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Research Report:

Conducting a Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems

by

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NOTICE

The U.S. Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to the Agency's peer and administrative review and has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

FOREWORD

This report was developed by the U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD), National Center for Environmental Assessment - Cincinnati Office (NCEA-Cin). It contains information concerning the conduct of risk assessments for mixtures of disinfection by-products (DBPs) across various drinking water treatment systems. Under 42 USC § 300 of the Safe Drinking Water Act Amendments of 1996, it is stated that the Agency will "develop new approaches to the study of complex mixtures, such as mixtures found in drinking water..." In addition, the EPA's Office of Water drafted a *Research Plan for Microbial Pathogens and DBPs in Drinking Water* that calls for the characterization of DBP mixtures risk (U.S. EPA, 1997a). This report reflects the current results relative to research in this area over the past five years. The report as a whole presents an illustrative DBP mixtures risk characterization; the summary of an expert scientific workshop on this subject; EPA conclusions and recommendations subsequent to the workshop; a conceptual cumulative risk approach; and ideas on future research needs.

This effort has resulted in the production of four reports contained in this document. Appendix I contains an initial report generated as a pre-meeting report to an April 1999 workshop on this subject. It is entitled, *Workshop Pre-meeting Report: The Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems* (U.S. EPA, 1999a) and was developed to detail the response addition approach to estimating DBP mixture risk that has recently been developed by NCEA-Cin. Having performed this initial assessment, NCEA-Cin scientists recognized a number of areas for improvement and held a workshop in April 1999 to examine the current method, present ideas to advance the approach, and come to some conclusions relative to new research and development directions. The resulting workshop report is presented as Report 2, entitled, *Workshop Report: The Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems.* Finally, EPA scientists have used the information developed in the April 1999 workshop to develop a number of conclusions and recommendations relative to this area of research and to develop a conceptual approach to performing a cumulative risk assessment. This information is presented as Report 1, entitled, *EPA Conclusions and Conceptual Approach for Conducting a Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems.*

An external review of this document was conducted June 21-22, 2000, with the primary goal of evaluating Report 1 on EPA's conclusions and conceptual approach. These reviewers were also invited to comment on the data, methods and discussions presented in Reports 1 and 2 or to add new information and perspectives to this document where needed. A final report containing the summary of the external review comments is contained in Appendix II.

To facilitate the production of this document, work was done under three contractual agreements. The illustrative example of a risk characterization was developed by Dr. Joshua Cohen, under contract #68-C6-0024 with TN & Associates,

Inc. The workshop was conducted on April 26-28, 1999, at EPA's Andrew W. Breidenbach Environmental Research Center in Cincinnati, Ohio, under contract #68-C7-0011 with SAIC, Inc, who also invited several of the expert scientists who participated. The proceedings of the workshop were then subcontracted to Syracuse Research Corporation and the report prepared by Dr. Pat McGinnis. The independent external review and preparation of comments was conducted under contract #68-C-99-238 with Versar, Inc.

EPA RESEARCHERS

This research on the risk assessment of DBPs was sponsored by U.S. Environmental Protection Agency (EPA), National Center for Environmental Assessment - Cincinnati Division (NCEA-Cin), Comparative Risk Project Team, in collaboration with members of the Cumulative Risk Team and the Risk Assessment Services Team. NCEA-Cin scientists conducted portions of this research, presented at the workshop, and are authors of this report. A number of other EPA scientists also contributed their ideas, provided discussions and review, and wrote text toward completion of this effort. These individuals are listed below.

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This document was subjected to an external review by an expert panel on June 20-21, 2000. A workshop report was generated and finalized in July 2000 (Appendix II). The final draft of this document was greatly influenced and enhanced by the interactions with the expert reviewers. The distinguished members of the expert panel, their affiliations and areas of expertise are:

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DOCUMENT CONTENTS

REPORT 1: EPA Conclusions and Conceptual Approach for Conducting a Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems. September 30, 2000.

REPORT 2: Workshop Report: Novel Methods for Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems. January, 2000.

APPENDIX I: Workshop Pre-meeting Report: The Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems. April, 1999. NCEA-C-0584

APPENDIX II: Peer Review Workshop Report: The Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems. July, 2000.

REPORT 1:

EPA CONCLUSIONS AND CONCEPTUAL APPROACH FOR CONDUCTING A RISK ASSESSMENT OF MIXTURES OF DISINFECTION BY-PRODUCTS (DBPs) FOR DRINKING WATER TREATMENT SYSTEMS

September 30, 2000

REPORT 1: TABLE OF CONTENTS

Page

FOREWORD iii

EPA RESEARCHERS v

EXTERNAL REVIEW PANEL vi

APRIL 1999 WORKSHOP PARTICIPANTS vii

DOCUMENT CONTENTS viii

LIST OF TABLES xiii

LIST OF FIGURES xiv

EXECUTIVE SUMMARY xv

1. INTRODUCTION R1-1

1.1. PURPOSE R1-1
1.2. STRUCTURE OF THE DOCUMENT R1-2
1.3. BACKGROUND R1-5

2. SUMMARY: CURRENT STATE OF THE SCIENCE R1-8

2.1. INTRODUCTION R1-8

2.1.1. Risk Assessment Paradigm for DBP Mixtures R1-9

2.2. MIXTURES RISK ASSESSMENT METHODS R1-11

2.2.1. Key Concepts R1-12
2.2.2. Data-Driven Approaches for Assessing Risks Posed by Chemical Mixtures R1-13
2.2.3. Risk Characterization and Uncertainty R1-15
2.2.4. Applying Mixtures Methods to DBP Mixtures Risk Estimation R1-23

2.3. DBP EXPOSURES R1-27

2.3.1. DBP Concentrations R1-33
2.3.2 Tap Water Exposure R1-36

Page

2.4. DBP HEALTH EFFECTS DATA (HAZARD IDENTIFICATION AND DOSE-RESPONSE) R1-38

2.4.1. Summary of Epidemiology Studies R1-39
2.4.2. Summary of Single Chemical Toxicology Studies R1-58
2.4.3. Summary of Mixtures Toxicology *In Vivo* and *In Vitro* Studies R1-70

2.5. THE UNIDENTIFIED FRACTION OF DBPS R1-82

2.6. RISK ASSESSMENT USING A RESPONSE ADDITION APPROACH R1-85

2.6.1. Development of Distributions of Risks R1-91

3. EPA'S MAIN CONCLUSIONS AND RECOMMENDATIONS BASED ON THE APRIL 1999 WORKSHOP R1-105

3.1. EPA RECOMMENDATIONS: INTEGRATION OF EPIDEMIOLOGIC AND TOXICOLOGIC DATA IN THE RISK ASSESSMENT R1-106

3.2. IMPROVEMENTS IN EXPOSURE CHARACTERIZATION R1-109

3.3. ACCOUNTING FOR POTENTIAL TOXICITY OF UNIDENTIFIED DBPs R1-112

3.4. RISK ASSESSMENT OF DEVELOPMENTAL AND REPRODUCTIVE EFFECTS R1-114

3.5. RISK ASSESSMENT OF CARCINOGENIC EFFECTS R1-116

3.6. ACCOUNTING FOR VARIABILITY AND UNCERTAINTY R1-118

3.6.1. Dose-Response Issues R1-118
3.6.2. Exposure Issues R1-120

3.7. MIXTURE RISK CHARACTERIZATION METHODS R1-121

REPORT 1: TABLE OF CONTENTS (cont.)

Page

4. CONCEPTUAL MODEL FOR A CUMULATIVE RISK APPROACH R1-124

4.1. MODEL CONSIDERATIONS AND REQUIREMENTS R1-124
4.2. CUMULATIVE RISK APPROACH R1-126

4.2.1 Relative Potency Factors R1-133
4.2.2. Cumulative Relative Potency Factors R1-142
4.2.3. Unidentified DBPs R1-147
4.2.4. Discussion R1-148

5. RESEARCH NEEDS R1-150

5.1. METHODS RESEARCH R1-150

5.2. RESEARCH ON APPLICATION OF A CUMULATIVE RELATIVE POTENCY FACTOR APPROACH R1-151

5.3. EPIDEMIOLOGIC RESEARCH R1-151

5.4. DEVELOPMENT OF TOXICOLOGIC DATA R1-152

6. REFERENCES R1-155

APPENDIX R1-1: Summary: ILSI Workshop on Unidentified DBPs R1-171

LIST OF TABLES

No.	Title	Page
1	Methods for Component Data	R1-16
2	Methods for Whole Mixture Data	R1-19
3	DBPs Commonly Found in Finished Drinking Water	R1-34
4	Summary of Interview-Based, Case-Control and Cohort Studies for Cancer	R1-41
5	Summary of Epidemiological Studies for Adverse Pregnancy Outcomes	R1-48
6	Verified DBP Assessments on EPA's Integrated Risk Information System (IRIS)	R1-59
7	Available Toxicity Data for DBP Mixtures	R1-71
8	Identified Disinfection By-Products (Set *k*) for the Response Addition Illustration	R1-89
9	Tap Water Consumption in the General Population (mL/kg-day) by 5-Year Age Groups	R1-96
10	DBP Concentrations Used in the Illustration	R1-97
11	Incremental Cancer Risk per mg/kg-day for Identified DBPs	R1-99
12	Hypothetical Characterization of the Toxicologic Properties of Five DBPs that are Liver Carcinogens in Animal Studies	R1-140
13	Hypothetical Example: Relative Potency Factors (RPF) and Equivalent Exposures for Five Liver Carcinogens	R1-141
14	Hypothetical Characterization of Several Relative Potency Factors for the Same DBP Mixture; Different Routes, Different Effects	R1-147

LIST OF FIGURES

No.	Title	Page
1	Schematic of DBP Mixtures Risk Assessment	R1-4
2	Flow Chart for Data-Driven Approach to Selection of Mixtures Risk Assessment Method (U.S. EPA, 1999c)	R1-14
3	Mapping of Risk Assessment Approaches to Drinking Water Health Effects Studies	R1-24
4	Typical Distribution of Disinfection By-Products	R1-35
5	Examples of DBPs in Groups A, B and C are Illustrated	R1-84
6	Process for Estimation of Risk for Unidentified TOX (Group B Chemicals)	R1-90
7	2 Stage Monte Carlo Analysis of Variability and Uncertainty, R = Y*C*S	R1-92
8	Monte Carlo Results for Lifetime Cancer Risk for a Chlorination System, R = Y*C*S	R1-94
9	Biological Marker Components in Sequential Progression from Exposure to Disease	R1-127
10	Schematic of CRPF Decision Process	R1-131
11	RPF Approach for Three Hypothetical Chemicals, Single Effect, Route and Duration	R1-137
12	RPF Approach for Three Hypothetical Chemicals, Two Exposure Routes	R1-139
13	Integration of Dose Addition and Response Addition to Mixture Risk for a Single Exposure Route	R1-144
14	Integration of Dose Addition and Response Addition to Estimate Mixture Risk for Two Exposure Routes	R1-145

EXECUTIVE SUMMARY

Human exposure to disinfection by-products (DBPs) in drinking water presents an example of a multiple chemical, multiple route exposure that is ubiquitous across all segments of the U.S. population, as well as the populations of many developed countries around the world. DBPs may be present in liquid, vapor, or aerosol form(s); can enter the body via ingestion, respiration, or dermal penetration; and may be metabolized before distribution to the target organ(s).

Disinfectants such as free chlorine, combined chlorine, ozone, and chlorine dioxide react with naturally occurring organic and inorganic material in the incoming source water to produce a variety of DBPs. Several hundred chemically distinct DBPs have been identified in the laboratory, but in general, as illustrated for the organic halogens in Figure E-1, approximately 50% of the DBPs is typically made up of an unknown number of unidentified chemicals (Miltner et al., 1990; Richardson, 1998; Weinberg, 1999).

Exposure to DBPs is a potential human health hazard; both the epidemiologic and toxicologic literature provide some evidence of potential adverse health effects. Taken as a whole, epidemiologic studies on chlorinated drinking water offer some evidence of an association with certain cancers, reproductive and developmental effects, warranting further investigation. In contrast, in whole mixture studies, toxic effects have not been observed when animals are exposed to finished drinking water, but there is evidence of mutagenicity in *in vitro* studies of drinking water extracts and concentrates. In *in vivo* studies at high doses of individual DBPs and some defined

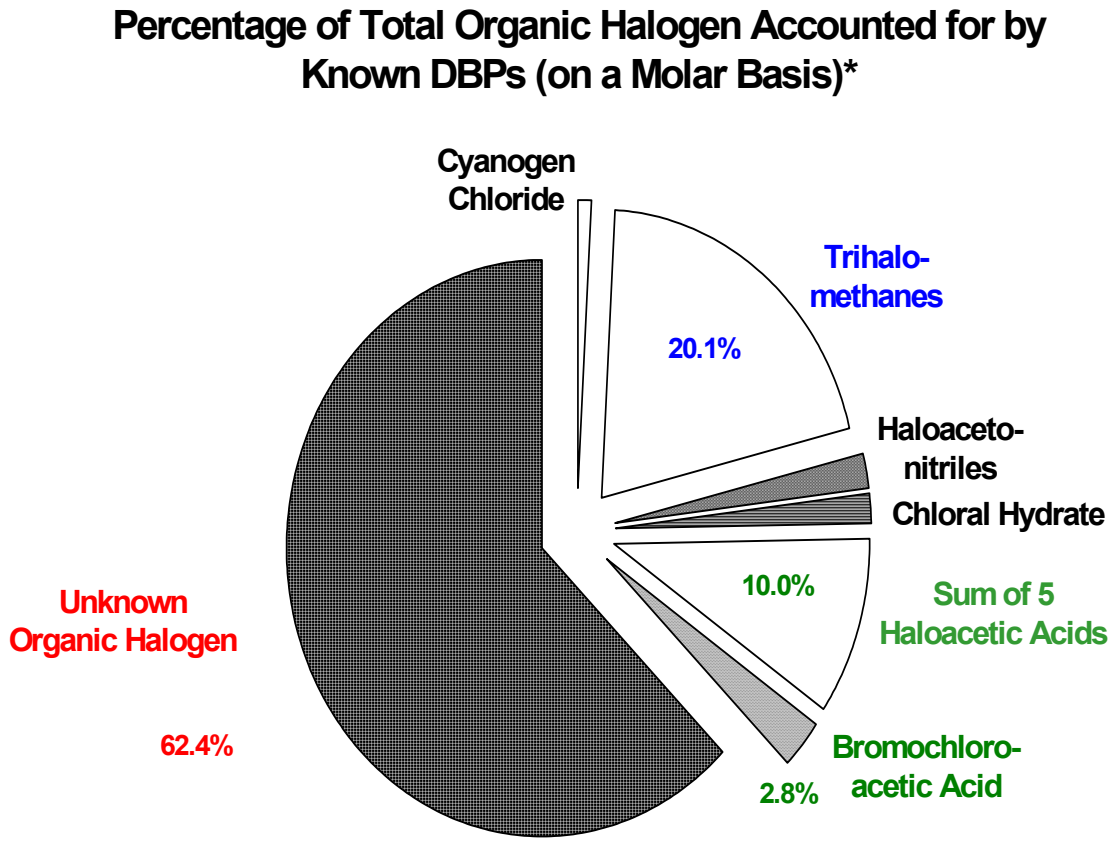


FIGURE E-1

Typical Distribution of Disinfection By-Products

Source: Stuart Krasner, Metropolitan Water District of So. California, 1999

DBP mixtures, there is evidence of carcinogenicity, reproductive and developmental effects, nephrotoxicity and hepatotoxicity. Thus, the existence of adverse human health effects from exposure to environmental levels of DBPs is certainly possible, but also highly uncertain.

The need to study the conduct of a risk assessment for DBP mixtures arose both as a mandate and also as a logical scientific direction. Under 42 USC § 300 of the Safe Drinking Water Act Amendments of 1996, it is stated that the U.S. Environmental Protection Agency (EPA) will "develop new approaches to the study of complex mixtures, such as mixtures found in drinking water..." In addition, the EPA's Office of Water drafted a *Research Plan for Microbial Pathogens and DBPs in Drinking Water* that calls for the characterization of DBP mixtures risk (U.S. EPA, 1997a). In response to these mandates, U.S. EPA's National Center for Environmental Assessment - Cincinnati (NCEA-Cin) began investigating the DBP mixture issue and developed a number of scientific interests that included: developing a method to compare DBP risks across various drinking water treatments; evaluating potential drinking water health risks by comparing and integrating toxicology and epidemiology data; and furthering the development of mixtures risk assessment methods for general use in evaluating environmental problems.

The risk assessment of disinfection by-product mixtures in drinking water addresses an important issue in environmental health and also facilitates risk assessment methods development. To improve its assessment of DBP mixture health risk, the NCEA-Cin has been exploring a number of novel approaches to generating realistic, central tendency estimates of potential health risks, despite data limitations and uncertainties. The purpose of this document is to detail the response addition

method developed to estimate DBP mixtures risk; discuss the state of DBP toxicity and exposure data; present available methods for mixtures risk characterization that may be applicable; explore alternative methodologies; and make recommendations for future applications and methodological developments. This effort has resulted in the production of three interrelated research reports and an external review report contained in this document, as follows:

- Report 1, September, 2000: EPA's conclusions, recommendations, conceptual approach, and future directions regarding the conduct of a DBP mixture risk assessment. Although new information and ideas not in Report 2 or Appendix I are included, Report 1 is not written as a stand-alone document; it is meant to be read in conjunction with Report 2 and Appendix I.

- Report 2, January, 2000: Summary of presentations and discussions at an April 1999 workshop where scientists examined an illustrative example of a DBP mixtures risk assessment, presented ideas to advance the approach, and recommended research and development directions.

- Appendix I, April, 1999: An illustrative example of a DBP mixtures risk assessment using a response addition approach developed by NCEA-Cin, including data, assumptions and statistical methods used. Shows resulting risk distributions and uncertainty analysis.

- Appendix II, July, 2000: External scientific review comments and recommendations, concentrated primarily on Report 1 of this document.

The authors of this document have chosen to evaluate DBP health effects using mixture risk assessment approaches, rather than assessing each chemical separately. These approaches acknowledge real human exposures, as well as account for any compounded effects from exposure to the low levels of multiple DBPs that are found in drinking water. Because toxic effects have not been observed in animal studies when the exposures are to low doses of DBPs and because the epidemiologic data are inconsistent across studies with only relatively weak to moderate associations noted, the existence of human health risks is questionable, but cannot be entirely dismissed.

If it is assumed, however, that the human health effects suggested in some epidemiologic studies are real, then one hypothesis that explains the discrepancies between the epidemiologic results and the lack of effects in animals exposed to finished drinking water (i.e., water that has undergone a disinfection process) is that there is an effect from exposure to the mixture of DBPs greater than what would be expected from a low level exposure to any individual DBP. The authors of this document have chosen this hypothesis — that adverse health effects exist and are attributable to exposure to the complex mixture — as the basic premise on which to build a risk assessment approach.

The EPA has both experience and guidance available to address the issue of DBP mixture risk estimation. The EPA generally follows the paradigm established by the National Academy of Sciences (NRC, 1983) when performing a human health risk assessment. This paradigm consists of a group of inter-related processes: hazard identification, dose response assessment, exposure assessment and risk characterization. These processes are also the basis for the current DBP mixtures risk assessment and are the elements that must be addressed in making improvements. The EPA began to address concerns over health risks from multiple chemical exposures in the 1980s and issued its *Guidelines for the Health Risk Assessment of Chemical Mixtures* in 1986 (U.S. EPA, 1986). Continued interest and research in this area and in multiple route exposures has resulted in other documents over the years (U.S. EPA, 1989a,b, 1990, 1999b). In 2001, the EPA is expected to release further guidance on the assessment of risks posed by exposures to chemical mixtures (U.S. EPA, 1999c, 2000a).

Three basic approaches are available for quantifying health risk for a chemical mixture, depending on the type of data available to the risk assessor (U.S. EPA, 1986, 1999c, 2000a). These approaches are: data on the complex mixture of concern; data on a similar mixture; or data on the individual components of the mixture or on their interactions. Figure E-2 illustrates that these three approaches can be mapped directly to three toxicity testing scenarios recommended by an International Life Sciences Institute (ILSI) expert panel on DBP mixtures toxicity (ILSI, 1998). Figure E-2 also shows the potential uses of such data for risk assessment.

The initial risk assessment was done to illustrate how DBP mixture risk could be quantified using occurrence data, DBP toxicity estimates, and human drinking water consumption rate data (U.S. EPA, 1998a, 1999a). (The details of this risk characterization, including exposure estimates, toxicity values and risk estimates are presented in full in Appendix I; presentations of this analysis from an April 1999 workshop are summarized in Section 2 of Report 2.)

This illustration was developed as a limited demonstration to evaluate:

- Whether sufficient data exist on exposure and toxicity to estimate DBP mixture risks
- If a reasonable risk assessment method for this effort is response addition (a component-based method for joining dose-response and exposure data to estimate risk for the mixture by estimating each individual chemical component's endpoint-specific risk at its measured exposure concentration and then summing these risks to yield the total mixture risk for that health endpoint)
- How to address and present the uncertainty and variability in the available data

Through the development of a reasonable set of assumptions regarding two hypothetical drinking water treatment interventions and the potential toxicity of the DBP

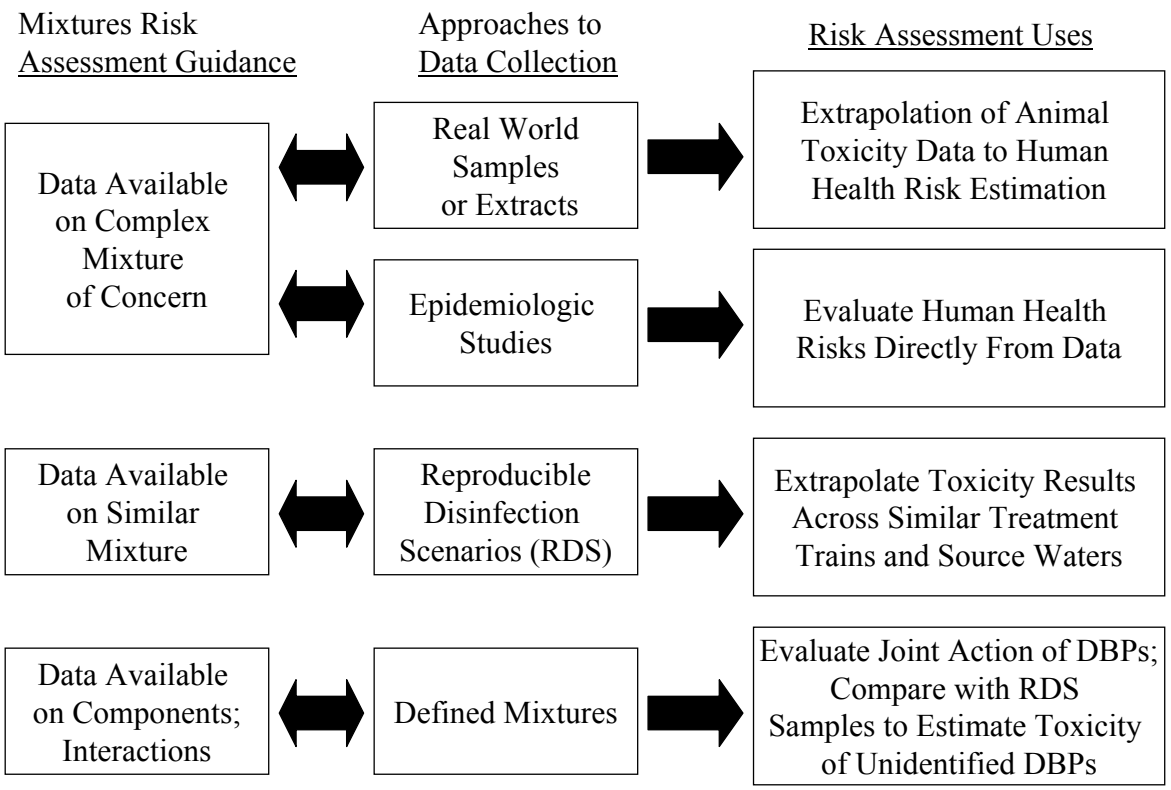


FIGURE E-2

Mapping of Risk Assessment Approaches to Drinking Water Health Effects Studies

mixtures, the illustration shows that facility-specific data can be used to develop distributions of DBP mixtures risk estimates for a drinking water treatment system. This illustration highlights critical areas where pertinent research could potentially change the outcomes of the analysis. The constraints of the illustration include:

- Comparison of only two alternative drinking water treatment technologies (a conventional chlorination treatment system and a pre-ozonation system followed by a conventional chlorination treatment system) with no comparison of gradations of application (e.g., changes in the levels of chlorination or ozone).
- Limitations of available input data for DBP concentrations and toxicity values and tap water consumption rates to develop distributions for conducting an uncertainty analysis.
- Constraints concerning the current scientific measurement and temporal distribution of concentrations of DBPs in treated drinking water from a single treatment system. Additionally, no attempt has been made to characterize the impact of the water distribution system on estimated DBP concentrations.
- Limitations in the understanding of the relationship between health effects and DBP exposures through drinking waters inherent in the risk assessments of these agents both collectively and individually.
- Evaluation of systems functioning normally without taking into account scenarios that may result from perturbation(s) or critical failures of the drinking water treatment plant.

In this approach, the epidemiologic data and the toxicologic data were used to identify the nature of the hazard posed by DBPs. In this case, cancer and reproductive and developmental effects were identified to be of concern from DBP exposures using both the epidemiologic and toxicologic data as corroborating evidence. Only the DBP toxicology data were used in the dose-response assessment; however, the epidemiologic attributable risk estimates were incorporated into the uncertainty analysis.

The response-addition model assumes that risk (unitless) is related to the concentration and potency of each individual component chemical as follows:

$$risk = Y \times \frac{1}{1000}\left[\sum_{i \in k} C_i S_i + \sum_{i \in u} C_i S_i\right] \quad \text{(E-1)}$$

where

Y = Tap water intake (L/kg-day)

C_i = Concentration of DBP_i (µg/L)

S_i = Incremental toxicity for DBP_i $(mg/kg\text{-}day)^{-1}$

1 mg = 1000 µg

k = Set of identified DBP

u = Set of unidentified DBP

Equation E-1 is a theoretical construct, as it requires information that is not known (i.e., *u*, the set of unidentified DBP, will never be completely analytically characterized as to chemical species). Measured data on total tap water consumption (Y) were available for the analysis (Ershow and Cantor,1989). For each of the identified DBPs that comprised set *k*, there was a measure of its concentration in tap water, C_i, and its incremental risk (S_i), so the summation, $\Sigma C_i S_i$, was calculated. For the unidentified DBPs, set *u*, these values were unknown, so the summation, $\Sigma C_i S_i$, had to be estimated.

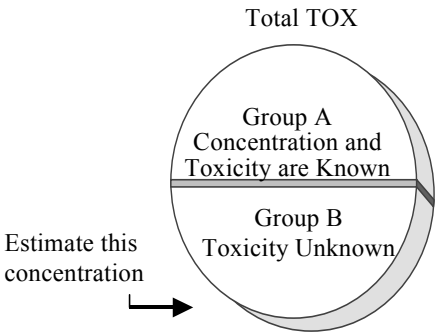
Figure E-3 shows the steps developed to estimate the potential toxicity of set *u* using data on the known DBPs (Group A), summary measures of Total Organic Halide (TOX), expert judgment, and Quantitative Structure Toxicity Relationship

Step 1

$$Risk_B = \frac{Conc_B}{Conc_A} * Risk_A$$

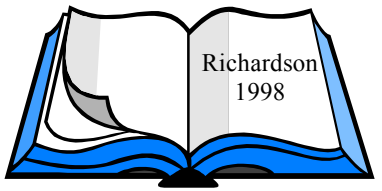
Assume equal Risk of Group A and Group B DBPs per unit of TOX for a specific health endpoint

Step 2



Step 3

Identify DBPs that may be present in Group B



Step 4

1) Assume that each member of Group B accounts for the same fraction of TOX

2) Use QSTR to classify health endpoints associated with individual Group B DBPs

Step 5

Assume that the % of Group B DBPs classified by QSTR as associated with an individual health endpoint represents the actual proportion of Group B's concentration that can be associated with the individual health endpoint

Step 6

1) Use information in steps 2-5 to calculate $Risk_B$ as shown in Step1.

2) Using assumption of response addition, add risks estimated for DBPs in Groups A and B.

FIGURE E-3

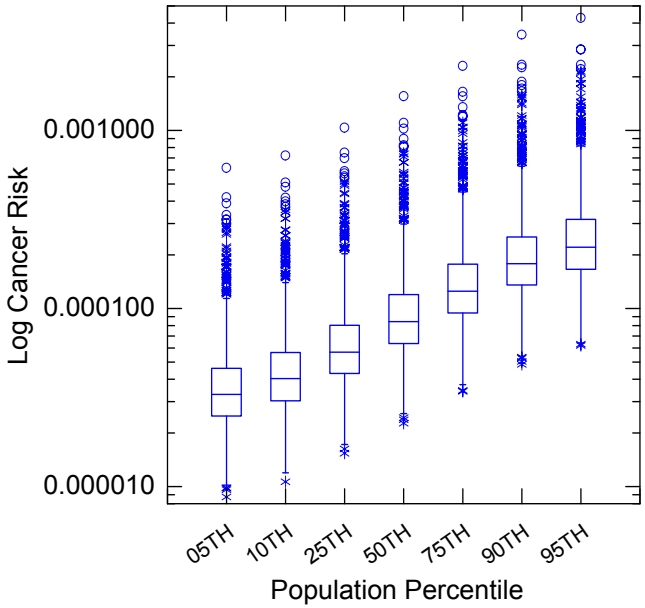
Process for Estimation of Risk for Unidentified TOX (Group B Chemicals)

(QSTR) modeling techniques. This process estimated risk only for the unidentified organic halides (Group B); the non-halogenated DBPs (Group C) were not included. The total endpoint-specific risk, using equation E-1, is the sum of the risks for the identified DBPs (Group A), as calculated from known toxicity and measurement data, and the unidentified DBPs (Group B), as estimated using Steps 1 through 6 of Figure E-3.

To address variability and uncertainty, a two-stage Monte Carlo analysis was performed to calculate distributions of DBP mixture risk. Input distributions were developed to quantify variability (heterogeneity) in the population tap water consumption rates (Y), (i.e., the range of plausible risks resulting from differences among members of the population) and to quantify uncertainty (i.e., the range of plausible risks for each individual corresponding to alternative plausible assumptions) for DBP concentration data (C_i) and DBP toxicity estimates (S_i). The result of such an analysis is the development of risk distributions, as shown in Figure E-4, that reflect variability on the X-axis and uncertainty on the Y-axis.

EPA held a workshop in April 1999 to examine the response addition illustration and to advance the development of methodology to assess health risk for mixtures of drinking water DBPs. The workshop assembled a multi-disciplinary group of scientists that worked together to formulate a range of approaches to solving this problem. They then determined the most practical and scientifically sound directions the EPA should take to improve the risk assessment (see Charge to Participants, Attendees in Report 2). As a result of the April 1999 workshop, EPA identified the major issues for consideration regarding improvement of the DBP mixtures risk assessment

Uncertainty of Toxicity Values (S) and Concentration Estimates (C)



Population Variability In Drinking Water Consumption Rates (Y)

FIGURE E-4

Monte Carlo Results for Lifetime Cancer Risk for a Chlorination System, R = Y*C*S

methodology. The Workshop Report (Report 2) relates a number of discussions and recommendations made by the participants. Each of these was considered by EPA within the context of the EPA's previous experience with DBP mixtures risk assessment and was evaluated for scientific validity, feasibility of application in the near term, data availability, consistency with other EPA guidelines and practices, and relevance to risk assessment goals and regulatory needs. The selected recommendations are presented in Section 3 of Report 1. These were determined to potentially have the most significant impact in the near term on improving the DBP mixtures risk assessment. Additionally, a number of longer term research needs were identified; these are presented in Section 5 of Report 1.

A major recommendation is to approach human health risks posed by DBPs as a cumulative risk problem that can account for:

- Multiple routes of exposure
- Any toxicologic similarity among chemicals in the mixture (beyond target organ effects)
- Temporal issues of exposure.

A conceptual model, Cumulative Relative Potency Factors (CRPF), was developed with the following goals:

- To develop a mixtures approach with the flexibility to integrate selected mixtures risk models based on an understanding of the toxic mode-of-action
- To consider the temporal nature of DBP exposures and variability of human activity patterns and address and appropriately integrate exposures through the three routes of primary concern for environmental pollutants: ingestion, dermal, and inhalation
- To address the main endpoints of concern in the epidemiologic literature: developmental and reproductive effects and cancer

- To identify the “risk-relevant” components of DBP mixtures. This may include organic halides that are not measured individually as well as DBPs that are not halogenated
- To estimate risks for various drinking water treatment trains, reflecting differences in the DBPs formed and their concentrations over time in the distribution system
- To generate central tendency risk estimates along with their associated probability distributions; such distributions of risks are needed to appropriately reflect both the uncertainty and variability found in these data
- To identify specific measures to incorporate into future epidemiologic investigations that could improve exposure classification
- To develop mixtures risk characterization approaches to be used in the evaluation of causality.

The goal of the conceptual approach is the integration across routes of Relative Potency Factor (RPF)-based risk estimates (U.S. EPA, 2000a) that are route-specific for toxicologically similar subclasses of DBPs for an effect-specific period of duration. Once several RPF risk estimates are generated, then the analyst can make some assumptions relative to the likely relationships of the across-subclass risks and determine if and how the subclasses should be combined (e.g., a response addition assumption would lead to summing these RPF risks) to estimate the total risk estimate for the mixture (Figure E-5). This approach is designed to produce a transparent cumulative risk assessment because assumptions about the toxicity and the interactions must be specifically identified.

The RPF approach has been proposed as an interim approach for characterizing health risks associated with mixtures of chemical compounds that have data indicating that they are toxicologically similar (U.S. EPA, 1999c). To develop an RPF-based

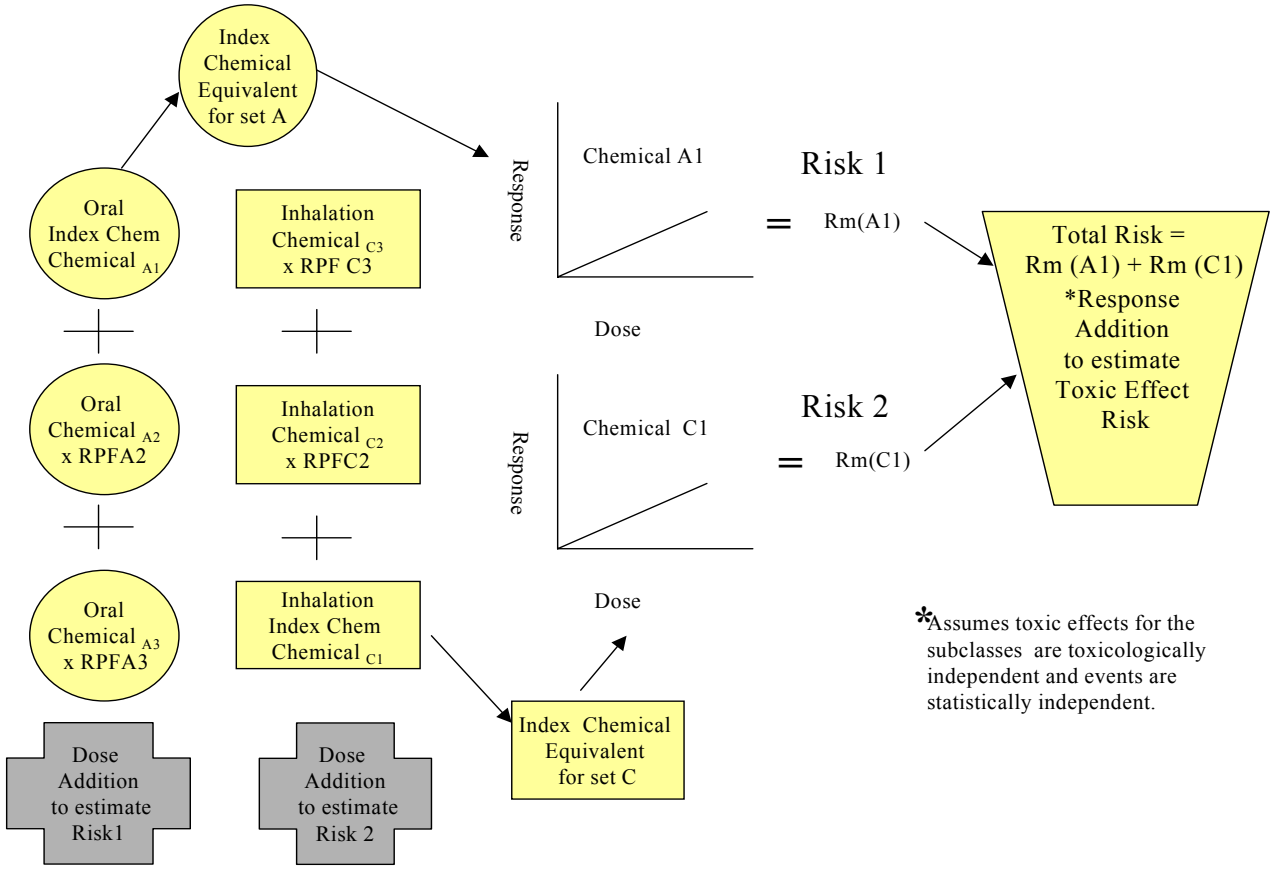


FIGURE E-5

Integration of Dose Addition and Response Addition to Estimate Mixture Risk for Two Exposure Routes

risk estimate for a class of chemicals, toxicologic data are needed at least for one component of the mixture (referred to as the index chemical), and scientific judgment is used to assess the relative toxicity of the other individual components in the mixture as well as of the mixture as a whole. The RPF approach assumes dose addition is appropriate for the related components that comprise the mixture or a subset of the mixture components. True dose addition assumes that the components of the mixture act by the same mode of action. The exposure level of each component in the mixture is scaled by its toxicity relative to that of the index chemical, resulting in an index chemical equivalent dose for each component (e.g., the columns of circles or rectangles in Figure E-5). This scaling factor (the RPF) is based on a comparison of relevant dose-response information between the index chemical and the component, including the results of toxicologic assays and analyses of structural similarity to other compounds of known toxicologic potential. For each component of the mixture, the RPF approach predicts an equivalent exposure in terms of the index chemical; these equivalent exposures are then summed to generate an index chemical-equivalent total mixture dose. The risk posed by the mixture is then estimated using the dose-response curve of the index chemical.

The development of RPF-based risk estimates and their integration with response addition in a CRPF approach addresses many of the shortcomings of the first response addition assessment; not all issues are addressed, however. The approach does not directly address the differences in risks for sensitive subpopulations or the contribution to the risk estimate that may be addressed by using what is known in the epidemiologic literature. In addition, application of CRPF promises to be a resource-intensive exercise that may be more technically correct than the application of response

addition, but, in the end, may not produce risk estimates very different in magnitude. Furthermore, an enormous problem lies in the fact that very few toxicity data are available for the dermal and inhalation routes of exposure.

The CRPF approach is a conceptual model for development of a cumulative risk assessment for DBP mixtures. It improves upon the initial response addition assessment by more carefully considering toxicologic similarities among chemicals, route of exposure, and physiologically-relevant time frames. It allows treatment system-specific exposures to be investigated and, although not specified in this discussion, does not preclude the use of human activity patterns and distribution system effects from being incorporated into the analysis. Risk estimates for the unidentified DBPs can also be included in the development of the RPF-based risk estimates. A probabilistic analysis and full risk characterization would be required with careful treatment of the variabilities and uncertainties examined and explained.

In summary, investigations into the potential human health risks from DBP mixture exposures are important to conduct because of both the ubiquitous nature of the exposures and the evidence of health effects in both the epidemiology and toxicology literature. In this research effort, we have made the following progress:

- NCEA-Cin has performed an assessment of human health risks for developmental and reproductive effects and cancer from exposure to DBP mixtures (Appendix I), using a response addition approach that incorporates data on the unidentified fraction of the DBPs and uses a probabilistic approach.

- NCEA-Cin has produced a workshop report (Report 2) that contains a wealth of information on the exposure, dose-response and risk characterization issues relative to DBP mixtures health risks that can be used by risk assessors interested in this area.

- NCEA-Cin has developed a new conceptual approach (Report 1), the Cumulative Relative Potency Factors (CRPF) method, for assessing

DBP mixtures health risks. The CRPF method improves on the response addition method by integrating data on mode of action and multiple routes of exposure over physiologically-relevant time frames.

- NCEA-Cin has recommended areas of research most critical for improving DBP mixtures health risk assessment (Report 1).

Improvements in the development of health risk estimates are needed, with the most important scientific directions to include:

- Integration of both human and animal toxicity data into the assessment
- Development of exposure models that incorporate dermal, oral and inhalation routes, human activity patterns, and measures of internal dose
- Collection of concentration data that are representative of real world drinking water samples, including additional information on the unidentified fraction of the DBPs
- Application of risk characterization methods that incorporate data on the toxic mode of action for the physiologically-relevant exposure time frame
- Consideration of sensitive subgroups in the population
- Analysis of variability in the data and uncertainty of the final risk estimates.

Research that addresses these improvements will be valuable not only to the human health risk assessment of DBP mixtures, but also to the advancement of chemical mixtures risk assessment methodology applicable to other environmental exposures.

1. INTRODUCTION

1.1. PURPOSE

The risk assessment of disinfection by-product (DBP) mixtures in drinking water addresses an important issue in environmental health and also facilitates risk assessment methods development. To improve its assessment of the DBP mixture health risk, NCEA-Cin has been exploring a number of novel approaches to generating realistic, central tendency estimates of potential health risks, despite data limitations and uncertainties. These include such risk characterization methods and adjuncts such as response addition, proportional-response addition, relative potency factors, dosimetry, quantitative structure activity relationships, development of distributions for relevant variables, and Monte Carlo simulation. The purpose of this document (i.e., Report 1, Report 2, and Appendix I) is to detail the response addition method that was initially developed to estimate DBP mixtures risk, discuss the state of DBP toxicity and exposure data, present available methods for mixtures risk characterization that may be applicable, explore alternative methodologies, and make recommendations for future applications and methodological developments.

The need to study the conduct of a risk assessment for DBP mixtures arose both as a mandate and also as a logical scientific direction. Under 42 USC § 300 of the Safe Drinking Water Act Amendments of 1996, it is stated that the EPA will "develop new approaches to the study of complex mixtures, such as mixtures found in drinking water..." In addition, the EPA's Office of Water drafted a *Research Plan for Microbial Pathogens and DBPs in Drinking Water* that calls for the characterization of DBP

mixtures risk (U.S. EPA, 1997a). In response to these mandates, NCEA-Cin began investigating the DBP mixture issue and identified a number of scientific interests, including: developing a method to compare DBP risks across various drinking water treatment interventions; evaluating potential drinking water health risks by comparing and integrating toxicology and epidemiology data; and furthering the development of mixtures risk assessment methods for general use in evaluating environmental problems.

