universally appropriate. ATSDR endorses the use of (mg/kg3/4)/day for dose scaling as a default, in the absence of empirical data, as suggested by the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET 1992).

The Agency recognizes, however, that the use of any default approach to scaling is a crude approximation and that all factors responsible for interspecies differences must be considered in dose/exposure conversions among species when selecting extrapolation methods. For these reasons, empirically derived data relevant to dose scaling are preferred and should be used preferentially when they are available. Extrapolation may not be necessary if epidemiologic data are used to assess potential carcinogenic risk; however, differences in individual sensitivity must be taken into account.

b) Pharmacokinetics and Pharmacodynamics:

ATSDR considers it important to conduct health studies in populations that have been exposed to carcinogens in the past or that are currently exposed to these agents. In assessing the potential carcinogenic risks of agents, information on the delivered target dose rather than the exposure dose may help in developing a more accurate assessment of the possible carcinogenicity of an agent. ATSDR encourages the development and use of physiologically based pharmacokinetic models for estimating the magnitude and time course of exposure to agents at target sites in animal models. Once data from the animal models have been appropriately validated, they can then be used to estimate corresponding target tissue doses in humans. Furthermore, ATSDR recognizes that estimation of lifetime cancer risks is further complicated when available data are derived from less than lifetime exposures and that pharmacokinetic insights may be of utility in addressing this issue.

c) Mechanistic Considerations and Modeling:

Health assessment for potential carcinogens must take into consideration dose-response relationships from all available relevant studies. In chronic bioassays, animals are often exposed to levels of the agent that are, for practical reasons, far higher than levels to which humans are likely to be exposed in the environment. Therefore, mathematical models are used to extrapolate from high to low dose. The selection of models depends on the known or presumed mechanism of action of the agent and on science policy considerations. In the absence of sufficient information to choose among several equally plausible models, preference will be given to the more conservative (i.e., protective) model.

The multistage model is widely used for low- dose extrapolation for genotoxic agents. It is based on the premise that a developing tumor proceeds through several different stages before it is clinically detectable. In the low-dose region, this multistage model is frequently linear, and it is assumed that a threshold, below which effects are not anticipated, does not exist. ATSDR recognizes that no single mathematical model is appropriate in all cases and that incorporation of new information on mechanism and pharmacokinetics, among other factors, will increase the usefulness and facilitate the selection of the most appropriate mathematical model. Existing mathematical models for low-dose extrapolation may not be appropriate for nongenotoxic agents. ATSDR believes that more information on biological mechanism is needed to determine if there are threshold exposure levels for nongenotoxic agents. For these reasons, where feasible, ATSDR will consider the presentation of a range of plausible potency estimates in conveying quantitative conclusions.

d) Individual vs. Population Risk--The Role of Molecular Epidemiology:

Recent advances in biomolecular technology have resulted in the development of highly sensitive methods for measuring biomarkers of exposure, effects, and susceptibility (Shields and Harris 1991; Johnson and Jones 1992). Biomarkers have the potential to serve as bridges between experimental and epidemiologic studies of carcinogens, insofar as they reflect biochemical or molecular changes associated with exposure to carcinogens.

Biomarkers, such as DNA adducts, may be used as indices of the biologically effective doses, reflecting the amount of the potential carcinogen or its metabolite that has interacted with a cellular macromolecule at the target site. Furthermore, markers of early biologic effect, such as activated

oncogenes and their protein products, and/or loss of suppressor gene activity, may indicate the occurrence of possibly irreversible toxic effects at the target site.

Genetic markers, such as certain aryl hydrocarbon hydroxylase isozymes, may suggest the presence of heritable predispositions or the effects of other host factors, such as lifestyle or prior disease. Thus, molecular epidemiology, by combining experimental models, molecular biology, and epidemiology, holds promise as a means to estimate individual cancer risk and to better define the health implications of hazardous waste sites for members of exposed populations (NRC 1991). However, it should be noted that more research is needed before biomarkers can be used as prognostic indicators. ATSDR strongly endorses the development of such analytical tools to better define exposures, effects, and risks, including individual risk, in the broad context of risk analysis.