1.2. STRUCTURE OF THE DOCUMENT

This effort has resulted in the production of three interrelated research reports and an external review report that are contained in this document as follows:

- Report 1, September, 2000: EPA's conclusions, recommendations, conceptual approach and future directions regarding the conduct of a DBP mixture risk assessment. Although new information and ideas not in Report 2 or Appendix I are included, Report 1 is not written as a stand-alone document; it is meant to be read in conjunction with Report 2 and Appendix I.

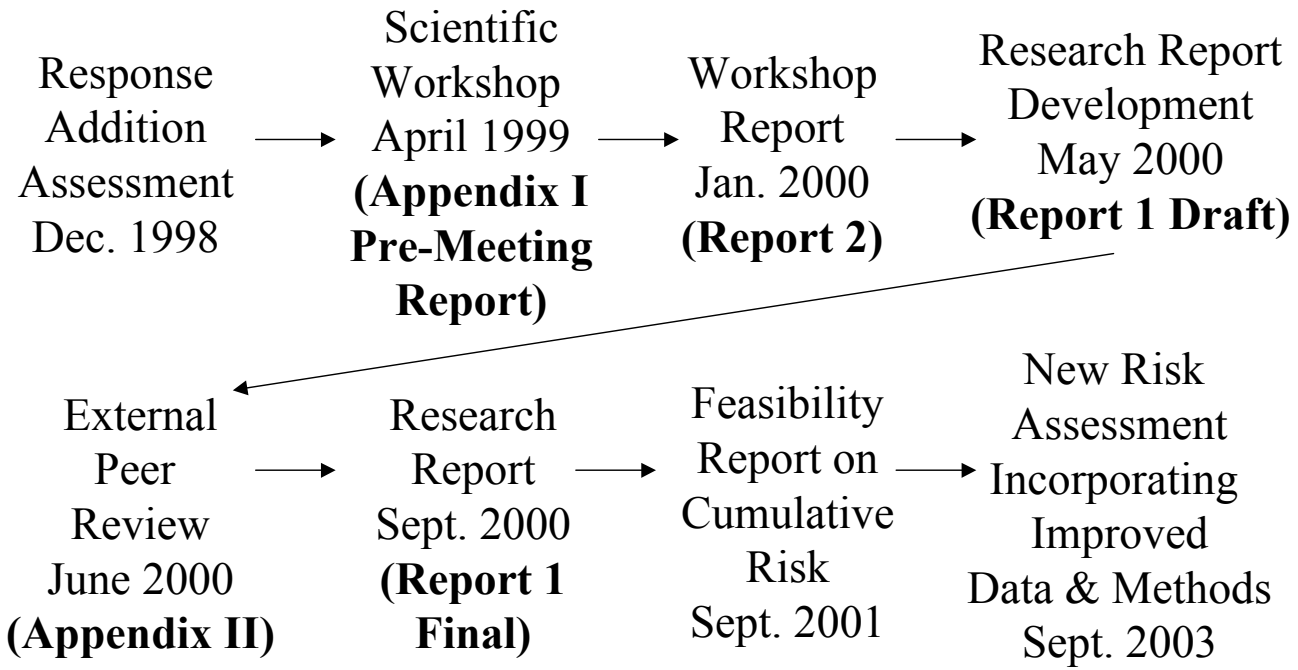
- Report 2, January, 2000: Summary of presentations and discussions at an April 1999 workshop where scientists examined an illustrative example of a DBP mixtures risk assessment, presented ideas to advance the approach, and recommended research and development directions.

- Appendix I, April, 1999: The illustrative example of a DBP mixtures risk assessment (using a response addition approach) developed by NCEA-Cin, including data, assumptions and statistical methods used. Shows resulting risk distributions and uncertainty analysis.

- Appendix II, July, 2000: External scientific review of the Research Report. Comments and recommendations are concentrated primarily on Report 1 of this document.

Figure 1 illustrates the process NCEA-Cin has followed to produce this document and projects subsequent activities in this research area. The initial assessment of the project in December 1998 (U.S. EPA, 1998a) was subsequently developed into a pre-meeting report for the April 1999 workshop on this subject entitled: *Workshop Pre-Meeting Report: The Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems* (U.S. EPA, 1999a) Appendix 1 details the response addition approach to estimating DBP mixture risk. During this initial assessment, NCEA-Cin scientists recognized a number of areas for improvement and held the April 1999 workshop to examine the response addition method, present ideas to advance the approach, and generate some conclusions relative to new research and development directions. The resulting workshop report is presented as Report 2 entitled: *Workshop Report: Novel Methods for Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems.* Finally, based on information developed in the April 1999 workshop, EPA scientists reached a number of conclusions relative to this area of research and developed an approach to the assessment of cumulative risk. This information is presented as Report 1, entitled *EPA Conclusions and Conceptual Approach for Conducting a Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems.* Report 1 is a composite document linked to Report 2 and Appendix I by pointers within the text to provide the reader with additional information on a topic area. Appendix II contains the external review report entitled: *Peer Review of the "Research Report: The Risk Assessment of Mixtures of Disinfection Byproducts (DBPs) for Drinking Water*

Figure 1
Schematic of DBP Mixtures Risk Assessment



Treatment Systems." As indicated in Figure 1, additional research and assessment work on DBP mixtures risk assessment is ongoing.

1.3. BACKGROUND

The authors of this document have chosen to evaluate DBP health effects using mixture risk assessment approaches, rather than assessing each individual chemical separately. These approaches acknowledge real human exposures, as well as account for any compounded effects from exposure to the low levels of multiple DBPs found in drinking water. Because toxic effects have not been observed in animal studies when the exposures are to low doses of DBPs and because the epidemiologic data are inconsistent across studies with only relatively weak to moderate associations noted, the existence of human health risks is questionable, but cannot be entirely dismissed. If it is assumed, however, that the human health effects suggested in some epidemiologic studies are real, then several hypotheses can be posed to explain the discrepancies between the epidemiologic results and the lack of effects in animals exposed to finished drinking water (i.e., water that has undergone a disinfection process). Such hypotheses include the following:

- There is an effect from exposure to the mixture of DBPs that is at least additive (if not synergistic) in nature, so that toxicology studies involving low levels of individual DBPs are inadequate to explain the health effects found in the positive epidemiologic data
- Effects in humans are the result of chronic, repetitive insult from daily exposure to DBP mixtures; effects in humans may occur only in sensitive individuals who are genetically predisposed or in high end consumers of drinking water
- Laboratory animals differ from humans in physiology, biochemistry, anatomy, genetic heterogeneity and lifestyle factors (e.g., high fat diets) that prevent demonstration of the same health outcomes across species

- Laboratory studies to date expose animals by only a single route, usually oral, so that effects resulting from a combined oral-dermal-inhalation exposure are not observed

- Effects in epidemiologic studies are the result of exposure to other environmental contaminants, such as metals, inorganic materials or pesticides in the drinking water, so that animal studies solely focused on DBPs will not corroborate epidemiologic findings.

Although it may be noted that these hypotheses are not mutually exclusive, the authors of this document have chosen the first hypothesis (that adverse health effects exist and are attributable to exposure to the complex mixture) as the basic premise on which to build a risk assessment approach.

The specific goals of the DBP mixtures risk assessment are the following:

- To compare DBP risks for drinking water treatment trains that reflect differences in DBP production and concentrations

- To make *reasonable risk estimates* for all endpoints of concern because of suggested cancer, reproductive and developmental effects in the epidemiologic literature

- To develop *distributions of risks* that reflect their uncertainty and variability for use in sensitivity analyses

- To incorporate information on both the *unknown and known DBPs* into the risk estimate.

The response addition approach (Section 2.5. of this report and Appendix I) was used as a first step in this process, although a number of factors were not addressed. Specifically, this initial assessment:

- Did not address *multiple exposure routes* (dermal, oral, inhalation)

- Did not assess multiple *time frames* or physiologically relevant time frames

- Did not use *epidemiologic data* for quantitative risk assessment

- Did not take into account *human activity patterns* to adjust exposure
- Did not make *dosimetric adjustments* to account for toxic mode of action, including consideration of pharmacokinetic and pharmacodynamic determinants of observed effect
- Did not address *unidentified by-products of disinfection other than* organic halides;
- Dd not use *alternative Quantitative Structure Activity Relationship models* in assessing potential toxicity of unidentified compounds
- Did not utilize *alternative mixtures risk characterization models* to derive estimates of risk.

These topics were addressed in the April 1999 workshop (Report 2) and have become the basis for proposing a new conceptual model for assessing DBP mixture risk.

2. SUMMARY: CURRENT STATE OF THE SCIENCE

2.1. INTRODUCTION

Humans are exposed concurrently and sequentially to chemical mixtures at various exposure levels. The by-products formed during chemical disinfection of water present an example of multiple chemical, multiple route exposure that is ubiquitous across all segments of the U.S. population, as well as the populations of many developed countries around the world. Human exposure to the chemicals formed as by-products of chemical disinfection of water is an example of both a concurrent exposure to a complex mixture of chemicals (the mixture of chemicals in the glass of water consumed today) and a temporally separated mixtures exposure (exposure to the DBPs in the glass of water consumed today is temporally separated from the DBPs consumed yesterday, as well as from the DBPs encountered during bathing in the morning).

The health benefits of chemical disinfection, i.e., dramatic decreases in both morbidity and mortality from water-borne diseases, are clearly evident (Regli et al., 1993). A consequence of water disinfection however, is low-level exposure to myriad DBPs. Disinfectants such as free chlorine, combined chlorine (monochloramine), ozone, and chlorine dioxide [the most common oxidants and disinfectants used (Singer, 1995)] react with naturally occurring organic and inorganic material in the incoming source water to produce a variety of DBPs. A number of factors influence the formation of DBPs: the type, concentration and point of application of the disinfectant; the type and concentration of organic and inorganic precursor material; the disinfectant contact

time; and source water characteristics of pH, bromide concentration and temperature (Singer, 1995; Fair, 1995). Several hundred chemically distinct DBPs have been identified in the laboratory but, in general, approximately 50% of the DBPs is made up of an unknown number of unidentified chemicals (Miltner et al., 1990; Richardson, 1998; Weinberg, 1999).

Human health risks from exposure to DBPs are of concern; both the epidemiologic and toxicologic literature provide some evidence of potential adverse health effects. Taken as a whole, epidemiologic studies on chlorinated drinking water offer some evidence of an association with certain cancers, and reproductive and developmental effects, warranting further investigation. In contrast, in whole mixture studies, toxic effects have not been observed when animals are exposed to finished drinking water, but there is evidence of mutagenicity in *in vitro* studies of drinking water extracts and concentrates. In *in vivo* studies at high doses of individual DBPs and some defined DBP mixtures, there is evidence of carcinogenicity, reproductive and developmental effects, nephrotoxicity and hepatotoxicity. Thus, the existence of adverse human health effects from exposure to environmental levels of DBPs is certainly possible, but also highly uncertain.

2.1.1. Risk Assessment Paradigm for DBP Mixtures. The EPA generally follows the paradigm established by the National Academy of Sciences (NRC, 1983) when performing a human health risk assessment. This paradigm consists of a group of interrelated processes: hazard identification, dose-response assessment, exposure assessment and risk characterization. These processes are also the basis for the

current DBP mixtures risk assessment and are the elements that must be addressed in making improvements. These elements are described briefly as follows:

1) Hazard Identification. Available data on biological endpoints are used to determine if the DBPs are likely to pose a hazard to human health. These data are also used to define the type of potential hazard, its severity, and the modes of action associated with the chemicals of interest. For mixtures, hazard identification must also consider potential interaction effects from exposure to the combination of DBPs and their combined doses.

2) Dose-Response Assessment. Data are used to estimate the concentrations of DBPs that may elicit an adverse effect in humans. The risk assessor may define a quantitative dose-response relationship usable for low dose exposure, often by applying mathematical models to the data. For mixtures, dose-response assessment must consider the potential for effects below individual chemical thresholds as well as incorporate judgments related to similarity of mode-of-action within or between mixtures.

3) Exposure Assessment. Exposure assessment uses available data relevant to population exposure, such as concentration data, tap water consumption patterns, and biomarker information to determine the extent to which a population is exposed to DBPs. Fate and transport of the DBPs in the environment, routes of exposure, pharmacokinetics and pharmacodynamics of the DBPs once in the body may all be considered in the exposure assessment. For mixtures, exposure assessment must take into account chemical characterization of unidentified DBPs in the complex mixture and the variability of the mixture in the distribution system over time.

4) Risk Characterization. This step in the paradigm summarizes assessments of human health, identifies human sub-populations at elevated risk, assesses exposures from multiple environmental media and describes the uncertainty and variability in these assessments. For mixtures, risk characterization must evaluate how well the assumptions made about interaction effects, toxicologic similarity of mixtures or their components, and exposure can be supported by the data. In both the exposure assessment and the dose-response assessment steps for a chemical mixtures risk assessment, the analyst must determine whether the mixture evaluated in the laboratory is "sufficiently similar" to the mixture encountered in the environment. This judgement of sufficient similarity between the "tested" mixture and the "environmental" mixture is a unique element of the risk characterization step in the chemical mixtures risk assessment paradigm.

2.2. MIXTURES RISK ASSESSMENT METHODS

The EPA began to address concerns over health risks from multiple chemical exposures in the 1980s and issued its *Guidelines for the Health Risk Assessment of Chemical Mixtures* in 1986 (U.S. EPA, 1986). Continued interest and research in this area and in multiple route exposures has resulted in other documents over the years (U.S. EPA, 1989a, 1989b, 1990, 1999b). In 2001, the EPA is expected to release further guidance on the assessment of risks posed by exposures to chemical mixtures (U.S. EPA. 1999c; 2000a). A number of publications provide additional depth and information on chemical mixtures toxicology and risk assessment methods for complex mixtures (see, e.g., Cassee et al., 1998; Hertzberg et al., 1999; Krishnan and Brodeur,

1991; Mumtaz et al., 1997a, 1998; NRC, 1988; Simmons, 1995a; Svendsgaard and Hertzberg, 1994; Teuschler and Hertzberg, 1995; Yang, 1994; Yang and Suk, 1998).

2.2.1. Key Concepts. Several important concepts have evolved relative to the evaluation of chemical mixtures (U.S. EPA, 1999c). The first is the role of toxicologic similarity which can be considered along a spectrum of information on toxicologic action from *mechanism-of-action,* specific molecular understanding of a toxicologic process (e.g., DNA damage due to adduct formation), to *mode-of-action*, a more general understanding of these processes at the tissue level in the body (e.g., centrilobular necrosis of the liver), to *toxicologic similarity*, toxicologic action expressed in broad terms such as at the target organ level (e.g., enzyme changes in the liver). Assumptions about toxicologic similarity play an important role in chemical risk assessment evaluations.

The second key concept is the assumption of similarity or, in contrast, independence of action. The term, *sufficiently similar mixture*, refers to a mixture very close in composition to the mixture of concern; differences in their components and their proportions are small; and the data from the sufficiently similar mixture can be used to estimate risk for the mixture of concern. The term, *similar components,* refers to the single chemicals within a mixture that act by the same mode-of-action and may have comparable dose-response curves; a component-based risk assessment can be performed. The term, *group of similar mixtures*, refers to chemically-related classes of mixtures that act by a similar mode-of-action, have closely related chemical structures, and occur together routinely in environmental samples, usually because they are generated by the same commercial process or remain after environmental

transformation; chemical mixtures risk assessments are conducted using knowledge about the shifts in chemical structure and relative potency of the components. Finally, the term, *independence of action*, refers to a group of mixture components for which the toxicity caused by any single component is not influenced by the toxicity of the other components; the probabilities of toxic effects for the individual components can be combined.

The third key concept is understanding language referring to toxicologic interactions, defined here as any toxic responses that are greater than or less than what is observed under an assumption of *additivity*. The term, *additivity*, is used when the effect of the combination of chemicals can be estimated directly from the sum of the exposure levels (dose addition), the sum of the responses (response addition) of the individual components, or the sum of the biological effects of the individual components (effects addition). The most general terms for interaction effects are synergism (i.e., greater than additive) and antagonism (i.e., less than additive).

2.2.2. Data-Driven Approaches for Assessing Risks Posed by Chemical Mixtures. Figure 2 (U.S. EPA, 1999c) describes the selection of a chemical mixture risk assessment method, beginning with an assessment of data quality and availability and progressing to a number of judgments relative to data type, chemical composition, and toxicologic activity to choose among risk assessment methods. The major concerns are whether the available data are on components or whole mixtures; whether the data are composed of either similar components or similar mixtures that can be viewed as acting by similar toxicologic processes; whether the mixture components act by the same mode of action or are functionally independent; and whether the data may be

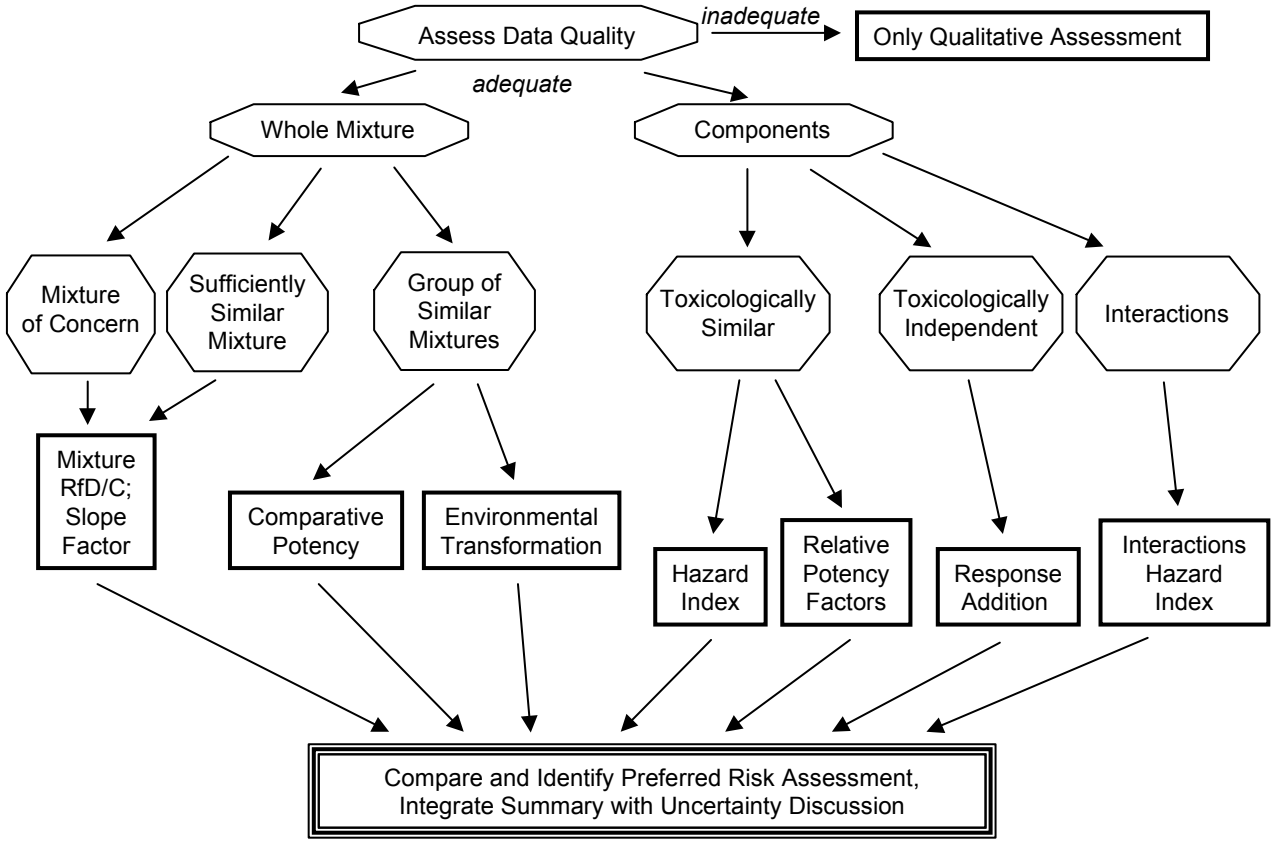


FIGURE 2

Flow Chart for Data Driven Approach to Selection of Mixtures Risk Assessment Method (U.S. EPA, 1999c)

grouped by emissions source, chemical structure or biologic activity. The results of such judgments point the risk assessor toward methods that are available for these specific types of data. Methods selected for whole mixtures depend on whether information is directly available on the mixture of concern or only on sufficiently similar mixtures or groups of similar mixtures. Methods available for component data depend on whether data on interactions are available, or whether the components act with a similar mode of action or are toxicologically independent. For all assessments based on data of adequate quality, the outcome is a quantitative assessment with a complete risk characterization and uncertainty discussion presented. Tables 1 and 2 contain short descriptions for many of the available methods indicated as endpoints in Figure 2, with references for further information.

Figure 2 is deceptively simple, as many of the issues presented in the diagram depend on scientific judgment or data that may not be readily available. In addition, there will often be mixtures for which whole mixture data and component data both exist, so the choice of method will not be clear (for example, both epidemiologic data and component toxicity data may exist). Furthermore, the true toxicologic mechanism-of-action is rarely known for a given mixture or even for most of its components; the judgments made of toxicologic similar action or independence of action, for example, will be uncertain. Thus, one approach that the risk assessor can take is to implement several of the methods that are practical to apply and evaluate the range of health risk estimates that are produced.

2.2.3. Risk Characterization and Uncertainty. Mixtures risk characterization requires the use of considerable judgment along with plausible approaches that must be

TABLE 1

Methods for Component Data

Approach [Type of Assessment]	Data Requirements	Strategy of Method	Ease of Use / Advantages	Assumptions	Limitations and Uncertainties	References
Response Addition [Risk Characterization for any Toxic Endpoint]	Toxicity data (measured in % responding) and exposure data on the mixture's components.	Risk estimated for each component using its dose-response curve at the exposure concentration. Component risks are added.	Easy to calculate. Data available on components (e.g., EPA's IRIS database)	Assumes toxicologic independence of action. Assumes interactions are not significant at low exposures.	Limited to low exposure doses. Slight overestimate of mixture's upper bound on risk when adding component upper bound risks. Individual risk estimates may vary in quality, accuracy.	U.S. EPA, 1989a. Chen et al., 1990. Cogliano, 1997.
Hazard Index, Target Organ Toxicity Doses [Risk Characterization for any Toxic Endpoint]	Toxicity and exposure data on mixture's components.	Scale individual component exposure concentrations by acceptable "safe" dose level. Add concentrations.	Easy to calculate. Data available on components (e.g., EPA's IRIS database)	Dose addition: same mode-of-action (same target organ), parallel dose-response curves for components.	Exposure data must be at low levels. Toxicity values across components may vary in their uncertainty. Individual risk estimates may vary in quality, accuracy.	U.S. EPA, 1989a. Mumtaz et al., 1997b.

TABLE 1 cont.						
Approach [Type of Assessment]	Data Requirements	Strategy of Method	Ease of Use / Advantages	Assumptions	Limitations and Uncertainties	References
Interaction-based Hazard Index [New Procedure for Risk Characterization of any Toxic Endpoint]	Toxicity and exposure data on components, interactions data on at least one pair of components.	Scale individual component exposure concentrations by acceptable "safe" dose level. Modify this term with data on binary interactions. Add concentrations.	Complicated to use. Offers a method for incorporating interaction effects using binary data, which are the most readily available interactions data.	Assumes binary interactions are the most important.	Limited interactions data are available. Binary interactions used to represent the interactions for the whole mixture. Individual risk estimates may vary in quality, accuracy.	Mumtaz and Durkin, 1992. Mumtaz et al., 1998 Hertzberg, et al., 1999.
Relative Potency Factors (RPFs) [New Procedure for Dose-Response Assessment of any Toxic Endpoint]	Toxicity and exposure data on components. One well-studied chemical. Toxicity data may be missing for some components.	Scale component exposures relative to potency of an index chemical. Add scaled concentrations. Estimate risk for sum using dose-response curve of index chemical.	Complicated to use. Data intensive. Requires some statistical modeling and judgment of RPFs. Offers interim method.	Dose addition: same mode-of-action (use surrogates), parallel dose-response curves for components. Applied to specific endpoint, route, duration.	Limited by data quality and similarity. May not have data from all routes of exposure of interest. Same mode-of-action across components may not be known. Judgment of relative potency factors required.	Hertzberg, et al., 1999.

TABLE 1 cont.

Approach [Type of Assessment]	Data Requirements	Strategy of Method	Ease of Use / Advantages	Assumptions	Limitations and Uncertainties	References
Toxicity Equivalence Factors (TEFs) [Dose-Response Assessment of any Toxic Endpoint]	Toxicity and exposure data on components. One well-studied chemical.	Scale component exposures relative to potency of an index chemical. Add scaled concentrations. Estimate risk for sum using dose-response curve of index chemical.	Complicated to use. Data intensive. Requires some statistical modeling and judgment of TEFs. Dioxin TEFs reviewed extensively.	Dose addition: same mode-of-action, parallel dose-response curves for components. Applied to all endpoints and exposure routes.	Rare data. Restricted by strong similarity, so few chemical classes will qualify. Same mode-of-action across components is established.	U.S. EPA, 1989b.
Geographic Site-Specific Assessment [Risk Characterization for Any Toxic Endpoint]	Toxicity data on commercial mixture and environmental exposure data on components.	Range of risk estimates for the commercial mixture are adjusted for environmental mixture composition.	Complicated to use. Data intensive. Offers method for incorporating effects of environmental degradation of the mixture.	Requires the user to make scientific judgements about the fate and transport of groups of chemicals.	Some data restricted by similarity. Restricted to specific conditions. Limited by data quality, accuracy.	U.S. EPA, 1996a Cogliano, 1998.

TABLE 2

Methods for Whole Mixture Data

Approach [Type of Assessment]	Data Requirements	Strategy of Method	Ease of Use / Advantages	Assumptions	Limitations and Uncertainties	References
Mixture of Concern Toxicity Value [Dose-Response Assessment]	Toxicity data on mixture of concern (e.g., epidemiologic data, human clinical studies, toxicology data on complex mixture).	Estimate dose-response toxicity value directly from data on complex mixture of concern, using the same procedures as those used for single chemicals.	Calculations are simple. Assesses whole mixture so potential toxicity of unknown components is accounted for.	Composition of the test mixture is functionally the same as the environmental mixture. Test data account for all sensitive endpoints.	Data are rarely available. Scientific judgments made of the chemical composition of the mixture; toxicologic relevance of the laboratory data to the environmental mixture may be weak.	U.S. EPA, 2000b. (see RfD for Arachlor 1016; cancer assessment for coke oven emissions)
Sufficiently Similar Mixture Toxicity Value [New Procedure for Dose-Response Assessment]	Toxicity data on a mixture judged as sufficiently similar to the mixture of concern for which no data are available.	Estimate dose-response toxicity value using data on the sufficiently similar mixture as a surrogate for data on mixture of concern; use same procedures as for single chemicals.	Calculations are simple. Assesses whole mixture so potential toxicity of unknown components is accounted for.	Composition of the sufficiently similar mixture is functionally the same as the environmental mixture. Test data account for all sensitive endpoints.	Availability of data is limited. Scientific judgments of sufficient similarity, chemical composition and stability of mixtures; toxicologic relevance of the laboratory data to the environmental mixture must be supported.	U.S. EPA., 1999c.

TABLE 2

Methods for Whole Mixture Data

Approach [Type of Assessment]	Data Requirements	Strategy of Method	Ease of Use / Advantages	Assumptions	Limitations and Uncertainties	References
Comparative Potency [Dose-Response Toxicity Values for Cancer, Genetic Toxicity]	Short-term data on several similar mixtures including mixture of concern; at least one data point from a chronic *in vivo* study	Estimate dose-response value using relationships across similar mixtures and similar assays to extrapolate to a value for mixture of concern.	Calculations involve some statistical modeling and toxicologic judgement. Allows use of short-term *in vitro* data	Assumes potency change for similar mixtures across assays is the same. Test data account for all sensitive endpoints.	Availability of data is limited. Scientific judgments of sufficient similarity relative to chemical composition and toxicologic activity of the mixtures must be supported.	Lewtas, 1985. Lewtas, 1988. Nesnow, 1990.

presented transparently. Mixtures composed of chemicals thought to have threshold effects must be assessed and presented carefully. A common interpretation is that mixtures with few components, each less than its respective threshold, pose no significant risk. For chemicals acting by the same mode-of-action, this conclusion can be in error because the joint exposures contribute to the same potential toxicity and effectively represent a cumulative dose. Thus, a dose-additive assessment should be performed (i.e., summing the component doses that are scaled for potency and estimating the risk for the total mixture dose). For a mixture of toxicologically dissimilar chemicals thought to be functionally independent, an assessment can be performed using response addition (i.e., summing the risks of the individual components). In this case, the mixture risk would likely be judged negligible, particularly if the threshold effects are considered minor. When the toxic effects are of major concern, such as cancer or developmental toxicity, the estimated mixture risk should be judged in the context of the effects, the shapes of the dose-response curves, and the characteristics of the exposed population (U.S. EPA, 1999c).

Whenever an assessment is based on component toxicity values, the risk characterization must discuss the quality of the individual chemical estimates used, including both exposure data and dose-response information. For example, cancer potency estimates are uncertain, as reflected by confidence levels and goodness-of-fit values when dose-response models are applied, as well as by qualitative descriptors of the weight of evidence that the chemical is a human carcinogen. Similarly, human exposure estimates can be uncertain because of water treatment system practices, source water characteristics or tap water consumption patterns. All these measures of

uncertainty and unevenness of component estimates must be described, at least in summary fashion, in the risk characterization.

Many of the variables that are quantified in a mixtures risk assessment can have multiple possible values, resulting in a need to address both variability and uncertainty when applying the methodology. First, a parameter's true value may be uncertain but may not vary across individuals in the population. In this case, the parameter has one true value for all individuals in the population but that value is not known. Second, a parameter's value may vary across individuals in the population but be treated as known with certainty. It is important to segregate the influence of uncertainty and variability because they give rise to two different sets of questions. Uncertainty raises the question of how precise the resulting risk estimates are. Variability raises the question of whether there are (identifiable) individuals in the population at a particularly elevated risk. Application of a probabilistic approach allows the results of an analysis to be used to quantify the distribution of plausible risks for the population. To implement the analysis, input distributions are developed for all variables thought to be variable or uncertain; such distributions are developed to reflect best estimates of the variables for use in simulations and should not be biased toward conservative estimates of risk.

Following the generation of a distribution of plausible risks, additional sensitivity and uncertainty analyses can be performed. An analysis of the relationship between the model input variables and the model output can identify those variables that have the greatest impact on the results. Such variables can then be targeted for future research efforts. In addition, both model and data set uncertainty should be examined. Model uncertainty is introduced when there is more than one plausible mathematical

formulation describing some quantity (e.g., different dose-response models can be used). Data set uncertainty is introduced when more than one data set can be used to quantify a parameter, and the data sets cannot be directly combined (e.g., health risks can be estimated using data from several different animal bioassays). Thus, these uncertainties can be examined by repeating the probabilistic analysis using different model or data set choices and comparing the results with those of the initial analysis. Such additional analyses provide information on the reliability of the initial analysis and are useful in planning new research activities.

2.2.4. Applying Mixtures Methods to DBP Mixtures Risk Estimation. Three basic approaches are available for quantifying health risk for a chemical mixture, depending on the type of data available to the risk assessor (U.S. EPA, 1986; 1999c; 2000a):

- Data on the complex mixture of concern
- Data on a similar mixture
- Data on the individual components of the mixture or on their interactions.

Figure 3 illustrates how these three scenarios can be mapped directly to three toxicity testing scenarios recommended by an International Life Science Institute (ILSI) expert panel on DBP mixtures toxicity (ILSI,1998). Figure 3 also shows the potential uses of such data for risk assessment.

In the first approach, toxicity data are available on the complex mixture of concern, which, in the case of DBPs, means data from real world drinking water samples or extracts. The quantitative risk assessment is done directly from these data, which can include either epidemiologic or toxicologic data. Although there are

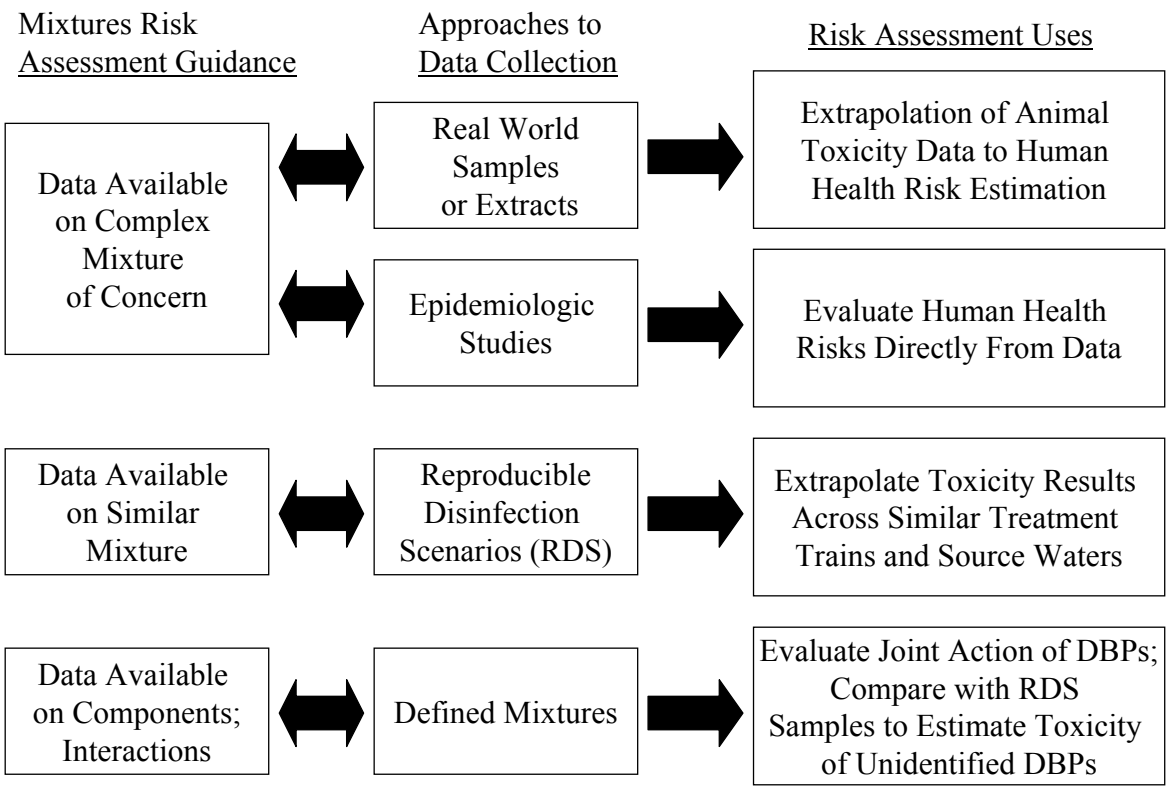


FIGURE 3

Mapping of Risk Assessment Approaches to Drinking Water Health Effects Studies

advantages to testing the complex mixture of concern, this can also be problematic. Toxicologic data from animal studies suffer from the uncertainties inherent in extrapolation to human health risk. Epidemiologic data appear to be superior in terms of evaluating humans directly, but these data suffer from confounding sources of potential toxicity that can be difficult to account for.

The second approach uses data on a "sufficiently similar" mixture, represented for DBPs by the toxicologic evaluation of Reproducible Disinfection Scenario (RDS) samples (i.e., water samples produced by controlling the characteristics of source water and then subjecting the samples to specific treatment trains). RDS samples may be classified as similar mixtures with toxicity data that may provide a measure of the expected toxicity of finished drinking water for a given treatment train and source water characterization. Data in an RDS toxicity database could be judged for similarity against data from a treatment plant by identifying and measuring the concentrations of DBPs in each, comparing component proportions across the mixtures, and contrasting available toxicity data on their components. For the RDS mixtures, the source of the mixtures is controlled and measured so comparisons can be made across similar treatment trains and source waters. Analytical chemistry is needed to characterize the composition and stability of the mixtures. Toxicity data on the RDS samples are used to characterize expected health effects. If the treatment plant data and the RDS mixture are judged to be similar, then the quantitative risk assessment for the treatment process may be derived from health effects data on the RDS sample.

Finally, the third mixtures risk assessment approach is to evaluate the DBP mixture through an analysis of data on its components. This approach maps to the ILSI

panel's testing of simple or "defined" mixtures of DBPs. For example, data from defined mixture experiments (and also single chemical studies) could be used to perform a risk assessment using a dose addition approach for DBPs thought to act by a similar mode-of-action and or a response addition method for estimates of risk for DBPs thought to be functionally independent. These particular procedures include a general assumption that interaction effects at low concentration levels either do not occur at all or are small enough to be insignificant to the risk characterization. Other, newer component-based approaches that incorporate interactions information into the risk estimates when such data are available are under development (Hertzberg et al., 1999; U.S. EPA, 1999c). For DBPs, toxicity and concentration data on the components of a mixture can be combined and added together (depending on the assumption used) to estimate mixtures risk. Again, analytical chemistry is needed to identify and quantify the components.

At least some data on DBPs exist for all these scenarios, so the method of risk characterization chosen depends on the availability of health effects data, the characterization of the exposure of interest, and the beliefs held relative to the toxicity of the DBPs in the complex mixture, their interaction potential, and their likely mode(s)-of-action. Given all the data collection, evaluation and expert judgments that must be performed, the risk assessor can then determine the most appropriate risk characterization method to apply (U.S. EPA, 1999c).

The doses associated with human exposure to DBPs are all below the levels that show adverse health effects when administered to animals, making extrapolation necessary and the existence of a threshold effect level an important consideration. A

major concern is whether unidentified chemicals may produce “surprise” interactions, even at low doses. Two major considerations in determining the likelihood of toxicological interactions among DBP mixtures are that the DBPs are present at low concentrations in drinking water and that a large number of compounds remain unidentified.

Typically, little interaction is expected at the doses associated with exposure to DBPs in drinking water. At the current, extremely low, environmental concentrations of DBPs, synergistic toxicological interactions are not thought to occur. However, the large number of uncharacterized compounds precludes completely ruling out the possibility. An additional consideration that may result in possible interactions is whether DBPs could accumulate in the body from constant exposure or whether there could be an accumulation of impacts from exposure to hundreds of different chemicals, each individually at a low level, but all acting (by the same mechanism or at different steps in the same pharmacodynamic process) on some precursor stage leading to an adverse health effect.

2.3. DBP EXPOSURES

The goal of an exposure assessment is to quantify the uptake of an agent or a group of agents that results from an individual’s or a population’s contact with environmental media (U.S. EPA, 1992; Paustenbauch, 2000). U.S. EPA (1992) defines exposure assessment as the qualitative or quantitative “determination or estimation of the magnitude, frequency, duration, and route of exposure.” Exposure assessments involve three general steps:

- Estimation of the occurrence and concentrations of an agent or group of agents in various media that individuals contact
- Characterization of specific contact rates with the media
- Calculation of the likelihood of an exposure, the resulting uptake and *biologically relevant* dose rates, e.g., average daily exposure in terms of mg/kg/day, peak exposure, or cumulative exposure.

Exposures to DBP mixtures ultimately depend on concentrations of DBPs at the tap (Olin, 1999). These concentrations at the tap depend upon fluxes in the DBP concentrations within the distribution system. Very few consumers drink water directly from a water treatment plant; most customers consume water that has passed through a water distribution system. The concentration of the individual DBPs depends on the water chemistry of the distributed water and the concentration and type of disinfectant. The concentration of disinfectant also depends on the water chemistry and the disinfectant demand associated with the distribution system. (For more details on exposure data, see Sections 2.2., 3.4., 3.5., 3.6. of Report 2.) Water quality varies throughout the distribution system because of changes taking place in the bulk phase of the water and conditions existing at the interface between the bulk phase and the pipe wall. To make exposure estimates more realistic, a series of dynamic models have been developed to predict the concentrations of some individual DBPs at various times in the distribution system (Clark, 1998; Clark and Sivaganesan, 1998).

Residence time in distribution systems affects DBP formation. In the United States, distribution systems are frequently designed to ensure hydraulic reliability, which includes adequate water quantity and pressure for fire flow as well as domestic and industrial demand. To meet these goals, large amounts of storage are usually

incorporated into system design, resulting in long residence times, which in turn may contribute to water quality deterioration.

Human exposure to DBPs is a classic complex exposure scenario (Olin, 1999). DBP exposure patterns can be characterized as a multiple route, daily exposure to a highly variable complex mixture of chemicals at low concentrations that inherently reaches the general population, including sensitive subpopulations. DBPs have been measured in tap water, vapors and aerosols. Some DBPs in tap water (e.g., chloroform) volatilize through heating during cooking, showering, etc. (e.g., Weisel and Chen, 1994; Giardino and Andelman, 1996). As a result, DBP exposures can occur through ingestion, inhalation, and dermal absorption.

Mathematical exposure models have been developed for each exposure route; several of these are summarized specifically for drinking water inhalation and dermal exposures in Olin, 1999. Paustenbauch (2000) provides a general review of exposure assessment and describes ingestion, inhalation and dermal exposure. The models predict exposures based on such factors as the physical and chemical properties of DBPs in water and assumptions concerning human activity patterns, as well as air exchange rates in buildings and room dimensions (Olin, 1999). Studies of human activity patterns in the U.S., such as tap water consumption distributions (including heated tap water consumption), showering and bathing frequency and duration distributions, provide contact rates for important exposure media (U.S. EPA, 1997b; Johnson et al., 1999). These data can be aggregated and used in exposure modeling to estimate DBP contact rates for the three primary exposure routes.

Mathematical models have been developed to estimate the absorbed doses from oral, inhalation, and dermal routes. Absorbed dose is defined by the U.S. EPA (1997b) as the amount crossing a specific absorption barrier through uptake processes. Report 2 describes an oral exposure model (Section 3.4.). In this model, DBP exposure is a function of the concentration in water and the daily quantity of water ingested. Some general models include a bioavailability parameter, although this was not included in this modeling effort. The model used described a potential dose (i.e., the quantity ingested). Both U.S. EPA (1994a) and Wilkes (1999), among others, describe inhalation exposure models. Wilkes (1999) describes a model for estimating the absorbed dose of drinking water contaminants including DBPs. The model estimates chemical exposures via inhalation of aerosols and vapors. These may be generated from a number of household uses including showers, clothes washers, dishwashers, and toilets. Bunge and McDougal (1999) describe two broad classes of dermal penetration models: membrane models and pharmacokinetic models. Both types of models can be used to estimate absorbed doses. To estimate the absorbed dose of chloroform from drinking water, Wilkes used an inhalation model and a membrane model for dermal exposure. His results showed that the inhalation route is dominant for compounds that have a higher volatility such as chloroform.

Further development of these models and extensions to DBP classes, such as the HAAs and HANs, will be useful both to refine human exposure estimates and obtain more relevant information from epidemiological studies (see Sections 4.1.1 and 4.8.1. of Report 2). Difficulties in measuring both irregular exposure patterns and variable DBP occurrence levels complicate interpretations of environmental epidemiological studies.

Some of the uncertainties have been discussed regarding the cancer literature (Murphy et al., 1999; Poole and Greenland, 1999; U.S. EPA,1998b). Epidemiologic studies that integrate more relevant exposure measures, data derived from mathematical models of DBP exposures, and biomonitoring data are being developed. These improvements may decrease many of the uncertainties in interpreting this literature in the near term. In the longer term, DBP biomarkers may prove useful for refining exposure measures, improving human dose-response assessment, and evaluating causality.

The development of quantitative measures of human exposure or effects from exposure to DBPs from the three primary environmental exposure routes has proven to be challenging. The development of biomarkers may aid the evaluation of these areas of DBP research. Biomarkers are observable properties of an organism that can be used to estimate prior exposure, to assess the underlying susceptibility of an organism, and to identify changes or adverse effects resulting from exposures. Biomarkers can occur at a number of functional levels within an organism: molecular, cellular, tissue, or whole organism. Biomarker monitoring may provide a sensitive indicator of exposure, susceptible subpopulations or individuals, or health. In the future, biomarkers offer the potential advantage of integrating exposure and dose-response functions. The development and use of these markers in human health risk assessment of environmental chemicals are under active investigation. The following three areas of biomarker research are being developed:

- Exposure biomarkers measure exogenous chemicals, metabolite(s) or the products of interactions with target molecules or cells in a compartment within an organism. This includes internal dosimeters of parent or metabolite concentrations and markers of biologically effective doses

- Susceptibility biomarkers indicate inherent or acquired properties of an organism that may lead to an increase in the internal dose or an increased level of the response resulting from exposure to a chemical or chemical class

- Effects biomarkers measure alterations of an organism that, depending on magnitude and nature, can indicate a potential or actual physical impairment or disease.

Some research efforts have focused on developing and evaluating biomarkers of exposures to individual DBPs. Based on work described in Wallace et al. (1987) and previous efforts in their laboratory, Weisel et al. (1999) evaluated two sets of exposure biomarkers: 1) measuring the THM levels in exhaled breath; and 2) measuring the urinary excretion rates and concentrations of dichloroacetic acid and trichloroacetic acid. The rapid metabolism of THMs in the liver reduces body burden and breath concentration following exposure; this rapid metabolism complicates the interpretation of breath concentrations. Although both chloroform and bromodichloromethane measurements taken immediately after shower exposures significantly correlated statistically with concentrations in water, these measures and collection approaches still need refinement before they can be used for purposes other than general markers of inhalation and dermal exposure.

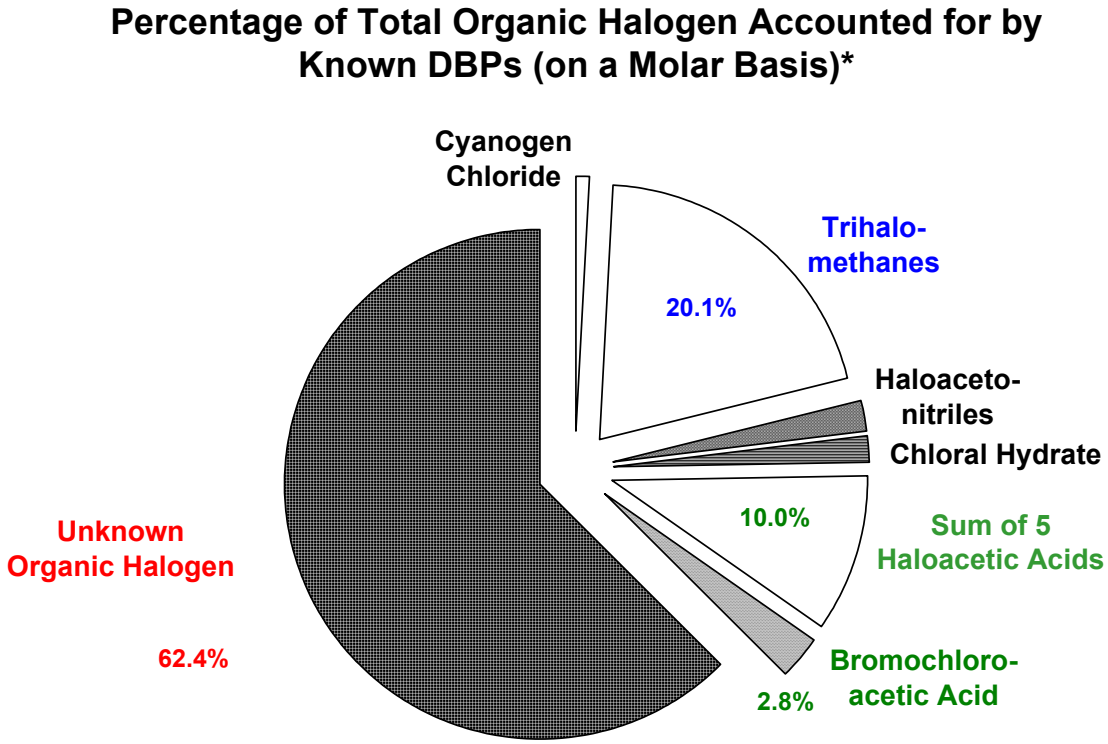
Pereira and Chang (1982) and Pereira et al. (1994) have developed blood biomarkers that eventually may be useful in estimating the exposure to total THM, but additional data are needed to describe the formation of adducts from individual THM chemicals. THMs are metabolized to dihalocarbonyl, which binds cysteine. This bound residue is metabolized, forming 2-oxothiazolidine-4-carboxylic acid, a urinary metabolite of THM chemicals. Although measuring 2-hydroxythiazolidine-4-carboxy acid in

hemoglobin or albumin and the urinary excretion of 2-oxothiazolidine-4-carboxylic acid would not distinguish individual THM chemicals from one another, it could serve as a biomarker for total exposure to THMs. Data describing levels of the different THMs in the drinking water and the rates at which each was metabolized could be used to approximate the percentage of hemoglobin adduct produced by each THM.

A similar mechanism exists for the HANs. This may complicate attributing of a given fraction of blood or urinary marker for THMs. Urinary dichloroacetic acid excretion rates were not correlated to concentrations in drinking water; however, trichloroacetic acid in the urine was a good marker of chronic exposure. Although these efforts are still evolving, the use of biomarkers of exposure shows promise.

2.3.1. DBP Concentrations. A health risk assessment may consider many DBPs, several hundred of which have been identified (Richardson, 1998). Chemicals commonly found in finished drinking water are listed in Table 3. Figure 4 illustrates a typical distribution of DBPs for a system that disinfects via a chlorination process, including many of the DBPs listed in Table 3. Figure 4 also demonstrates the common fact that more than 50% of the organic halogens produced by chlorination disinfection are unidentified chemicals (62.4% in this instance). Similarly, less than 40% of the by-products of ozonation have been identified (Weinberg, 1999). In general, these unidentified DBPs include not only the organic halogens, but also non-halogenated compounds in the water. Thus, the risk assessment must take into account that part of the chemical exposure to humans that includes an unknown number of unidentified chemicals likely to be found at extremely low concentrations.

TABLE 3 DBPs Commonly Found in Finished Drinking Water
Trihalomethanes (THMs) Chloroform ($CHCl_3$), Bromodichloromethane (BDCM), Chlorodibromomethane (CDBM), Bromoform ($CHBr_3$)
Haloacetic Acids (HAAs) Chloroacetic acid (CAA), Dichloroacetic acid (DCA), Trichloroacetic acid (TCA), Bromoacetic acid (BAA), Dibromoacetic acid (DBA), Bromochloroacetic acid (BCA)
Haloacetonitriles (HANs) Dichloroacetonitrile (DCAN), Trichloroacetonitrile (TCAN), Bromochloroacetonitrile (BCAN), and Dibromoacetonitrile (DBAN)
Aldehydes Formaldehyde, Acetaldehyde
Haloketones 1,1,1-Trichloropropanone, 1,1,1-Dichloropropanone
Other miscellaneous DBPs e.g., Bromate, Chloral Hydrate, Chloropicrin



Courtesy of Stuart Krasner, Metropolitan Water District Of So. California, 1999

FIGURE 4

Typical Distribution of Disinfection By-Products

Assessing exposure to chemical mixtures of DBPs entails consideration of several broad issues not encountered in single chemical risk assessments. First, when assessing the current state of the analytic chemistry of DBPs, not only are the accuracy and reliability of the measurement techniques critical, but also whether all of the toxicologically relevant components have been identified (i.e., are there unidentified components of the mixture?) or if the entire mixture has been measured at the points of contact over time. Second, it should also be determined whether the key environmental reactions have been identified and reaction rates measured. Important changes in the concentrations of the DBP mixture components in the medium(a) of concern at the point(s) of human contact must be identified (i.e., are all of the exposed individuals receiving exposures to the same compounds, etc.). Finally, the bioavailability of the mixture components must also be assessed. Important uncertainties must be identified (and perhaps quantified): uncertainty based on imperfect analytic methods (e.g., some constituents may not be characterized by the analytic technique that represents the current state-of-the-science); extrapolations between concentrations at measurement points and points of human exposure; unknown transformation reactions to the mixture in the environment; and bioavailability. Each of these uncertainties in the risk assessment must be discussed and accounted for in the final risk characterization.

2.3.2. Tap Water Exposure. Human exposure occurs only when an agent comes into contact with the human membranes. For most individuals, DBPs primarily are encountered indoors. The primary uses of indoor water are faucet use (drinking, cooking, hand washing, etc), showering/bathing, toilet use, clothes washing and dish washing (U.S. EPA, 1997b). DBPs may be present in liquid, vapor, or aerosol form(s),

can enter the body via ingestion, respiration, or dermal penetration, and may be metabolized before distribution to the target organ(s).

The fate of DBPs in tap water depends on the water temperature and the nature of use (Olin, 1999). For example, volatile DBPs are released when water is heated for cooking and bathing; showering leads to increases in aerosolized DBPs; volatilization and aerosolization of DBPs may be more limited during other water uses. The concentrations of DBPs in the air also are dependent on the original concentrations in the tap water, the volume of water used per activity, and structural characteristics (e.g., room dimensions, air flow patterns, etc.). For example, showering can utilize large volumes of heated water.

For the oral route, DBP exposure can be estimated as a function of total tap water consumed (L/kg-day), including all water from the household tap consumed directly as a beverage or used to prepare foods and beverages. The studies of Ershow and Cantor (1989) of the U.S. population and the Canadian Ministry of National Health and Welfare (1981), presented in U.S. EPA (1997b) can be used to derive consumption estimates. In addition, the Continuous Survey of Food Intake by Individuals (CSFII) data (1994-1996) is currently undergoing evaluation within the EPA. Water consumption data are also available for some subpopulations (e.g., pregnant women (Ershow et al., 1991), persons with AIDs). Differences in DBP exposures occur because of other factors, such as heated vs. unheated tap water or changes in consumption patterns (e.g., in CSFII, increased use of bottled water).

Human activity patterns greatly influence DBP exposures via inhalation and dermal routes. Human activity patterns including time spent at each activity as well as

location within a building are needed to assess exposure through other non-ingestion routes. These activity patterns need to include encounters with DBPs that occur when others are showering or washing clothes. The influence of human activity patterns on estimated exposures to individual DBPs and DBP classes needs to be evaluated.

2.4. DBP HEALTH EFFECTS DATA (HAZARD IDENTIFICATION AND DOSE-RESPONSE)

Data from both epidemiologic and toxicologic studies indicate that human health effects from DBP exposure are of concern, but neither discipline has been able to confirm this with confidence. DBPs typically occur at low levels in drinking water at which general toxic effects from exposure to the environmental mixture have not been found in animal studies. In contrast, epidemiologic studies of chlorinated drinking water exposures in humans suggest weak associations with bladder, rectal and colon cancer and limited evidence of reproductive and developmental effects. A limited number of toxicology studies (for both cancer and non-cancer endpoints) exists on defined DBP mixtures (i.e., simple mixtures of 2-5 chemicals) that have been performed primarily using the trihalomethanes and the haloacetic acids. Results indicate that:

- Concurrent exposures tended to be consistent with dose-addition or antagonism, whereas temporally separated exposures tended to result in a greater than additive response
- The mixing ratio of the components comprising the mixture may influence the toxic outcome
- Interactive effects appear to be dose-dependent, a finding consistent with mixtures research in general (i.e., synergism or inhibition are expected interaction effects at high-dose levels, while dose additivity is more commonly observed in lower portions of the mixture dose-response curve) (Simmons et al., 2000a).

There is evidence in single chemical animal studies, at high DBP dose levels, of carcinogenicity, reproductive effects, developmental effects, and other toxic effects, particularly in the kidney and liver. Finally, there is evidence of mutagenicity and of additivity using embryo cultures from exposure to extracts of finished drinking water in *in vitro* studies.

2.4.1. Summary of Epidemiology Studies. Since the early 1970s, a large number of epidemiologic studies of varying design and quality have been published in the scientific literature. The studies have focused almost exclusively on chlorinated drinking water and its association with cancer rather than on individual chemical exposures. Reproductive and developmental epidemiologic studies on this topic first appeared in the literature in the late 1980s. However, only recently have investigators collected information to quantitatively estimate exposures to individuals from different chemical families and species of DBPs and begun to study disinfectants other than chlorine. The purpose of this section is to provide a brief overview of the existing epidemiologic literature suggesting a potential hazard from exposure to disinfected drinking water and its associated DBPs.

2.4.1.1. Cancer Studies — Several types of epidemiological studies have been conducted to assess the association between cancer and chlorinated drinking water, including ecological, cohort, and case-control designs, evaluating both incident and decedent cancer cases. These studies differ in their basic approach and the evidence they provide about the possible causality of an epidemiological association between chlorinated drinking water and cancer. These studies are not reviewed in detail in this document. However, a summary of the more methodologically sound studies (e.g.,

those based on incident cases that have interviews and some from of individual exposure estimates) is provided in Table 4. The studies are described further in U.S. EPA (1998a,b).

The results from these studies have not been used quantitatively for the current risk assessment exercise because most of the exposure contrasts were confounded by water source and none of the designs allowed for a comparison of the drinking water treatment practices of interest to the current problem. In addition, recent research has demonstrated evidence of publication bias, a form of selection bias, in the cancer literature, where studies with inverse or null associations may not have been published or submitted for publication by the investigators (Poole, 1997; Poole and Greenland, 1999; Murphy et al., 1999).

Based on the entire cancer-chlorinated drinking water epidemiology database, there is better evidence for an association between exposure to chlorinated surface water and bladder cancer than for other types of cancer. However, the latest bladder cancer study (Cantor et al., 1998) notes several inconsistencies in results among the studies for smokers/nonsmokers and males/females (Lang et al., 1998), and the evidence is still considered insufficient to judge which water contaminants may be important. Evidence for a role of THMs is weak at this time. A possible explanation for the apparent discrepancies in findings for smokers and never-smokers among studies may reside in water quality and water treatment differences in the respective study areas, with resulting variations in the chemical composition of by-product mixtures.

TABLE 4

Summary of Interview-based Case-control and Cohort Studies for Cancer*

Overview	Population	Exposure Assessment	Analysis
Reference: Cantor et al., 1998 *Type of study*: case-control (incidence) *Cancer site(s)*: bladder; 5 other sites also studied	*Population base*: residents of Iowa. *Cases*: 1,123 bladder cancers, ages 40-85 yrs., histological confirmation of all cases, identified primarily through State Health Registry of Iowa *Controls*: 1,983 age-gender-race frequency matched sample of the general population; no previous cancer diagnosis	*Exposure measure*: mailed questionnaire obtained estimates of fluid and tap water consumption, residential and water source history; duration of use of chlorinated surface water, unchlorinated ground water, fluid and tap water consumption. *Ascertainment of D/DBPs*: water source and treatment from water company records and recent measures of water contaminants such as THMs.	*Method*: logistic regression adjusted for potential confounders, such as age, farm occupation, diet, physical activity, cigarette smoking. *Findings*: little overall association between bladder cancer risk and exposure to chlorination by-products. Bladder cancer risk increased with exposure duration , but opposite trends were found in males and females; further analyses that included total lifetime and average lifetime THM levels show all risk increases are apparently restricted to male smokers.
Reference: Cantor et al., 1987 *Type of study*: case-control (incidence) *Cancer site(s)*: Bladder (National Bladder Cancer Study)	*Population base*: white U.S. residents in 10 locations. *Cases*: 2,805, age 21-84, diagnosed 1977-1978, identified from tumor registries. *Controls*: 5,258 from general population; frequency matched to cases by sex, age, and geographic area; identified through phone sampling (to age 64) or sample of Medicare roster (age 65 and over).	*Exposure measure*: duration of use of chlorinated surface water vs. nonchlorinated ground water; tap water consumption. *Ascertainment of D/DBPs*: information on water source (surface vs. ground) and chlorination from survey of utilities; residential history, and level of consumption of tap water and beverages, by personal interview.	*Method*: logistic regression; adjusted for age, gender, study area, smoking, usual or high-risk occupation, and urbanicity of place of longest residence. *Findings*: for whites with >59 years exposure to chlorinated water overall OR = 1.1 (0.8-1.5), non-smokers OR = 2.3 (1.3-4.2), current smokers OR = 0.6 (0.3-1.2); for whites with 40-59 years exposure to chlorinated water overall OR = 1.0 (0.8-1.3), non-smokers OR = 1.4 (0.9-2.3), current smokers OR = 0.7 (0.5-1.2); for those with 40-59 years of chlorinated surface water use, OR for highest quintile of tap water consumption relative to lowest quintile = 1.7 (p for trend = 0.006); for those with $\geq$60 years of use, OR = 2.0 (p for trend = 0.014).

TABLE 4 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: McGeehin et al., 1993 *Type of study*: case-control *Cancer site(s)*: bladder (incidence)	*Population base*: white Colorado residents from the State Cancer Registry. *Cases*: 327. *Controls*: 261 frequency matched by gender and 5-year age group randomly selected from cancer registry during same period, excluding lung and colorectal cancers.	*Exposure measure*: residential history and level of tap water consumption; duration of use of chlorinated/chloraminated surface water, chlorinated/unchlorinated ground water, bottled water; tap water consumption. *Ascertainment of D/DBPs*: information on water source and chlorination or chloramination from site visit to water utilities; water quality data collected for total THMs, chlorine residual, and nitrates.	*Method*: logistic regression adjusted for smoking, coffee, history of kidney stones and familial bladder cancer, and occupation. *Findings*: OR for bladder cancer = 1.8 (1.1-2.9) for >30 years' exposure to chlorinated water. Cases consumed more tap water per day than controls ($p<0.01$); OR for bladder cancer = 2.0 (1.1-2.8) for cases consuming >5 glasses of tap water. Risk of bladder cancer decreased with increased duration of exposure to chloraminated surface water ($p<0.01$); OR = 0.6 (0.4-1.0) for those consuming chloraminated water >40 years. Level of total THMs, residual chlorine, or nitrates not associated with bladder cancer risk controlling for years of exposure.
Reference: Freedman et al., 1997 *Type of study*: nested case-control *Cancer site(s)*: bladder (incidence)	*Population base*: white residents of Washington County, MD, included in 1975 county census. *Cases*: 294 new cases reported to Washington County cancer registry, 1975-1992. *Controls*: 2,326 frequency matched by age and gender, randomly selected from 1975 census.	*Exposure measure*: chlorinated vs. nonchlorinated drinking water (Municipal, vs. nonmunicipal source); fluid consumption not obtained. *Ascertainment of D/DBPs*: information on water treatment from prior study; drinking water source obtained in 1975 county census.	*Method*: logistic regression adjusted for age, sex, smoking level and history, urbanicity, marital status, education. *Findings*: OR = 1.2 (0.9-1.6) using 1975 measure of exposure to chlorinated vs. nonchlorinated water; slight gradient of increasing risk with increasing duration of exposure noted only among smokers; further stratification by gender showed elevated ORs to be restricted to subcategory of male smokers.

TABLE 4 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: King and Marrett, 1996 *Type of study*: case-control *Cancer site(s)*: bladder (incidence); colon and rectal cancers also studied, but results not yet reported	*Population base*: residents of Ontario, Canada, ages 25-74 years. *Cases*: 696. *Controls*: 1545 age-gender frequency matched sample of the general population from households randomly selected from residential phone listings; controls also used to study colon and rectal cancer and age-gender distribution based on that expected for all 3 sites combined.	*Exposure measure*: mailed questionnaire/telephone interview obtained estimates of fluid and tap water consumption, residential and water source history: duration of use of chlorinated surface water, unchlorinated ground water, fluid and tap water consumption. *Ascertainment of D/DBPs*: water source and treatment from water company records and questionnaire; combined with model to estimate past total THMs summer levels (annual peak value) by year.	*Method*: logistic regression adjusted for age, gender, education, cigarette smoking, caloric intake. *Findings*: bladder cancer risk increased with increasing number of years exposure to chlorinated surface water, but was statistically significant only for lengthy exposures. OR for bladder cancer = 1.41 (1.09-1.81) for >34 years exposure to chlorinated surface water compared to <10 years exposure. OR for bladder cancer =1.44 (1.10-1.88) for exposure to >1956 ug/l-years THMs compared to <584 ug/l-years; risk increases by 11% with each 1,000 ug/L THMS-years. Results provide no support for an interaction between volume of water consumed and years of exposure to THMs level >49 ug/L. Among those with relatively homogenous exposures for >29 years, trend for increased bladder cancer risk with increased THMs levels (p=0.006) and OR for bladder cancer = 1.39 (1.09-1.79) for chlorinated surface water compared to ground water.
Reference: Young et al., 1987 *Type of study*: case-control *Cancer site(s)*: colon (incidence)	*Population base*: WI residents, age 35-90. *Cases*: 347 new cases reported to WI Cancer Registry over 2-year period. *Controls*: 639 new cases of non-gastrointestinal/urinary tract cancer reported to registry; also 611 population controls, a random sample of WI drivers.	*Exposure measure*: high or medium vs. low lifetime exposure (and period-specific exposure) to total THMs. *Ascertainment of D/DBPs*: water source and treatment from water company records and questionnaire; combined with model to estimate past total THM levels by year; residential history, drinking water sources, and use of tap water from self-administered questionnaire.	*Method*: logistic regression; adjusted for age, sex, and urbanicity of residence. *Findings*: for lifetime exposure: for high exposure group, OR = 0.93 (0.55-1.57) using cancer controls and 0.73 (0.44-1.21) using population controls; for medium-exposure group, OR = 1.05 (0.66-1.68) using cancer controls and 1.10 (0.68-1.78) using population controls.

TABLE 4 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: Cragle et al., 1985 *Type of study*: case-control *Cancer site(s)*: colon (incidence)	*Population base*: white NC residents with residency 10 years. *Cases*: 200 new cases over 18-month period from 7 NC hospitals, resident in NC 10 years. *Controls*: 407 non-cancer hospital patients with admission date nearest diagnosis date of case, matched to case in age, race, gender, vital status, and hospital.	*Exposure measure*: duration of exposure to chlorinated drinking water (none vs. 1-15 years vs. 16-25 years), 1953-1978. *Ascertainment of D/DBPs*: queried local water treatment plants about water source and treatment; residential history by questionnaire (phone or self-administered).	*Method*: logistic regression adjusted for sex, age, genetic risk, dietary fiber, region of NC, urban residence, smoking, alcohol use, education, and number of pregnancies. *Findings*: for age 60: OR = 1.38 (1.10-1.72) for longer exposure and 1.18 (0.94-1.47) for shorter exposure; for age 70: OR = 2.15 (1.70-2.69) and 1.47 (1.16-1.84); for age 80: OR = 3.36 (2.41-4.61) and 1.83 (1.32-2.53).
Reference: Hildesheim, 1998 *Type of study*: case-control *Cancer site(s)*: colon and rectal cancers (incidence)	*Population base*: residents of Iowa *Cases*: 560 colon cancers, 537 rectal cancers ages 40-85 yrs., histological confirmation of all cases, identified primarily through State Health Registry of Iowa *Controls*: 1983 age-gender-race frequency matched sample of the general population; no previous cancer diagnosis Cases and controls studies had at least 70% of lifetime drinking water exposures documented	*Exposure measure*: mailed questionnaire obtained estimates of fluid and tap water consumption, residential and water source history; duration of use of chlorinated surface water, unchlorinated ground water, fluid and tap water consumption. *Ascertainment of D/DBPs*: water source and treatment from water company records and recent measures of water contaminants such as THMs.	*Method*: logistic regression adjusted for potential confounders, such as age, farm occupation, diet, physical activity, cigarette smoking, urbanicity. *Findings*: No association between colon cancer and estimates of past chlorination by-product exposure. Rectal cancer risk increased siginificantly with duration of exposure to chlorinated surface water and increasing lifetime THMs exposure; larger odds ratios found among those with low fiber intake and low levels of physical activity.

TABLE 4 cont.			
Overview	Population	Exposure Assessment	Analysis
Reference: Doyle, 1997 *Type of study*: cohort *Cancer site(s)*: Eleven anatomic sites including bladder, colon, rectum, liver, kidney, pancreas, breast (incidence)	*Population base*: 36,127 female residents of Iowa in Women's Study, ages 55-69; followed for cancer incidence and mortality thru 12/93 *Exposed*: Women served by 100% surface water or mixed surface and groundwater *Unexposed*: Women served by 100% groundwater (referent category)	*Exposure measure*: mailed questionnaire for drinking water source; other info obtained at baseline 1986 via questionnaire *Ascertainment of D/DBPs*: mailed questionnaire for drinking water source; water company records and statewide survey used for recent measures of water contaminants for 4 specific THMs	*Method*: Cox proportional hazards regression, adjusting for age, smoking, education, physical activity, vegetable and fruit intake, total calorie intake, and anthropomorphic measures. *Findings*: Compared to consumers of 100% groundwater, RR for colon cancer were 1.67 (95% CI=1.07, 1.52) for consumers of 100% surface water, 1.52 (95% CI=1.08, 2.14) for consumers of mixed ground and surface sources; elevated risk for combined total cancer also noted; significant dose-response noted for colon with increasing chloroform exposure; no elevated risks observed for rectal cancer; bladder cancer RR inconsistent.

Studies with historical water exposure information; 95% confidence interval for OR in parentheses unless otherwise noted.

This continues to reinforce the need for better exposure assessments in this literature to reduce the possibility of missing a true risk because it has been diluted by nondifferential exposure misclassification.

Expert evaluations over the past 20 years of the epidemiological data for chlorinated drinking water/DBPs and cancer have been made by the National Academy of Science (NAS), International Association for Research on Cancer (IARC), EPA, International Society for Environmental Epidemiology (ISEE), International Life Sciences Institute (ILSI), Health Canada, and the World Health Organization International Programme on Chemical Substance (WHO-IPCS) among others. In general, the consensus is that the data have limitations and that a conclusion as to a causal relationship cannot be drawn (IARC, 1991; Neutra and Ostro, 1992; Craun et al. 1993; U.S. EPA, 1994b, 1997c; Reif et al., 1996; Mills et al., 1998).

To improve this body of literature, EPA has an ongoing project to acquire more complete chemical occurrence and water quality data that can be used to develop models for predicting the historic levels of THM occurrence (and in some cases, haloacetic acids) in specific geographic areas where epidemiologic studies have been performed, e.g., Iowa and Ontario, Canada (Murphy et al., 2000). The models, developed with historical data from water utilities, will be used to re-evaluate the exposure assessment component of certain recently completed studies, which will then be appropriately reanalyzed. This research should help reduce some of the uncertainties and problems outlined above, particularly the need for valid,

unconfounded exposure measures that can separate effects of water source from the DBPs and other chemical constituents in the water source.

2.4.1.2. Reproductive and Developmental Studies — Although fewer in number than the body of cancer literature, epidemiological studies of reproductive and developmental outcomes also have been performed. The outcomes considered have included stillbirth, spontaneous abortion, low birth weight, intrauterine growth retardation, somatic effects, and various birth defects including cardiac and neural tube defects. Almost all of these studies examined multiple outcomes and multiple exposure variables and most have used different operational definitions for study endpoints and exposures. A summary of this literature is given in Table 5 and a more detailed description can be found in U.S. EPA (1998a).

In 1993, an expert scientific panel convened by EPA and ILSI (ILSI, 1993; Reif et al., 1996) reviewed the epidemiologic literature on reproductive and developmental endpoints and DBP and disinfectant exposures. They concluded that the research in this area was in a very early and evolving stage and that the studies should be viewed as preliminary. A second expert panel convened by EPA in 1997 reviewed more recently completed studies and reached a similar conclusion. Although several studies have suggested that increased risks of neural tube defects and miscarriage may be associated with THMs or selected THM species, additional studies are needed to determine whether the observed associations are causal. The epidemiologic literature on adverse reproductive and developmental outcomes is still very sparse and must

TABLE 5

Summary of Epidemiological Studies for Adverse Pregnancy Outcomes*

Overview	Population	Exposure Assessment	Analysis
Reference: Magnus et al., 1999 *Type of Study:* cross-sectional, semi-ecological (database linkage) *Outcome(s):* Primary–presence of any birth defect (all conditions with ICD-8 codes 740.0-759.9, plus umbilical and ventral hernias (551.1-551.2); secondary outcomes were neural tube, cardiac, respiratory tract, urinary tract, and oral cleft defects	*Population base:* all 181,361 children born and listed in Norwegian Birth Registry 1993-95; eligible for study were 141,077 children from municipalities with available water exposure information; linked to national registry of birth defects recorded during 1st week of life (n=2,608 defects) *Exposed:* births in municipalities with chlorination and high color *Comparison:* births in municipalities with no chlorination and low color (baseline referent), plus other chlorine/color combinations	*Exposure Measure:* based on municipality of residence of mother at time of the birth; chlorination practice of municipality (proportion chlorinated), weighted mean water color(as mg Pt/L) as surrogate for dissolved organic carbon *Ascertainment of disease/other risk factors:* maternal age and parity from birth registry; categorized indicators for place of birth (clinic hospitals), geographic placement (in relation to regional/urban centers), population density, industrial profile	*Method:* computed prevalence rates (95% CIs) of defects per 100 live births; logistic regression to estimate adjusted ORs *Findings:* chlorination/high color vs. no chlorination/low color comparisons For all studied birth defects OR = 1.14 (0.99-1.31) Neural tube defects OR = 1.26 (0.61-2.62) Major cardiac defects OR = 1.05 (0.76-1.46) Respiratory defects OR = 1.07 (0.52-2.19) Urinary defects **OR = 1.99 (1.10-3.57)** Oral cleft defects OR = 0.94 (0.64-1.42)

TABLE 5 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: Klotz and Pyrch, 1999 *Type of Study:* population-based case-control *Outcome(s):* neural tube defects (NTDs)	*Population base:* all New Jersey births 1993-1994; *Cases:* 112 neural tube defects ascertained through NJ Birth Defects Registry and Fetal Death Registry (n=76 spina bifida only, 19 anencephaly only, 8 encephalocele only, 9 combination defects) *Controls:* 248 randomly selected from all NJ births; term births <2,500 g and infants with other defects excluded	*Exposure Measure:* estimated on basis of mother's residence at time of neural tube closure (1st month of gestation), using water utility data for individual & THMs; post-birth in-home water sample collection for THMs, total and free chlorine, haloacetonitriles (HANs), haloacetic acids (HAAs) timed to coincide with critical window 1 yr. earlier. *Ascertainment of disease/other risk factors:* Birth certificates plus interviews, interviewers blinded to exposure status of participants; pregnancy & medical history, parental occupation; behaviors & exposures for 3 mo. before & 1 mo. after conception including tap water ingestion, showering, bathing, swimming; use of water filters and vitamin use.	*Method:* prevalence ORs calculated with logistic regression; exposure categories based on prior studies *Findings:* For subjects with known residency at conception– public monitoring data concurrent w/ 1st month of pregnancy: surface vs. ground source OR = 1.6 (0.9 - 2.8) TTHMs (ppb) 40+ vs. <5 **OR = 1.7 (1.0 - 3.1)** in-home tap water sample 1 yr after 1st month of pregnancy: surface vs. ground source OR = 1.7 (0.8 - 3.6) TTHMs (ppb) 40+ vs. <5 OR = 2.0 (0.9 - 4.9) No association with total tap water or cold tap water ingested, irrespective of THM levels; HAAs (ppb) 35+ vs. <3 OR = 1.2 (0.5 - 2.6) HANs (ppb) 3.0+ vs. <0.5 OR = 1.3 (0.6 - 2.5)

TABLE 5 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: Dodds et al., 1999 *Type of Study:* retrospective cohort *Outcome(s):* low (LBW) & very low birth weight (VLBW) (<2500g, <1500g, respectively); preterm delivery (<37 wks gestation); small for gestational age (SGA) (bottom 1/10 of wt. dist. for Canadian live births); stillbirth (birth of nonliving fetus ≥500g); congenital anomalies (NTDs, cleft lip & palate, major cardiac defects, chromosomal abnormalities; outcomes not mutually exclusive	*Population base:* Nova Scotia, Canada women residing in area with municipal surface water with singleton birth or pregnancy termination for major fetal anomaly between 1/1/88-12/31/95, ascertained through Atlee Perinatal Database and Fetal Anomaly Database (93,295 singleton deliveries resulting in 50,755 included, eligible women) *Exposed:* 3 TTHMs exposure categories, calculated for different relevant time intervals (50-74, 75-99, ≥100 µg/L) *Comparison:* TTHMs 0-49 µg/L, calculated for different relevant time intervals	*Exposure Measure:* mother's residence at delivery linked to geographic areas served by each public utility; linear regression models applied to existing TTHM monitoring data on basis of observations by yr, month, and facility to generate average exposures *Ascertainment of disease/other risk factors:* maternal age & smoking, parity, prenatal class attendance, prepregnancy weight, sex of infant (from Perinatal Database); neighborhood family income	*Method:* Prevalence ratios (PRs) or relative risks (RRs) calculated with Poisson regression models *Findings:* TTHMs during last 3 mos. of pregnancy: no association with SGA, LBW, VLBW or preterm birth, all RRs approx. 1.0 TTHMs during first 2 mos. of pregnancy: little evidence of any important association with cleft or cardiac defects (intermediate exposures appeared protective) TTHMs 1 mo. before & 1 mo. after conception: intermediate exposures appeared protective for NTDs; for ≥100 vs. 0-49 µg/L RR=1.18 (0.67-2.10) TTHMs 3 mos. before conception: no clear pattern of ↑prevalence with ↑TTHMs for chromosomal abnormalities for ≥100 vs. 0-49 µg/L RR=1.38 (0.73-2.59) TTHMs ave. throughout pregnancy–stillbirths for ≥100 vs. 0-49 µg/L **RR=1.66 (1.09-2.52)**

TABLE 5 cont.			
Overview	Population	Exposure Assessment	Analysis
Reference: Gallagher et al., 1998 *Type of study:* Retrospective Cohort *Outcome(s):* Low birth weight (≤5 lbs, 8 ozs), preterm delivery (<37 weeks gestation), term-low birth weight (≥37 wks gestation and ≤5 lbs, 8 ozs)	*Population base:* 8,259 births 1990-93 in 2 Colorado municipal water districts comprising 86 census blocks. Excluded were: 6,214 births from 58/86 census blocks with no THM monitoring information; births <400 g, those outside 28-42 weeks gestation, multiple births, and births to nonwhite mothers; 1,893 births remained for study *Exposed:* Women exposed to >20 ppb TTHMs in 3rd trimester (n births =354 @ 21-40 ppb, 192 @ 41-60 ppb, 73 @ ≥61 ppb, 649 unknown THMs) *Comparison:* Women exposed to ≤20 ppb THMs (n=625 births total) served as referent group	*Exposure Measure:* Maternal address at time of birth used to establish residence during pregnancy; THMs exposure was modeled based on hydraulic characteristics of water system and THMs levels from quarterly monitoring program; sufficient information was available to estimate THMs exposure for mothers in 28 census block groups. Exposure score for each birth calculated as median of all THM concentrations measured in distribution system during 3rd trimester (n= 1,244 births) *Ascertainment of Disease/Risk Factors:* From birth certificates for maternal smoking, parity, maternal age, education, employment during pregnancy, prenatal care, and marital status.	*Method:* Logistic regression, adjusted for maternal smoking, parity, age, education, employment, prenatal care, and marital status if differed from crude analysis by more than 10% *Findings* (3rd trimester exposures): For low birth weight, OR=2.1 (1.0-4.8) for TTHMs ≥61ppb vs. THMs ≤20 ppb (n=8 vs. 34, respectively) For preterm delivery, OR=1.0 (0.3-2.8) for TTHMs ≥61ppb vs. THMs ≤20 ppb (n=4 vs. 36, respectively) For term-low birth weight, **OR=5.9 (2.0-17.0)** for TTHMs ≥61ppb vs. THMs ≤20 ppb (n=6 vs. 11, respectively)

TABLE 5 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: Waller et al., 1998 *Type of study:* Cohort *Outcome(s):* Spontaneous abortion (pregnancy loss at ≤20 wks. gestation, confirmed by medical records or physician interview; ectopic, molar, and electively terminated pregnancies excluded)	*Population base:* 5144 women members of Kaiser Permanete Medical Care Program in California 1989-91, age ≥17, ≤13 weeks gestation, with known date of last menstrual period (LMP) ; of 7457 eligible women, 6179 agreed to participate, 5342 successfully interviewed, and pregnancy outcomes established for 99% of those interviewed. *Exposed:* several different exposure groups created using various combinations of tap water consumption levels, and total and individual THM levels: High personal TTHM exposure = >5 glasses/day cold tapwater and TTHM level ≥75 µg/L *Comparison:* low personal exposure = <5 glasses/day cold tapwater, or having TTHM level <75 µg/L, or receiving water from utility providing >95% groundwater (see last column for individual THM cutpoints)	*Exposure Measure*: Water source based on address and interview to determine the glasses of bottled and tap water consumed per day in the week before interview and at their LMP; 97% of cohort assigned to water supply; THMs data from 1989-92 obtained from water supplies (at least quarterly at distribution taps) available for 96% of cohort; person's THMs exposure was estimated using average level of THMs for water supply with sample dates within the women's first trimester (77% of cohort) or within 30 days (4%) or annual average from the year of the midpoint of the first trimester (9%); analogous procedures used for TTHMs and individual THMs *Ascertainment of Disease/Risk Factors:* Pregnancy outcomes from hospital records of KPMCP, CA birth registry, follow-up interviews; interviews for information about demographics; previous pregnancy; consumption of alcohol, tobacco, and caffeine; employment.	*Method:* Logistic regression, adjusted for maternal age, employment during pregnancy, gestational age, history of pregnancy loss, race, cigarette smoking, and child's gender. *Findings:* For spontaneous abortion For TTHM ≥75 vs. <75 OR=1.2 (1.0-1.5) For High vs. low personal exposure All women: **OR = 2.0 (1.1-3.6)** Women not employed **OR = 3.0 (1.2-7.9)** Women employed OR = 1.5 (0.8-2.8) For high exposure to dichlorobromomethane (≥18 µg/L and ≥5 glasses/day) vs. low exposure (adjusted for covariates and all THMs simultaneously) **OR=3.0 (1.4-6.6)**

TABLE 5 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: Kanitz et al., 1996 *Type of study:* Cross-sectional *Outcome(s):* Low birth weight (≤2500 g), preterm delivery (≤37 weeks gestation), small body length (≤49.5 cm), small cranial circumference (≤35 cm), neonatal jaundice N.b.–study likely suffers from selection bias, evidenced by frequency distrbutions for variables that are out of the normal range for the population, among other things; the reported comparisons may not reflect the true underlying risks.	*Population base:* Births 1988-89 at Galliera Hospital, Genoa, and Chiavari Hospital, Chiavari, Italy, to mothers residing in each city. *Exposed:* 548 women in Genoa exposed either to filtered water disinfected with chlorine dioxide (Brugneto River wells and Reservoir and surface water) or chlorine (Val Noci Reservoir); THMs in chlorinated water varied from 8-16 ppb and in chlorine dioxide disinfected water 1-3 ppb. *Comparison:* 128 women in Chiavari with untreated well water.	*Exposure Measure:* Water source based on address (undisinfected well water, chlorine, chlorine dioxide, or both). *Ascertainment of Disease/Risk Factors:* Hospital records for information about all outcomes and mother's age, smoking, alcohol consumption, education level; family income from municipal records.	*Method:* Logistic regression, adjusted for maternal age, education, income, smoking, and child's gender. *Findings:* For chlorine dioxide vs. untreated well water: small cranial circumference **OR=3.5 (2.1-8.5)** short body length **OR=2.0 (1.2-3.3)** low birth weight OR=5.9 (0.8-14.9) preterm delivery OR=1.8 (0.7-4.7) neonatal jaundice **OR=1.7 (1.1-3.1)** For chlorine vs. untreated well water: small cranial circumference **OR=2.4 (1.6-5.3)** short body length **OR=2.3 (1.3-4.2)** low birth weight OR=6.0 (0.6-12.6) preterm delivery OR=1.1 (0.3-3.7) neonatal jaundice OR=1.1 (0.7-2.8)

TABLE 5 cont.			
Overview	Population	Exposure Assessment	Analysis
Reference: Savitz et al., 1995 *Type of study:* Population based case-control (interviews) *Outcome(s):* Low birth weight (<2500 g), miscarriage, preterm delivery (<37 weeks gestation)	*Population base:* Medically treated miscarriages in Alamance County, NC, 9/88 to 8/91; preterm deliveries and low birth weight infants at 6 hospitals in Orange and Durham Counties, 9/88 to 8/89 and Alamance County, 9/88 to 4/91. *Cases:* 261 miscarriages of 418 eligible, 412 preterm of 586 eligible, and 296 low birth weight of 782 eligible; all with complete data about water source; 126, 244, and 178 with complete data for THMs *Controls:* Live birth immediately following a preterm or low birth weight case of the same race and hospital; for miscarriages, 237 controls of 341 eligible,122 with data for THMs; for preterm and low birth weight, 543 controls of 782 eligible with complete data about water source, 333 with data for THMs.	*Exposure Measure:* Water source (private well, community water, bottled); water consumption (glasses per day); THMs levels and dose (level x consumption) *Ascertainment of Exposure:* Water source from interview and address; community water system – quarterly average measures of THMs at a sampling point nearest the address of participant and at an appropriate time (4th week of pregnancy for miscarriage and 28th week for preterm and low birth weight).	*Method:* Logistic regression, adjusted for maternal age, race, hospital (preterm, low birth weight), education, smoking, alcohol consumption, poverty level, marital status, education, employment and nausea (miscarriage) as needed. *Findings:* For miscarriages, OR=1.0 (0.7-1.6) community vs. private well; OR=1.6 (0.6-4.3) bottled vs. private well; OR=0.8 (0.5-1.1) 4 or more vs. 3 or fewer glasses/day; OR=1.2 (O.6-2.4) for THMs 81.8-168.8 vs. 40.8-59.9 ppb; OR=0.6 (0.3-1.2) for THMs dose 275.1-1171 ppb vs. 40.8-139.9(ppb x glasses/day). For preterm, OR=0.9 (0.7-1.2) community vs. private well; OR=0.8 (0.4-1.4) bottled vs. private well; OR=0.8 (0.6-1.0) 4+ vs. 1-3 glasses/day; OR=0.9 (O.6-1.5) for THMs 82.8-168.8 vs. 40.8-63.3 ppb; OR=0.9 (0.6-1.3) for THMs dose 330.9-1171 ppb vs. 44.0-169.9 (ppb x glasses/day). For low birth weight, OR=1.0 (0.7-1.4) community vs. private well; OR=0.8 (0.4-1.6) bottled vs. private well; OR=0.6 (0.6-1.1) 4+ vs. 1-3 glasses/day; OR=1.3 (O.8-2.1) for THMs 82.8-168.8 vs. 40.8-63.3 ppb; OR=0.8 (0.5-1.3) for THMs dose 330.9-1171 ppb vs. 44-169.9 (ppb x glasses/day).