B. Institutional Experience:

A central theme of ATSDR's Cancer Policy Framework is the development of a construct that will facilitate optimal decisions in the Agency's human health assessment programs. Therefore, the Agency's Cancer Policy Framework places primary emphasis on the scientific judgment, peer review, and expertise/knowledge of the scientific community including ATSDR and other federal agencies, such as NTP, EPA, OSHA, the National Institute for Occupational Safety and Health (NIOSH), and the Food and Drug Administration (FDA), and other organizations with significant programs in this area, such as IARC. Although they are useful as adjuncts to the decision-making process, ATSDR places less weight on generic, algorithmically derived conclusions than on biomedical judgment and institutional experience.

C. The Role of Emerging Scientific Principles and Techniques:

ATSDR believes that its Cancer Policy Framework is best viewed as a dynamic and continuously evolving instrument intended to mirror the scientific community's new insights into and understanding of carcinogenicity. Since cancer risk analysis typically involves significant uncertainty associated with required extrapolation and assumption, it is anticipated that as knowledge and understanding of the carcinogenic process matures, the Agency's Cancer Policy Framework will have to be modified accordingly. Additional data on metabolic pathways and pharmacokinetics, species variability, and mechanistic insights may better define the relevance of animal data to humans. Similarly, research findings on biomarkers (e.g., DNA adducts) may better explain their significance in relation to carcinogenic risk. Other areas of research that may reduce uncertainty in risk analysis include: the development of model systems to assay compounds that influence the promotion and progression of initiated cell populations, the study of factors that influence cell proliferation, and the development of tests for chromosomal rearrangements and oncogene and suppressor gene functions. New information from each of these areas of research will further understanding of carcinogenesis and thereby serve to reduce current uncertainties in risk analysis.

V. Analysis of Carcinogenic Risk

ATSDR views risk analysis as a multidimensional endeavor encompassing expert judgment, peer review, and risk assessment (NRC 1983), as well as risk communication and risk management (CEQ 1989). Of pivotal importance to credible risk analysis efforts is a systematic identification of uncertainties attendant to each of the components and subcomponents of risk analysis. Such uncertainty is often obscured in the typically linear progression from the elements of risk assessment as defined by the National Research Council (NRC 1983) to elements of risk management and risk communication. As a result, algorithmically derived numerical risk estimates tend to be conveyed in an artificially precise manner and sometimes used inappropriately in decision-making. This artificial appearance of precision can lead decision makers to rely heavily on numerical risk estimates. Although ATSDR recognizes the utility of numerical risk estimates in risk analysis, the Agency considers these estimates in the context of the variables and assumptions involved in their derivation and in the broader context of biomedical opinion, host factors, and actual exposure conditions. The actual parameters of environmental exposures

must be given careful consideration in evaluating the assumptions and variables relating to both toxicity and exposure. Particular attention must be paid to the differences in conditions under which empirical data used in the development of a risk estimate were derived and the actual environmental exposure conditions being assessed as well as host factors.

A. Risk Characterization:

In risk characterization, all information derived from each step of the assessment of carcinogenic risk is integrated and used to project the frequency and severity of the adverse health effects in exposed populations. ATSDR places a premium on a critical evaluation and presentation of all environmental, biological, and statistical uncertainties in the final assessment. Furthermore, the Agency will carefully reexamine the quality of the studies used to support all conclusions and compare data across similar studies that are relevant to specific assessments. When appropriate, ATSDR will employ plausible ranges associated with default exposure, toxicological, and other assumptions/policy positions. These may include ranges of default values such as the range of pulmonary ventilation rates (i.e., 8-20 m3/day), human body weight (i.e., 10-60 or 70 kg), or ranges based on the use of low-dose extrapolation models (i.e., logit, probit, multistage, etc.).

B. Risk Communication:

ATSDR recognizes that the needs of the clients of risk analysis must be well understood by those involved in the assessment process. There must be feedback and interaction between practitioners and clients, including risk analysts, risk managers, risk communicators, and the public. Furthermore, ATSDR considers that education and training efforts related to public health assessment are essential to effective communication. ATSDR endorses the use of principles of risk communication as articulated by the National Research Council (NRC 1989; CCEHRP 1992).

C. Risk Management:

Risk management decisions should be based on a wide range of issues relevant to risk analysis, including medical opinion, epidemiology, and professional judgment, along with socioeconomic factors and technical feasibility. Although ATSDR does not engage in risk management per se, the Agency does provide technical information and professional judgment to be employed as part of that process. As such the Agency places a premium on enhancing communication and feedback among those engaged in the components of risk analysis and management.

VI. References

ATSDR. 1989. Statement of organization, functions, and delegations of authority. Agency for Toxic Substances and Disease Registry. Federal Register 54:33617.