TABLE 5 cont.			
Overview	Population	Exposure Assessment	Analysis
Reference: Bove et al., 1995 *Type of study*: Cross-sectional *Outcome(s):* All surveillance birth defects (30 diagnoses), low birth weight, small for gestational age, and preterm births.	*Population base:* All live singleton births (80,938) and fetal deaths (594) 1/85 to 12/88 in 75 New Jersey. *Exposed:* Women exposed to THMs, volatile and other organics from municipal water sources; 32,493 women exposed to >20 ppb THMs during 1st trimester. *Comparison:* Women exposed to low levels of organics or THMs; 19,841 women exposed to (≤20 ppb THMs; a comparison group of all live births that were not low birth weight, small for gestational age, and had no birth defects was also considered.	*Exposure Measure:* Water source and THMs based on address on birth certificate; THMs data (at least 4 samples each quarter) from locations in the water system 1984-88 were used to estimate monthly exposures to correspond with each gestational month of each birth and death. *Ascertainment of Disease/Risk Factors:* Birth defects were obtained from NJ Birth Defects Registry; birth and fetal death certificates provided information about maternal risk factors: race, age, education, marital status, prenatal care, previous stillbirth or miscarriage and child's gender; no information on smoking, alcohol consumption, and maternal occupation.	*Method:* Logistic regression, adjusted for maternal age, race, and education, previous stillbirth or miscarriage, prenatal care, and child's gender. *Findings:* Unadjusted results reported because adjustment did not alter results by >15%. Analyses considered exploratory by authors. Mean decrease in birth weight among term births was 70.4 g (40.6-82.6) for THMs >100 vs. THMs ≤20 ppb; for small for gestational age, **OR=1.5 (1.2-1.9)** for THMs >100 vs. THMs ≤20 ppb; for oral clef defects, **OR= 3.2 (1.2-7.3)** for THMs >100 vs. THMs ≤20 ppb;. For THMs >80 vs. THMs ≤20 ppb: all birth defects **OR=1.6 (1.2-2.0)** CNS defects **OR=2.6 (1.5-4.3)** neural tube defects **OR=3.0 (1.3-6.6)** major cardiac defects OR=1.8 (1.0-3.32.0)

TABLE 5 cont.

Overview	Population	Exposure Assessment	Analysis
Reference: Aschengrau et al., 1993 *Type of study:* Nested case-control with interviews *Outcome(s):* Congenital anomalies (live/stillborrn infant with 1 or more anomalies), stillbirths (without anomalies), and neonatal deaths (live-born infants without anomalies, dying within 1 week of birth)	*Population base:* Cohort of 14,130 obstetric patients who delivered from 8/77 to 3/80 at Boston Hospital for Women (83% of all delivery patients). *Cases:* 1314 congenital anomalies; 121 stillbirths; 76 neonatal deaths (1039, 77, and 55 cases in study, respectively) *Controls:* 1490 randomly selected women who delivered infants alive at discharge and without anomalies (1177 in study)	*Exposure Measure:* Water source (surface, ground, or mixed; chlorine or chloramine); and routine water analyses of minerals, metals, and other chemicals (no THMs); analyses closest to date of conception (median interval 3.3 months). *Ascertainment of Exposure/Covariates:* Address (at time of pregnancy outcome or 1st trimester if available) used to assign water exposures; interview used to collect information about maternal habits and demographic characteristics.	*Method:* Logistic regression, adjusted for maternal age, race, hospital payment method, history of anomaly, alcohol consumption, and water source. *Findings:* For chlorinated vs. chloraminated surface water Stillbirths OR = 2.6 (0.9-7.5) congenital anomalies, neonatal deaths OR-=1.0 (no reported CI) All major malformations OR = 1.5 (0.7-2.1) Respiratory defects OR = 3.2 (1.1-9.5) Urinary tract defects OR = 4.1 (1.2 -14.1)

TABLE 5 cont.			
Overview	Population	Exposure Assessment	Analysis
Reference: Kramer et al., 1992 *Type of study:* Population based case-control without interviews *Outcome(s):* Low birth weight (<2500 g), preterm delivery (<37 weeks), intrauterine growth retardation (IGR, <5th percentile of weight for gestational age)	*Population base:* All live singleton infants born 1/89 to 6/90 to non-Hispanic, white women from Iowa towns with 1,000 to 5,000 inhabitants that delivered 100% of public water from a single source. *Cases:* Three case groups – 159 low birth weight infants, 342 preterm deliveries, 187 infants with IGR (case groups not mutually exclusive) *Controls:* Three groups, randomly selected on a 5:1 basis – 795 (from infants weighing ≥2500 g); 1710 (randomly selected from infants with ≥37 wks. gestation), and 935 (randomly selected from infants with reported gestational age, excluding those ≤22 or ≥44 weeks)	*Exposure Measure:* Water source (surface, shallow or deep wells) and THMs levels from a 1987 state water survey. *Ascertainment of Exposure/Covariates:* Water source and THMs levels from address at birth; birth certificate used to obtain information about maternal age, marital status, smoking, parity, prenatal visits, and education.	*Method:* Logistic regression, adjusted for maternal age, smoking, marital status, education, prenatal care, number of previous children. *Findings:* For chloroform ≥10 ppb vs. non detectable levels: Low birth weight OR = 1.3 (0.8-2.2) Preterm delivery OR = 1.1 (0.7-1.6) IGR **OR = 1.8 (1.1-2.9)** For dichlorobromomethane ≥10 ppb vs. non detectable levels: IGR OR = 1.7 (0.9-2.9) For organic halides≥100 ppb vs. non detectable: IGR OR = 1.8 (0.9-3.4) For chloroform ≥10 ppb vs. non detectable levels in deep wells (≥150 feet): IGR OR = 2.4 (0.8-7.5) For chloroform ≥10 ppb vs. non detectable chloroform levels in shallow wells (<150 feet): IGR OR = 2.2 (0.7-6.8)

* 95% confidence interval in parentheses for ORs and RRs except for Bove et al., (1995) (90% CI). Bold OR/RR indicates increased risk with a CI that excludes the null value of 1.0. Information presented is intended to highlight positive findings in these studies; original articles should be consulted for complete results and details of study design, implementation and analysis

increase in both number and quality before quantitative use of the results can be considered.

2.4.2. Summary of Single Chemical Toxicology Studies. Taken as a body of literature, single chemical toxicology studies on DBPs have produced effects in the same target organ systems (but not always the same site) as those observed in the positive epidemiology studies (i.e., for developmental and reproductive effects and cancer). Toxicologic data are available for some of the more common DBPs, but not for the hundreds of potential DBPs described in Section 2.3. As shown in Table 6, information is available on the Agency's Integrated Risk Information System (IRIS) database (U.S. EPA, 2000b) for only a few DBPs; these are chloroform ($CHCl_3$), bromoform ($CHBr_3$), bromodichloromethane (BDCM), chlorodibromomethane (CDBM), dichloroacetic acid (DCA), trichloroacetic acid (TCA), formaldehyde and chloral hydrate (CH), all of which have shown some evidence of carcinogenicity in the toxicologic literature. Most of the data used to evaluate these DBPs are for oral exposures; little information is available on the toxic effects of inhalation or dermal exposures. For these DBPs and for an increasing number of additional DBPs, toxicologic studies are available that show evidence of carcinogenicity, mutagenicity, reproductive and developmental effects, hepatotoxicity, nephrotoxicity and other toxic effects in high-dose, single chemical studies. (For more detailed information, see Section 2.3. of Report 2 and Appendix I). This section highlights the toxicologic issues associated with individual chemical studies of significant concern in the development of a DBP mixture risk assessment.

TABLE 6

Verified DBP Assessments On EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 2000b)

Compound [CAS Registry No.]	Reference Dose[a] (Date) [No RfCs Available]	Carcinogenic Risk	
		Oral Slope/ WOE Classification[b] (Date)	Oral Unit Risk Inhalation Unit Risk
Chloroform [67-66-3]	1 E-2 mg/kg/day (09/01/92)	6.1 E-3 / B2 (03/01/91)	1.7 E-7 $(\mu g/L)^{-1}$ 2.3 E-5 $(\mu g/m^3)^{-1}$
Bromodichloromethane [75-27-4]	2 E-2 mg/kg/day (03/01/91)	6.2 E-2 / B2 (03/01/93)	1.8 E-6 $(\mu g/L)^{-1}$ -
Dibromochloromethane [124-48-1]	2 E-2 mg/kg/day (03/01/91)	8.4 E-2 / C (01/01/92)	2.4 E-6 $(\mu g/L)^{-1}$ -
Bromoform [75-25-2]	2 E-2 mg/kg/day (03/01/91)	7.9 E-3 / B2 (01/01/91)	2.3 E-7 $(\mu g/L)^{-1}$ 1.1 E-6 $(\mu g/m^3)^{-1}$
Trichloroacetic Acid [76-03-9]	-	- / C (03/01/96)	- -
Dichloroacetic Acid [79-43-6]	-	- / B2 (03/01/96)	- -
Chloral Hydrate [75-87-6]	2 E-3 mg/kg/day (02/01/96)	- / -	-
Formaldehyde [50-00-0]	2E-1 mg/kg/day (09/01/90)	none / B1 (05/01/91)	- 1.3E-5 $(\mu g/m^3)^{-1}$

[a] Reference Dose is an oral human exposure level below which deleterious non-cancer effects are not expected to occur. RfC (Reference Concentration) is the analogous inhalation value.

[b] Oral Slope per mg/kg-d; U.S. EPA(1986) recommended that carcinogens be classified on the weight of evidence for cancer using both animal and human data. Although these are changed in the new proposed guidelines (U.S. EPA, 1996b), many of the 1986 classifications remain on IRIS and are defined as follows:

Group A (Human Carcinogens) includes chemicals for which there is sufficient human epidemiologic evidence linking exposure with cancer risk.

Group B (Probable Human Carcinogens) includes chemicals for which the weight of evidence for human carcinogenicity is limited but the weight of animal data is sufficient.

Group C (Possible Human Carcinogens) includes chemicals for which there is limited animal evidence in the absence of human data.

Group D (Not Classifiable as to Human Carcinogenicity) includes chemicals that lack available (adequate) data.

Group E (Evidence of Non-Carcinogenicity for Humans) includes chemicals for which adequate data are available that do not demonstrate a risk for cancer.

2.4.2.1. Carcinogenicity from Exposure to DBPs — The cancer process involves several distinct events: initiation, promotion and progression. Chemical carcinogens act through initiation and/or promotion; progression is related to the internal biology of the tumor, governed largely by tumor type. Genotoxic chemical carcinogens interact directly with the DNA and impart an initiating effect. This adverse change in the DNA can be repaired or may remain long enough to be replicated and passed on to daughter cells. These cells may then clonally expand to form tumors. Epigenetic chemical carcinogens do not directly interact with the DNA of the organism, but alter processes that govern cellular homeostasis. Disruption of cellular homeostasis allows initiated cells to expand to become tumors. Tumor promoters (e.g., phthalates) are carcinogens that may be encountered at doses predicted to be without adverse effect. This type of carcinogen (epigenetic, tumor promoter) may demonstrate a distinct dose level (threshold), below which the production of tumors is not evident.

As stated above, some evidence of carcinogenic response has been observed for all of the DBPs in Table 6; the chemical-specific information presented here is found on IRIS (U.S. EPA, 2000b). For the THMs, kidney tumors were seen in male rats exposed to $CHCl_3$. BDCM is structurally similar to other known animal carcinogens, is mutagenic, and produced tumors at multiple sites in multiple species. CDBM is mutagenic and produced liver tumors in female mice only at doses that also produced liver damage. $CHBr_3$ is genotoxic and induced neoplastic lesions in the large intestines in rats. For the two haloacetic acids in Table 6, an increased incidence of hepatocellular adenoma and carcinomas was found in male and female mice exposed to DCA, and although TCA produced tumors in male and female mice, there is no

evidence of carcinogenicity in rats. Finally, squamous cell carcinomas were found in male rats exposed to formaldehyde by inhalation. Although a cancer assessment is not available on IRIS for CH, in a recent study, it was found to be carcinogenic (hepatocellular neoplasia) in the male mouse, but not in the rat (George et al., 2000).

For several of these DBPs, however, questions regarding the strength of the carcinogenic evidence remain. In particular, an expert panel cancer assessment (U.S. EPA, 1998c) of $CHCl_3$ that employed methodology from the 1996 proposed Cancer Risk Assessment Guidelines (U.S. EPA, 1996b), found increasing evidence that the carcinogenic mechanism of action for $CHCl_3$ is not relevant at the low concentrations found in drinking water. Similar issues are being raised for the haloacetic acids. In addition, several of the THM cancer studies were performed using corn oil as the dosing vehicle, confounding the carcinogenic results (see Section 2.4.2.3. below).

2.4.2.2. Developmental and Reproductive Effects from Exposure to DBPs —

Human epidemiologic studies identifying reproductive and developmental toxicities have stimulated increased laboratory testing in this area. Qualitatively, DBPs (especially, the haloacetic acids and haloacetonitriles) have been shown to adversely affect reproduction and development in animals. Studies of reproductive and developmental toxicity effects of DBPs, summarized elsewhere (and in EPA, 1999d), demonstrated alterations in sperm morphology, motility and count; decreased levels of fertility; spontaneous resorptions; decreased fetal body weight; and visceral, cardiovascular and craniofacial malformations. Studies have shown alterations in sperm parameters at the lowest doses tested. The haloacetic acids have also produced male infertility in rats. Although effects on sperm morphology and/or motility indicate a

potential reproductive hazard, ascribing decreased fertility (a quantifiable measure of adverse effect) to the test chemical may be somewhat conservative. Changes in sperm motility, morphology or number do not necessarily translate into decreased fertility, owing to the high degree of redundancy in sperm production. Nonetheless, these observations are indicative of risk. Because of the epidemiologic link to cardiovascular malformations in humans, animal studies were undertaken, through which confirmatory data have been generated. Additional studies are aimed at investigating the potential epidemiologic link between spontaneous abortion in humans and demonstrated additional developmental toxicities with DBPs.

Seven of the 11 haloacetic acids (MCA, DCA, TCA, MCA) and haloacetonitriles (DCAN, TCAN, BCAN) have been subjects of developmental toxicity studies by a single group of investigators (e.g., Christ et al., 1995; Randall et al., 1991; Smith et al., 1988, 1989a,b, 1990, 1992). Three of the haloacetic acids (DCA, MBA, DBA) have been the subjects of male reproductive studies by another group of investigators (e.g., Linder et al.,1994) (see Sections 2.3. and 3.8. of Report 2 for references and additional details). All of these studies were conducted in rats using gavage administration. The results for developmental toxicity were positive. For reproductive toxicity, the dihalogenated haloacetic acids gave positive results, but MBA gave negative results. An additional chemical, the haloacetonitrile, DBAN, was tested in a short-term developmental and reproductive toxicity screening study in rats by the NTP (1992), with negative results. Evaluation of these data sets listed by dose-response modeling showed that visceral malformations, particularly cardiovascular (interventricular septal defects, defects between ascending aorta and right ventricle, and levocardia) and smaller fetal size

(body weight and crown-rump length) appeared to be the most sensitive endpoints in common for these chemicals.

For the THMs, BDCM is of most concern for the developmental and reproductive endpoints. An epidemiology study (Waller et al., 1998) associated exposures to BDCM in the drinking water to spontaneous abortions. Klinefelter et al. (1995) reported that the exposure of rats to BDCM in drinking water, significantly decreased sperm velocity. As with the carcinogenic data, both the vehicle of administration and the possibility that the mechanism of toxicity is not active at environmental exposure levels are of concern for this data set.

2.4.2.3. Vehicle and Route Considerations — Toxicity data are often derived from animal studies and generally include the administration of high doses of a chemical. There is a crucial interplay between dose, dose rate, pharmacokinetics/ internal concentrations, mode/mechanism of action and saturable biologic processes. The application of Haber's Law (concentration times time) may not hold true for orally administered compounds and for some compounds encountered via the inhalation route. For instance, the administration of a single bolus delivered via gavage in a vehicle that promotes rapid absorption of the chemical may produce absorption patterns that would not be replicated in a human exposure to the same chemical via the same route. Studies with $CHCl_3$, BDCM, and the haloacetonitrile compounds have involved the delivery of the chemicals via gavage in vehicles which may be problematic. For example, $CHCl_3$ administered as a single gavage bolus in corn oil produces peak concentrations and toxicities greater or more detrimental than those observed from the

same dose (expressed as mg/kg/day) via drinking water spread over time through multiple dosing (Simmons and Pegram, 1998).

While exposure to DBPs in drinking water is generally assumed to be through ingestion of drinking water, the actual exposure pattern is more complex. Tap water is used for cooking, washing household materials and showering/bathing. These uses indicate that DBPs in drinking water are encountered via dermal and inhalation pathways, as well as by ingestion. Although the DBPs encountered at low doses through the consumption of drinking water are each virtually 100% bioavailable (they are all absorbed with nearly 100% efficacy in the GI tract), the internal doses developed as a function of inhalation or dermal exposure are not so uniform. In showering, both the inhalation and dermal routes are relevant. Differential volatility and efficacy at which DBPs are absorbed by the blood (governed by blood:air partitioning) largely determines the internal doses attained from inhalation exposure. THMs have very low boiling points, reasonably high vapor pressures, and low molecular weights. Thus, they readily volatilize during showering or bathing. Jo et al. (1990) measured $CHCl_3$ in breath following showering while unclothed and clothed in a water-occlusive rubber suit. Because $CHCl_3$ in the exhaled breath of individuals wearing rubber suits was approximately half that of individuals showering unclothed, these data may indicate that (for $CHCl_3$) the magnitude of dermal exposure is roughly equivalent to that from the inhalation route. In contrast to $CHCl_3$'s physical chemical properties (non-polar, well-halogenated, highly lipophilic, highly volatile, low molecular weight) and high degree of dermal penetration, the haloacetic acids, haloacetonitriles, and other higher molecular weight DBPs have lower boiling points and vapor pressures and thus are volatilized with

much less efficiency. Thus, inhalation exposures favor the delivery of volatile DBPs over non-volatile DBPs.

However, the dermal delivery of DBPs, is generally less well characterized. The dermal absorption of $CHCl_3$ in humans increases when $CHCl_3$ in tap (bath) water was encountered during bathing at higher temperatures than when bathing at lower temperatures (Corley et al., 2000). Increased blood circulation to the skin promotes higher absorbance of $CHCl_3$. This physiological adaptation to heat likely increases the absorbance of other DBPs, as well. Several factors distinguish the dermal penetrability of chemicals, including DBPs. Higher degrees of lipophilicity promote dermal absorbance. The lipophilicity of DBPs (measured as octanol:water partitioning, logP) spanned a range of more than 100-fold. The degree to which lipophilicity dictates dermal penetration indicates that the differential dermal absorption of DBPs produces marked differences in their internal doses, even when encountered under similar concentrations and conditions.

2.4.2.4. Pharmacokinetics and Target Organ Concentrations — While the EPA regulates chemical exposures based on the dose expressed as milligrams encountered per kilogram of body mass per day (mg/kg/day), the rate at which this dose is encountered may significantly affect its toxicity. The administration of test chemicals via the most likely route of human exposures is difficult when actual exposures may be through drinking water encountered over the course of a day. Although investigators can maintain the same route (oral) by dissolving the chemical in a dosing vehicle (water, corn or olive oil, tricaprylin, etc.) and administering it orally, the rate at which these chemicals enter the body and the resulting internal concentrations of the chemical in

target organs for toxicity differ from those produced by the same daily dose (mg/kg/day) delivered in multiple, lower doses (e.g., hepatic concentrations of $CHCl_3$ resulting from temporally-dispersed drinking water exposure are lower than those resulting from a bolus corn oil gavage exposure). This sometimes marked difference in internal concentrations may affect toxic response through several mechanisms; two examples hinge on metabolism and cellular damage.

Attaining higher internal concentrations (resulting from higher doses) of a toxicant can recruit additional (or secondary) enzymes to the disposition of chemicals. This can result in the production of qualitatively different (and differentially toxic) metabolites at higher doses than at lower doses. This may become evident when doses, potentially spread over the course of a day, are concentrated into a single dose and administered in a vehicle promoting rapid absorption and delivery to tissues. On the other hand, some chemicals may be metabolized, regardless of dose, to produce toxic metabolites. However, lower concentrations of the toxic metabolites may produce cellular responses that can be corrected by the normal functioning of the cell. Cellular damage and necrosis can be repaired (or replaced) to some degree, but when the extent of injury increases the rate of cellular replication to the point that efficient DNA repair (a normal function) cannot take place, then the potential for mis-formation of DNA and genetic damage exists. This mis-formation of DNA can lead to the development of cancer. This phenomenon may complicate the extrapolation of high dose toxicity to lower doses, and makes the identification of the mode of action (MOA) all the more critical. Certainty about potential dose-dependency of the MOA reduces uncertainty in the extrapolation to lower doses.

For several chemicals whose toxicity is mediated through a common MOA, and that may be encountered in combination, an estimate of their combined toxicity may be accomplished by combining their doses. In addition to information on MOA, pharmacokinetic information about the chemicals allows for a more thorough evaluation of the toxic interaction of mixtures, regardless of their MOA. When these chemicals are active in their parent form, their metabolism reduces their toxic impact. However, one of the chemicals may reduce the body's ability to metabolize the others, resulting in prolonged residence time in the body and greater opportunity for interaction with biological (target) tissues. The elucidation of general and specific pharmacokinetic parameters thus enhances the ability to ascertain or estimate the effect of multiple chemical exposures.

2.4.2.5. Mode of Action — Determination of MOA and any dose-dependency of the MOA is helpful when evaluating dose-response. BDCM's carcinogenic response may involve metabolism through the glutathione S-transferase pathway, but this may not be relevant at low doses or low internal concentrations. BDCM produces genetic damage in bacteria into which rat glutathione S-transferase theta class enzyme has been transfected, but not in the same bacterial strain lacking this enzyme (DeMarini et al., 1997). In mammals, lower doses of BDCM are metabolized by the mixed function oxidase system, but higher doses of BDCM may saturate this mechanism and recruit the glutathione S-transferase metabolic system. Thus, the delivery of the test chemical via methods that may not mimic the human exposure scenario may produce results that must be carefully extrapolated to humanly-relevant doses and delivery schedules. This differential effect with respect to dose (target organ concentration) has been recognized

in the Agency's treatment of $CHCl_3$ risk; is being investigated with respect to BDCM risk; and complicates the interpretation of developmental toxicity results obtained with haloacetonitrile compounds delivered via gavage in tricaprylin. The results obtained from research animals treated via gavage with boli of high doses of toxicants may provide overly conservative estimates of risk when extrapolated to humans in the absence of adequate pharmacokinetic, metabolism and MOA considerations.

2.4.2.6. Bromate — When source waters are high in bromide and ozone is the primary chemical disinfectant, brominated compounds are produced in greater quantities than chlorinated DBPs; bromate, in particular, is produced. Drinking water studies of rats exposed to bromate have shown the production of kidney tumors (males and females) and peritoneal mesotheliomas (males only) (Kurokawa et al., 1983). Although these results indicate that bromate is a complete carcinogen, additional experiments in this study demonstrated its tumor promoting activity in the kidney and that the lowest dose producing kidney tumors was 6.5 mg/kg/day (doses employed were 0.7, 1.3, 2.5, 5.6, 12.3 and 33.4 mg/kg/day). Interestingly, no increase in liver tumors followed initiating treatment (with EHEN). Kurata et al. (1992) treated rats with acute doses of bromate followed by promoting doses of barbital sodium to examine tumor initiating activity, but could demonstrate none. The lack of tumor initiating activity may support the theory that longer durations are necessary to initiate tumors or that bromate produces renal tumors through promotional activity.

An evaluation of the impact of bromate (delivered as either KBrO3 or NaBrO3) indicates that these chemicals, but not KBr, induce alpha-2-micro-globulin accumulation in the kidneys of male, but not female, rats (Umemura et al., 1993). These data,

coupled with the lack of renal carcinogenicity in mice and hamsters (Kurokawa et al., 1986; Takamura et al., 1985), raise the question of the relevancy of bromate-induced renal tumors to the evaluation of cancer risk in humans. The involvement of alpha-2-micro-globulin as an exclusive mechanism of tumorigenicity in rat kidneys is confounded by the finding of renal tumors in female rats (Kurokawa et al., 1983). Alternately, the production of oxidative stress in renal tissue may stimulate cell replication, resulting in tumor promotion (Umemura et al., 1995). Although the finding of renal tumors in female rats may reduce the perceived importance of alpha-2-micro-globulin as an event modifying renal carcinogenicity, its association with male rat kidney tumors may indicate that the mechanism may increase the incidence of tumors in male rats beyond the incidence in female rats. This may raise questions about the validity of carcinogenic risk estimates for bromate, as they are mainly based on the incidence and dose-response relationship demonstrated for male rat kidney tumors.

Consistent with the finding of renal toxicity in rodents, humans acutely exposed to bromate (potassium and/or sodium bromate) in permanent hair wave neutralizing solutions have demonstrated severe renal damage as well as permanent hearing loss. There are no available published reports on the potential of bromate to produce developmental toxicity. Recently, published data (DeAngelo et al., 1998) have confirmed the multisite carcinogenicity of bromate in rats. A slight dose-response was noted for kidney tumors in mice. The U.S. EPA (2000b) has considered this evidence supportive of earlier MCL (0.01 mg/L) and MCLG (zero) values.

Bromate also produces oxidative injury in tissues, as evidenced by the formation of characteristic 8 hydroxy-deoxyguanine adducts. Oxidative stress may be a tumor

promotional event. DeAngelo and co-workers (Crosby et al., 2000; DeAngelo et al., 1998; and Wolff et al.,1998) have examined the effect of potassium bromate on tumors other than kidney in rats and mice. They have demonstrated that bromate induces a high number of tumors in the tunica vaginalis of the testicle of rats, and that these tumors can spread through the mesentary to other parts of the viscera. Tumor prevalence at this site was 25% in a 2-year bioassay, while only 1% of rats demonstrated renal carcinogenicity. These results identify a site much more sensitive to carcinogenesis than the kidney and offer additional carcinogenesis dose-response data for risk assessment considerations. These authors pointed out the unique anatomy and physiology of this tumor site, and recommend specific attention to those factors that may uniquely influence toxicity/carcinogenicity at this site.

2.4.3. Summary of Mixtures Toxicology *In Vivo* and *In Vitro* Studies. A number of toxicology studies are available on mixtures of DBPs, ranging across a variety of effects, including mutagenicity, carcinogenicity, hepatotoxicity, nephrotoxicity, developmental toxicity, neurological effects and changes in pharmcokinetics (Table 7). Historically, the majority of research with DBP mixtures has focused on toxicologic assessment of concentrated drinking water samples, with an emphasis on detection of mutagenicity. In the 1990s, there has been an increased interest in research on simple DBP mixtures, with a general focus on interactions either among the trihalomethanes (THMs) or among the haloacetic acids (HAAs). This initial focus on the within-class interactions among the THMs and the HAAs is understandable because the vast majority of single-chemical toxicology research on DBPs has focused on these two important chemical classes, resulting in the identification of carcinogenic,

TABLE 7

Available Toxicity Data for DBP Mixtures

DBP Mixture[a]	Effects/Species/ Duration	Dose Combinations[b]	Results	References
Complex mixture; extracts of finished drinking water	Mutagenicity in *Salmonella* plate incorporation assay	-	Chlorine-highly mutagenic; Chloramine-slightly mutagenic; Ozone-no apparent effect	DeMarini et al., 1995; Patterson et al., 1995
Binary mixture: Ratios of $CHCl_3$:$CHBr_3$	Mortality, circulatory, neurological effects in medaka fish; 96 hours	1:1 ratio of 20, 30, 40, 50 ppm tmd	Dose-additivity observed at low doses; antagonism at 50ppm	Hartley et al., 1999
Binary mixture: Ratios of $CHCl_3$:BDCM	Hepatotoxicity in rats; acute	1:1 ratio of 0.5-3 mmol/kg tmd	Dose-additivity observed at all doses	Keegan et al., 1997
Binary mixture: Ratios of $CHCl_3$:BDCM	Hepatotoxicity in mice; 14 days	1:1 ratio of 0.1, 1, 3 mmol/kg/day tmd; 2.7:1 ratio of 1,3 mmol/kg/day tmd	Dose-additivity observed at all doses	Simmons et al., 2000b
Quaternary mixture: Ratios of $CHCl_3$:$CHBr_3$: BDCM:CDBM	Hepatotoxicity in mice; 14 days	0.65:0.01:0.24:0.1 ratios of 0.872 tmd	Dose-additivity observed	Gennings et al., 1997

TABLE 7 cont.

DBP Mixture[a]	Effects/Species/ Duration	Dose Combinations[b]	Results	References
Quaternary mixture: Ratios of $CHCl_3$:$CHBr_3$: BDCM:CDBM	Blood concentrations of $CHCl_3$, $CHBr_3$, BDCM, CDBM; acute	1:1:1:1 ratios of 1.0 mmol/kg tmd	Antagonistic toxicokinetic interaction	da Silva et al., 1999a
Binary mixtures: Ratios of $CHCl_3$:$CHBr_3$: BDCM:CDBM	Blood concentrations of $CHCl_3$, $CHBr_3$, BDCM, CDBM; acute	1:1 ratios of each binary combination of 1.0 tmd	Antagonistic toxicokinetic interaction	da Silva et al., 1999b
Binary mixtures: Ratios of DCA:TCA and TCA:DCA	Metabolism in mice; 14 days pretreatment in water, acute challenge	15.5 mmol DCA/L: 100 mg TCA/kg; 12.2 mmol TCA/L: 100 mg DCA/kg	DCA pretreatment had no effect on TCA metabolism; TCA pretreatment had no effect on DCA metabolism	Gonzalez-Leon et al., 1999
Binary mixtures: Ratios of DCA:TCA	Hepatic tumor promotion in MNU-initiated mice; 50 weeks	1.3:1, 2.6:1, 4.2:1, 0.6:1 ratios of 13.8, 21.6, 31, 40.6 mmol/L tmd, respectively	At highest tmd only, DCA increased TCA-induced tumor promotion	Pereira et al., 1997
Binary mixtures: Ratios of DCA:$CHCl_3$ and TCA:$CHCl_3$	Hepatic and renal toxicity in rats; acute, sequential, pre-treatment with DCA or TCA	1.5:1, 3.9:1 ratios of each binary combination of 1.55, 3.08 mmol/kg tmd	DCA increased $CHCl_3$ hepatotoxicity and nephrotoxicity; TCA increased $CHCl_3$ nephrotoxicity	Davis, 1992

TABLE 7 cont.				
DBP Mixture[a]	Effects/Species/ Duration	Dose Combinations[b]	Results	References
Binary mixtures: Ratios of DCA:$CHCl_3$	Hepatic toxicity in rats; acute, sequential, pre-treatment with DCA	0.8:1, 0.36:1 ratios of 5.57 and 11.8 mmol/kg tmd	DCA increased $CHCl_3$ hepatotoxicity	Yang and Davis, 1997a,b

[a] Chloroform ($CHCl_3$), Bromodichloromethane (BDCM), Chlorodibromomethane (CDBM), Bromoform ($CHBr_3$), Dichloroacetic acid (DCA), Trichloroacetic acid (TCA), Dibromoacetic acid (DBA), Bromochloroacetic acid (BCA)

[b] tmd = total mixture dose (i.e., sum of the component doses)

developmental, hepatotoxic and nephrotoxic effects of concern. In addition, the THMs and HAAs are among the most commonly occurring DBPs and are present at relatively high concentrations compared to other DBPs. One notable exception to the within-class investigations has been examination of the effect of dichloroacetic acid (DCA, a HAA) on chloroform ($CHCl_3$, a THM) toxicity.

The generation of DBP mixtures data is essential to refine human health risk assessment methods under development and efficient experimental designs and statistical approaches for mixtures (Simmons et al., 2000a; Teuschler et al., 2000). Because several available risk assessment methods are based on additivity assumptions, their use to estimate DBP mixtures risk should be grounded by toxicity data supporting these assumptions. Although the number of studies on defined DBP mixtures is still small, several conclusions may be drawn from this body of literature. First, the nature of the observed interaction (additive, nonadditive) may depend on whether the multiple chemical exposure is concurrent or temporally separated. Second, the mixing ratio of the components comprising the mixture may affect the toxic outcome and account for apparent inconsistencies across studies. Third, interactive effects appear to be dose-dependent (e.g., synergism and antagonism are expected interaction effects at high dose levels, while dose additivity is more commonly observed in lower portions of the mixture dose-response curve). This dose-dependence may account for inconsistencies across studies that appear to have conflicting outcomes, but are actually working in different sections of the dose-response curve. In general, these conclusions are consistent with the current state of knowledge in mixtures research.

2.4.3.1. Complex Mixtures of DBPs — DeMarini et al. (1995) and Patterson et al. (1995) examined the mutagenic potency of extracts prepared from water that had undergone one of several different disinfection treatments. The DBPs present in the drinking water were concentrated by extraction techniques that resulted in concentration of the semi-volatile and nonvolatile organics and the loss of the volatile organics. Mutagenicity was assessed in the *Salmonella* plate incorporation assay (Patterson et al. employed strains TA100, TA98, TA97 and TA102, with and without metabolic activation, and DeMarini et al. used strains TA98 and TA100 without metabolic activation).

According to their findings, raw water (i.e., water that has not undergone chemical disinfection) has a very low level of mutagenic activity. Compared to raw water, chlorination greatly increases the mutagenicity of water. Ozonation alone has very little apparent effect on the mutagenic activity of water. Chloramination alone increases the mutagenicity of water, but to a lesser extent than chlorination. Prior treatment with ozone decreases the mutagenicity associated with either chloramination or chlorination. Generally, the addition of metabolic activation decreases mutagenic activity. The mutation spectra produced by the various drinking water extracts resemble those produced by MX (3-chloro-4(dichloromethyl)-5-hydroxy-2(5H)-furanone, a highly mutagenic DBP).

2.4.3.2. Defined Mixtures of Trihalomethanes — To date, the binary combination of $CHCl_3$ and bromoform ($CHBr_3$) has been evaluated in a Japanese medaka (*Oryzias latipes*) embryo lethality/developmental toxicity assay and the binary combination of $CHCl_3$ and bromodichloromethane (BDCM) has been examined for

hepatotoxicity in both mice and rats. In the fish assay, medaka were exposed concurrently to $CHCl_3$ and $CHBr_3$ for 96 hours (Hartley et al., 1999). The measured effect was based on the combined incidence of death and severe neurological/circulatory effects expected to result in death. The data were analyzed using a response surface model (Gennings et al., 1997), built under the assumption of dose-addition, and then used to test for departures from dose additivity. Of the four concentrations tested at a 1:1 mixing ratio of $CHCl_3$:$CHBr_3$, deviation from dose additivity was detected only at the highest tested concentrations of 25 ppm $CHCl_3$: 25 ppm $CHBr_3$, where antagonism was observed. At all lower concentrations (10:10, 15:15, 20:20), the toxicity of the mixtures did not depart from that predicted by dose additivity.

The binary interaction of $CHCl_3$ and BDCM was evaluated in mice (female, CD-1) and rats (male, F-344) following concurrent oral exposure in an aqueous vehicle (Keegan et al., 1997; Simmons et al., 2000b). Hepatotoxicity was assessed by serum indicators of hepatic damage in rats 24 hours after acute exposure and in mice after 14 days of daily dosing. Rats were exposed to total mixture dosages ranging from 0.5 to 3.0 mmol/kg at a 1:1 mixing ratio. In the mouse experiment, three mixture groups were exposed to total mixture dosages of either 0.1, 1.0 or 3.0 mmol/kg/day at a mixing ratio of 1:1 $CHCl_3$:BDCM; another two mixture groups were exposed to total mixture dosages of either 1.0 or 3.0 mmol/kg/day at a mixing ratio of 2.7:1 $CHCl_3$:BDCM. The 2.7:1 mixing ratio of $CHCl_3$:BDCM was selected based on the average seasonal proportions of these two chemicals at 35 U.S. water treatment facilities (Krasner et al., 1989). In

both species, there was little or no apparent deviation from dose additivity at the tested mixing ratios and chemical concentrations.

The hepatotoxicity of a mixture of the four THMs ($CHCl_3$, $CHBr_3$, BDCM, and chlorodibromomethane [CDBM]) has been evaluated (Gennings et al., 1997, 1999) in mice under an experimental protocol similar to that described above for the binary combination of $CHCl_3$ and BDCM. The four THMs were administered in an aqueous vehicle to female CD-1 mice by concurrent daily oral exposure for 14 days. The mixing ratio of the four THMs was selected based on their average seasonal proportions at 35 U.S. water treatment facilities (Krasner et al., 1989). The proportions, on a mmol basis, were 0.65 $CHCl_3$: 0.01 $CHBr_3$: 0.24 BDCM: 0.10 CDBM. The total mixture dosage was 0.872 mmol/kg/day. The threshold additivity model was used to predict the serum level of sorbitol dehydrogenase (SDH), a serum indicator of hepatotoxicity, expected under an assumption of dose additivity. The predicted mean SDH value for the mixture was 40.5 IU/l with 95% prediction limits of 31.9 and 49.1. The experimental mean SDH response was 43.9 IU/l. The close correspondence between the predicted and the observed mixture response indicated that hepatotoxicity, as measured by this serum indicator, did not deviate from the level predicted under dose additivity.

In contrast to the dose additivity reported for the hepatotoxicity of the four THMs (Gennings et al., 1997), other investigators (da Silva et al., 1999a) have reported an apparent antagonistic toxicokinetic interaction among the four THMs. Male Sprague-Dawley rats were exposed acutely by oral administration to 0.25 mmol/kg of each THM alone or to a four-THM mixture containing 0.25 mmol/kg of each chemical for a total mixture dosage of 1.0 mmol/kg. For each THM, administration in the mixture resulted in

increased blood concentrations when compared to single chemical administration, indicating decreased metabolism. Work in progress (da Silva et al., 1999b) has compared, for all six possible binary combinations of the four THMs, blood THM concentration following oral exposure to 0.5 mmol/kg of each THM alone with the blood THM concentration resulting from exposure to binary combinations at a total mixture dosage of 1.0 mmol/kg (i.e., containing 0.5 mmol/kg of each THM). Similar to what was seen with the four-THM mixture, exposure to the THMs in binary combination resulted in an increase in blood concentration when compared to single chemical administration.

Several reasonable hypotheses can be constructed to explain the apparent conflict between the dose additivity among the THMs for hepatotoxicity based on serum indicators reported by Simmons et al. (2000b) and the metabolic antagonism among the THMs reported by da Silva et al. (1999a) One explanation may lie in the definition of additivity applied in these studies. The conclusions drawn by Simmons et al. are based on the concept of dose addition. Although the underlying model of additivity used by da Silva et al. is not stated, the results of their work appear to be based on the concepts of response or effect addition. These models of chemical interaction are based on different mathematical constructs and toxicological assumptions about mechanism of action (U.S. EPA, 1986, 1999c). Thus, they do not necessarily result in the same conclusion regarding additivity or nonadditivity (Gessner, 1988).

Another possible hypothesis lies with the endpoints chosen for examination. Serum indicators such as SDH are generally considered sensitive markers of hepatotoxicity; it is possible that other measures of hepatotoxicity would respond differently. The two research groups used different species and strains/stocks of

animals and the differing results may reflect either species or strain differences in chemical response. Rarely has the same mixture or multiple chemical exposure been tested in more than one species or strain. Finally, differences in chemical interactions between these studies could be the result of differences in the mixing ratios employed. Simmons et al. used environmentally-based ratios that included very small proportions of $CHBr_3$ (1% of the mixture, for an actual dosage of 0.012 mmol/kg/day), a relatively toxic THM. In contrast, da Silva et al. used a 1:1 mixing ratio, resulting in much larger dosages of $CHBr_3$, namely, 0.25 and 0.5 mmol/kg.

2.4.3.3. Defined Mixtures of Haloacetic Acids — Gonzalez-Leon et al. (1999) examined the effect of pretreatment with DCA on the pharmacokinetics of trichloroacetic acid (TCA) in male B6C3F1 mice. Similarly, they examined the effect of pretreatment with TCA on the kinetics of DCA. Mice were exposed for 14 days to drinking water containing either 2 g DCA/L (~15.5 mmol DCA/L) or water containing 2 g TCA/L (~12.2 mmol TCA/L). On the 15th day, the DCA pretreated mice were challenged with 100 mg TCA/kg, and the TCA-pretreated mice were challenged with 100 mg DCA/kg. The authors found pretreatment with DCA had no apparent effect on TCA metabolism, and pretreatment with TCA had little or no apparent effect on DCA metabolism.

Pereira et al. (1997) assessed hepatic tumor promotion in methyl-nitrosourea (MNU)-initiated female B6C3F1 mice that had been exposed chronically to mixtures of TCA and DCA via their drinking water. The mice were initiated at 15 days of age with MNU; they received DCA alone (7.8, 15.6 or 25 mmol/L), TCA alone (6.0 or 25 mmol/L) or mixtures of DCA and TCA (7.8 mmol DCA/L + 6.0 mmol TCA/L, 15.6 mmol DCA/L + 6.0 mmol TCA/L, 25 mmol DCA/L + 6.0 mmol TCA/L, 15.6 mmol DCA/L + 25 mmol

TCA/L) in the drinking water from 6 to 50 weeks of age. With response expressed on a per mouse basis (altered hepatic foci/mouse and total hepatic proliferative lesions/mouse), the authors reported that 6.0 mmol TCA/l had little effect on DCA-induced tumor promotion in mice that received either 7.8, 15.6 or 25 mmol DCA/L. DCA at 15.6 mmol/L appeared to increase TCA-induced tumor promotion in mice that received 25 mmol TCA/L but not in mice that received 6.0 mmol TCA/L. Experiments are in progress to test the effect of binary combinations of $CHCl_3$ and DCA or $CHCl_3$ and TCA on hepatic tumor promotion (Pereira and Kramer, 1999).

Comparing the work of Pereira et al. with that of Gonzalez-Leon et al., it can be noted that these two research groups are investigating different regions of the TCA dose-response curve. The dose level of TCA appears to affect whether DCA enhances TCA-induced tumors. DCA had no detectable enhancing effect in combination with 6.0 mmol TCA/L but has an apparent enhancing effect at 25 mmol TCA/L. The dose level of TCA, 25 mmol/L, at which an apparently greater than additive effect on tumor promotion occurred is 2-fold higher than the dose of TCA shown to have little or no effect on DCA metabolism.

2.4.3.4. Defined Mixtures of Trihalomethanes and Haloacetic Acids — In the only example of cross-class mixtures of DBPs found, Davis (1992) examined the effects of pretreatment with either DCA or TCA on $CHCl_3$ hepatic and renal toxicity in male and female Sprague-Dawley rats. Pretreatment with DCA (administered by gavage 27, 10 and 3 hours prior to $CHCl_3$) at 0.92 mmol DCA/kg (but not 2.45 mmol DCA/kg) increased $CHCl_3$ (~0.63 mmol $CHCl_3$/kg by i.p. injection) hepatic toxicity 24 hours after $CHCl_3$ administration. Both 0.92 and 2.45 mmol DCA/kg increased the

nephrotoxicity of this dosage of $CHCl_3$. A similar pretreatment regimen with TCA at 2.45 mmol TCA/kg (but not at 0.92 mmol TCA/kg) enhanced the renal, but not the hepatic, toxicity of $CHCl_3$ (~0.63 mmol $CHCl_3$/kg), 24 hours after $CHCl_3$ administration. The enhancement of $CHCl_3$ toxicity by the HAAs was gender specific, with increased toxicity seen in female, but not male, rats. Further experimentation with the same rat stock (female and male Sprague-Dawley) with DCA revealed that pretreatment with 2.45 mmol DCA/kg (27, 10 and 3 hours prior to $CHCl_3$) resulted in increased hepatic toxicity at both 3.12 and 9.35 mmol $CHCl_3$/kg in female rats and at 3.12 mmol $CHCl_3$/kg in male rats (Yang and Davis, 1997a). In addition to the differences in $CHCl_3$ dosage between these two studies, the nutritional status of the rats differed; Davis (1992) rats received feed ad libitum whereas the Yang and Davis (1997a) rats were fasted for 20 hours prior to $CHCl_3$ administration.

Based on the results of a series of experiments (Yang and Davis, 1997a,b; Yang et al., 1996), the mechanism by which DCA potentiates $CHCl_3$ hepatotoxicity appears to be linked to hepatic CYP2E1 induction by DCA. Treatment with DCA under the same dosage regimen used in the interaction studies (2.45 mmol DCA/kg, 27, 10 and 3 hours prior to termination) resulted in increased hepatic CYP2E1 activity as measured by both aniline hydroxylation and p-nitrophenol hydroxylation and in increased amounts of CYP2E1 protein as measured by immunoblot analysis (Yang et al., 1996). As the concentration of 3-hydroxybutyrate was also increased, the induction of hepatic CYP2E1 may be an indirect effect of DCA (Yang et al., 1996). Research to elucidate the mechanism(s) underlying nonadditive interactions is important, because a mechanistic understanding provides a rational basis for extrapolation of toxicologic

information across dose, route, length of exposure, and to other species (Simmons, 1994, 1995b). This dose-dependence may account for inconsistencies across studies that appear to have conflicting outcomes, but are actually working in different sections of the dose-response curve. In general, these conclusions are consistent with the current state of knowledge with regard to mixtures research. For risk assessment purposes, the behavior of multiple chemicals at low dose levels is critical to support the methodology used to assess health risks.

2.5. THE UNIDENTIFIED FRACTION OF DBPS

As illustrated in Figure 4, generally more than half the DBPs in drinking water consist of unidentified material, yet measures of the concentrations and potential toxicity of such material are critical to performing a risk assessment. Measures generally available include: Total Organic Carbon (TOC); DBPs routinely monitored either individually or as summary concentrations (e.g., total THMs, HAAs); and Total Organic Halides (TOX). Although it is not standard practice, methods are available to proportion the TOX into total organic chlorine (TOCl) and total organic bromine (TOBr). These distinctions are important because when source waters high in bromide are treated with ozone or chlorine, higher levels of the brominated compounds are produced. Concern over the toxicity of brominated compounds has increased as newer epidemiology and toxicology data indicate these compounds may be more toxic than their chlorinated analogues. The formation of bromate, a highly toxic DBP, is of particular concern because it can be formed in relatively large amounts as a by-product of ozonation processes applied to high bromide source water.

DBPs can be divided into three groups that reflect their analytic chemistry (Figure 5). A small number of halogenated DBPs (Group A), which account for up to 50% of the total organic halides in treated drinking water, can be quantitated by routine gas chromatography (GC). Examples of Group A DBPs are reported by Miltner et al. (1990) and Weinberg (1999). The set of halogenated DBPs that cannot be quantitated by routine GC comprises Group B. Several hundred Group B DBPs have been identified qualitatively through GC and mass spectrometry (MS), but most of them have not been quantitatively measured. Examples of Group B DBPs are reported by Richardson (1998). Other members of Group B are suspected to be present in drinking water but have not yet been identified. Finally, a third group consisting of non-halogenated organic compounds (Group C) also exists. Some members of Group C have been identified, but many others are suspected to be present in drinking water but remain identified to date. The measured TOX concentration can be used to identify the quantity of material that comprises Group B. The organic halogen concentration of each member of Group A can be quantified and summed, yielding the fraction of the TOX concentration that may be accounted for by Group A. The organic halide concentration associated with Group B is the difference between the TOX and the organic halide concentration associated with Group A. In general, some Group C DBPs are measured individually (e.g., formaldehyde), and TOC is also measured routinely.

Assessing the risks posed by exposures to Group B compounds is complicated because 1) all members of Group B have probably not been identified; 2) the quantity of each component is not known; and 3) the toxicity of most of the compounds that have

Halogenated DBPs	Non-Halogenated DBPs
Group A • Haloacetonitriles • Trihalomethanes • Haloacetic Acids	Group C • Formaldehyde • Hydrogen Peroxide • Carboxylic Acids • Ketoaldehydes • Ketoacids
Group B • Haloketones • Halonitromethanes • Haloaldehydes	

FIGURE 5

Examples of DBPs in Groups A, B, and C are Illustrated

been found has not been tested in bioassays. If it is assumed that the toxicity of those Group B compounds identified through GC and MS (from the same drinking water sample as the Group A compounds) is representative of the toxicity of the entire Group B, then the toxic potential of individual compounds in this set can be estimated by Quantitative Structure Toxicity Relationship (QSTR) models (e.g., Moudgal et al., 2000). Such models predict toxicologic bioassay results for untested substances based on the degree of similarity between the molecular attributes of the untested compound and previously tested compounds.

2.6. RISK ASSESSMENT USING A RESPONSE ADDITION APPROACH

The initial assessment illustrates how DBP mixture risk may be quantified using a two-stage Monte Carlo analysis of DBP occurrence data, DBP toxicity estimates, and human drinking water consumption rate data (U.S. EPA, 1998a, 1999a). (The details of this risk characterization, including exposure estimates, toxicity values and risk estimates, are presented in full in Appendix I; presentations of this analysis from the workshop are summarized in Section 2. of Report 2.) The drinking water source was a pilot-scale drinking water treatment plant (Miltner et al., 1990), designed to simulate several drinking water treatment system configurations. Two of these for which risk estimates were developed included a conventional chlorination treatment system and a pre-ozonation system followed by a conventional chlorination treatment system.

This illustration was developed as a limited demonstration to evaluate: 1) whether sufficient data exist on exposure and toxicity to estimate DBP mixture risks; 2) if response addition is a reasonable risk assessment method for this effort; and 3) how to address and present the uncertainty and variability in the available data. Through the

development of a reasonable set of assumptions regarding two hypothetical drinking water treatment interventions and the potential toxicity of the DBP mixtures, the illustration shows that facility-specific data can be input to the response addition model to develop DBP mixtures risk estimates for a drinking water treatment system. This illustration highlights critical areas where pertinent research could potentially change the outcomes of the analysis. The constraints of the illustration include the following:

- Comparison of only two alternative drinking water treatment technologies and no comparison of gradations of application (e.g., changes in the levels of chlorination or ozone)

- Limitations of available input data for DBP concentrations and toxicity values and tap water consumption rates to develop distributions for conducting an uncertainty analysis

- Constraints concerning the current scientific measurement and the temporal distribution of concentrations of DBPs in treated drinking water from a single treatment system. Additionally, no attempt has been made to characterize the impact of the water distribution system on estimated DBP concentrations

- Limitations in the understanding of the relationship between health effects and DBP exposures through drinking waters inherent in the risk assessments of these agents both collectively and individually

- Evaluation of systems functioning normally without taking into account scenarios that may result from perturbation(s) or critical failures of the drinking water treatment plant.

In this approach, epidemiologic and toxicologic data were used in the hazard identification to identify the nature of the hazard posed by DBPs. In this case, cancer, reproductive and developmental effects were identified to be of concern from DBP exposures using both the epidemiologic and toxicologic data as corroborating evidence. Only the DBP toxicology data were used in the dose-response assessment; however,

the epidemiologic attributable risk estimates were incorporated into the uncertainty analysis.

This illustration uses a response-addition approach, a component-based method for joining dose-response and exposure data, to estimate risk for the mixture. The strategy of the method is to estimate each individual chemical component's endpoint specific risk at its measured exposure concentration and then sum these risks to yield the total mixture risk for that health endpoint. The response-addition model assumes that risk (unitless) is related to the concentration and potency of each individual component chemical as follows:

$$risk = Y \times \frac{1}{1000}\left[\sum_{i \in k} C_i S_i + \sum_{i \in u} C_i S_i\right] \quad (1)$$

where

Y = Tap water intake (L/kg-day)

C_i = Concentration of DBP_i (µg/L)

S_i = Incremental toxicity for DBP_i $(mg/kg\text{-}day)^{-1}$

1 mg = 1000 µg

k = set of identified DBP

u = set of unidentified DBP

Equation 1 is a theoretical construct, as it requires information that is not known (i.e., *u*, the set of unidentified DBP, will never be completely analytically characterized

as to chemical species). Measured data on total tap water consumption (Y) were available for the analysis (Ershow and Cantor,1989). For each of 15 identified DBPs (Table 8) that compromised set *k*, there was a measure of its concentration in tap water, C_i, and its incremental risk (S_i), so the summation, $\Sigma C_i S_i$, was calculated. For the unidentified DBPs, set *u*, these values were unknown, so the summation, $\Sigma C_i S_i$, had to be estimated.

Figure 6 shows the steps developed to estimate the potential toxicity of set *u* using summary measures, expert judgment, and modeling techniques. This process estimated risk only for the Group B organic halides that were unidentified; the Group C chemicals (non-halogenated DBPs) are not included here.

- Step 1. It was assumed that the risk for the unidentified DBPs (Group B) associated with a health endpoint (e.g., developmental effects) is equal to that of the identified DBPs (Group A) for the same health endpoint per unit of organic halide concentration (in µg Cl/L). This assumption allowed for the unidentified DBP risk to be calculated as a weighted average of the risk from the identified components. Thus, an estimate of the concentration of unidentified DBPs that could be associated with the health endpoint was required.

- Step 2. The organic halide concentration (in µg Cl/L) of the entire Group B was calculated by subtracting the sum of the Group A DBPs from the Total Organic Halide (TOX) material. In the illustration, roughly 57% of the TOX was associated with Group B DBPs (U.S. EPA, 1999a).

- Step 3. Those DBPs that had been found in laboratory experiments under similar treatment scenarios were selected for use in estimating the toxicity of Group B. In the illustration, 70 and 62 of the halogenated DBPs identified by Richardson (1998) were chosen as representative of all of the halogenated DBPs in the Miltner et al. (1990) study for the chlorination system and the pre-ozonation followed by chlorination system, respectively.

TABLE 8

Identified Disinfection By-Products (Set *k*) for the Response Addition Illustration

DBP with Reproductive/Developmental Data	DBP with Carcinogenicity Data
Monochloroacetic Acid (MCA)[a]	Bromodichloromethane (BDCM)
Dichloroacetic Acid (DCA)	Chlorodibromomethane (CDBM)
Trichloroacetic Acid (TCA)	Bromoform ($CHBr_3$)
Monobromoacetic Acid (MBA)	Chloral Hydrate (CH)
Dibromoacetic Acid (DBA)	Dichloroacetic Acid (DCA)
Bromochloroacetic Acid (BCA)	Trichloroacetic Acid (TCA)
Dichloroacetonitrile (DCAN)	Bromate
Trichloroacetonitrile (TCAN)	Chloroform[b] ($CHCl_3$)
Bromochloroacetonitrile (BCAN)	
Dibromoacetonitrile (DBAN)	
Bromodichloromethane (BDCM)[a]	

[a] MCA and BDCM were excluded from the reproductive and developmental risk assessments because threshold parameters were modeled for all endpoints.

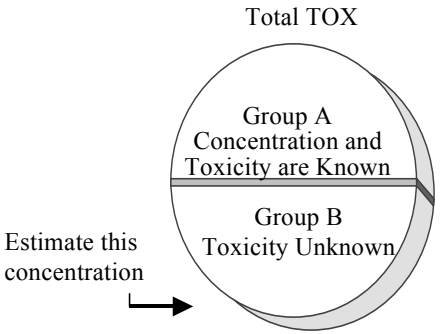
[b] Chloroform was excluded from the risk assessment because the mechanism of action for carcinogenicity was thought not to be active at its environmental concentration.

Step 1

$$Risk_B = \frac{Conc_B}{Conc_A} * Risk_A$$

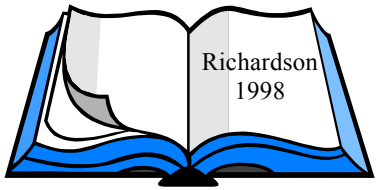
Assume equal Risk of Group A and Group B DBPs per unit of TOX for a specific health endpoint

Step 2



Step 3

Identify DBPs that may be present in Group B



Step 4

1) Assume that each member of Group B accounts for the same fraction of TOX

2) Use QSTR to classify health endpoints associated with individual Group B DBPs

Step 5

Assume that the % of Group B DBPs classified by QSTR as associated with an individual health endpoint represents the actual proportion of Group B's concentration that can be associated with the individual health endpoint

Step 6

1) Use information in steps 2-5 to calculate $Risk_B$ as shown in Step1.

2) Using assumption of response addition, add risks estimated for DBPs in Groups A and B.

FIGURE 6

Process for Estimation of Risk for Unidentified TOX (Group B Chemicals)

- Step 4. The QSTR model was used to classify each of the selected Group B DBPs as either associated with a health endpoint or not, resulting in the calculation of a percentage of Group B DBPs associated with the health endpoint. In the illustration, QSTR models in TOPKAT© were used to assess the toxicity of each of the Group B DBPs (Moudgal et al., 2000). The fractions of Group B DBPs found to be associated with cancer and developmental toxicity were 58% and 42%, respectively, for the chlorination system and 55% and 56%, respectively, for the pre-ozonation followed by chlorination system. Because TOPKAT© did not have a reproductive toxicity model, the developmental toxicity values were also used as surrogates for the fraction of Group B DBPs that may be associated with inducing reproductive toxicity.

- Step 5. The percentage of Group B DBPs associated with the health endpoint was extrapolated directly to estimate the proportion of the Group B organic halide concentration that could be associated with the health endpoint.

- Step 6. Using the ratio of Group B to Group A organic halide concentrations associated with the health endpoint of concern, the risk for the Group B DBPs was calculated as shown in Step 1.

The total endpoint-specific risk, using Equation 1, is the sum of the risks for the identified DBPs (Group A), as calculated from known toxicity and measurement data, and the unidentified DBPs (Group B), as estimated using Steps 1 through 6.

2.6.1. Development of Distributions of Risks. For the illustration, a two-stage Monte Carlo analysis was performed, as shown in Figure 7, to calculate distributions of DBP mixture risk using Equation 1. Input distributions were developed to quantify variability (heterogeneity) in the population tap water consumption rates (Y), (i.e., the range of plausible risks resulting from differences among members of the population) and to quantify uncertainty (i.e., the range of plausible risks for each individual corresponding to alternative plausible assumptions) for DBP concentration data (C_i) and DBP toxicity

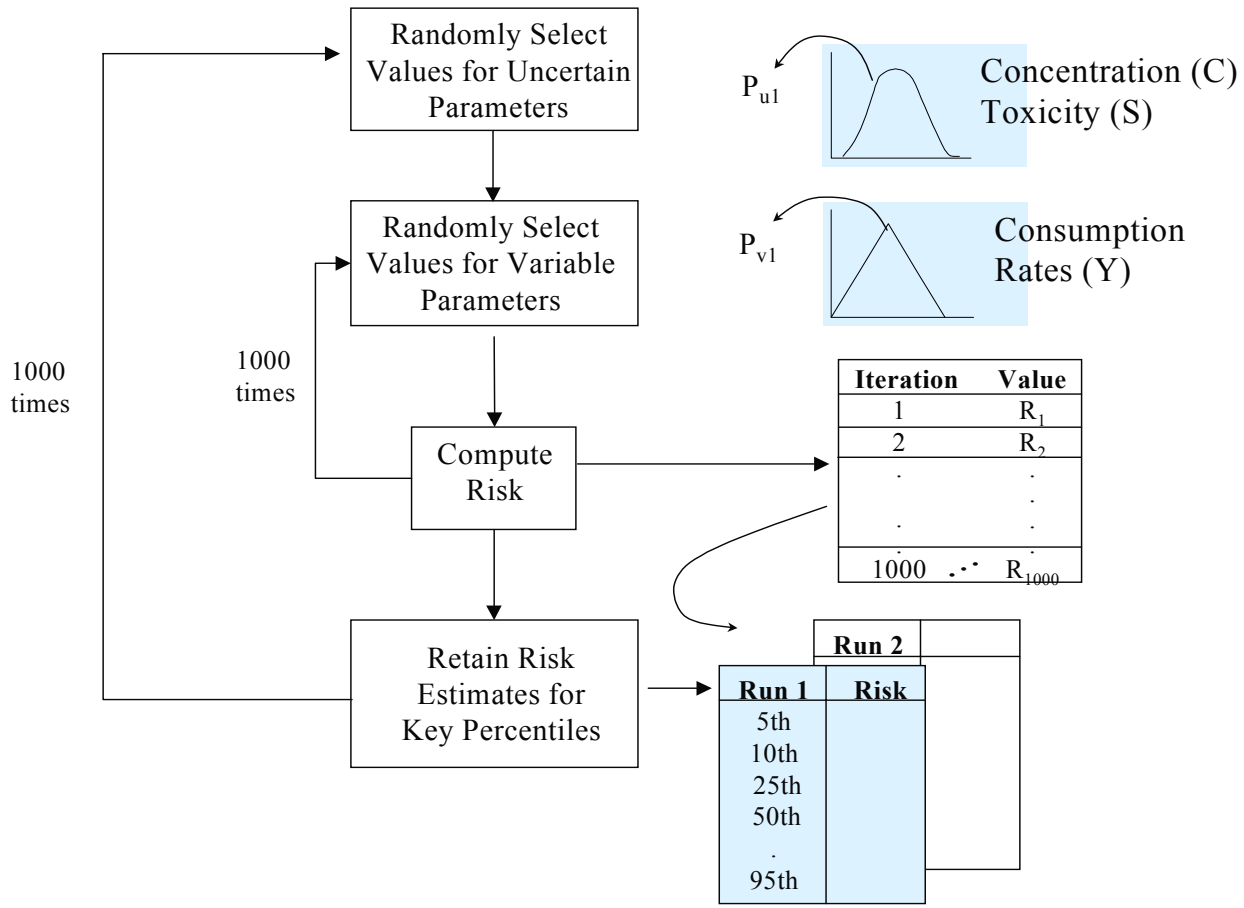


FIGURE 7

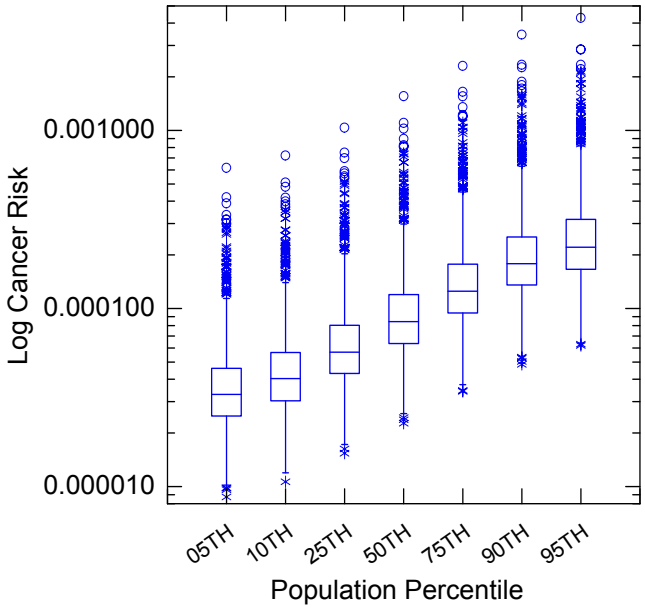
2-Stage Monte Carlo Analysis of Variability and Uncertainty, R = Y*C*S

estimates (S_i). The result of such an analysis is the development of risk distributions, as shown in Figure 8, that reflect variability on the X-axis and uncertainty on the Y-axis.

Variability was quantified by holding uncertain assumptions fixed and computing risk estimates corresponding to different values for parameters that vary among members of the population. Uncertainty was quantified by computing risk for several "representative" members of the population, such as the median individual and the 95th percentile individual. Values for uncertain parameters (e.g., cancer slope factors and DBP concentrations) were randomly selected and held constant, and then 1000 sets of values for the variable parameters (e.g., water consumption, L-kg/day) were randomly drawn (corresponding to 1000 iterations of the inner loop) and used to compute 1000 estimates of risk. After ranking the 1000 risk estimates from the inner loop, some key population summary statistics estimates (i.e., 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles) were retained (Figure 8). The simulation then proceeded to the next iteration of the outer loop, selecting new random values for the uncertain parameters and then executing 1000 new iterations of the inner loop. The outer loop was ultimately executed 1000 times, yielding 1000 estimates of each of the key population summary statistic risk estimates.

2.6.1.1. Tap Water Consumption (Y) — DBP exposure was assumed to be a function of total tap water consumed. All water from the household tap consumed directly as a beverage or used to prepare foods and beverages was considered tap water. The studies of Ershow and Cantor (1989) of the U.S. population and the Canadian Ministry of National Health and Welfare (1981), presented in U.S. EPA

Uncertainty of Toxicity Values (S) and Concentration Estimates (C)



Population Variability In Drinking Water Consumption Rates (Y)

FIGURE 8

Monte Carlo Results for Lifetime Cancer Risk for a Chlorination System, R = Y*C*S

Exposure Factors Handbook (1997b) were used to derive consumption estimates. The illustration approach quantified tap water consumption by fitting lognormal distributions to age-specific intake data for the U.S. population developed by U.S. EPA (1997b), based on Ershow and Cantor (1989) and shown in Table 9. The water consumption of some subpopulations was evaluated and found not to differ from the general population estimates. The illustration did not, however, evaluate exposure routes other than oral, compare differences in DBP exposures from heated vs. unheated tap water, or account for potential changes in consumption patterns (e.g., increased use of bottled water) since the time of data collection by Ershow and Cantor (1989).

2.6.1.2. DBP Concentrations in Drinking Water (C_i) — Concentration data (in µg/L) for individual DBPs in the illustration (one with chlorination only and one with chlorination following pre-ozonation) were adapted from a paper by Miltner et al., (1990), resulting from a study in which Ohio River water was treated in a pilot plant and then subjected to a simulated distribution system for each of the treatment trains. Table 10 lists the resulting concentration data used in the case study. These data are slightly different from the Miltner et al. (1990) paper because the means and confidence limits were recalculated from the sampling data assuming a normal distribution and substituting half the detection limit for non-detects instead of zero, which was used in the original publication. The notable exception is that the concentrations for bromate were not sampled at the time of the study and have been estimated using more recent information.

TABLE 9

Tap Water Consumption in the General Population (mL/kg-day)
by 5-Year Age Groups[a]

Age (Years)	Population Percentile							Arith-metic Mean[b]
	5	10	25	50	75	90	95	
0 to 4	9.14	13.66	23.71	38.5	57.4	82.89	103.03	44.4
5 to 9	8.56	12.14	18.36	27.72	40.78	56.1	65.56	31.2
10 to 14	5.4	8.06	12.72	19.28	28.06	38.02	44.56	21.3
15 to 19	3.9	5.7	9.6	14.8	21.5	29	35	16.3
20 to 24	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
25 to 29	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
30 to 34	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
35 to 39	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
40 to 44	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
45 to 49	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
50 to 54	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
55 to 59	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
60 to 64	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
65 to 69	8.7	10.9	15.1	20.2	27.2	35.2	40.6	21.9
70 to 74	8.7	10.9	15.1	20.2	27.2	35.2	40.6	21.9
75 to 79	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4
80 to 84	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4
85 +	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4

[a] Ershow et al. (1989) cited in U.S. EPA (1997b)

[b] The arithmetic mean value for each age group was computed by fitting a lognormal to the percentile values listed and computing the arithmetic mean corresponding to that distribution's geometric mean and geometric standard deviation.

TABLE 10

DBP Concentrations Used in the Illustration (Adapted from Miltner et al., 1990)

Chemical	Ozone/Chlorination System			Chlorination System		
	Mean Conc (µg/L)	Low 95% Conc (µg/L)	Upp 96% Conc (µg/L)	Mean Conc (µg/L)	Low 95% Conc (µg/L)	Upp 96% Conc (µg/L)
CHCl3	39.55	34.70	44.40	55.50	52.20	58.80
CHBrCl2	21.10	20.90	21.40	24.40	21.90	26.90
CHBr2Cl	13.00	12.20	13.80	10.20	8.80	11.60
CHBr3	1.50	1.10	1.80	0.35	0.00	0.84
CH	5.80	4.90	6.80	4.20	3.60	4.70
MCA	1.46	1.37	1.54	1.44	1.30	1.60
DCA	19.30	18.00	20.60	30.85	28.40	33.30
TCA	10.00	8.90	11.20	20.10	18.60	21.70
MBA	0.28	0.22	0.34	0.29	0.24	0.33
DBA	1.98	1.74	2.20	1.50	1.30	1.70
BCA	6.70	6.50	6.90	8.50	8.30	8.60
DCAN	2.60	2.20	3.00	3.50	2.70	4.20
TCAN	0.05	0.05	0.05	0.20	0.05	0.30
BCAN	1.65	1.44	1.85	1.90	1.50	2.30
DBAN	0.55	0.31	0.78	0.15	0.03	0.27
Bromate*	4.00	3.40	4.60	0.00	0.00	0.00

* Bromate was not measured in the Miltner et al. (1990) study, but was estimated using subsequent measurements from the same laboratory (see Appendix I).

2.6.1.3. Toxicity Estimates (S_i) — The toxicity estimate for each identified DBP was assumed to be lognormal with a geometric mean equal to the 50th percentile and 95th percentile values, as shown for cancer slope factors in Table 11. Although the confidence intervals reported for toxicity estimates that were fit using maximum likelihood techniques are theoretically normal. However, the relative magnitude of the 50th and 95th percentile values of the slope factors for many compounds, along with the constraint that the slope factor must be non-negative, indicates that the true confidence intervals must be skewed to the right. The lognormal distribution was used to approximate this skew.

All dose-response modeling was performed using a linearized multistage procedure, with a threshold parameter included in the model for the developmental and reproductive endpoints. In the illustrative example, carcinogenicity dose-response data were selected based on expert evaluations of the toxicology literature (i.e., Agency reviews [U.S. EPA, 2000b; Bull and Kopfler, 1991]) and used in the response addition procedure to estimate human health risks (see Section 4.3.1. of Appendix I). For cancer, each identified DBP's dose-response was assumed to be linear with no threshold for each DBP identified as a carcinogen through *in vivo* toxicologic evaluations. The exception to this was chloroform, whose mechanism of action for cancer was not considered to be active at the exposure concentrations in the Miltner et al. (1990) study.

In the illustrative example (see Section 4.3.2., Appendix I), a careful toxicological review was done for each DBP identified in the *in vivo* toxicology literature to evaluate

TABLE 11

Incremental Cancer Risk per mg/kg-day for Identified DBPs

Chemical	Weight of Evidence Classification[a]	Slope Factor $(mg/kg\text{-}day)^{-1}$			GSD	Observed Effect
		MLE	95th Percentile UCL	GM		
BDCM	B2	5.7×10^{-3}	6.2×10^{-2}	5.7×10^{-3}	4.3	Renal adenomas and adenocarcinomas
CDBM	C	7.2×10^{-4}	8.4×10^{-2}	7.2×10^{-4}	18.0	Hepatocellular adenomas and adenocarcinomas
CHBr3	B2	3.4×10^{-4}	7.9×10^{-3}	3.4×10^{-4}	6.8	Neoplastic lesions in large intestine
CH	C	4.1×10^{-2}	1.3×10^{-1}	4.1×10^{-2}	2.0	Hepatocellular adenomas and adenocarcinomas
DCA	B2	1.4×10^{-3}	1.0×10^{-1}	1.4×10^{-2}	13.4	Hepatocellular adenomas and adenocarcinomas
TCA	C	4.9×10^{-2}	8.4×10^{-2}	4.9×10^{-2}	1.4	Liver neoplasms
Bromate	B2	3.2×10^{-1}	4.9×10^{-1}	3.2×10^{-1}	1.3	Renal adenomas and adenocarcinomas
CHCl3[b]	B2	3.1×10^{-2}	6.1×10^{-3}	3.2×10^{-3}	1.5	Renal tumors

[a] Chemicals classified as B2 have sufficient evidence of carcinogenicity in animals but inadequate or a lack of evidence in humans. For chemicals classified as C, there is limited evidence of carcinogenicity in animals and inadequate or a lack of evidence in humans.

[b] Chloroform was excluded from the risk assessment because its mechanism of action for cancer is not thought to be active at environmental concentrations for either treatment train.

Chemical Key: BDCM - Bromodichloromethane
CDBM - Chlorodibromomethane
CHBr3 - Bromoform
CH - Chloral Hydrate
DCA - Dichloroacetic Acid
TCA - Trichloroacetic Acid
CHCl3 - Chloroform

the observed DBP dose-related developmental and reproductive effects (e.g., resorptions, fetal deaths, malformations, fetal weight, sperm abnormalities). Then, for each DBP, all endpoints were individually modeled using a linearized multistage procedure with a threshold parameter. For those dose-response data for which the threshold parameter was not statistically significantly different from zero, the most sensitive endpoint was selected for inclusion in the response addition procedure to estimate human health risks. (In all cases in which the threshold parameter was different from zero, the exposure concentrations were below the threshold estimate, so risk was estimated to be zero.) To model continuous endpoints, the analysis first converted them into quantal endpoints by designating a cutpoint in the upper tail of the effect's distribution in the control animal data. The cutpoint was selected to represent a toxicologically adverse effect (see Appendix I).

2.6.1.4. Uncertainty Analysis — As discussed fully in Appendix I, the risk estimates for each health effect (i.e., cancer and reproductive/developmental toxicity) were quantified by combining exposure estimates with toxicity coefficients for the identified DBPs and adding these to the risks estimated for the unidentified DBPs. It is recognized that there is considerable uncertainty in these risk estimates because of many factors. Following the generation of a distributions of plausible risks, additional sensitivity and uncertainty analyses were performed. An analysis of the relationship between the model input variables and the model output identified those variables that had the greatest impact on the results. For each health condition (cancer, developmental toxicity, and reproductive toxicity), the set of parameters having the greatest influence on the determination of risk was identified by using linear regression

to model the population mean risk as a function of the uncertain parameters. Uncertainty in the slope factor estimates accounted for the largest portion of the parametric uncertainty in risk estimates for the cancer endpoints. However, the concentration of unidentified total organic halide (TOX) DBP contributed the largest portion of the parametric uncertainty in the developmental and reproductive toxicity endpoints.

Not all of the sources of uncertainty, however, were quantified within the two-stage Monte Carlo procedure. Some of these uncertainties were examined by repeating the probabilistic analysis using different models, data sets or alternative assumptions and comparing the results with the initial analysis. Such additional analyses provided information on the reliability of the initial analysis and were useful in planning new research activities. A summary of the results for the additional analyses made in the illustration is presented below.

A. Exposure Uncertainties

1) The assumption that tap water ingestion dominates intake

2) The use of *total* tap water intake, rather than another estimate of tap water intake such as unheated tap water

The exposure assumption that ingestion dominates intake could be significant if other routes of exposure result in much more efficient uptake or metabolism of the DBPs. Total tap water intake as the relevant measure of exposure is unlikely to be important. Although there is some speculation that heating tap water may remove some of the volatile DBP, restricting attention to the intake of only unheated water affects the

estimate of risk by at most a factor of 2, indicating that this assumption is not a relatively important source of uncertainty.

B. Toxicity Uncertainties

1) Use of QSAR to quantify the proportion of unidentified DBPs associated with a health endpoint

2) The assumption that the unidentified DBPs pose the same risk as the identified DBPs per concentration of organic halide

3) The assumption that the mechanism of action for chloroform carcinogenicity is not active at levels found in drinking water

4) Use of animal toxicology data to quantify the toxicity estimate or slope factor (S_i), instead of epidemiologic data

5) The assumption that the slope factors (S_i) are statistically independent

The proportion of unidentified DBPs associated with a health endpoint was quantified using QSAR. The range of risks associated with the extreme alternative assumptions of 0% or 100% generally spanned a factor of approximately 5 to 10, suggesting that this assumption does not substantially contribute to uncertainty.

The assumption that the unidentified DBPs pose the same risk as the identified DBPs was evaluated by assuming alternatively that the unidentified DBP pose only 50% the risk as the identified DBPs per concentration, and that the unidentified DBPs pose twice the risk as the identified DBPs per concentration. The results indicate that this range of assumptions corresponds to a range of risk estimates spanning a factor of approximately 5 to 10.

The assumption that chloroform's mechanism of action for cancer is not active at the levels in drinking water affects the overall risks by approximately 1.2 to 1.4, despite the concentration data for chloroform (in this illustration) that show it is large and exceeds that of many of the other DBPs. Whether chloroform is a carcinogen at environmentally relevant exposure levels affects the cancer risk estimates for two reasons. First, because the concentration of chloroform exceeds that of many other DBPs, its potential contribution to carcinogenicity is substantial. The assumption of a threshold dose-response for carcinogenicity removes its contribution from the risk estimate. Second, because chloroform's concentration is large compared to that of other DBPs, its classification as a carcinogen affects the estimated risk associated with exposure to unidentified DBPs. Specifically, if it is not classified as a carcinogen, its potency is removed from the weighted average used as an estimate of the typical potency of an unidentified DBPs. Because chloroform's assumed potency is less than the weighted average potency of the other identified DBPs, removing it from consideration (by assuming it does not behave as a carcinogen at environmentally relevant doses) increases the weighted average potency of the set of identified DBPs. These two influences on risk work in opposite directions and hence, partially cancel each other out.

Risk estimates computed under the assumption that for each health endpoint, the slope factors are perfectly correlated, do not differ substantially from the risk estimates computed under the assumption that these quantities are statistically independent. This finding indicates that the assumption of statistical independence is not an important source of uncertainty.

In place of the animal bioassay data used to quantify DBP carcinogenicity, the epidemiology literature could be used. Calculations made using epidemiologic information suggest a broad range of risks, ranging from zero to risks that may be substantially larger than those determined from the animal data. Thus, the weak to moderate findings for cancer using the epidemiologic data may be considered important; the risk estimated from the animal studies could be an underestimate. Because of these uncertainties, it is conceivable that the plausible range of risks from exposure to the DBP mixtures is very broad and could include zero.

3. EPA's MAIN CONCLUSIONS AND RECOMMENDATIONS BASED ON THE APRIL 1999 WORKSHOP

EPA held a workshop in April 1999 to examine the response addition illustration and to advance the development of methodology to assess health risk for mixtures of drinking water DBPs. The goal of the workshop was to assemble a multidisciplinary group of scientists to formulate a range of possible approaches to solving this problem and then provide guidance on the most practical and scientifically sound directions the EPA should take to improve the risk assessment (see Charge to Participants, Attendees in Report 2). Based on the results of this workshop, in this section, EPA recommends certain issues for consideration regarding improvement of the DBP mixtures risk assessment methodology. In Report 2 of this document are many discussions and recommendations from workshop participants. Each of these was considered by EPA within the context of the Agency's previous experience with DBP mixtures risk assessment and evaluated for scientific validity, feasibility of application in the near-term, data availability, consistency with other Agency Guidelines and practices, and relevance to risk assessment goals and regulatory needs. The recommendations selected are presented in this section. They potentially have the most significant, near-term impact on improving DBP mixtures risk assessment. Additionally, EPA identified a number of longer term research needs; these are presented in Section 5 of this Report.

3.1. EPA RECOMMENDATIONS: INTEGRATION OF EPIDEMIOLOGIC AND TOXICOLOGIC DATA IN THE RISK ASSESSMENT

Both epidemiologic and toxicologic approaches can potentially contribute valuable information to understanding potential human health risks from exposure to DBPs in drinking water. EPA's risk assessment of DBP mixtures could be improved by integrating both types of data in at least a weight-of-evidence evaluation, if not a quantitative approach. Such an effort, however, would have to take into account both the similarities and significant differences between human and animal data.

A credible risk characterization effort considers all available data, so for the DBP assessment, the incorporation of both epidemiologic and toxicologic data is important. (For discussions and recommendations from the April 1999 workshop, see Sections 3.10., 4.7., 4.8.7. of Report 2.) To combine both toxicology and epidemiology data into a risk characterization, it is recommended that the following areas of research be explored.

1) *Approach.* Investigate the use of expert judgment approaches (Evans et al., 1994; Sielken, 1995; Fayerweather et al., 1999), that combine the risk estimate calculated from each data source (i.e., from the available animal and human studies) with an expert judgment projection of the likelihood that each risk estimate is certain. The result is a kind of weighted average of the risk estimates. An equation, for example, to calculate the risk, R, of a health effect from a certain exposure may be similar to:

$$R = \sum_{i=1}^{n} \delta_i R_i \qquad (2)$$

where:

n = the number of data sets available

δ_i = is an expert judgment weight of the certainty the risk estimate for that data set is correct; the sum of the δ_i for n risk estimates equals 1

R_i = the risk calculated for data set i.

Rationale. Each data set, deemed to be of adequate quality, is used to produce a quantitative risk estimate. Thus, when the choice of data set is unclear, an arbitrary decision is not required. Furthermore, some sense of the quality and appropriateness of each data set can be factored into the calculation using expert judgment. For DBP mixtures risk estimation, for which the epidemiologic data are important and the calculated risks are relatively large, but the associations are weak, this offers a way to influence the outcome of the risk estimation process that otherwise may default to only using the animal toxicology data, while acknowledging the uncertainties in the databases for both data sources. This approach also offers the opportunity to develop distributions of risks that may be useful for comparisons and risk ranking efforts.

2) *Approach.* Evaluate differences in biology, exposure (including internal dose), and dose-response between animals and humans including:

- Elucidating the underlying modes-of-action that result in the expression of different health effects within the same target organ systems between humans and experimental animals
- Considering sensitive subpopulations, such as pregnant females, that may (or may not) respond differently between animals and humans
- Evaluating the enormous differences across species and within human exposures relative to duration, DBP concentration levels, lifestyle factors, and activity patterns that affect contact
- Identifying differences in physiology, biochemistry, anatomy, and metabolic responses that may produce disparate health outcomes.

Rationale. Human DBP exposures are generally lower than those used in animal studies. For DBP exposures, the health effects observed in these two types of studies are not always exactly the same (e.g., mostly liver and kidney tumors are observed in animal bioassays of DBPs, and bladder, colon and rectal tumors are associated with chlorinated drinking water in some epidemiologic studies), although similar target systems may be involved for each. Dose dependence of such tumor sites resulting from differences in exposures between animal studies and the epidemiologic literature may also be a factor.

Also, animal studies are often conducted using different routes than those to which the human population is exposed. Route-to-route and high-to-low dose extrapolations of data should take into account differences in how the DBPs are metabolized and distributed in the body. For example, after the ingestion of low concentrations of DBPs, nearly complete metabolism occurs during the first pass through the liver, while the inhaled and dermally-absorbed compounds are distributed throughout the body prior to hepatic metabolism. By contrast, because of high doses in animal studies, there generally is incomplete metabolism of the compounds, even when ingested. Thus, careful evaluation of the factors that affect toxicity for both humans and animals and identification of the differences in these factors will improve future risk assessments.

3) *Approach.* Convene a “Blue Ribbon” panel to identify the important issues regarding better characterization of the uncertainties associated with interpreting the epidemiologic literature and how best to quantify the human health risks of cancer and exposure to drinking water disinfectants and by-products (see Section 4.7. of Report 2 for additional details). The general composition of the panel should include epidemiologists, toxicologists, and quantitative analysts who have experience in complex problem solving. The primary interest of the panel is to objectively evaluate current studies and analyses of their results, identify the uncertainties, and recommend ways to reduce these uncertainties. They would also oversee the implementation of projects and tasks specifically designed to address the relevant issues.

Rationale. Both epidemiologic and toxicologic approaches contribute valuable information to the risk assessment process, but difficulties occur in incorporating epidemiologic results into the quantitative risk assessment. Better characterization of the uncertainties associated with the underlying epidemiologic literature is needed. When attempting to quantify human health risks, it should be recognized that available epidemiologic data are insufficient to establish a causal association

between DBP and cancer or reproductive risks. Epidemiologists and toxicologists express confusion about how to interpret study findings because of inherent differences in the design, execution, and analysis of the studies. Of particular concern are the non-comparability of the water exposures studied, methodological differences among the studies, internally inconsistent findings within studies, and the lack of consensus regarding causality for bladder, colon, and rectal cancers. The literature on reproductive and developmental effects is currently too sparse to use for quantitative risk assessment. One problem in attempting to interpret epidemiologic findings is incompletely presented dose-response information. Use of continuous data (where available) improves both the sensitivity and the power of the analyses.

3.2. IMPROVEMENTS IN EXPOSURE CHARACTERIZATION

In developing DBP exposure estimates, comprehensive exposure models should be developed. These should incorporate the range of individual DBP concentrations at both the treatment plant and within the distribution system over the etiologically relevant time period; location and time spent in the distribution system; differences in the mixture of DBPs during the exposure period caused by changes in water sources or treatment practices; water use and consumption patterns that may affect ingestion, inhalation and dermal exposures; other human behavioral activities or characteristics that may affect exposure; and household/workplace characteristics. (For discussions and recommendations from the April 1999 workshop, see Sections 3.4., 3.5., 3.6., 4.1. and 4.8.1. of Report 2.) Recommendations for improving the exposure characterization include:

1) *Approach.* Develop better concentration data on DBPs in finished drinking water throughout the distribution system. Use data from the Information Collection Rule (ICR) as a source of distributional data on concentrations of THMs, HAAs, bromate, and aldehydes in water systems throughout the United States.

Rationale. These data help characterize DBP mixture exposures representative of specific source waters and drinking water treatment scenarios, including measures of seasonal fluctuations and variance in concentration data across geographic regions of the United States. It may be noted, however, that the limited number of samples within any system indicates that the full extent of the variability will likely not be captured by the ICR data.

2) *Approach.* Develop models that include multi-route exposures (i.e., oral, dermal and inhalation) when conducting risk assessments for DBPs. Consider the form in which consumption occurs (e.g., if water is heated before consumption, volatile organic compounds are driven off; thermally unstable compounds decrease; the concentration of non-volatile compounds may be increased because of water evaporation and volume reduction; inhalation exposures to the volatile compounds may be increased).

Rationale. DBPs have been measured in tap water and indoor air; some DBPs in tap water (e.g., chloroform) volatilize through heating during cooking, showering, etc. (e.g., Olin, 1999; Weisel and Chen, 1994; Giardino and Andelman, 1996). As a result, DBP exposures can occur through ingestion, inhalation, and dermal absorption. The inhalation exposure for volatile DBPs and dermal exposure to highly lipophilic DBPs can result in exposures equivalent to ingestion for median water uses. Thus when comparing risks from different water sources and treatment practices, which may result in different DBPs and concentrations, it is critical to include all exposure routes.