CCEHRP. 1985. Risk assessment and risk management of toxic substances. A report to the Secretary, Department of Health and Human Services (DHHS) from the Executive Committee, Committee to Coordinate Environmental Health and Related Programs (CCEHRP).

CCEHRP. 1992. Draft Report. Recommendations to improve health risk communication. Subcommittee on Risk Communication and Education, Committee to Coordinate Environmental Health and Related Programs (CCEHRP), Department of Health and Human Services, Public Health Service.

CEQ. 1989. Risk analysis: A guide to principles and methods for analyzing health and environmental risks. Council on Environmental Quality. Washington, D.C. NTIS: PB89-137772.

EPA. 1986a. Guidelines for carcinogen risk assessment. US Environmental Protection Agency: Part II. Federal Register 51:33992-34003.

EPA. 1986b. Final draft. Reference values for risk assessment. US Environmental Protection Agency. Prepared by Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment. Cincinnati, OH.

FCCSET. 1992. Draft Report. A cross-species scaling factor for carcinogen risk assessment based on equivalence of (mg/kg3/4)/day. Federal Coordinating Council for Science, Engineering, and Technology. Federal Register 57:24152-24173.

IARC. 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1-42, supplement 7. Lyon, France: International Agency for Research on Cancer.

Johnson BL, Jones DE. 1992. ATSDR's activities and views on exposure assessment. Journal of Exposure Analysis and Environmental Epidemiology, Suppl. 1:1-17.

NAS. 1991. Human exposure assessment for airborne pollutants. National Academy of Sciences. Washington, DC, p. 3.

NRC. 1983. Risk assessment in the federal government: Managing the process. National Research Council. National Academy Press, Washington, DC

NRC. 1989. Improving risk communication. National Research Council. National Academy Press. Washington, DC

NRC. 1991. Environmental epidemiology. Public health and hazardous wastes, volume I. National Research Council. National Academy Press, Washington, DC

NTP. 1991. Sixth annual report on carcinogens. National Toxicology Program, US Department of Health and Human Services, Public Health Service.

OSHA. 1980. Identification, classification and regulation of potential occupational carcinogens. Occupational Safety and Health Administration, Department of Labor. Code of Federal Regulations. 29 CFR 1990, Chapter XVII.OSTP. 1985. Chemical carcinogens: A review of the science and its associated principles. Office of Science and Technology Policy. Federal Register 50:10372-10442.

Shields PG, Harris CC. 1991. Molecular epidemiology and the genetics of environmental cancer. JAMA 266:681-687.

Appendix A: Classification of Carcinogens

Table 1. Classification of carcinogens

EPA	IARC	NTP	OSHA
(Group A) Human Carcinogen	(Group 1) Carcinogenic to Humans	Human Carcinogen	Category I
(Group B1, B2) Probable Human Carcinogen	(Group 2A) Probably Carcinogenic to Humans	Reasonably Anticipated to be a Carcinogen	Category II
(Group C)	(Group 2B)		

Possible Human Carcinogen	Possibly Carcinogenic to Humans
(Group D) Not Classifiable as to Human Carcinogenicity	(Group3) Not Classifiable as to Human Carcinogenicity
(Group E) Evidence of Non-Carcinogenicity for Humans	

Appendix B: Response to Public Comments

Identification of Submitters

Submitter #1 is Board of Scientific Counselors, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia.

Submitter #2 is Richard A. Lemen, Ph.D., National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Atlanta, Georgia.

Submitter #3 is Richard B. Rothenberg, M.D., National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Submitter #4 is Malcolm D. Williams, D.V.M., Ph.D., Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, Georgia.

ATSDR thanks these submitters for their reviews of the document. The reviews were constructive and provided valuable perspectives in preparing the ATSDR Cancer Policy Framework.

General Comments

Submitter #1, Comment 1, believes that the draft document submitted at the November 6, 1992, meeting reflects appropriately the recommendations of the Board in April 1992, and that the revised version of the document need not be reviewed by the Board. Major revisions, as a result of the Board's review in April 1992, include (1) addition of a Foreword to better describe the historical background, the needs of the Agency, and the intent of the Cancer Policy Framework, (2) clarification of the intent of the document, especially in relation to risk assessment activities of the Environmental Protection Agency and other relevant federal agencies and organizations, and (3) clarification of the use of biomarkers, and caution in communicating individual risk.