3) *Approach.* Recognize the etiologically-relevant exposure period, that is, the time frame over which exposure should be evaluated, and use this information in assessing risks.

Rationale. To evaluate the appropriate time period, it is necessary to consider the endpoint of interest: for acute effects (including reproductive or developmental), peak or average daily exposure may be needed, whereas for cancer, annual or integrated, longer-term exposure estimates may be required. A second consideration is to determine how the time frame over which exposures are expected to occur overlaps with the time frame(s) over which damage or effects occur at the molecular, cellular, tissue, or organ level. Both pharmacokinetic and pharmacodynamic studies are needed to address these temporal issues.

4) *Approach.* Develop tap water consumption and human activity pattern data for potentially sensitive subpopulations identified in epidemiology and toxicology studies that better characterize contact with the DBPs in different media. Potentially sensitive subpopulations include pregnant women, lactating women, and young children. Examine changes in water use and consumption patterns that occur during pregnancy and during the period of time in which women lactate (i.e., children obtain a larger quantity of milk from their mothers or wet nurses over time and then consumption decreases until nursing ceases.) For young children, examine the changes in DBP exposures that result from changes in activity patterns as they develop. Dermal exposures in newborns should be examined. Both mathematical models and biomarkers could be used in such evaluations.

Rationale. Data and models exist that can be used for this effort (e.g., tap water consumption for the general population and for pregnant women are available [U.S. EPA, 1997b]). Mathematical exposure models exist for use in risk assessments (e.g., Olin, 1999) based on physical/chemical properties of DBPs in water and assumptions concerning human activity patterns, as well as air exchange rates in buildings and room dimensions (ILSI, 1998). Studies of U.S. human activity patterns, such as tap water consumption distributions (including heated tap water consumption) and showering and bathing frequency and duration distributions, provide contact rates for important exposure media (U.S. EPA, 1997b). These data can be aggregated and used in the exposure assessment to estimate DBP contact rates for the three primary exposure routes.

5) *Approach.* Develop of additional mathematical models to predict the formation of DBPs similar to formation model for individual THMs developed by Clark and Sivaganesan (1998). DBPs of interest would include the HAAs , HANs, and chlopicrin.

Rationale. These data will help characterize DBP concentrations in the distribution system and provide additional data on the variations in levels of various DBPs. These variations depend upon the source waters and drinking water treatment systems considered and should include estimates of seasonal fluctuations and variance in concentration data across geographic regions of the United States.

3.3. ACCOUNTING FOR POTENTIAL TOXICITY OF UNIDENTIFIED DBPs

The DBP mixtures risk assessment should address the complex mixture in addition to those chemicals routinely identified. It should also determine if exposures to the unidentified compounds are of toxicologic concern. (For discussions and recommendations from the April 1999 workshop, see Sections 4.2. and 4.8.2. of Report 2.) Thus, to improve the methodology for estimating risks that incorporates information on the unidentified chemicals, the following recommendations are made:

1) *Approach.* Evaluate the assumption made in the illustrative example that the DBP mixture risks for Groups A and B are equal, per concentration of organic halide material. An initial evaluation of this assumption could be performed by assembling distributions of easily available data, such as LD_{50}s, for each Group (where Group B chemicals must be identified using existing laboratory data) and comparing them for similar central tendency estimates and variability. LD_{50}s can be derived by modeling experimental animal data or estimated using QSTR models.

   Rationale. In the uncertainty analysis for the illustration, the assumption that the unidentified DBP pose the same risk per concentration as the identified DBP was evaluated by assuming alternatively that the unidentified DBP pose only 50% the risk as the identified DBP per concentration, and that the unidentified DBP pose twice the risk as the identified DBP per concentration. The results indicated that this range of assumptions corresponds to a range of risk estimates spanning a factor of approximately 5 to 10, which may be a significant difference depending on the severity of the effect being evaluated. Research to examine this assumption will reduce the uncertainty in this calculation.

2) *Approach.* Improve the chemical characterization of Groups B and C. One approach to this problem is to solicit the opinions of expert organic chemists who work in the analytical field as to the types of compounds comprising Groups B and C. Some of this work has already occurred through two workshops held in 1998 (see Appendix R1-A) and 2000 (for summary, see U.S. EPA, 2001).

   Rationale. It is likely that the non-halogenated compounds comprising Groups A, B and C differ substantially. These differences are likely to

include molecular weight, functional molecular subunits, and number of halogens. Although formed through the same process, compounds in Group C may be quite different than DBPs comprising Groups A and B. It is important to examine modes-of-action associated with these agents as well as target organ toxicity and interaction effects. For example, formaldehyde is a likely component of Group C and is classified on EPA's IRIS system as a probable human carcinogen; there is also an RfD based on histopathological changes in the intestinal tract.

3) *Approach.* Once a set of chemicals is selected to represent the Group B and C DBPs, QSTR models can be used to estimate their toxicity. Improvements can be made in this process by using alternative QSTR models:

- Use various QSTR models to provide more confidence in the toxicity predictions. Such an effort may yield various conflicting predictions, so that multiple "answers" are provided for analysis. However, this information could be examined as a body of data and considered under a weight of evidence scheme; multiple "answers" could be examined by expert judgment. One important distinction among models that may explain different "answers" is to consider whether the models are asking equivalent questions that will provide directly comparable information.

- Examine and estimate the misclassification errors for the various QSTR models used.

- Examine the range of predictions from various QSTR models and make risk predictions on that basis, e.g., by using zero as the lower bound and predicting the upper bound by assuming a worst case.

Rationale. The use of QSTR modeling of toxicity carries with it a degree of uncertainty that must be acknowledged and estimated. In the illustration, only one model was applied to the Group B DBPs to estimate the proportion of the unidentified TOX that could be associated with a given health endpoint. The range of risks associated with the extreme alternative assumptions of 0% or 100% generally spanned a factor of approximately 5 to 10. Although this is a reasonable range for this illustration, the range may be significantly different depending on the source water characteristics and treatment trains being examined. Research to examine this assumption will reduce the uncertainty in this calculation.

4) *Approach.* Perform a statistical evaluation of the certainty that chemicals are indeed present in the DBP mixture. When toxicity data on such chemicals are then used in the risk assessment, the likelihood that the compounds are truly present in the DBP mixture can be used as a weighting factor in the actual risk estimation or taken into account in the uncertainty analysis.

Rationale. The illustration gives equal weight to the risks estimated for the Group A and B DBPs, despite the fact the we are certain the Group A DBPs are present and only estimate that the Group B DBPs are present. Furthermore, within the Group B DBPs, there is a range of uncertainty because, for example, some Group B DBPs are clearly formed by the disinfection process, where others are suspected of being formed by the analytical chemistry methods themselves. Similar issues exist for the Group C DBPs.

5) *Approach.* Evaluate experimental and environmental DBP mixtures for sufficient similarity.

Rationale. Because of the variability in DBP mixtures, development of statistical and toxicologic criteria to evaluate the concept of sufficient similarity among DBP mixtures is potentially useful in comparing the relative risks posed by different types of DBPs, including the unknown fraction. For example, these types of approaches may prove valuable for comparing toxicities of and exposures to drinking waters with elevated brominated DBP levels to those containing elevated chlorinated DBP concentrations. They could also be used to make comparisons of exposure and toxicity among these two groups. Evaluation of the changes in concentrations of individual DBPs as the mixture travels through the distribution system (Clark and Sivaganesan, 1998) may also be useful in the comparisons of relative risks posed by different DBP mixtures.

3.4. RISK ASSESSMENT OF DEVELOPMENTAL AND REPRODUCTIVE EFFECTS

The assessment of developmental and reproductive risks can be improved by using more appropriate dose-response models and evaluating the relationships between the animal study endpoints and the human effects of concern. (For discussions and recommendations from the April 1999 workshop, see Sections 3.2., 3.3., 4.4. and 4.8.4. of Report 2.) The following recommendations are made:

1) *Approach.* To assess human risk from animal developmental toxicity data and account for possible intrafetal correlations, consider modeling the risk of *any* treatment-related developmental effect, rather than focusing on a specific effect. One method would be to aggregate the observed effects in the animal bioassay prior to running the chosen dose-response model. Another alternative is to model several endpoints together using a multivariate normal model.

Rationale. When only one data set (e.g., reduced fetal body weight in males) is finally selected out of several possibilities (e.g., visceral malformations, reduced fetal body weight in females, neural tube defects, etc.) for risk estimation, much information is lost. When it can be shown that modeling data sets together is both biologically and statistically reasonable (e.g., Stiteler et al., 1993; Vater et al., 1993; Velazquez et al., 1994), then efforts should be made to combine them in the modeling procedure.

2) *Approach.* A model such as the log-logistic model with underlying beta-binomial response variability is recommended for modeling a single quantal endpoint instead of the linearized multistage procedure used in the illustrative example.

Rationale. Such models account for the correlated nature of the results from typical developmental toxicity data sets (and from many reproductive toxicity data sets) and allow estimates of the fetal probabilities of response as a function of dose or exposure (and other covariates such as litter size). Usually, the modeling of developmental toxicity studies is limited by the fact that individual fetal data are not generally reported in the literature, requiring separate modeling of each endpoint. For the DBP analysis, however, such data are available. It is generally more appropriate to model individual embryo/fetal responses and control for litter effects, as opposed to litter-based summaries of response (e.g., litters with one or more affected fetuses are considered to be the responding litters) because more information is utilized in the analysis.

3) *Approach.* Explore different ways to model continuous endpoints. Instead of converting them into quantal endpoints by estimating a cutpoint beyond which effects are considered to be adverse, the analysis can model changes in the continuous variable itself (e.g., changes in mean birth weight) as a function of dose.

Rationale. Modeling the continuous variable itself allows the results to be linked to sequellae known or thought to be caused by changes in the continuous endpoint (e.g., adverse affects in the infant linked to low birth weight, or infertility linked to low sperm count), thus addressing the issue of relating effects observed in animal studies to human health effects. That is, the dose-response relationship for the continuous endpoint in animals could be projected to humans using a pharmacokinetic or allometric dose scaling procedure. Then, the implications for human risk using human data can be interpreted in the context of the continuous parameter (or its human analogue) to human clinical outcomes of concern. Such an analysis should, of course, be limited to parameters that have human analogues strongly related to adverse outcomes of concern. An advantage of the use of continuous intermediate parameters such as birth weights is that they are more amenable to epidemiologic study and measurement of population effects than the often rare quantal effects.

3.5. RISK ASSESSMENT OF CARCINOGENIC EFFECTS

To improve the mixtures risk assessment for carcinogenicity, additional research is needed to provide better mechanistic information, epidemiologic exposure characterizations and statistical modeling. (For discussions and recommendations from the April 1999 workshop, see Sections 3.1., 3.10., 4.3. and 4.8.3. of Report 2.) The following recommendations are made:

1) *Approach.* Improve statistical treatment of uncertainty in the cancer potency estimates, including animal-to-human extrapolation, selection of data set, cancer mechanisms and statistical sampling error. Methods exist for determining minimal estimates of uncertainty from the biological literature. For example, using the EPA's upper confidence limit (UCL) estimate of risk (U.S. EPA, 2000b) as approximately a 95th percentile value (1.6449 standard deviations above the median) and representing uncertainties as log-normally distributed about a median estimate at about 0.072 times the EPA UCL, then the geometric standard deviation of the lognormal distribution representing uncertainties is $10^{[\log(.0724)/1.6449]}$ = 4.93 (Hattis and Goble, 1991; Hattis and Barlow, 1996; Hattis and Minkowitz, 1996). Work by Crouch (1996) and by Kodell et al. (1996) showed a GSD of 10.5-11. A scale can be used, then, to understand the difference between particular percentiles of log normal distributions (e.g.,

between the 5th and 95th percentile). This is one approach for showing central tendency and range of variability.

Rationale. Uncertainty/confidence distributions should be derived for cancer potency estimates for chemicals for which bioassay data exist. Methods in the literature can be used in the near term to provide better estimates of inter-individual variability in the population than the lognormal distributions used in the illustration.

2) *Approach.* Explore the assumption of independence versus similarity of carcinogenic modes of action across DBPs, which is critical to understanding if DBP risk estimates should be calculated using response addition (independence) or dose addition (similarity).

Rationale. The degree of similarity of mode of action that would negate the assumption of independence is not known and is likely to be dose-dependent. A particular toxic endpoint (e.g., liver tumors) might arise from many different mechanisms, which may or may not be independent.

3) *Approach.* Investigate the toxicology literature for each carcinogenic DBP and determine the likelihood that its mechanism-of-action for cancer is not active at environmental exposure levels.

Rationale. The mode of carcinogenic action of the DBPs is important in assessing whether the carcinogenic mode of action has a threshold. The question of response thresholds is critical primarily when significant extrapolation is needed from experimental or observational exposures to those of interest and because animal bioassay exposures are generally several orders of magnitude higher than human exposures to finished drinking water. Several important points of scientific uncertainty exist for the assessment of risk from threshold compounds.

4) *Approach.* Assess the quality of existing epidemiological studies, evaluating the likely DBP mix in the areas where the studies were conducted; determine the feasibility of developing water quality models to better estimate historical exposures to specific DBPs.

Rationale. A number of analytic epidemiological studies have been conducted to assess the cancer and reproductive or developmental risks that may be associated with consumption of chlorinated drinking water. Results differ among the studies conducted in various geographic areas. For studies with minimal sources of bias, these differences may be the result of possible differences in water exposures to various disinfection

by-products (DBPs) in the study areas. To decrease the uncertainties associated with the interpretation of this body of literature, it is necessary to develop better assessment methods for the DBPs and other exposures of interest. Results of such efforts could be used for possible re-analysis of recent, well-conducted analytic epidemiological studies.

3.6. ACCOUNTING FOR VARIABILITY AND UNCERTAINTY

The illustrative example addressed both variability and uncertainty (see Section 2.5. of Report 2 and Sections 2.2., 2.3., 2.4., 5.2., 5.3. of Appendix I). When available, data were used to estimate distributions for parameters such as slope factors, DBP concentrations and tap water consumption values. These distributions were then used in a two-stage Monte Carlo analysis to generate distributions of risk estimates, and uncertainty analyses were further developed to analyze the effect of uncertain assumptions on the results.

3.6.1. Dose-Response Issues. Because a response addition approach is used to estimate DBP mixtures risk in the illustrative example, slope factors, calculated using the linearized multistage procedure, are one set of key parameters used to characterize both the cancer and non-cancer risks. While this model has precedent for carcinogens, the 1996 proposed Cancer Guidelines (U.S. EPA, 1996b) indicate other models should be used if they are biologically more appropriate. Furthermore, model uncertainty is of great concern for the non-cancer endpoints, as other models are available that account for such variables as litter effects and the existence of thresholds. The following issues and modeling techniques relative to accounting for variability and uncertainty in the dose-response assessment can be applied to both the cancer and noncancer endpoints. The caveat is that some other toxicity marker may be used in place of a

slope factor in future analyses, particularly for the noncancer endpoints. (For discussions and recommendations from the April 1999 workshop, see Sections 3.7., 4.6. and 4.8.6. of Report 2.)

1) *Approach.* Use data comparing potency in animals and humans for a generic set of chemicals to quantify the distribution of plausible human potency estimates associated with the DBP-potency estimates inferred from the animal toxicity data sets.

   Rationale. Some work has been done on this for the cancer endpoint (see Allen et al., 1988, 1998; Shipp et al., 1989). In the workshop, it was demonstrated that the distribution of human cancer potency estimates corresponding to a slope-factor estimate inferred from an animal toxicity data set can be characterized as lognormal with a GSD of approximately 10 (see Section 3.1. of Report 2 of this document).

2) *Approach.* Use a Monte Carlo simulation or bootstrapping techniques to develop human slope factor distributions. When determining the value of a human slope factor to use for a set of simulations, take the animal-based slope factor estimate (which itself could be sampled from the distribution representing its stochastic uncertainty) and then sample from a distribution of human inter-individual sensitivities developed for the endpoint of interest (e.g., for cancer, a lognormal distribution having a mean equal to that animal-based estimate and a GSD of 10).

   Rationale. In the illustrative example, the slope factors are treated as uncertain values that are input as lognormal distributions into the Monte Carlo procedure to determine uncertainty and variability associated with the risk estimates. The estimates of these slope factors can be improved by using real data to determine the shape and parameters of the distribution.

3) *Approach.* Consider both data set uncertainty and model uncertainty in any risk characterizations.

   Rationale. Both the current approach and the bootstrapping method described above use a single animal data set and require the choice of a particular dose-response model. Both of these choices affect the uncertainty of the distribution produced. For many of the more common DBPs, multiple (animal) data sets exist that provide alternative slope factor estimates, and in some cases, studies exist in which no adverse

effects were observed. A variety of dose-response models are available, several of which may provide an acceptable fit to a single data set, but may provide very different slope factor estimates, particularly when extrapolating into the low-dose region of the curve. Such uncertainties should be investigated and accounted for in the Monte Carlo analysis.

4) *Approach.* Use the expert judgment method described above (Section 3.1.) with Equation 2 to evaluate model uncertainty for each toxicologic or epidemiologic data set. Model each data set using all dose-response functions or other risk methods that are biologically plausible and statistically appropriate (e.g., demonstrates a statistically significant goodness-of-fit). Then, for a given data set, produce a weighted average of the risk estimates for the exposure of interest as described above.

Rationale. This approach provides an evaluation of model uncertainty. Experts can "compare" the results of independent models. This quality of each model can be factored into the model uncertainty analysis.

5) *Approach.* Characterize uncertainty in the hazard identification step when evaluating DBPs.

Rationale. This is a fundamental source of uncertainty whether relying on animal bioassays or epidemiologic studies. There are clearly differences between chemicals in the degree of certainty that they are indeed capable of causing health effects in humans, particularly at the low environmental exposure levels for DBPs. To be most useful, the uncertainty should be characterized quantitatively so it is reflected in the risk estimates that are compared.

3.6.2. Exposure Issues. Even at the most fundamental level, concentrations of some of the DBPs are uncertain for any given treatment system simply because the identity of those DBPs is unknown. Above and beyond this fundamental difficulty, there are uncertainty and variability issues that need to be recognized in relation to both concentration and subsequent exposures. Variability and uncertainty in the exposure estimates can be improved by considering changes over time. (For discussions and

recommendations from the April 1999 workshop, see Sections 3.4., 3.5., 3.6., 4.1., 4.6., 4.8.6. of Report 2.)

1) *Approach.* For tap water consumption data, derivation of a distribution for temporal variation should be investigated to provide information different from that representing inter-individual variations.

   Rationale. Because tap water intake is one of the key parameters determining exposure (once a set of DBP concentrations is given), some care must be taken in interpreting and using the tap water intake data to derive distributions characterizing variability and/or uncertainty. Of particular concern here is the lack of differentiation between percentiles of consumption across individuals and percentiles across days of consumption. It is believed that the available consumption data (presented in Ershow and Cantor, 1989) were averaged over 3-day periods. Such information on temporal variation might be important when considering the impact of some noncancer endpoints, where a long-term average daily dose may not be the most appropriate determinant of response.

2) *Approach.* Characterize the variance and uncertainty in concentration data according to the time over which the assessment is made and the dimensions of the exposure area (e.g., one treatment plant, one region, national).

   Rationale. Measurement error associated with collection of concentration data (for which there is substantial laboratory involvement) is likely to be a significant contributor to uncertainty. Also, seasonal variation in source water characteristics and geographic variation should be taken into account when appropriate for the scope of the assessment.

3.7. MIXTURES RISK CHARACTERIZATION METHODS

As detailed in Section 2.1.2., any risk characterization approach needs to address the interconnected elements of the risk assessment paradigm that include hazard identification, dose response assessment, exposure assessment and risk characterization with an uncertainty analysis. Investigations are needed into how well

different risk characterization methods work with the DBP data. (For discussions and recommendations from the April 1999 workshop, see Sections 3.8., 3.9., 3.10., 4.1., 4.5. and 4.8.5. of Report 2.)

1) *Approach.* Evaluate multiple chemicals and multiple routes of exposure for several endpoints over time. The DBP mixture risk assessment should be approached using the principles of cumulative risk. Although cumulative risk is a fairly new area of research, the results of existing efforts can be used to apply cumulative risk assessment principles to DBP mixtures. Specifically, Agency efforts in this area include guidance on evaluating multiple pathways of exposure (U.S. EPA, 1999b), guidance on the health risk assessment of chemical mixtures (U.S. EPA, 1999c), and documentation on cumulative risk that will soon be available from the Office of Pesticides and from the National Center for Environmental Assessment's Risk Assessment Forum.

   Rationale. Drawing on points that have been made in Sections 3.1. to 3.4. of this document, it is clear that the risk assessment of DBPs is a multifaceted problem that includes population exposures to multiple chemicals over a lifetime. Data developed on inhalation and dermal exposures indicate that these pathways may contribute significant amounts of DBPs. Furthermore, it may be proposed that differences in risk estimates made from the epidemiologic data vs. the animal toxicity are different because the animals are not exposed via multiple routes and durations are too short as compared with human exposures.

2) *Approach.* Apply and compare several types of risk characterization methods to evaluate additivity, to include response-addition, relative potency factors (dose-addition), and proportional response addition.

   Rationale. The use of risk characterization methods other than response addition may be important, for example, for developmental endpoints, when different DBPs affect development at the same stages or critical periods. For example, the haloacetic acids and haloacetonitriles that have been tested for developmental toxicity produce a spectrum of effects in the postimplantation period including postimplantation loss, depression of fetal body weight and crown-rump length, and visceral and skeletal malformations. Thus, for these DBPs, the critical periods appear to be similar, and mode of action may be considered as similar, so a dose addition approach would be more appropriate. However, when mode of action and timing of effects are unknown, a comparison of risk values under different assumptions offers a range of risk estimates

under additivity, which is important because synergistic or anatagonistic responses are not likely to occur at the low environmental levels at which DBPs occur.

4. CONCEPTUAL MODEL FOR A CUMULATIVE RISK APPROACH

As noted above, several different risk characterization methods have been recommended for estimating DBP mixtures risk: response-addition, relative potency factors and proportional response addition (Section 3.7.). Detailed examples are available within this document for the DBP mixtures problem for the oral route only using response addition (Appendix I) and proportional response addition (Section 3.8. of Report 2). Although each of these approaches has its strengths, neither of these examples accounts for 1) multiple routes of exposure, 2) any toxicologic similarity among chemicals in the mixture (beyond target organ effects), and 3) temporal issues of exposure.

Section 4.1. presents a conceptual model that accounts for multiple routes of exposure over time and toxicologic similarity of the components. This approach will be expanded in an NCEA report on the feasibility of performing cumulative risk assessments for non-cancer and cancer endpoints for mixtures of drinking water disinfection by-products via inhalation, dermal, and oral exposures; the projected completion date of this feasibility report is 2001.

4.1. MODEL CONSIDERATIONS AND REQUIREMENTS

Currently, it is feasible to approach human health risks posed by DBPs as a cumulative risk problem. The current effort (Appendix I) to quantify human cancer risk from exposure to DBP mixtures using animal data from the oral route alone produces risk estimates several orders of magnitude lower than those projected using positive

epidemiologic data on chlorinated drinking water exposures in the study population (other epidemiologic data indicate that risks posed may be negligible). If one assumes that DBP exposures cause human cancers and that the positive epidemiologic results provide unbiased quantitative estimates of the cancer risk posed by chlorinated water exposures, then the discrepancy between risk estimates from the toxicological data and the positive epidemiologic studies requires explanation. Several reasons for the discrepancy are postulated, including failure to accurately extrapolate dosimetry between animals and humans; failure to account for contribution to risk from inhalation and dermal exposure routes; and failure to integrate the data according to the level of organization at which the effects were observed (e.g., population, target organ, cellular).

The goals of a cumulative risk assessment for DBPs build upon those of the current DBP mixture risk assessment (Appendix I). The goals of a new methodology would include:

- To develop a mixtures approach that incorporates the flexibility to integrate selected mixtures risk models based on an understanding of the mode-of -action
- To consider the temporal nature of DBP exposures and variability of human activity patterns; address and appropriately integrate exposures through the three routes of primary concern for environmental pollutants: ingestion, dermal, and inhalation
- To address the main endpoints of concern in the epidemiologic literature: developmental and reproductive effects and cancer
- To identify the “risk-relevant” components of DBP mixtures, this may include organic halides not measured individually as well as DBPs that are not halogenated

- To estimate risks for various drinking water treatment trains, reflecting differences in those DBPs formed and their concentrations over time in the distribution system

- To generate central tendency risk estimates along with their associated probability distributions; such distributions of risks are needed to appropriately reflect both the uncertainty and variability found in these data

- To identify specific measures that could be incorporated into future epidemiologic investigations to improve exposure classification

- To develop mixtures risk characterization approaches that can be used in the evaluation of causality.

4.2. CUMULATIVE RISK APPROACH

Three general approaches for addressing additivity associated with low doses components of a chemical mixture exist (see Section 2.2.). Dose addition assumes the mixture components share an MOA; thus, doses of individual components can be added together after being appropriately scaled for relative potency. Response addition assumes component risks for a given target organ or tissue can be added given the components' effects are toxicologically and statistically independent. Finally, effects addition assumes health outcomes attributable to individual components can be added together, assuming that the toxicodynamics are similar across components. To incorporate MOA data into the risk assessment, a dose-addition approach is investigated here.

MOA refers to a continuum describing the key events and processes starting from the point of toxicant-cell interaction and leading to the onset of a health endpoint (see Figure 9). The MOA may involve several levels of toxicologic analysis and

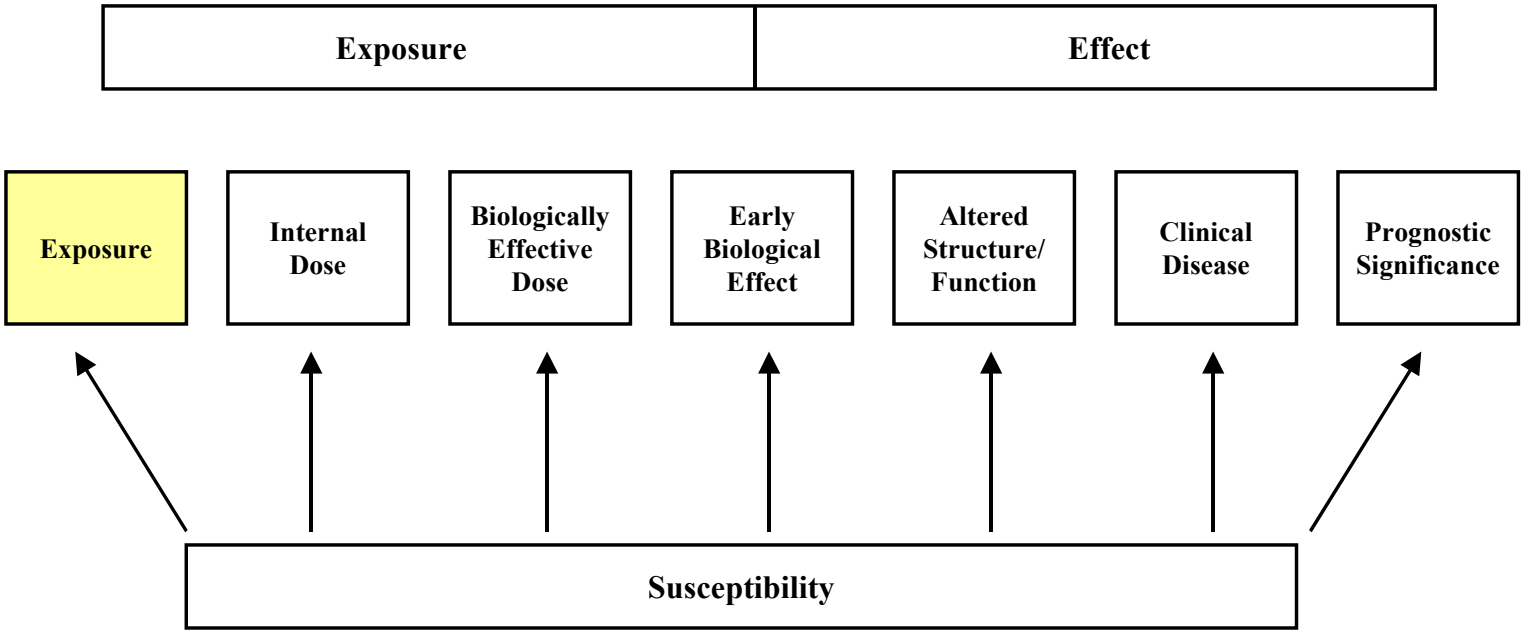


FIGURE 9

Biological Marker Components in Sequential Progression from Exposure to Disease

Source: Schulte (1989)

influence based on the structural hierarchy of animal bodies: intracellular, intercellular, tissue, organ, organ system, whole organism. Less is known about MOA as contrasted with the term mechanism-of-action, which implies a detailed molecular description of the induction of a health effect (see Section 2.2.1.).

Both ILSI (1999) and Wilkinson et al. (2000) have documented the complexities associated with assessing risks posed by chemical classes exhibiting a common MOA. These reports describe a range of chemical mixture risk assessment methods that could be applied to a set of pesticides that exhibit a shared MOA, the organophosphates (OP). The potential utility of the hazard index approach (U.S. EPA, 1999c), a chemical mixtures approach that requires dose response and exposure data for each component, and a relative potency factors approach (detailed below) are presented in each. Wilkinson and collaborators also detail a combined margin of exposure approach, which is conceptually related and mathematically similar to the hazard index approach. The ILSI report describes an exposure schematic that can combine exposure estimates for inhalation, oral and dermal exposure routes; Olin (1999) also describes conceptually similar approaches for assessing exposures to drinking water contaminants and details additional exposure considerations for combining estimates from multiple exposure routes. Wilkinson et al. (2000) and Rhomberg (1999) elucidate the temporal considerations that impact an assessment of risks posed by multiple chemicals. Specifically, they both conclude the internal dose of the components matters more than the timing of the exposures.

Cumulative risk assessment, as used in this document, examines the potential for increased risks by considering multiple chemical exposures through multiple routes

over multiple time frames. Cumulative risks are conjectured to occur under a number of conditions:

- When exposures (through multiple routes) to a group of chemicals that act through a common mechanism of toxicity occur within a physiologically-relevant time frame

- When exposures occur (through multiple routes) to a group of chemicals that impact different parts of a pharmacodynamic pathway that lead to a toxic response given the temporal considerations of the impacts (e.g., repair processes)

- When risks of a toxic effect estimated for each component using the component's dose-response curve at the exposure concentration are additive, given temporal considerations of the response

- When there are synergistic interaction effects associated with exposures to two different chemicals (or dose-additive chemical groups) that occur over a physiologically-relevant time frame.

The physiologic time frame can reflect the pharmacokinetics (PK) or the pharmacodynamics (PD) associated with exposures to specific components of the chemical mixture. PK is the study of the fate of chemicals in the body; it deals with absorption, distribution, biotransformation, and elimination. PD is the study of biochemical and physiological effects of chemicals and their mechanisms of action. The PK depend on exposure routes and patterns (e.g., duration, magnitude, and frequency). Although four conditions are listed previously in this section, only a cumulative risk approach arising from exposures to groups of chemicals that act through a common mechanism of toxicity within a physiologically-relevant time frame is described.

Figure 10 illustrates the decision processes that would be undertaken to apply this approach. The decision diagram is presented from left to right, although some

steps may be interative. The initial step is to evaluate the MOA data for the components of a chemical mixture. If the components share a common MOA, then it may be possible to develop a cumulative relative potency factors approach. This assumes that component data for individual exposure routes meet criteria established for implementing an RPF approach; specifically, one component is well studied and has a dose-response function available for the effect of interest, and it is reasonable to conclude from available data on toxicity or chemical structure that all components share a common MOA (U.S. EPA, 1999c). If the components do not meet the criteria, then some other assessment approach should be considered.

The next step is to evaluate the exposure scenario. By which routes are individuals exposed and over what time frames do these exposures occur? Three exposure routes are typically considered when assessing risks posed by environmental mixtures: dermal, oral, and inhalation. DBP exposures occur through all three routes. Similarly, the time frame of DBP exposures is thought to be intermittent throughout the period of time spent indoors. Concentrations of volatile DBPs (e.g., THMs) increase when activities such as showering, cooking, and clothes washing occur. Dermal exposures occur through activities such as bathing and hand washing, and oral exposures occur through drinking water and consuming water in or on foods.

The next step is to assess the impact of absorption, distribution, biotransformation, and elimination on the DBP components as they are absorbed

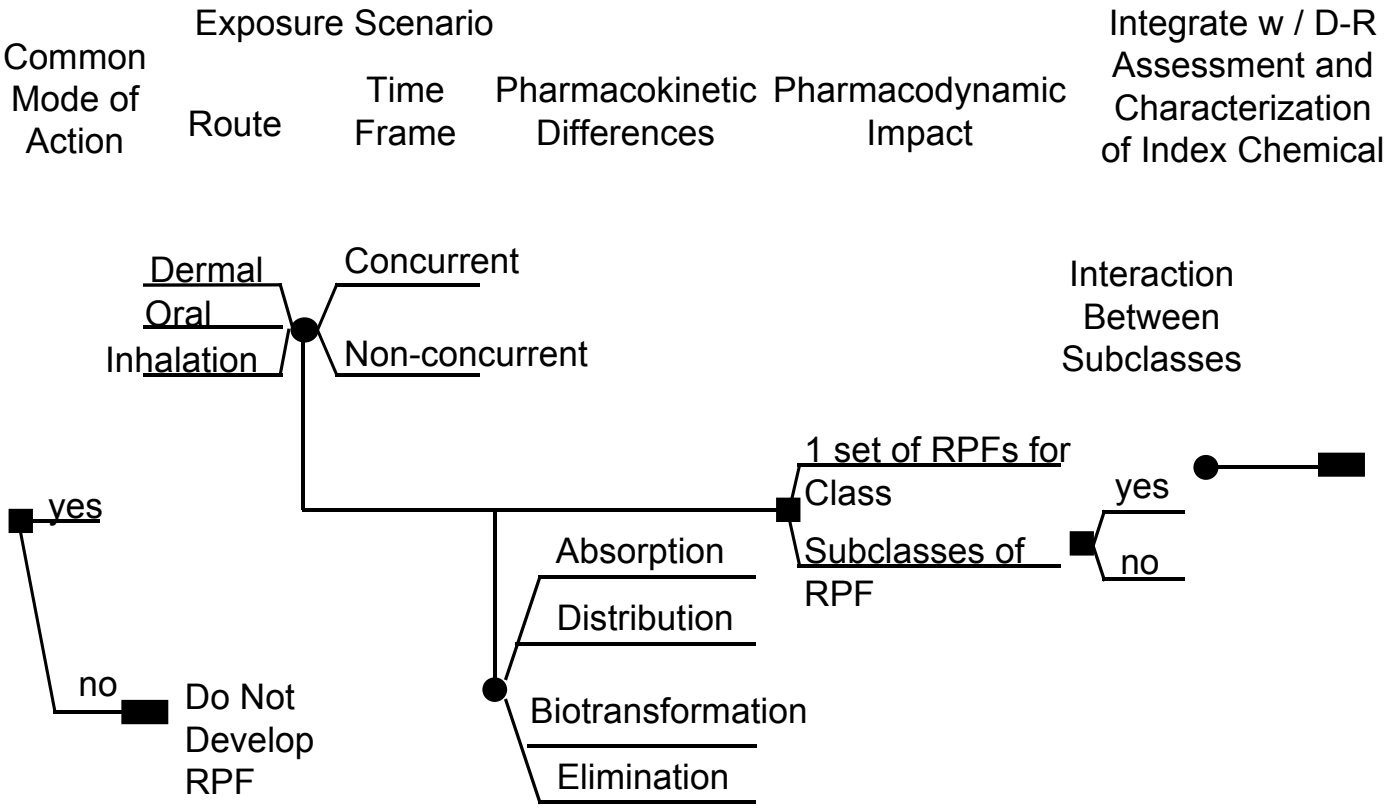


FIGURE 10

Schematic of CRPF Decision Process

through the various exposure routes. Specifically, are there differences in internal dose arising from the multiple route exposures? For example, when environmental concentrations of chloroform are absorbed through the intestines, they appear to be rapidly biotransformed in the liver. Inhaled chloroform is not biotransformed by the liver as rapidly because it is not subjected to first pass effects.

The next step is to assess the PD differences. Do the components of the mixture share a common MOA at environmental doses in the biological moiety(ies) of interest? Can the MOA be plausibly linked to adverse health outcomes? If the data are generated in laboratory animals, is there a comparable human MOA? If the components are consistent across routes, PK, and PD properties, then it may logical to develop a single set of RPFs for the compound class under evaluation. If they vary, then it may be logical to split the class into two or more subclasses and pose the question as to the type of interactions that exist between the classes. The final step is to develop an equivalent index chemical concentration. This exposure assessment is then integrated with the dose-response function of the index chemical to quantitatively estimate risk.

To implement this approach, it is critical to identify the assumptions made and explain the basis for these assumptions. Typically, the data upon which to base many of these decisions does not exist or may be difficult to interpret; expert judgement or surrogate data may be used to facilitate decision making. In these cases, the uncertainty introduced into the quantitative exposure assessment should be described. The identification of uncertainty in mixtures risk assessments is critical (U.S. EPA, 1986, 1999c). The goal is to develop a transparent assessment, so that key assumptions can be readily identified and evaluated.

The goal of the conceptual approach is the integration across routes of RPF-based risk estimates that are route specific for toxicologically similar subclasses of DBPs for an effect-specific period of duration. Once several RPF risk estimates are generated, then the analyst can make some assumptions relative to the likely relationships of the across-subclass risks and combine them (e.g., a response addition assumption leads to summing these RPF risks) to yield the total risk estimate for the mixture. This approach produces a transparent cumulative risk assessment because assumptions about the toxicity and the interactions must be specifically identified.

4.2.1. Relative Potency Factors. The RPF approach has been proposed as an interim approach for characterizing health risks associated with mixtures of chemical compounds that have data indicating they are toxicologically similar (U.S.EPA, 1999c). To develop an RPF-based risk estimate for a class of chemicals, toxicologic data are needed for at least for one component of the mixture (referred to as the index chemical), and scientific judgment is used to assess the relative toxicity of the other individual components in the mixture as well as of the mixture as a whole. The RPF approach assumes dose addition is appropriate for the related components that comprise the mixture. True dose addition assumes the components of the mixture act by the same MOA. If they are reasonable, these assumptions predict the toxicity of the mixture by using the dose-response curve of the index chemical.

The exposure level of each component in the mixture is scaled by its toxicity relative to that of the index chemical resulting in an index chemical equivalent dose for each component. This scaling factor (the RFP) is based on a comparison of relevant dose-response information between the index chemical and the component, including

the results of toxicologic assays and analyses of structural similarity to other compounds of known toxicologic potential. When data are available, the RPF can be adjusted to account for intake and for dosimetry. For each component of the mixture, the RPF approach predicts an equivalent exposure in terms of the index chemical; these equivalent exposures are them summed to generate an index chemical equivalent total mixture dose. The risk posed by the mixture is then estimated using the dose-response curve of the index chemical. This estimate of risk developed through equivalent index chemical exposure should be considered an interim and approximate estimate of risk that should be revised as more complete and better data are generated.

The application of an RPF approach may be limited based on available data to specific exposure routes, specific health endpoints, or specific members of a class of compounds that have similar PD and possibly PK properties. Application of an RPF approach when conducting a cumulative risk assessment allows the analyst to 1) subdivide a class of chemicals that exhibit a common toxic endpoint but different PD properties into toxicologically appropriate subclasses; 2) incorporate differences in toxicity based on exposure route and exposure time frame into this subdivision; and 3) appropriately limit the cumulative risk assessment to certain health endpoints based on available data. The RPF method requires that a quantitative uncertainty analysis or qualitative description of uncertainty be included in the risk characterization. To apply RPF to the DBP mixture problem for a single effect and route, the basic model would be as follows:

$$R_m(k) = f_k\left(\frac{1}{1000} * Y^* C_m(k)\right) \quad (3)$$

where:

$R_m(k)$ = mixture risk for a given endpoint (unitless) as a function of an index chemical k

f_k = dose response function of an index chemical k (a well-studied chemical in the mixture), requiring the 1/1000 conversion factor of mg to µg when dose units are mg/kg-day

Y = tap water intake rate (L/kg-day)

$C_m(k)$ = concentration of the mixture in units of index chemical k (µg/L) [see Equation 4 below for calculation of $C_m(k)$.]

The RPF is based on dose addition, which carries with it the assumption of a similar MOA for the mixture components, so each component can be considered a dilution of the index chemical. To the extent that data are available, division of the DBPs into subclasses could be performed by incorporating all relevant biological information regarding toxicant-target interactions and response processes (e.g., it would be important to distinguish between carcinogens that directly interact with and damage DNA versus those that operate through epigenetic or nonmutagenic mechanisms such as receptor-mediated pathways and hormonal or physiological disturbances).

The index chemical is likely to be chosen because it is a well studied chemical for which the endpoint of interest has been observed, and its dose-response curve for that endpoint is available. The concentrations of the other DBPs in the group then are expressed as the index chemical by developing a scaling factor, the RPF. Then, the total mixture dose is estimated as:

$$C_m(k) = \sum_{i=1}^{n} \left(RPF_i * C_i \right) \quad (4)$$

where:

$C_m(k)$ = mixture exposure concentration expressed as the index chemical k (µg/L)

n = number of components in the mixture

RPF_i = proportionality constant relative to the toxic potency of the index chemical, k, for the ith mixture component

C_i = measured concentration of the ith mixture component (µg/L).

Calculation of an RPF_i involves making an estimate of relative potency for each chemical compared with the index chemical. When data are available, dosimetric adjustments, commensurate with level of effect observation and MOA, can be made during this calculation to provide route-specific estimates of a cumulative internal dose surrogate to adjust the RPF_i.

Figure 11 presents a simple hypothetical RPF case for a single effect, route, and duration. Chemical A1 is the index chemical. Equivalent concentrations of chemical components A2 and A3 are developed and these are summed to estimate the index chemical equivalent exposure for the simple mixture.