Response: No response is required.

Submitter #2, Comment 1, states that the document is generally sound and addresses most of the major issues.

Response: No response is required.

Submitter #2, Comment 2, notes that there is no discussion of why an additive interactive model was chosen over a multiplicative model and asks why in all cases an additive model would be used.

Response: ATSDR believes that no single approach is appropriate for all risk assessments of multiple chemical exposures. Furthermore, at present, there is no consensus on the appropriate use of a particular multiplicative model within the scientific community. Given the paucity of empirical data and the complexity of this issue, ATSDR assumes that, in the absence of information regarding the interactive effects of hazardous substances, their effects are additive. The rationale for this position has been further clarified in the document.

Submitter #2, Comment 3, asks how people identified as highly exposed or at increased risk of cancer will be treated regarding medical surveillance and follow-up, results notification, risk communication, and confidentiality of information.

Response: ATSDR believes that the Submitter's comments are beyond the scope of this document. These topics are more appropriately discussed in specific health assessment guidelines.

No change will be made in the document, although ATSDR will consider the development of such guidelines in response to specific programmatic needs, as appropriate.

Submitter #2, Comment 4, suggests that the discussion of "individual vs. population risk - the role of molecular epidemiology" should convey more caution about whether individual risk assessment is warranted and how soon approaches may be available. Furthermore, the Submitter notes that there is a danger in basing a prediction of an individual's risk of cancer on measurements of one or a few markers. According to the Submitter, such reductionist approaches are misleading and could both create anxiety and cause interventions to be targeted too narrowly.

Response: ATSDR concurs with the Submitter's concerns and has emphasized the sentence, "However, it should be noted that more research is needed before biomarkers can be used as prognostic indicators," with italics and bolding in the revised document. [See Section IV. A. 2. d, third paragraph].

Submitter #3, Comment 1, believes that there is some lack of clarity in the overall use of language which may result from the jargon of risk assessment and the area in which ATSDR works. The Submitter states that a reader who is not familiar with the issues might benefit from substitution for some of the jargon. The Submitter cites two examples: 1) "cancer potency factor" vs. "EPA potency factor" and 2) 10-6 in ATSDR public health assessments.

Response: ATSDR concurs and has revised the document accordingly. [See SPECIFIC COMMENTS, ATSDR response to Submitter #3, Comment 2 (II.B. Quantitative Practice), and Comment 3 (II.C.- Exposure Assessment), respectively].

Submitter #3, Comment 2, believes that italics are difficult to read because they give the sense that everything is special or everything is emphasized. Furthermore, the Submitter indicates that when bold is added, it becomes even more difficult to read and suggests using both forms of emphasis judiciously.

Response: ATSDR concurs and has used italics with bolding for emphasis only in the revised document.

Submitter #4, Comment 1, believes that overall, the document is clearly written, concise, and scientifically sound.

Response: No response is required.

Specific Comments

Executive Summary

Background

Submitter #2, Comment 1, asks for clarification of a sentence on page 1, second paragraph, namely, if the sentence is meant to read "……biomedical judgment peer review….." or if these are separate items. The Submitter believes that the latter makes more sense.

Response: ATSDR has revised the sentence to read "Risk analysis is a multidimensional endeavor encompassing biomedical judgment, peer review, and risk assessment……"

Analysis of Hazard and Risk

(a) Qualitative Issues

Submitter #3, Comment 1, requests clarification of the sentence "ATSDR believes that although an agent may not have been demonstrated to be a carcinogen in a well-designed and well-conducted epidemiologic study, a potential association between exposure to the agent and human cancer cannot be ruled out." The Submitter believes that the sentence, as currently written, implies that even if the agent has not been demonstrated to be a carcinogen in a "good" study, it might still be one. Furthermore, the Submitter states that this suggests that ATSDR does not believe in epidemiologic data.

Response: As stated in the Cancer Policy Framework, ATSDR believes that epidemiologic studies are an invaluable resource in public health decisions. Therefore, in evaluating the potential human cancer risks, ATSDR assigns a higher weight to well-designed and well-executed epidemiologic studies than to animal studies of comparable quality. However, ATSDR believes that a nonpositive study does not necessarily indicate that the agent may not be shown to be carcinogenic in future epidemiologic investigations or in follow-up studies. No change will be made in the document.

(b) Quantitative Issues

Submitter #2, Comment 2, asks for clarification of "cancer potency" vs. "potency factors, developed by the EPA." (Also, see Section IV.B., first paragraph).

Response: ATSDR has clarified the issue by using the term, "cancer potency factors," throughout the revised document.

Risk Analysis

Submitter #1, Comment 1, asks for clarification of the sentence "ATSDR will employ the plausible ranges associated with default exposure, toxicological, and other assumptions/policy positions."

Response: ATSDR has clarified this sentence by adding the following to the revised document, namely, "These may include ranges of default values such as the range of human pulmonary ventilation rates (i.e., 8-20 m3/day), human body weight (i.e., 10-60 or 70 kg), or ranges based on the use of low-dose extrapolation models (i.e., logit, probit, multistage, etc.)." Submitter #2, Comment 3, asks for clarification of the sentence "ATSDR will employ the plausible ranges associated with default exposure, toxicological, and other assumptions/policy positions."

Response: See ATSDR response to Submitter #1, Comment 1 above.

I. Preface

A. Background

Submitter #2, Comment 4, notes two typographical errors in the first paragraph, and suggests removing the comma after "Comprehensive" and move (CERCLA) to after 1980.

Response: ATSDR concurs and has made the suggested changes.

II. Current Practice within ATSDR

B. Quantitative Practice

Submitter #3, Comment 2, requests clarification of "cancer potency factors" vs. "EPA potency factors" in the first two sentences of the first paragraph.

Response: ATSDR has revised the second sentence to read "In some instances, cancer potency factors, derived by EPA, are employed....."

C. Exposure Assessment

Submitter #2, Comment 5, asks if ATSDR intends to adopt EPA risk estimates. Furthermore, the Submitter indicates that if ATSDR is not going to perform low- dose modeling then it might also consider alternative estimates of risk from other federal (e.g., OSHA, NIOSH, or FDA) and state (e.g., California OSHA) organizations.

Response: Although ATSDR does not "adopt" risk estimates used by any particular federal or state agency, the Agency does "report" risk estimates as derived by EPA and other relevant agencies and organizations insofar as they are useful in risk characterization. No change will be made in the document.

Submitter #2, Comment 6, disagrees with the sentences, "The linkage of exposures to cancer occurrence is qualitative rather than quantitative. Thus, causal inferences in risk characterization are limited." The Submitter believes that the second sentence does not seem to be supported by the first one.

Response: ATSDR concurs with the Submitter, and has revised the second sentence to read "Thus, the Agency's current use of dose-response relationships in risk characterization is limited."

Submitter #3, Comment 3, requests clarification of "10-6" in ATSDR public health assessment.

Response: ATSDR has revised the sentence to read "...(e.g., one case of cancer in 1,000,000)...."

III. ATSDR Policy Statement on Exposure to Carcinogens

A. Exposure Duration and Frequency

Submitter #2, Comment 7, notes that the premise that ATSDR weighs all relevant information on a particular exposure scenario in developing its public health assessment is appropriate. However, the Submitter considers that the term "lower dose exposures" may be better than "exposure to lower doses." Furthermore, the Submitter believes that the terms "acute, intermediate, and chronic exposure" do not equate to duration alone but to a combination of duration and intensity. The Submitter suggests rewording.

Response: The term, "lower dose exposures," is used in the revised document, as suggested by the Submitter. However, ATSDR defines "acute, intermediate, and chronic exposure" as durations only, consistent with usage in the ATSDR toxicological profiles.

Submitter #4, Comment 1, suggests that it may be informative to the reader for ATSDR to indicate the definition of acute, intermediate, and chronic duration.

Response: ATSDR concurs and has defined acute, intermediate, and chronic duration as 14 days, 15- 364 days, and 365 days, respectively, in the revised document. D. Exposure Modeling

Submitter #2, Comment 8, agrees with ATSDR's position that uncertainty associated with risk assessment methods should be clearly articulated.

Response: No response is required.

F. Behavior

Submitter #4, Comment 2, suggests that the heading, "Host Factors" may be more appropriate than "Behavior" because the multitudinous factors within the host that may affect the development of cancer upon exposure are not all related to behavior.

Response: ATSDR concurs and has changed the heading to "Host Factors" and revised the text accordingly.

Submitter #4, Comment 3, suggests the word "other" be deleted from the sentence "...status and other lifestyle variables...."

Response: ATSDR concurs and has made the suggested change.