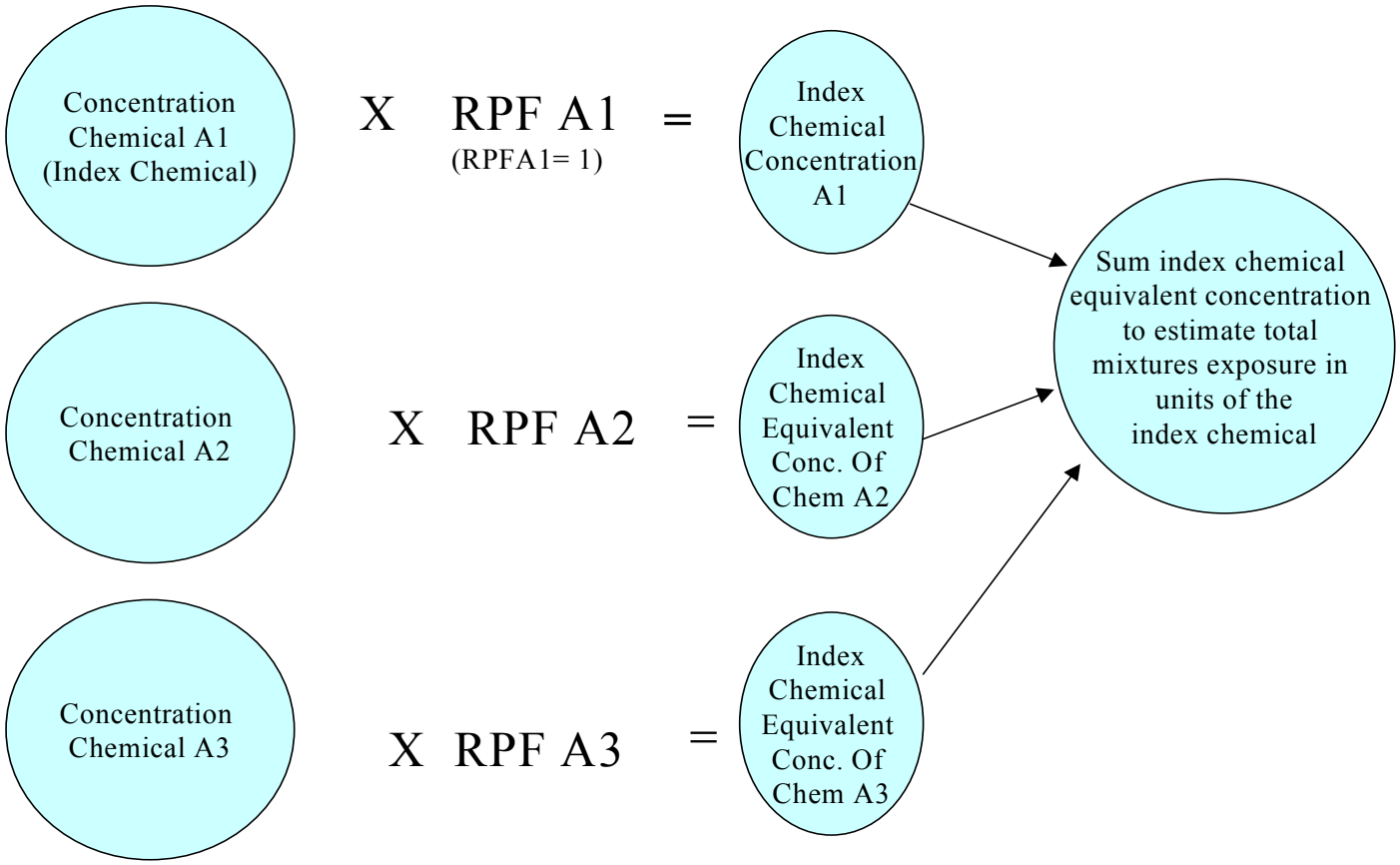


FIGURE 11

RPF Approach for Three Hypothetical Chemicals, Single Effect, Route, and Duration

Figure 12 presents a simple hypothetical RPF case for a single effect over a consistent time frame of exposure for two exposure routes. The oral exposure of chemical A1 again serves as the index chemical for both oral exposures to chemicals A2 and A3 and for exposures to chemical A1 through the inhalation route. Equivalent concentrations of chemicals A2 , A3, and inhaled A1 are developed and these are summed to estimate the index chemical equivalent exposure for the simple mixture. The equivalent exposure is compared to the dose-response function of the index chemical to estimate a risk. The assumptions or dosimetry data supporting the route-to-route conversion for inhaled and oral chemical A1 would need to be clearly identified.

Tables 12 and 13 provide example calculations for a hypothetical subclass of five DBPs that are liver carcinogens acting by the same MOA after oral ingestion. Table 12 illustrates some of the considerations related to data set evaluations, including data availability and quality and differences in species and study durations. ED_{01} values are estimated from each chemical's critical study for use in the RPF approach; these should be adjusted for dosimetry if enough data are available. The index chemical, k, exhibits the best quality data set. For purposes of illustration, Table 13 shows a feasible set of calculations that could be used to produce a risk estimate for this mixture using a RPF approach. Ratios of the ED_{01} of the index chemical to the i^{th} chemical's ED_{01} provide an RPF_i for that chemical. The measured concentration, C_i, of the i^{th} chemical is then multiplied by its RPF_i to adjust it to an index chemical equivalent concentration. In this example, the risk for the mixture, $R_m(k)$, is then estimated by multiplying the sum of these equivalent concentrations, $C_m(k)$, by the unit risk of the index chemical. The

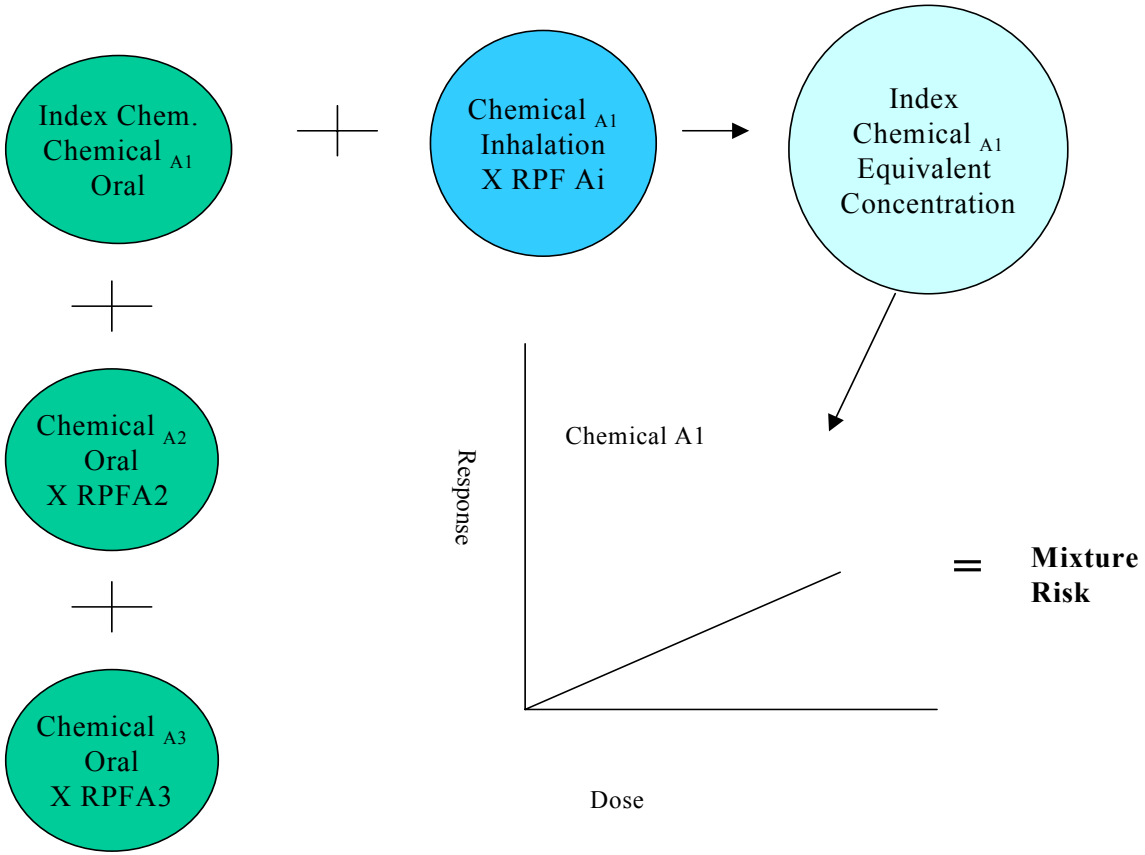


FIGURE 12

RPF Approach for Three Hypothetical Chemicals, Two Exposure Routes

TABLE 12

Hypothetical Characterization of the Toxicologic Properties of Five DBPs that are Liver Carcinogens in Animal Studies

DBP	Study ED_{01} (μg/L)	Test Species	Duration of Critical Study	Data Set Characteristics
DBP_1 (Index Chemical)	5.6E+3	Rat	2 years	Extensive. Many well conducted and documented studies for a broad spectrum of endpoints in multiple species. Human confirmation of relevance of effects.
DBP_2	4.2E+3	Mouse	2 years	Good. Many well conducted and documented studies for a broad spectrum of endpoints in multiple species.
DBP_3	1E+3	Rat	90 days	Poor. Few poorly documented studies.
DBP_4	2.2E+1	Dog	2 years	Good. Many well conducted and documented studies for a broad spectrum of endpoints.
DBP_5	7.7E+1	Rat	90 days	Limited. Few studies but well conducted.

TABLE 13

Hypothetical Example: Relative Potency Factors (RPF) and Equivalent Exposures for Five Liver Carcinogens

DBP	Study* ED_{01} (μg/L)	Relative Potency Factor (RPF_i) using Index Chemical DBP_1 [$ED_{01,1}$ /$ED_{01,i}$]	Measured Exposure Concentration (μg/L) [C_i]	DBP_1 Equivalent Concentration (μg/L) [RPF_i X C_i]
DBP_1	5.6E+3	1.0	24.4	24.4
DBP_2	4.2E+3	1.3	10.2	13.6
DBP_3	1.0E+3	5.6	0.001	0.006
DBP_4	2.2E+1	2.6E+2	0.003	0.76
DBP_5	7.7E+1	7.2E+1	0.01	0.72
Total [C_m]				39.5
% of Equivalent Concentration from DBP_1			62%	
Cancer Risk [R_m] from Exposure to DBP_1 Equivalent Concentration (DBP_1 Unit Risk = 2.4 E-6 per μg/L)			9.5E-5	

* For purposes of illustration, these doses represent the actual experimental doses converted to units of μg/L. In actual practice, this is where dosimetric adjustments and interspecies scaling factors would be applied to provide more appropriate dose surrogates to develop the RPF.

index chemical accounts for 62% of the risk; there is fairly good confidence in this risk estimate (given the judgment of the dose-response data).

4.2.2. Cumulative Relative Potency Factors. The RPF approach described in Section 4.2.1. yields a single risk estimate for a subclass of toxicologically similar chemicals for a specified endpoint and time frame. Combining risk information across these chemical subclasses would require assumptions about the interrelationship of the risk estimates. Given such assumptions, the total mixture risk for endpoint h (expressed as R_{Th}) could then be calculated as a function of the subclass risks (each risk expressed as route-specific (w), chemical subclass (m) risk, R_{mw}). For example, if response addition were assumed (i.e., that toxic effects for the subclasses are toxicologically independent and events are statistically independent at low dose levels), then a simple summation of the subclass risks would be:

$$R_{Th} = \sum_{m=1}^{s} \sum_{w=1}^{j} R_{mw} \tag{5}$$

where:

$$R_{mw}(k) = f_{kw}\left(\frac{1}{1000} * Y_w C_{mw}(k) \right) \tag{6}$$

for the toxicologically similar chemical subclasses and exposure routes (oral, dermal, inhalation) with a route-specific water intake rate Y_w. The index chemical equivalent concentrations for each subclass would be calculated as:

$$C_{mw}(k) = \sum_{i=1}^{n} \left(RPF_{iw} * C_{iw} \right) \quad (7)$$

where:

w = route of exposure fixed as oral (w=o), dermal (w=d), or inhalation (w=i)

$C_{mw}(k)$ = mixture exposure concentration expressed as the index chemical for route w

n = number of components in the s mixture group for route w

RPF_{iw} = proportionality constant relative to the index chemical, k, for the ith mixture component for route w

C_{iw} = exposure concentration of the ith mixture component for route w

In the case of a simple summation of subclass risks shown above, response addition is applied, carrying with it the assumption that the R_{mw} are biologically independent, which may or may not be appropriate for the data. If other statistical or biological behavior is more appropriate (e.g., if the effects and, hence, the risks are correlated), then other functions of the R_{mw}, the multiple route RPFs, may be applied.

To illustrate the integration of dose addition and response addition, Figures 13 and 14 conceptualize the cumulative risk for two hypothetical mixtures. In Figure 13, humans are exposed to the components of this mixture from a single route of exposure. In Figure 14, humans are exposed to the components of this mixture from two different routes. For both cases, the logic for combining the RPF-based risk estimates is the same. Based on limited data, the components are considered to have two different

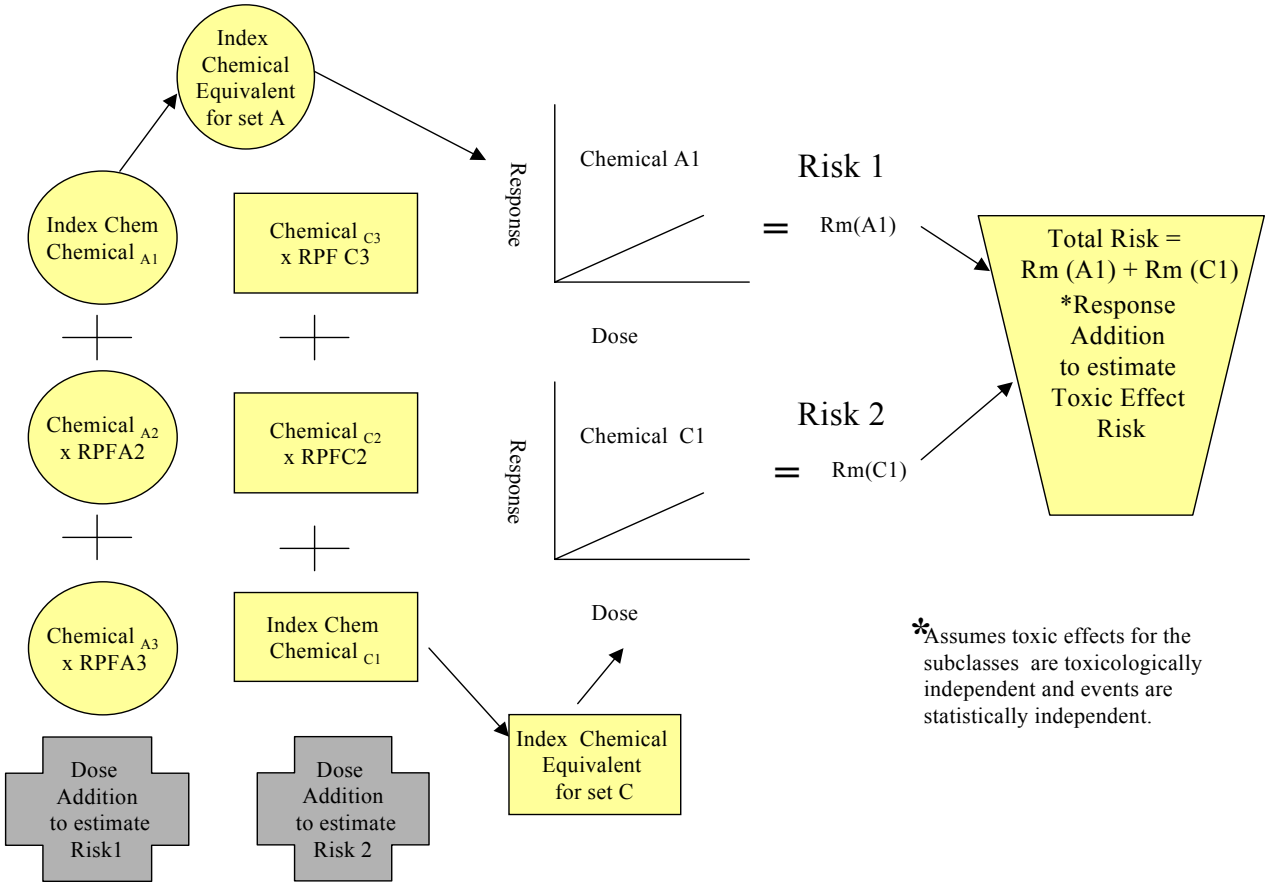


FIGURE 13

Integration of Dose Addition and Response Addition to Mixture Risk for a Single Exposure Route

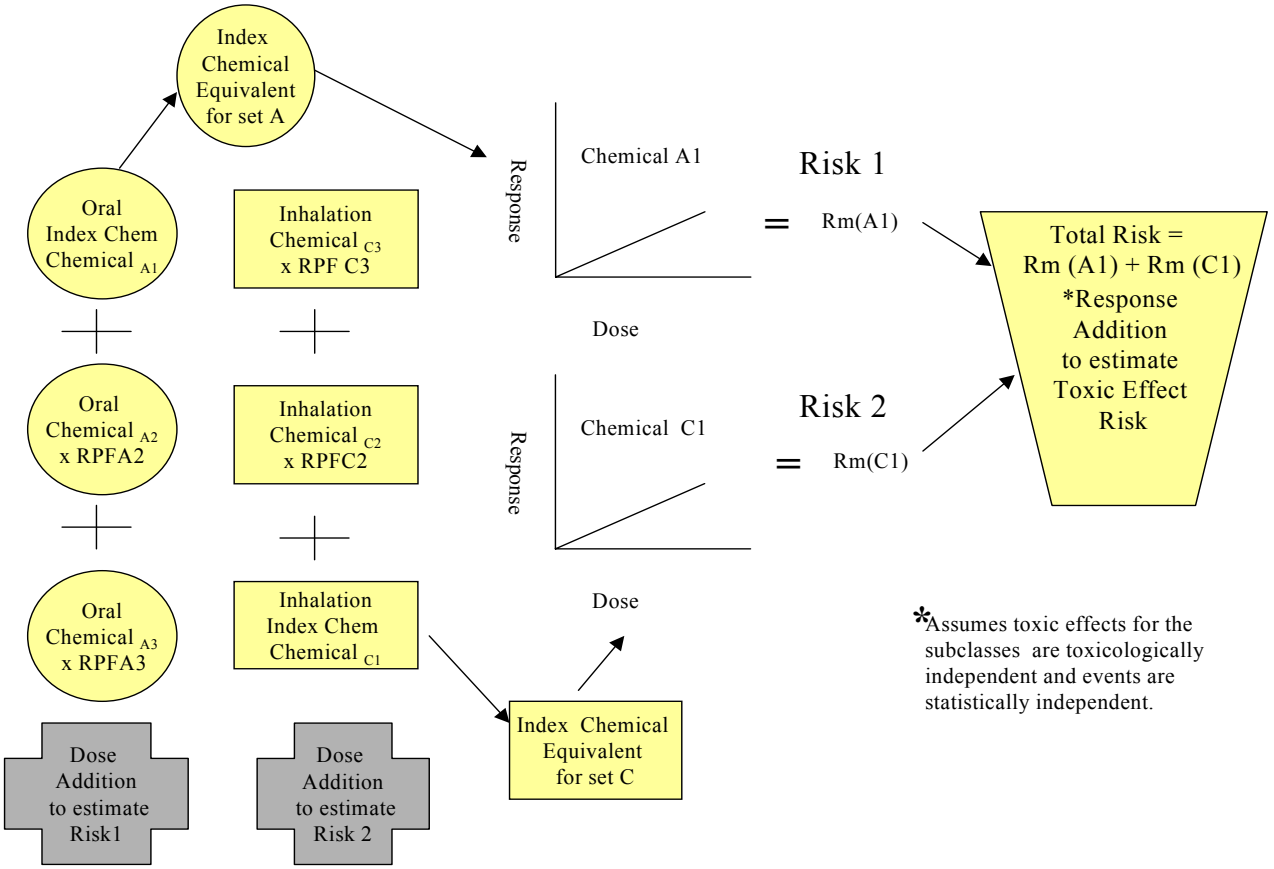


FIGURE 14

Integration of Dose Addition and Response Addition to Estimate Mixture Risk for Two Exposure Routes

MOA. Because of this, the components are subdivided into two sets for development of RPFs. Toxicity data (measured in % responding) is available for chemicals in both sets. An index chemical is determined and index chemical equivalent exposure concentrations are developed for each set. The toxicological evidence from the two index chemicals indicates that the same target organ is affected. The low environmental concentrations lead to exposure assessments in the low dose region. In this exposure region, component interactions are assumed not to be significant. The MOA data indicate there is toxicologic independence of action. Based on these data, response addition is selected as an appropriate method to estimate the risk associated with the two index chemical equivalent concentrations. Risks are estimated for each index chemical using its dose-response curve at the index chemical equivalent exposure concentration. The component risks from each RPF set are added.

Table 14 continues the illustration (see Tables 12 and 13) by presenting a hypothetical characterization of three RPF risk estimates that have been made for the same DBP mixture, but for different exposure routes (Figure 14) and different cancer sites. Ways to combine these risks depend on what is known about the independence of the toxicologic mechanism of action for the groups of chemicals and their route- and chemical-specific effects. If these three effects are considered functionally independent, then the mixture risk is based on a response addition assumption, Equation 5. The total mixture risk of any cancer is their sum (e.g., $R_m(k) = 9.5E\text{-}5 + 4.9E\text{-}5 + 2.2E\text{-}5 = 1.7E\text{-}4$). If the assumptions of toxicologic or statistical independence cannot be met, then other functions of the risks could be used or the maximum of the three risks may serve as the mixture risk estimate.

TABLE 14

Hypothetical Characterization of Several Relative Potency Factors
For the Same DBP Mixture; Different Routes, Different Effects

Index Chemical (DBP)	Equivalent Concentration / Unit Risk	Attributable to Index Chemical	Mixture Risk Estimate	Route of Exposure	Toxicologic Effect of Concern
DBP_1	39.5 (μg/L) 2.4 E-6 $(\mu g/L)^{-1}$	62%	9.5E-5	Oral	Liver Cancer
DBP_q	27.3 (μg/L) 1.8E-6 $(\mu g/L)^{-1}$	69%	4.9E-5	Oral	Kidney Cancer
DBP_r	1.7 $(\mu g/m^3)$ 1.3E-5 $(\mu g/m^3)^{-1}$	55%	2.2E-5	Inhalation	Kidney Cancer

4.2.3. Unidentified DBPs. The initial response addition assessment shown in Section 2.6. estimated an additional amount of risk for the unidentified DBPs by determining a fraction of the unidentified DBPs that can be associated with a given health endpoint and assuming equal risk per concentration of organic halide material for both the measured and the unidentified components of the mixture. A similar approach could be applied during development of the RPF risk estimates, using information from either laboratory data or from Quantitative Structure Toxicity Relationship models. The index chemical equivalent concentration, $C_m(k)$, could be adjusted to reflect the concentration of the unidentified DBPs, C_u, that can be associated with the subclass being evaluated. A relative potency factor, RPF_u, for the unidentified DBPs in C_u could be estimated using what is known about the likely chemical characterization of the unidentified DBPs (see

Section 2.5. and Appendix R1-A). For the same end point and route of exposure, Equation 4 could then be adjusted by using C_u and RPF_u to increase the value of $C_m(k)$, reflecting the contribution of the unidentified DBPs to that subclass of toxicologically similar chemicals.

4.2.4. Discussion. The development of RPF-based risk estimates and their integration with response addition in a CRPF approach addresses many of the shortcomings of the first response addition assessment in Appendix I: Workshop Pre-meeting Report, but not all issues are addressed. As shown above, the approach does not directly address the differences in risks for sensitive subpopulations or the contribution to the risk estimate that may be addressed by using what is known in the epidemiologic literature. In addition, application of CRPF promises to be a resource-intensive exercise that may be more technically correct than the application of response addition, but, in the end, may not produce risk estimates very different in magnitude. Furthermore, an enormous problem lies in the fact that very little toxicity data are available for the dermal and inhalation routes of exposure.

The CRPF approach described here is a conceptual model for development of a cumulative risk assessment for DBP mixtures. As shown, it improves on the initial response addition assessment (Appendix I: Workshop Pre-meeting Report) by more carefully considering toxicologic similarities among chemicals, routes of exposure, and dosimetry. It allows for treatment system-specific exposures to be investigated and, although not specified in this discussion, does not preclude the use of human activity patterns and distribution system effects from incorporation into the analysis. A

probabilistic analysis and full risk characterization would be required with careful treatment of the variabilities and uncertainties examined and explained.

5. RESEARCH NEEDS

DBP mixtures research is essential to establishing, explaining and estimating any substantive human health risks from exposure to the low levels of DBPs found in drinking water. Such research can serve to bridge the gap between the weak to moderate associations with cancer and developmental effects suggested in the epidemiologic literature and effects found only at high-dose levels of DBPs in single-chemical animal bioassays. To strengthen the risk assessment, a multidisciplinary research approach is needed that includes investigations of statistical methods and quantitative analyses, risk assessment methodologies, toxicologic effects, epidemiologic cohorts, and exposure assessment. Section 3 presented approaches that have the potential to be applied in the near term. The research ideas presented here represent long-term needs that are also considered important to improving the DBP mixture risk assessment.

5.1. METHODS RESEARCH

- Develop more scientifically credible distributions of toxicity coefficients for all endpoints (e.g., slope factors, effective dose levels) for use in probabilistic assessments.

- Investigate dose-response models for developmental and reproductive effects that include parameters for threshold and litter effects and incorporate multiple endpoints.

- Develop comprehensive exposure models that incorporate multiple routes, human activity patterns, multiple chemicals, and endpoint-specific timing of exposures.

- Apply alternative methods to Monte Carlo analysis (e.g., bootstrapping, Latin Hypercube, analytic solutions) to addressing uncertainty analysis and sensitivity analysis.

5.2. RESEARCH ON APPLICATION OF A CUMULATIVE RELATIVE POTENCY FACTOR APPROACH

- Define subclasses of DBPs based on exposure route, chemical structure, physicochemical attributes of chemicals, and MOA considerations (components may be in more than one subclass depending on route of exposure).

- Determine relationships among subclasses from a toxicologic perspective, including MOA, PK, PD, and consideration of what level of organization the effect measure was observed. Use relationships to develop appropriate assumptions and methods for combining RPF-based risks.

- Refine and apply dosimetric adjustment methods using case studies. Parallel suites of model structures are needed across all three routes (oral, inhalation, and dermal) based on inhalation reference concentration methods as a platform for consistency (U.S. EPA, 1994a). New model structures can be extended to include key determinants of MOA: dose surrogates to incorporate PK and PD parameters and processes at both portal-of-entry and systemic sites of toxicity. These dose surrogates can be constructed to be commensurate with the level of observation of the effect measure (population or cellular).

- Refine exposure assessments to consider water use issues (bathing, cooking, dishwashing), effects of heating water on chemical composition, human activity patterns and the human condition at time of exposure (age, weight, health status).

5.3. EPIDEMIOLOGIC RESEARCH

- Continue to rule out non-causal explanations for epidemiologic findings by examining reasonable alternative hypotheses for positive study results. To decrease the uncertainties associated with the interpretation

of this body of literature, it is necessary to develop better assessment methods for the DBPs and other exposures of interest.

- Expand ongoing or planned epidemiologic studies to include measures of dermal and inhalation exposures and human activity patterns for use in cumulative risk assessments.

- Quantitatively identify the model and data uncertainties in the exposure-response analysis used in the epidemiologic literature.

- Define susceptibility responses for general population and sensitive subpopulations.

- Develop and use biomarkers of exposure in future analytical epidemiologic studies because this can help reduce exposure misclassification. Instead of classifying epidemiologic study participants in a broad exposure category (e.g., as being exposed to disinfected water or to water without disinfection), measure and identify specific DBPs and consider the water usage, consumption rates and human activity patterns to better estimate exposure.

- Promote understanding of the problems associated with using a single aggregate number from a meta-analysis of the epidemiologic data for quantitative risk assessment, including considerations of whether causality can be established; take into consideration possible publication bias (i.e., when studies that fail to find an association, or find responses in different sites, are not published and not available for meta-analysis)

5.4. DEVELOPMENT OF TOXICOLOGIC DATA

- Conduct toxicologic studies to determine effects caused by inhalation and dermal DBP exposure and enrich the database for cumulative risk assessment.

- Use physiology-based pharmacokinetic models for the different DBPs, combined with available information on mode of action to provide insight into patterns of tumor development in animals and humans. In addition, use both *in vivo* and *in vitro* studies to help identify components of chlorinated water that may be associated with effects seen in the

positive epidemiologic studies (e.g., bladder cancer, spontaneous abortion).

- Study gene-environment interactions (e.g., CYP2E1, GST, acetyl) to identify subpopulations for further epidemiologic study; epidemiologic studies focusing on colon polyps could provide important information.

- Generate DBP mixtures data useful to refine human health risk assessment methods under development and efficient experimental designs and statistical approaches for mixtures. Mixtures of THM and HAA have a limited database already. Future directions include the evaluation of more cross-class mixtures of the THM and HAA, eventually adding other DBPs of concern, such as bromate, and screening for combinations of DBPs that may exhibit additivity or interaction effects.

- Conduct carefully designed experiments to estimate the toxicity of complex mixtures of DBPs produced by using reproducible disinfection scenarios or extracts of finished drinking water. Using these data in conjunction with the data on defined mixtures, estimates can then be made of the potential toxicity of unidentified DBP material in finished drinking water.

- Conduct studies to determine the mode(s)-of-action of DBPs, the mechanism(s) underlying any identified nonadditive interactions and their relevance to humans for cancer, developmental, and reproductive effects. Mode-of-action is difficult to determine, but is critical not only to understanding toxicity, but also to the development of statistical risk models based on biologic assumptions (e.g., independence of action, similar toxicologic action).

- Link exposure to biokinetic models so differences in toxicokinetics can aid in interpreting time, route, and cross species extrapolations. Include considerations of dosimetry and level of organization of the toxic response (e.g., cellular vs. population-based) in the risk assessment.

- Apply appropriately genetically altered (transgenic) animal models when the mechanism of action has been determined at the genetic level to determine the quantitative contribution of that mechanism to the chemical's overall toxicity.

- Develop appropriate laboratory test systems as a screen for the myriad of DBPs that have been identified in finished drinking water. Investigations into short-term screening tests for DBP mixtures, such as *in vivo* systems (e.g., developmental effects/cancer in medaka; mutagenicity in the frog embryo (FETAX) assay) or *in vitro* procedures (e.g., carcinogenicity in Syrian hamster embryo (SHE) cell transformation assay; developmental effects in whole embryo culture systems) are needed to identify the potential toxicity of DBP mixtures. The most toxic mixtures can then be tested in appropriate rodent test systems for reproductive, developmental, hepatotoxic, nephrotoxic, carcinogenic or immunotoxic effects.

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APPENDIX R1-A

Summary: ILSI Workshop on Unidentified DBPs

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Summary: ILSI Workshop on Unidentified DBPs

In February, 1998, the International Life Sciences Institute (ILSI) held a workshop entitled *Identification of new and uncharacterized disinfection by-products in drinking water*, with the goal of developing an analytical strategy for the identification, quantification, and prioritization of the full range of potential disinfection by-products in drinking water. The emphasis was on predicting, identifying, and quantifying potential DBPs not currently recovered from drinking water. Experts from different disciplines were brought together at this workshop to achieve this goal. The final report resulting from this workshop was published in 1999 and summarized the goals, presentations and key conclusions and recommendations for identifying new drinking water DBPs. Issues addressed included predictive chemistry, isolation and concentration techniques, analytic methods and development of analytical strategies.

The predictive chemistry session (Session 2) focused on predicting the types of DBPs that may be formed as a result of the disinfectant used for treatment. An overview of what is currently known about DBPs was presented, followed by predictions of reactions and the chemistry involved to form potential organic and inorganic DBPs. Disinfectants addressed included chlorine, chlorine dioxide, chloramine, ozone, and their combinations. An overview of what is known about natural organic matter (NOM) was presented to increase understanding of the precursor material that forms many DBPs. Also discussed were the by-products formed when these disinfectants are used

in the pulp and paper industry, followed by a toxicological viewpoint to indicate the types of chemicals that might be of concern with respect to absorption in the body. Compounds proposed to potentially be formed (but have not yet been identified) include bromo-amines and bromochloro-amines, peroxy-nitrites, nitric oxide and other inorganic nitrogen species, compounds resulting from reactions of chemicals with inorganics (including carbonates as percursor materials), chloroketamines and N-chloroketamines, chloroaldamines and N-chloroaldamines, nitroso-amines, compounds resulting from the reaction of carbohydrates with disinfectants, polar/non-extractable compounds (including polyalcohols, polycarboxylic acids, polyamines, and reactions of disinfectants with poly ethoxylate surfactants), sulfur-containing compounds (including sulfoxides and sulfones resulting from the reactions of disinfectants with sulfur-containing amino acids), iodate, imines, nitriles, organic peroxides, and higher molecular weight compounds (>500 amu). It was suggested that it may be useful to obtain basic information on these, such as molecular weights, functional groups, marker atoms, etc., even though complete structural identification is probably not feasible. The general consensus of this session was that toxicology should drive the analytical chemistry, e.g., fractionation followed by toxicity screens could be used to focus identification efforts on those fractions of treated drinking water that have an indication of toxicity. A need was also expressed to further characterize reactions of disinfectants with NOM to better predict potential DBPs.

Sessions 3 and 4 from the ILSI workshop assessed isolation and concentration techniques and analytical methods, respectively. Session 3 focused on sample preparation techniques to enhance recovery and eventual identification of unknown

DBPs. Methods were presented whereby conventional liquid-liquid extraction, solid phase extraction, and purging/headspace techniques could be combined with derivatization reactions to make both the non-polar and highly polar compounds more amenable to chromatographic analysis. Tandem mass spectrometry (MS/MS) was also suggested for identifying non-volatile DBPs. Session 4 centered on techniques that have been used mostly for analyses other than drinking water, but have the potential for identifying unknown DBPs in drinking water. Techniques presented that are not commonly used by the drinking water community include ^{13}C NMR (nuclear magnetic resonance), tetramethyl ammonium hydroxide thermochemolysis, high volume injection gas chromatography/ mass spectrometry (GC/MS), vibrational spectroscopy, membrane introduction MS (MIMS), online membrane extraction, preconcentration capillary electrophoresis/MS, capillary liquid chromatography (LC)/MS, LC/MS/MS, LC/diode array detection, and LC with amperometric detection.

Session 5 discussed the development of analytical strategies, which included the need for a shared database containing DBP mass spectra and other pertinent information for use in identifying the unknown DBPs. Other needs included methods utilizing more advanced instrumentation (mentioned above); further characterization of unidentified polar, non-volatile total organic halide (TOX) and NOM; new biological and toxicological screening tools to help guide research; re-evaluation and expansion of predictive surrogates for DBP formation; and clarification of the range of molecular sizes and concentrations of DBPs to focus research on the unidentified DBP fraction.

January 2000

Report 2:

April 26-28, 1999 Workshop Report on

Novel Methods for Risk Assessment of Mixtures of Disinfection By-Products (DBP) for Drinking Water Treatment Systems

National Center for Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, Ohio

FOREWORD

This report contains information concerning research sponsored by the U.S. Environmental Protection Agency's (EPA) National Center for Environmental Assessment - Cincinnati Office (NCEA-Cin) on the risk assessment of mixtures of disinfection by-products (DBP) across various drinking water treatment trains. Under 42 USC § 300 of the Safe Drinking Water Act Amendments of 1996, it is stated that the Agency will “develop new approaches to the study of complex mixtures, such as mixtures found in drinking water...” This report reflects the current results relative to research in this area over the past five years by presenting an illustrative risk characterization, the results of an expert scientific workshop, and recommendations on the most scientifically credible way for the Agency to proceed, including future research needs.

In the course of estimating DBP mixtures risk for applications of the Agency’s Comparative Risk Framework Methodology and Case Study (U.S. EPA, 1998), NCEA-Cin has been exploring a number of novel approaches for estimating cancer, developmental and reproductive risks to human health from drinking water exposures. These include such risk characterization methods as response addition, proportional-response addition, quantitative structure activity relationships, development of distributions for input parameters, and Monte Carlo simulation techniques. The goal of these efforts is to estimate human health risks that result from exposures to a range of DBP that are produced through chemical disinfection of drinking waters for comparison with risks from exposure to pathogenic microbes. This document details the current methods in use, discusses the state of the toxicity and exposure data, presents available methods for mixtures risk characterization that may be applicable, explores alternative methodologies, and make recommendations for future applications and future methodological developments. Discussions include the assumptions, statistical techniques, and toxicologic bases for the risk methods.

To facilitate the production of this document, work was done under two contractual agreements. The illustrative example of a risk characterization was developed by Dr. Joshua Cohen (then with Gradient Corporation), under contract #68-C6-0024 with TN & Associates, Inc. The workshop was put together and conducted under contract #68-C7-0011 with SAIC, Inc., who also invited several of the expert scientists who participated. The proceedings of the workshop were then subcontracted to Syracuse Research Corporation and the report prepared by Dr. Patricia McGinnis and Heather Printup.

EPA RESEARCHERS

This research on the risk assessment of disinfection by-products was sponsored by NCEA-Cin's Comparative Risk Project Team and the Cumulative Risk Team. The NCEA-Cin scientists who conducted portions of this research, presented at the workshop, and are authors of this report include (listed alphabetically):

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This research was presented and reviewed by a group of workshop participants in April 1999, with a workshop report generated in November 1999. That report has been incorporated into this document. The distinguished workshop participants included:

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CHARGE TO THE WORKSHOP PARTICIPANTS

Workshop on the Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems
US EPA, Cincinnati, Ohio
April 26-28, 1999

Purpose

The U.S. EPA's National Center for Environmental Assessment - Cincinnati Office (NCEA-Cin) is holding a workshop to examine the current methodology being used for the risk assessment of mixtures of drinking water disinfection by-products (DBPs) and to further its development. The goal of the workshop is to bring together a multi-disciplinary group of scientists who will work together to create the range of possible approaches to solving this problem and then reach consensus on the most practical and scientifically sound directions the EPA should take to improve the risk assessment. It is anticipated that a workshop report will be produced that will detail the current methods in use, discuss the state of the exposure, toxicity and epidemiologic data, present available methods for mixtures risk characterization that may be applicable, explore alternative methodologies, and make recommendations for future applications and future methodology or data development. Discussions should include the assumptions, statistical theory, and biological rationale for the recommended risk characterization methods. This workshop report will be used as the basis for an EPA report, as background for research planning, and as information for improving the current DBP mixtures risk assessments.

Specific Questions for the Workshop Participants

- Which aspects of the current approach to estimation of DBP risks are correct and appropriate and which ones need to be revisited? Specifically address the topics of concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, use of Monte Carlo procedures, handling of uncertainty and variability, and the appropriateness of assumptions and endpoints used for mixtures risk estimation.

- How can we incorporate epidemiologic data into the risk assessment and still maintain the ability to compare risks across drinking water treatment options?

- How can we incorporate expert judgment into the risk estimates?

- How do we handle the toxicity of unidentified DBPs or of identified DBPs for which little or no data exist? Is it appropriate to use data on a similar chemical as surrogate data for another chemical?

- For developmental, reproductive and non-genotoxic carcinogenicity, how can we handle the concept of thresholds? Is it reasonable to suggest that a mixtures

toxicity threshold exists that is possibly well below the thresholds for the individual chemicals?

- Is it appropriate to combine dose-response data from individual chemicals and use them in a mixtures risk assessment when their specific endpoints differ (e.g., both visceral malformations and crown rump length shortening to estimate developmental risks; or both liver and kidney tumors for cancer risk)?

- Human cancer risks, largely based on animal data, are interpreted by the Agency as "the lifetime excess cancer risk per the exposure." How should analogous developmental and reproductive risks be interpreted for the mixtures risk estimate?

- Are there newer data and methods that EPA should be considering in order to improve these risk assessments? Specifically address advancements in dose-response modeling, analytical chemistry, exposure characterization, mixtures risk assessment methods, probabilistic techniques, quantitative structure activity relationships, and methods for estimating risk for the unidentified DBPs.

Background

Human health risk from exposure to disinfection by-products (DBPs) in drinking water is of concern because of the widespread daily exposure to this complex mixture. Although it is clear that water disinfection is effective in preventing waterborne microbial illnesses, it was recognized as early as 1974 that there are potential health risks from exposure to chemical by-products of disinfection processes. DBPs are produced when disinfectants such as chlorine, ozone, chloramine or chlorine dioxide react with naturally occurring organic matter in the water. The most common DBPs on which concentration data are available include the trihalomethanes (THM), haloacetic acids (HAA), haloacetonitriles, haloketones, aldehydes, bromate, chloral hydrate, and chloropicrin, among others (Jacangelo et al., 1989; Krasner et al., 1989; Lykins et al., 1994; Miltner et al., 1990). More recently, Richardson (1998) identified approximately 250 DBPs from various disinfection scenarios. Of the identified DBPs, less than 20 have been subjected to toxicity studies of sufficient quality for use in risk assessment.

Data from both epidemiologic and toxicologic studies indicate that human health effects from DBP exposure are of concern, but neither discipline has been able to confirm this with confidence. DBPs typically occur at low levels in drinking water at which general toxic effects from exposure to the environmental mixture have not been found in animal studies (Bull et al., 1982; Kavlock et al., 1979). In contrast, epidemiologic studies of chlorinated drinking water exposures in humans suggest weak associations with bladder, rectal and colon cancer (Cantor et al., 1985; McGeehin et al., 1993; King and Marrett, 1996; Cantor et al., 1997; Freedman et al., 1997) and limited evidence of reproductive and developmental effects (Bove et al., 1995; Kramer et al., 1992; Swan et al., 1998; Waller et al., 1998). Although there are few studies available on defined mixtures of DBPs, evidence exists of dose-additivity for liver effects in mice exposed to mixtures of trihalomethanes (THM) (Gennings et al., 1997) and of

synergistic activity by mixtures of dichloroacetic acid (DCA) and trichloroacetic acid (TCA) for promotion of cancer (Pereira et al., 1997). The majority of the available DBP toxicity data consists of single chemical *in vivo* or *in vitro* studies. There is evidence in single chemical animal studies at high DBP dose levels of carcinogenicity, reproductive effects, developmental effects, and other toxic effects, particularly in the kidney and liver (Bull and Kopfler, 1991; NTP, 1985, 1986, 1989; Smith et al., 1989a). Finally, there is evidence of mutagenicity from exposure to extracts of finished drinking water in *in vitro* studies (Kool et al., 1981; Loper et al., 1978; Nestmann et al., 1982).

The U.S. EPA has pursued the estimation of risk of adverse effects from exposure to chemical mixtures since the early 1980s and has published the *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986) and its subsequent *Technical Support Document on Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1990). The health risk assessment issue for DBPs is appropriately defined as a mixtures problem because the human exposure in finished drinking water is to a mixture of DBPs, not to single chemicals. Many factors are involved in determining the mixture of substances that may be found in finished drinking water (e.g., type and characteristics of source water; type of disinfection used: chlorine, chloramine, chlorine dioxide, ozone; additional treatments such as enhanced coagulation, granular activated carbon, reverse osmosis; ranges of pH levels, etc.). To further complicate the exposure scenario, the composition of DBPs and pathogens constantly changes within the distribution system as well as through the heating of water for personal use (e.g., boiling, showering), so that the human exposure varies with time, activity pattern and location.

The NCEA-Cin's risk assessment goal is to make reasonable central tendency estimates of human health risks that reflect changes in the DBPs that are produced and in their concentrations and that are comparable across different drinking water treatment types and source water characteristics. A distributional approach to expressing the uncertainty or variability around these best estimates is also needed. An examination of the epidemiologic literature suggests that cancer, reproductive and developmental endpoints are the human health effects of concern in the drinking water; thus these effects must be included in the risk estimate with their uncertainty appropriately described. Several factors contribute to the uncertainty of estimating risks associated with DBPs: stochastic uncertainty in bioassay data; extrapolation of animal-derived toxicity values to humans; variation in the presence and concentrations of DBPs in the drinking water, seasonal variations in source water conditions, the presence of sometimes large amounts of unidentified halo-organic materials, variations in drinking water intake, and the assumptions that are made as the basis for estimating the mixtures risk.