G. Current, Past, and Potential Exposure

Submitter #2, Comment 9, suggests that the sentence "Carcinogenic effects may result in populations not only from current exposure to agents but also from past and/or potential exposures" be rephrased since potential exposures cannot produce carcinogenic effects, although such effects can be predicted.

Response: ATSDR concurs and has revised the sentence to read "Carcinogenic effects may occur in populations not only as a result of current exposure to agents but also from past exposures. Furthermore, based on current knowledge of the agents, these adverse health effects might be predicted from potential exposures."

H. Summary

Submitter #2, Comment 10, notes that for most pre- construction occupational exposure assessment, modeling is a necessity. The Submitter reasons that due to high variability in site characterization and environmental data, there are many cases where modeling will be a better predictor of exposure than empirical data. Therefore, the Submitter suggests rewording the policy statement to end after "exposures to carcinogens should be treated on a case-by-case basis" and delete "rather than, hypothetical basis."

Response: ATSDR concurs and has made the suggested change.

IV. ATSDR Policy Statement on Health Assessment of Carcinogens

A. Analysis of Hazard and Risk

1. Qualitative Issues

b) Mechanistic Inference and Species Concordance

Submitter #1, Comment 2, suggests deleting the phrase "somatic mutation" from this section.

Response: ATSDR concurs and has made the suggested change.

Submitter #2, Comment 11, notes that the definition of "epigenetic" is at variance with the meaning attributed in the document.

Response: ATSDR believes that the definition of "epigenetic" in the document is consistent with that in the scientific literature, e.g., Cohen SM, Ellwein LB. Genetic Errors, Cell Proliferation, and Carcinogenesis. Cancer Research 51:6493-6505, 1991, and Williams GM, Weisburger JH, Chapter on Chemical Carcinogens. Casarett and Doull's Toxicology--The Basic Science of Poisons, Third Edition. No change will be made in the document.

Submitter #2, Comment 12, suggests that the sentence "Carcinogenesis is generally viewed as a multistage process, proceeding from somatic mutation, initiation through promotion, and progression" be rephrased to either: "Carcinogenesis is generally viewed as a multistage process, proceeding from

initiation (somatic mutation), through promotion, and progression" or "Carcinogenesis is generally viewed as a multistage process, proceeding from initiation, through promotion, and progression."

Response: ATSDR concurs and has revised the sentence to read "Carcinogenesis is generally viewed as a multistage process, proceeding from initiation, throughpromotion, and progression."

Submitter #2, Comment 13, suggests that the fifth sentence in this paragraph, "For example, carcinogenic effects of some agents may result from nonphysiologic responses such as extensive organ damage or formation of calculi," should be rephrased to read "For example, carcinogenic effects of some agents may result from nonphysiologic responses with a threshold such as extensive organ damage or formation of calculi." Furthermore, the Submitter suggests including the reference, Cohen SM, Ellwein LB. Cell Proliferation in Carcinogenesis. Science 249: 1007-1011, 1990, if needed.

Response: Based on available information, it is not possible to derive definitive conclusions with regard to the issue of threshold for agents acting via epigenetic mechanisms. Furthermore, this is supported by the reference suggested by the Submitter (see section entitled, "Classification of Chemicals for Human Risk Assessment" in the reference). Therefore, the sentence will not be revised.

Submitter #4, Comment 4, requests clarification of the sentence, "For example, carcinogenic effects of some agents may result from nonphysiologic responses such as extensive organ damage or formation of calculi in the urinary tract." The Submitter suggests replacing the above sentence with "For example, carcinogenic effects of some agents may be associated with predisposing pathologic factors such as extensive organ damage...."

Response: The examples quoted, such as extensive organ damage, are results of exposure to agents and are not preexisting pathological factors. The document has been revised to read "For example, carcinogenic effects of some agents may result from nonphysiologic responses to the agents such as extensive organ damage or formation of calculi in the urinary tract."

d) Role of Epidemiologic Data

Submitter #2, Comment 14, suggests that the sentence in the first line of the third paragraph should read, "....an agent may not have been shown [to] be..."

Response: ATSDR concurs and has made the suggested change.

Submitter #2, Comment 15, suggests the paragraph break between the first and second paragraph be changed for better presentation of the information, namely, the first paragraph will address epidemiology in general and the second paragraph will address both descriptive and analytical epidemiologic studies.

Response: ATSDR concurs and has made the suggested change.

Submitter #2, Comment 16, asks for clarification of the sentence in the first paragraph, i.e., "ATSDR assigns a higher weight to well-designed and well-executed epidemiologic studies."

Response: ATSDR has revised the sentence to read "ATSDR assigns a higher weight to well-designed and well-executed epidemiologic studies than to animal studies of comparable quality."

g) Chemical Interaction

Submitter #2, Comment 17, suggests that additive may be the default position between synergism and antagonism and, thus, might very well be the best factor.

Response: ATSDR concurs with the Submitter. No change is required in the document. (Also, see ATSDR response to Submitter #2, Comment 2, in section on General Comments).

2. Quantitative Issues

a) Dose Scaling

Submitter #2, Comment 18, suggests revising the second sentence of the second paragraph, by replacing the phrase "empirically derived data" with "scientifically calculated values."

Response: ATSDR believes it to be most relevant to use data which are derived from experiments and observations (as opposed to technically supported calculations), whenever such data are available. Therefore, the phrase, "empirically derived data," will not be changed in the document.

d) Individual vs. Population Risk--The Role of Epidemiology

Submitter #2, Comment 19, notes that in the second sentence of the second paragraph, "oncogenies" should be "oncogenes."

Response: ATSDR concurs and has made the suggested change.

Submitter #2, Comment 20, suggests that the first sentence of the third paragraph, "Genetic markers, such as aryl hydrocarbon hydrolase..." should read "Genetic markers, such as certain aryl hydrocarbon hydrolase isozymes..."

Response: ATSDR concurs and has made the suggested change.

B. Institutional Experience

Submitter #2, Comment 21, suggests that ATSDR mention NIOSH in this Section.

Response: ATSDR concurs and has made the suggested change.

V. Analysis of Carcinogenic Risk

Submitter #2, Comment 22, considers some language to be confusing and presents a revision of the paragraph in this section, starting with the sentence, " As a result...." In addition, the Submitter states that some words are too complex (e.g., "probity" in Section I.C. Scope and "moieties" in Section IV. C. The Role of Emerging Scientific Principles and Techniques.

Response: ATSDR has adopted the revised version of the paragraph for Section V., as suggested by the Submitter, with the exception of the first revised sentence. Furthermore, ATSDR has replaced "probity" with "value," and the phrase "...the significance of such moieties...." has been changed to "...their significance..."

Submitter #2, Comment 23, suggests revising the sentence next to the last sentence of the first paragraph, by replacing the phrase "empirically derived data" with "scientifically calculated values."

Response: ATSDR believes the phrase, "empirically derived data" (revised as "empirical data" per Submitter #2, Comment 22) to be appropriate in the context of the paragraph; therefore, no change will be made. (Also, see ATSDR response to Submitter #2, Comment 18, in Section IV.A.2.a) Dose Scaling.

A. Risk Characterization

Submitter #2, Comment 24, asks for clarification of the sentence "ATSDR will employ the plausible ranges associated with default exposure, toxicological, and other assumptions/policy positions."

Response: ATSDR has clarified this sentence by adding the following to the revised document, namely, "These may include ranges of default values such as the range of human pulmonary ventilation rates (i.e., 8-20 m3/day), human body weight (i.e., 10-60 or 70 kg), or ranges based on the use of low-dose extrapolation models (i.e., logit, probit, multistage, etc.)."

B. Risk Communication

Submitter #2, Comment 25, suggests replacing the word "clients" with "users" in the first two sentences because the identity of the "clients" is not clear to the Submitter.

Response: ATSDR believes that the word "clients" is appropriately used in the context of this Section. No change will be made.

Appendix

Submitter #2, Comment 26, notes that the OSHA classification of carcinogens is listed incorrectly. The OSHA carcinogen standard (29 CFR 1990) lists two categories (I and II) of carcinogens. The four categories that are listed by ATSDR in the Appendix were proposed by OSHA in 1977, but the final standard reduced these cancer categories to two. Furthermore, the Submitter indicates that ATSDR should mention the OSHA cancer policy under "Qualitative Practice" in Section II.A. and Section IV.A.1.a.

Reponse: ATSDR concurs and has made the suggested changes.

Page last reviewed: June 25, 2001
Page last updated: June 25, 2001
Content source: Agency for Toxic Substances and Disease Registry

---

Agency for Toxic Substances and Disease Registry, 4770 Buford Hwy NE, Atlanta, GA 30341
Contact CDC: 800-232-4636 / TTY: 888-232-6348