Currently, the NCEA-Cin method assumes a response addition model as a component-based method for joining dose-response and exposure data to estimate both cancer and noncancer risks from exposure to the complex mixture of DBPs. Response addition carries with it an assumption that the components of the mixture are considered to be functionally independent of one another at low exposure levels; a similar mode of action or similar effects across chemicals are not required. Response

addition has often been assumed to estimate cancer risks for a mixture because of the assumed absence of component thresholds. Alternatively, for both cancer and noncancer endpoints, it is possible that a mixtures threshold exists that would potentially be lower than any of the individual components' thresholds, such that estimation of mixtures risk at these individual subthreshold dose levels is reasonable.

Dose-addition is generally preferred for noncancer endpoints; an assumption is required of similar mode of action across all chemical components of the mixture. Dose-addition would be another reasonable choice for the noncancer endpoints as it also addresses the issue of a mixtures toxicity threshold. A Toxicity Equivalence Factor approach, such as was used for dioxin (US EPA, 1989a), is a possibility for DBP risk estimation for those chemicals with a similar mechanism of action. NCEA-Cin has also been investigating the use of a proportional-response addition model for developmental and reproductive endpoints. Proportional-response addition is a hybrid of dose addition and response addition, where risk is estimated for individual components at the total mixture dose and then scaled back by the proportion of the component in the mixture; this approach requires similar effects across chemicals. Other approaches for cancer and noncancer could certainly be taken, each associated with its own set of assumptions and limitations. For example, it is feasible to use human cancer, reproductive or developmental data from the epidemiologic literature to develop risk estimates. However, these data do not distinguish the risks across various treatment technologies and are, therefore, not currently being used for estimating health risks across specific treatment trains and source waters. Expert judgment scenarios have been suggested in the literature for assessing the uncertainty of carcinogenic potency (Evans et al., 1994a, 1994b) and for combining both epidemiologic and toxicologic data in the risk assessment (Sielken, 1995). These expert judgment methods should be considered as ways to improve the DBP risk assessment. A final approach is to develop toxicity data directly on drinking water mixtures or similar mixtures that represent specific treatment trains and source water; to date, these data are not available for mixtures risk assessment.

AGENDA

Workshop on the Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems

April 26, 1999 - Room 130

8:30-8:45 Welcome
Terry Harvey

Introductions and Purpose of Workshop, Logistics, Charge to Participants, Discussion and Clarification of Charge
Facilitator (Gunther Craun/Glenn Rice)

8:45-9:15 Overview of Risk Assessment Objectives - Present Theory and Current Equation for Estimation of DBP Mixtures Risk Using Response Addition
Linda Teuschler

9:15-9:45 Overview of Exposure Considerations - Engineering concerns, Source Water Characteristics, Unidentified TOX, Tap water consumption Data
Glenn Rice

9:45-10:00 Break

10:00-10:30 Overview of Toxicology/Carcinogenicity Animal Data for Use in Quantitative Risk Estimation
John Lipscomb

10:30-11:00 Overview of Available Quantitative Epidemiologic Data - Cancer, Developmental, Reproductive Endpoints
Pat Murphy

11:00-11:30 Presentation of Monte Carlo Results of DBP Mixtures Risk Estimates
Josh Cohen

11:30-12:30 Open discussion of Current Data & Methodologies - first impressions, criticisms, first thoughts on ways to improve, identification of major issues
Facilitator (Gunther Craun/Glenn Rice)

12:30-1:30 Lunch

1:30-2:00 Dose-Response Data Modeling Improvements - Cancer
Dale Hattis

2:00-2:30 Dose-Response Data Modeling Improvements - Developmental Data
Bruce Allen

2:30-3:00 Dose-Response Data Modeling Improvements - Reproductive Data
Dale Hattis

3:00-3:15 Break

3:15-3:45 DBP Concentration Data Variability, ICR Data
Pat Fair

3:45-4:15 DBP Human Exposure Estimates, Multi-route
Cliff Weisel

4:15-4:45 Probabilistic Approaches to Developing Distributions of Risks
Bill Huber

4:45-5:30 Open discussion of Dose-Response, Exposure and Probabilistic Approaches - Identification of major issues
Facilitator (Gunther Craun/Glenn Rice)

April 27 - Room 130
(Extra Breakout Room 402)

8:30-9:00 Response Addition, Dose Addition, Proportional Response Addition Methods
Bill Stiteler

9:00-9:30 New mixtures methodologies: Relative Potency Factors, Toxic Equivalency Factors w/Response Addition
Rick Hertzberg

9:30-10:00 Incorporating Epidemiologic Data and Toxicologic Data into the Risk Estimate Using Expert Judgment
George Gray

10:00-10:15 Break

10:15-11:00 Open discussions of Mixtures Methods and Expert Judgment Approaches - Identification of major issues
Facilitator (Gunther Craun/Glenn Rice)

11:00-12:00 Identification of Primary Areas of Focus - Self Organization into Breakout Groups
Facilitator (Gunther Craun/Glenn Rice)

12:00-1:00 Lunch

1:00-2:15 Breakout Groups - brainstorming / discussion / consensus recommendations

2:15-2:30 Break (Change groups)

2:30-3:45 Breakout Groups - brainstorming / discussion / consensus recommendations

3:45-4:00 Break (Reconvene as large group)

4:00-5:00 Report out to larger group
Facilitator (Gunther Craun/Glenn Rice)

5:00-5:30 Identification of Major Areas of Focus - Self Organization into Breakout Groups
Facilitator (Gunther Craun/Glenn Rice)

5:30 Dinner Out as a Group

April 28 - Room 130
(Extra Breakout Room 402)

8:30-9:45 Breakout Groups - consensus discussions

9:45-10:00 Break (Reconvene as large group)

10:00-11:00 Report out to larger group
Facilitator (Gunther Craun/Glenn Rice)

11:00-12:00 Consensus Building of Best Directions and Group Recommendations for this methodology
Facilitator (Gunther Craun/Glenn Rice)

12:00-1:00 Lunch

1:00-3:00 Consensus Building of Best Directions and Group Recommendations for this methodology - Writing assignments
Facilitator (Gunther Craun/Glenn Rice)

3:00-3:15 Break

3:15-5:00 Writing initial drafts for final report

TABLE OF CONTENTS

Page

FOREWORD ii

EPA RESEARCHERS iii

WORKSHOP PARTICIPANTS iv

CHARGE TO THE WORKSHOP PARTICIPANTS v

AGENDA ix

LIST OF TABLES xvii

LIST OF FIGURES xxi

1. INTRODUCTION R2-1

2. CRFM: CURRENT DATA AND METHODS R2-6

2.1. PRESENTATION: OVERVIEW OF RISK ASSESSMENT OBJECTIVES: PRESENT THEORY AND CURRENT EQUATION FOR ESTIMATION OF DBP MIXTURES USING RESPONSE ADDITION (L.K. Teuschler) R2-6

2.2. PRESENTATION: OVERVIEW OF CHEMICAL EXPOSURE CONSIDERATIONS IN THE CASE STUDY OF THE U.S. EPA's COMPARATIVE RISK FRAMEWORK METHODOLOGY (CRFM): ENGINEERING CONCERNS, SOURCE WATER CHARACTERISTICS, UNIDENTIFIED TOX, TAP WATER CONSUMPTION (G. Rice) R2-18

2.2.1. Characteristics of the Source Water R2-19
2.2.2. Alternative Treatment Systems R2-20
2.2.3. Concentrations of DBP in Treated Waters: Distributions . R2-20
2.2.4. Contact R2-23

2.3. PRESENTATION: OVERVIEW OF TOXICOLOGY/ CARCINOGENICITY ANIMAL DATA FOR USE IN QUANTITATIVE RISK ESTIMATION (J. Lipscomb) R2-27

2.3.1. Developmental and Reproductive Effects R2-28
2.3.2. Cancer R2-30

TABLE OF CONTENTS (cont.)

Page

2.4. PRESENTATION: OVERVIEW OF AVAILABLE QUANTITATIVE EPIDEMIOLOGIC DATA: CANCER, DEVELOPMENTAL, REPRODUCTIVE ENDPOINTS (P. Murphy) R2-36

2.5. PRESENTATION: MONTE CARLO RESULTS OF DBP MIXTURES RISK ESTIMATES (J. Cohen) R2-40

2.6. PARTICIPANT DISCUSSION: CURRENT DATA AND METHODOLOGIES R2-57

3. NOVEL METHODS FOR MIXTURES R2-62

3.1. PRESENTATION: DOSE-RESPONSE MODELING IMPROVEMENTS: CANCER (D. Hattis) R2-62

3.2. PRESENTATION: MODELING IMPROVEMENTS - DEVELOPMENTAL DATA (B. Allen) R2-66

3.3. PRESENTATION: DOSE-RESPONSE MODELING IMPROVEMENTS: REPRODUCTIVE TOXICITY (D. Hattis) R2-76

3.4. PRESENTATION: DBP HUMAN EXPOSURE ESTIMATES: MULTI-ROUTE (C. Weisel) R2-85

3.5. PRESENTATION: DBP CONCENTRATION DATA VARIABILITY, ICR DATA (P. Fair) R2-108

3.6. PRESENTATION: HUMAN EXPOSURE ESTIMATES: WATER CONSUMPTION (R. Schoeny) R2-111

3.7. PRESENTATION: PROBABILISTIC APPROACHES TO DEVELOPING DISTRIBUTIONS OF RISKS (W. Huber) R2-115

3.7.1. Variability and Uncertainty R2-115
3.7.2. Maximum Likelihood Estimation R2-118
3.7.3. Mixtures of Distributions R2-120
3.7.4. Summary R2-127

3.8. PRESENTATION: PROPORTIONAL RESPONSE ADDITION (W. Stiteler) R2-127

TABLE OF CONTENTS (cont.)

Page

3.8.1. Introduction R2-127
3.8.2. Methods R2-130
3.8.3. Results R2-146
3.8.4. Future Directions R2-150

3.9. PRESENTATION: NEW MIXTURES METHODOLOGIES: RELATIVE POTENCY FACTORS, TOXIC EQUIVALENCY FACTORS WITH RESPONSE ADDITION (R. Hertzberg) R2-151

3.9.1. Relative Potency Factors R2-151
3.9.2. Interaction-based Hazard Index R2-156
3.9.3. More Complex Mixtures R2-161

3.10. PRESENTATION: EXPERT JUDGMENT FOR ASSESSING RISK: TOXICOLOGY AND EPIDEMIOLOGY (G. Gray) R2-162

3.10.1. Overview of Expert Judgment in Risk Assessment R2-162
3.10.2. Expert Judgment in Epidemiologic Questions R2-164
3.10.3. Expert Judgment in Toxicologic Questions R2-165
3.10.4. Summary R2-173

3.11. PARTICIPANT DISCUSSION: IDENTIFICATION OF MAJOR ISSUES R2-176

4. GROUP DISCUSSION R2-180

4.1. EXPOSURE GROUP R2-182

4.1.1. Use of Full Exposure Models R2-182
4.1.2. Exposure Variability Extrapolations R2-186
4.1.3. Sampling Location Impact on DBP Concentrations R2-187
4.1.4. Data Considerations for Exposure Routes R2-189
4.1.5. Bounding of Exposure Values R2-190
4.1.6. Recommendations R2-190

4.2. UNIDENTIFIED DBP GROUP R2-191

4.2.1. DBP “Layers” R2-191
4.2.2. The MX Concern R2-199
4.2.3. Documenting Statistical Models for Risk Assessment . . . R2-200

TABLE OF CONTENTS (cont.)

Page

4.3. CANCER RISK R2-202

4.3.1. What Approaches Can Incorporate the Various Data on Health Effects and Still Allow for Comparing Risks Across Treatment Options? R2-203
4.3.2. What Questions Regarding Cancer Could be Addressed by Expert Judgment? R2-205
4.3.3. How Can the Use of Dose-Response Information for Cancer Risk be Improved? How Should We Address the Idea of Low Dose Non-Linearity for Cancer? R2-207
4.3.4. How Should Data be Used for Different Sites or Effects in a Mixture Risk Assessment? R2-211

4.4. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY GROUP R2-214

4.4.1. Improving the use of Animal Developmental and Reproductive Toxicity Data R2-214
4.4.2. Predicting Human Risk from Animal Developmental and Reproductive Data R2-218

4.5. MIXTURES RISK CHARACTERIZATION R2-222

4.5.1. Identification of Approaches that Incorporate Data on DBP Health Effects into the Risk Assessment R2-222
4.5.2. Improving the Current Approach to Estimate the Risks Posed by DBP Exposures R2-222
4.5.3. Handling the Toxicity of DBP, or of Identified DBP, for which Little or No Data Exist R2-224
4.5.4. Handling the Concept of Threshold and the Unidentified DBP R2-225
4.5.5. Interpretation of Human Developmental and Reproductive Risks Based on Animal Data R2-227
4.5.6. Summary R2-228

4.6. UNCERTAINTY AND VARIABILITY GROUP R2-228

4.6.1. Approaches for Evaluation of Uncertainty and Variability R2-228
4.6.2. Characterization of Uncertainty Influencing Estimates of the Cancer Slope Factor R2-230

TABLE OF CONTENTS (cont.)

Page

4.6.3. Characterization of Uncertainty Influencing Estimates of the Noncancer Dose-Response R2-235
4.6.4. Uncertainty Associated with Exposure and Concentration Data R2-237
4.6.5. Uncertainty Associated with Unknown DBP Fractions . . . R2-239

4.7. TOXICOLOGY/EPIDEMIOLOGY AND EXPERT JUDGMENT . . R2-241

4.7.1. Issues for Blue Ribbon Panel Discussion R2-243

4.8. CONCLUSIONS, FUTURE RESEARCH AND RECOMMENDATIONS OF THE BREAKOUT GROUPS R2-253

4.8.1. Exposure R2-253
4.8.2. Unidentified DBP R2-255
4.8.3. Cancer R2-256
4.8.4. Reproductive and Developmental R2-259
4.8.5. Mixtures Risk Characterization R2-262
4.8.6. Variability and Uncertainty R2-264
4.8.7. Toxicology, Epidemiology and Expert Judgment R2-268

5. REFERENCES R2-271

LIST OF TABLES

No.		Page
2-1	Total Organic Halides (TOX, µg Cl/L) in Simulated Distribution (Stored) Pilot Plant Waters	R2-15
2-2	TOPKAT® QSAR Predictions by Endpoint for Known DBP Not in the Miltner et al. (1990) Sample, Filter-Cl_2 Treatment Train; Number Associated with Toxicity	R2-16
2-3	TOPKAT® QSAR Predictions by Endpoint for Known DBP Not in the Miltner et al. (1990) Sample, O_3-Filter-Cl_2 Treatment Train; Number Associated with Toxicity	R2-17
2-4	DBP Measured Concentrations and Fractional Halogen Contribution in Water Treated Using the Baseline Treatment Technology	R2-21
2-5	DBP Measured Concentrations in Water Subjected to the Ozone Pretreatment Technology	R2-22
2-6	Tap Water Consumption in the General Population (ml/kg-day) by 5-Year Age Groups	R2-26
2-7	Disinfection Byproducts Considered in CRFM Case Study	R2-29
2-8	Incremental Developmental Toxicity Risk for Identified DBP	R2-31
2-9	Dose-Response Modeling for Developmental Toxicity	R2-32
2-10	Incremental Reproductive Toxicity Risk for Identified DBP	R2-33
2-11	Dose-Response Modeling for Reproductive Toxicity	R2-34
2-12	Incremental Cancer Risk for Identified DBP	R2-35
2-13	Reproductive and Developmental Endpoints Studies in Human Epidemiologic Studies of DBP	R2-38
2-14	Plausible Range of Population Average Risk Values	R2-45
2-15	Proportion of Parametric Uncertainty in Cancer Risk Explained	R2-49
2-16	Proportion of Parametric Uncertainty in Developmental Toxicity Risk Explained	R2-50

LIST OF TABLES (cont.)

No.		Page
2-17	Proportion of Parametric Uncertainty in Reproductive Toxicity Risk Explained	R2-51
2-18	Impact of Alternative Assumptions for a_h on Estimated Risk (Expected Value of the Population Mean Risk)	R2-53
2-19	Impact of Alternative Assumptions for the Relative Toxicity of Unidentified DBP *vs.* Known DBP on Estimated Risk (Expected Value of the Population Mean Risk)	R2-55
2-20	Calculation of Total TOX Cancer Slope Factor Using Morris et al. (1992) Meta Analysis Results	R2-58
3-1	Indicated Variability for Non-Redundant Data Sets By Activity Category	R2-63
3-2	Uncertainties in Carcinogenic Risk Estimates For Genetically-Acting Agents, as Inferred from Three Case Studies of PBPK-Based Risk Analyses	R2-64
3-3	A Scale For Understanding Lognormal Variability Fold Differences Between Particular Percentiles of Lognormal Distributions	R2-67
3-4	Example of a Combined Presentation of Variability and Uncertainty Variability and Uncertainty for a Conventionally Assessed 10^{-6}/Lifetime 95% Upper-Confidence-Limit Individual Cancer Risk--260 Million People Exposed - Uncertainty Dimension (Z)-	R2-68
3-5	Calculated Toxic Equivalency Factors (TCA Dose Equivalents) for the Potency of Various DBP for Reducing Fetal Weights in Animals	R2-89
3-6	Chloroform Breath Concentrations by Exposure Route	R2-96
3-7	Chloroform Dose for Shower Study	R2-97
3-8	Summary of Population Dose - mg	R2-100
3-9	Comparison of Air THM Concentration ($\mu g/m^3$) for Low and High Water Groups	R2-103

LIST OF TABLES (cont.)

No.		Page
3-10	Mean (Median) THM Breath Concentrations (μg/m^3) After a Shower	R2-104
3-11	Pearson/Spearman Correlation Coefficients (r^2): THM Water Concentration or THM Exposure with Exhaled Breath	R2-105
3-12	Community Water Ingestion (L/person/day) (Consumers and Non-Consumers)	R2-114
3-13	Advantages and Disadvantages of Maximum Likelihood Estimation (MLE)	R2-121
3-14	Availability of Developmental and Reproductive Dose-Response Data for Haloacetic Acids and Haloacetonitriles Found in Drinking Water	R2-138
3-15	Developmental and Reproductive Toxicity Data Sets for Haloacetic Acids and Haloacetonitriles	R2-140
3-16	Example Data Sets: DCA (Smith et al., 1992, Teratology 46: 217-223)	R2-144
3-17	Example Risk Estimate for Developmental Toxicity in Humans Exposed to Haloacetic Acids and Haloacetonitriles in Drinking Water at Concentrations Determined in Pilot Study, Jefferson Parish (Mississippi River) Following Chlorine Treatment	R2-148
3-18	Example Risk Estimate for Developmental Toxicity in Humans Exposed to Haloacetic Acids and Haloacetonitriles in Drinking Water at Concentrations Determined in Pilot Study, Ohio River, Following Chlorine Treatment and Simulated Distribution	R2-149
3-19	Differences Between TEF and RPF for Chemical Classes	R2-152
3-20	Weight-of-Evidence Classification for Mixture Interactions	R2-154
3-21	Weight-of-Evidence Scores for Mixture Interactions	R2-155
3-22	Distributional Approach to Expert Judgment	R2-175

LIST OF TABLES (cont.)

No.		Page
4-1	Workshop Breakout Discussion Group and Participants	R2-181
4-2	Objectives for a “Blue Ribbon Panel”	R2-244

LIST OF FIGURES

No.		Page
2-1	Comparative Risk Assessment Framework Overview	R2-7
2-2	Comparative Risk Framework Methodology Case Study	R2-8
2-3	Human Exposure Pathways.	R2-24
2-4	Two Stage Monte Carlo used in CRFM Case Study	R2-41
2-5	Quantification of Uncertainty and Variability using Two-Stage Monte Carlo Analysis.	R2-43
2-6	Lifetime Cancer Risk: Filter-Cl_2 Treatment	R2-46
2-7	Lifetime Cancer Risk: O_3-Filter-Cl_2 Treatment	R2-46
2-8	Reduction in Lifetime Cancer Risk Achieved by Adding Ozone Pretreatment	R2-46
2-9	Lifetime Developmental Toxicity Risk: Filter-Cl_2 Treatment	R2-47
2-10	Lifetime Developmental Toxicity Risk: O_3-Filter-Cl_2 Treatment	R2-47
2-11	Reduction in Lifetime Developmental Toxicity Risk Achieved by Adding Ozone Pretreatment	R2-47
2-12	Lifetime Reproductive Toxicity Risk: Filter-Cl_2 Treatment	R2-48
2-13	Lifetime Reproductive Toxicity Risk: O_3-Filter-Cl_2 Treatment	R2-48
2-14	Reduction in Lifetime Reproductive Toxicity Risk Achieved by Adding Ozone Pretreatment	R2-48
3-1	Estimated Likelihood Distribution for Cancer Potencies for Genetically-Acting Carcinogens – Log Plot	R2-65
3-2	Estimated Probability Distribution for Cancer Potencies for Genetically-Acting Carcinogens – Linear Plot	R2-65
3-3	Beta Distributions	R2-70
3-4	Multinomial Models	R2-74

LIST OF FIGURES (cont.)

No.		Page
3-5	BBDR of 5-Fluorouracil: Shuey et al., 1994	R2-75
3-6	BBDR Modeling: Leroux et al., 1996	R2-77
3-7	Log Log Plot of the Relationship Between Total Motile Sperm Count and Pregnancy “Hits” Per Menstrual Cycle (Data of Brasch et al., 1994)	R2-79
3-8	Relationship Between Weight at Birth and Infant Mortality	R2-80
3-9	Expected Effect of a 1% Reduction in Birth Weights on the Distribution of Overall Infant Deaths Per 1000 Babies Born in the Total Population	R2-82
3-10	Effect of Cigarette Smoking on Birthweight; 1990 Data for All Races, All Gestational Ages	R2-83
3-11	Effect of Maternal Residence on Mean Birth Weight	R2-84
3-12	Data of Smith et al. (1988) on the Fetal Weight Response to Trichloroacetonitrile	R2-86
3-13	Data of Christ et al. (1995) on the Fetal Weight Response to Bromochloroacetonitrile	R2-87
3-14	Data of Smith et al. (1989) on the Fetal Weight Response to Trichloroacetic Acid	R2-88
3-15	Results of Regression Analysis of the Fraction of Control Fetal Weight Response in Grouped Categories of TCA Equivalents	R2-90
3-16	Exposure Framework	R2-91
3-17	Biomarker Continuum	R2-92
3-18	Shower Air Concentrations vs. Water Concentration	R2-95
3-19	Chloroform Breath Concentrations After Showering	R2-95
3-20	Breath Concentration vs. Water Concentration	R2-95

LIST OF FIGURES (cont.)

No.		Page
3-21	Breath Concentration Normalized to Water Concentration with Water Temperature and Duration	R2-95
3-22	TCAA Ingestion Exposure vs. Urinary Excretion	R2-106
3-23	TCAA Urinary Excretion Exposure and Water Concentration	R2-107
3-24	Example: NIRS Radon Data	R2-122
3-25	Burmaster and Wilson's Fit	R2-123
3-26	Burmaster and Wilson's fit as PDFs	R2-124
3-27	Roeder's MDP for k=1 Supports Burmaster and Wilson	R2-126
3-28	$A \cup B$	R2-131
3-29	Complete Negative Correlation	R2-131
3-30	Complete Positive Correlation	R2-131
3-31	Proportional Response Addition (Total Dose Held Fixed)	R2-133
3-32	Linear Model Evaluated at d_1 and at $d_1 + d_2$	R2-134
3-33	Proportional Response Addition for a Binary Mixture	R2-136
3-34	Hypothetical Dose-Response Curves for Different Mixtures of Two Noncompetitive Agonists with Equal Intrinsic Activities but Differing Affinities for the Receptor	R2-157
3-35	Probability of Relative Risk for Cancer Predicted by Epidemiologists A, B, C from a Lifetime of Residential Exposure to Chlorinated Drinking Water	R2-166
3-36	The Chloroform Probability Tree	R2-168
3-37	Constructing Risk Distributions for Chloroform Project. Example of Path by One Expert	R2-170
3-38	Results for Individual Experts for 100 ppb Chloroform in Drinking Water Tumor Induction at Any Site	R2-171

LIST OF FIGURES (cont.)

No.		Page
3-39	Lifetime Cancer Risk from Drinking Water with 100 ppb of Chloroform	R2-172
3-40	Combined Results from Experts Considered Self-Weighting	R2-174
4-1	"Layer" Analogy for Chemicals in Water (Exact Proportions of Layers is Not Known)	R2-193
4-2	Possible Approach for Comparing Toxicity of Known and Unknown Components	R2-198
4-3	Margin of Exposure Approach for Carcinogens.	R2-209
4-4	Application of Proportional Response Addition to Cancer ED_{10} (POD)	R2-213

1. INTRODUCTION

Humans experience a widespread daily exposure to a complex mixture of disinfection by-products (DBP) in finished drinking water. Although waterborne microbial illnesses are clearly prevented by disinfection processes, an unfortunate side-effect is exposure to potentially harmful DBP, produced by the reaction of disinfectants with naturally occurring organic matter in the water. Concentration data are available on relatively few DBP, including trihalomethanes (THM), haloacetic acids (HAA), haloacetonitriles (HAN), haloketones, aldehydes, bromate, chloral hydrate, and chloropicrin, among others (Jacangelo et al., 1989; Krasner et al., 1989; Lykins et al., 1994; Miltner et al., 1990). However, Richardson (1998) has identified several hundred potential DBP resulting from different types of disinfectants.

Toxicologic and epidemiologic data each provide some evidence that human health effects may result from DBP exposure. Weak associations have been suggested by epidemiologic studies of chlorinated drinking water exposures in humans, primarily for bladder, rectal, and colon cancer (Cantor et al., 1985, 1997; Freedman et al., 1997; King and Marrett, 1996; McGeehin et al., 1993). Recent publications have also suggested possible reproductive and developmental effects (Bove et al., 1995; Kramer et al., 1992; Swan et al., 1998; Waller et al., 1998). Studies that have exposed animals to finished drinking water do not support the epidemiologic findings. That is, general toxic effects have not been observed at low, environmental concentrations (Bull et al., 1982; Kavlock et al., 1979). In contrast, toxicologic evidence of carcinogenicity, reproductive effects, developmental effects, and other toxic effects are seen in high-dose, single chemical studies (Bull and Kopfler, 1991; NTP, 1985, 1986, 1989; Smith et

al., 1989). There is also evidence of mutagenicity from exposure to extracts of finished drinking water in *in vitro* studies (Kool et al., 1981; Loper et al., 1978; Nestmann et al., 1982). Although there are few studies available on defined mixtures of DBP, evidence exists of dose-additivity for liver effects in mice exposed to mixtures of THM (Gennings et al., 1997) and of promotion of cancer by mixtures of dichloroacetic acid (DCA) and trichloroacetic acid (TCA) (Pereira et al., 1997).

Risk assessment questions surround the issues of establishing, explaining, and estimating any substantive human health risks from exposure to the low levels of DBP found in drinking water. Because toxic effects are not observed in animal studies when the exposures are to low doses and because the epidemiologic data are inconsistent across studies with only relatively weak associations noted, the existence of human health risks is questionable, but cannot be entirely dismissed. If it is assumed, however, that the human health effects suggested in epidemiologic studies are real, then several hypotheses can be posed to explain the discrepancies between the epidemiologic results and the lack of effects in animals exposed to finished drinking water. Such hypotheses include: (1) there is an effect from exposure to the mixture of DBP that is at least additive (if not synergistic) in nature, so that studies involving low levels of individual DBP are inadequate to explain the health effects found in the positive epidemiologic data; (2) effects in humans are due to the chronic, repetitive insult from daily exposure to DBP mixtures; (3) animal studies differ from human exposures in ways such as differences in physiology, biochemistry, anatomy, and life style factors (e.g., high fat diets) that prevent them from demonstrating the same outcomes; (4) laboratory studies to date expose the animals to only a single route, usually oral, so that

effects due to dermal or inhalation exposure are not observed; (5) effects in epidemiologic studies are due to exposure to other environmental factors such as metals and inorganic materials in the drinking water or concurrent exposures to industrial pollutants in urban areas or pesticides in agricultural areas so that animal studies solely focused on DBP will not corroborate epidemiologic findings.

Testing of these hypotheses is a useful approach for investigating the potential risks from exposure to mixtures of DBP; studies can be designed to address these hypotheses. These hypotheses also have implications for the way risk assessments are performed for comparisons across drinking water treatment technologies. Such hypotheses suggest that traditional methods that characterize “safe levels” for single chemicals by individual routes are likely to underestimate risk from exposure to the complex mixture. The inadequacies of such methods are numerous. They fail to examine potential risk from exposure to multiple chemicals (DBP, as well as pesticides, metals, etc.). They neglect to account for interaction effects among chemicals or for decreased thresholds for effects that occur as a result of a total mixture dose, rather than an individual chemical dose. They do not account for risk due to simultaneous multiple route exposures (oral, dermal, and inhalation). They fail to provide a range of risk estimates that reflect multiple toxicity data sets, considerations of mechanism, or both animal and epidemiologic data. They do not consider the impact of the constant daily human exposure to finished drinking water, nor do they take into account human activity patterns that influence exposure. These particular concerns have caused risk assessors to focus on methods that are novel and are able to account for more variables than just a single chemical exposure that may be influencing risk.

The U.S. EPA has developed a Comparative Risk Framework Methodology (CRFM) and Case Study (U.S. EPA, 1998) that presents a method for evaluating the cost-effectiveness of drinking water treatment technologies relative to the health consequences incurred by their utilization. Human health endpoints of concern include gastrointestinal illness and death from exposure to pathogens, as well as cancer illness and death, and reproductive and developmental effects from exposure to DBP. The case study was developed to illustrate that the CRFM is feasible to implement. Within the case study, a mixtures risk assessment approach (i.e., response addition) was employed to estimate risk from exposure to the DBP for only the oral route of exposure. A Monte Carlo simulation provided for endpoint-specific distributions of risk estimates that included some sources of uncertainty and also incorporated the variability of human tap water consumption rates.

The motivation behind producing this document was to explore the potential world of available data and methodologies for improving the current approach in the CRFM and to identify data gaps and future research needs in this subject area. Chapter 2 of this report summarizes the CRFM approach. In this chapter, NCEA-Cin scientists and contractors presented an overview of the CRFM for the workshop participants and attendees. (The full pre-meeting report for the workshop is contained in Appendix I.) Chapter 3 summarizes the presentations by the multi-disciplinary group of scientists involved in the workshop. These scientists explored alternative methods for exposure, dose-response assessment and risk characterization and their potential application to DBP mixtures. Chapter 4 presents a synopsis of the two days of brain-storming and discussion by various “breakout” groups. These groups tackled the eight

questions posed in the *Charge to the Workshop Participants.* Herein recommendations for future applications and future methodological developments are made.

2. CRFM: CURRENT DATA AND METHODS

2.1. PRESENTATION: OVERVIEW OF RISK ASSESSMENT OBJECTIVES: PRESENT THEORY AND CURRENT EQUATION FOR ESTIMATION OF DBP MIXTURES USING RESPONSE ADDITION (L.K. Teuschler)

The EPA has developed a CRFM for the comparison of health risks resulting from exposure to disinfection by-products (DBP) and microbes in drinking water. Human exposure to DBP in drinking water can be characterized as multiple chemical, multiple route, low-level, and highly variable. Although human health effects resulting from these exposures are uncertain, epidemiologic and toxicologic data suggest a concern for several endpoints including cancer, and developmental and reproductive effects. In order to compare DBP chemical risks within the CRFM, EPA needs to make central tendency risk estimates with probability distributions for each of these endpoints of concern.

Figure 2-1 shows an overview of the CRFM that combines the NAS Risk Assessment Paradigm methodology with a public health approach, a Cost-Effectiveness Analysis, to evaluate new drinking water treatment technologies in light of the gains in health units relative to the cost in dollars to achieve those gains. The disparate health endpoints for comparison include cancer illness and death, and developmental and reproductive effects for disinfection by-products and gastrointestinal illness and mortality for microbial exposures. The CRFM goes further than just estimating risks utilizing the paradigm and develops a common health metric for use in making risk comparisons between DBP and microbes (e.g., *Cryptosporidium* infections). In order to illustrate the CRFM, the Agency has developed a case study. Figure 2-2 highlights the exposure conditions and the use of the paradigm for chemical

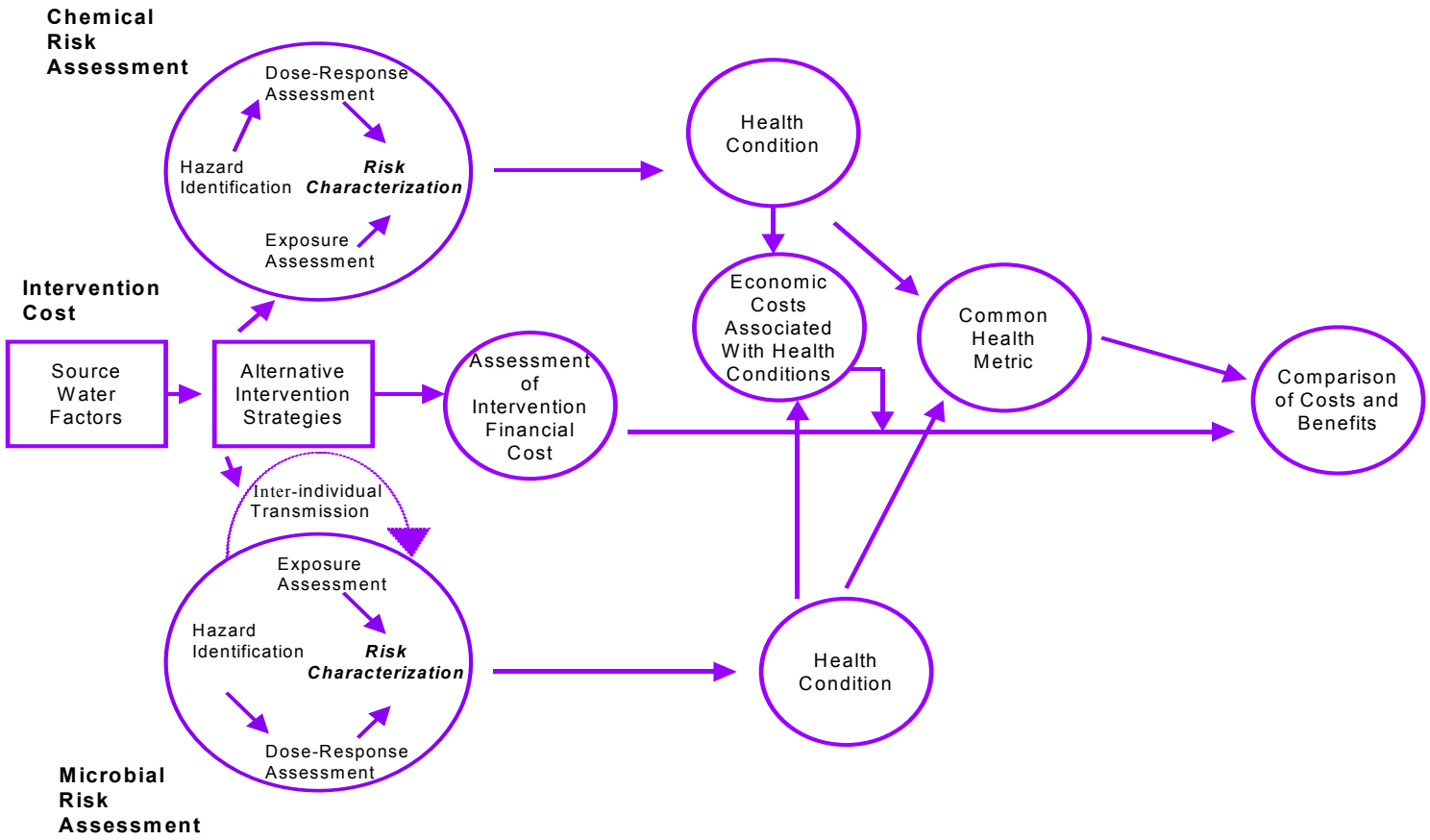


FIGURE 2-1

Comparative Risk Assessment Framework Overview

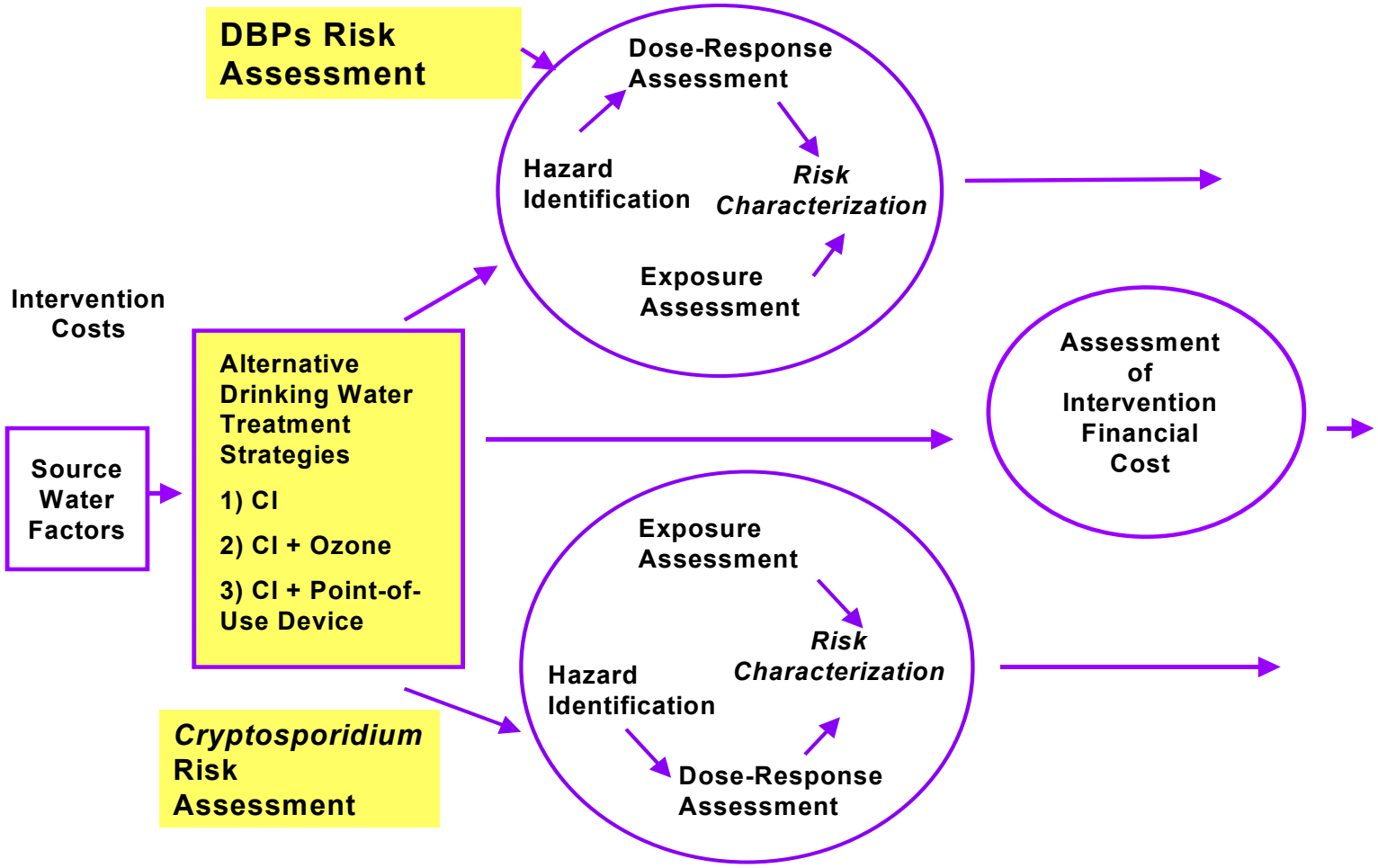


FIGURE 2-2

Comparative Risk Framework Methodology Case Study

risks in the case study that are the focus of the current workshop. In the illustrative case study, the alternative drinking water treatment disinfection strategies that are compared are: (1) filtration, post-chlorination; (2) pre-ozonation, filtration, post-chlorination; and (3) filtration, post-chlorination, point-of-use device (e.g., an in-home filter system).

The goals of the DBP risk estimation in the CRFM are to:

- compare DBP risks across drinking water treatment trains that reflect differences in which DBP are produced, as well as shifts in their concentration levels,
- make reasonable, useful risk estimates (other than zero) for all endpoints of concern because the epidemiologic and toxicologic evidence, although not conclusive, raise concern for cancer, and developmental and reproductive effects that need to be represented in the CRFM,
- develop distributions of risks in addition to central tendency estimates (not conservative, high-end estimates) that reflect their uncertainty and variability for use in the Monte Carlo and sensitivity analyses, and
- incorporate information on both the *measured* and *unmeasured* DBP into the risk estimate, as approximately 60% of the DBP in drinking water are represented only as summary measures (e.g., total organic halides) and are not identified as single chemicals.

A number of factors contribute to DBP risk uncertainty. These include:

- stochastic uncertainty in bioassay data,
- extrapolation to human risk estimates from animal dose-response toxicity data (when epidemiologic data are not available),
- variation in the presence and concentrations of DBP in the drinking water,
- seasonal (and other) variations in source water conditions,
- variations in human drinking water intake, and other uses of water,

- assumptions for estimating mixtures risk that carry requirements and limitations,
- contribution to risk by the inhalation and dermal exposure routes.

The current case study uses a response-addition model, a component-based method for joining dose-response and exposure data, to estimate risk for the mixture. The strategy of the method is to estimate the individual chemical component risks for a given health endpoint at the measured exposure concentration for each component and then sum these risks to yield the total mixture risk. This method assumes that the components of the mixture are functionally *independent* of one another in producing the effects (risks) at *low* exposure levels. Thus, evidence of a similar mode of action or similar toxic effect across chemicals is not required. Historically, this method has been used for estimation of cancer risks for a chemical mixture, but less often for noncancer endpoints that are thought to be threshold effects. Response-addition was applied to the DBP because of the need to compare DBP risks for the endpoints of concern at extremely low human exposures. For risk to a particular health endpoint, response-addition assumes that risk (unitless) is related to the concentration and potency of each individual component chemical as follows:

$$risk = Y \times \frac{1}{1000} \sum_{i \in All\ DBPs} C_i S_i \qquad (2\text{-}1)$$

where:

Y = Tap water intake (L/kg-day)

C_i = Concentration of DBP_i (µg/L)

S_i = Incremental risk for DBP_i $(mg/kg\text{-}d)^{-1}$

1 mg = 1000 µg

Equation 2-1 is reasonable if the concentration of all the DBP components in tap water are known (i.e., analytically characterized as to chemical species). However, only some of the DBP have been chemically characterized and their concentrations measured. Since there are always some DBP that are unidentified and thus, not chemically measured in the drinking water, the health risk can then be expressed as in terms of both the measured as well as the unmeasured DBP, as shown in Equation 2-2.

(2-2)

$$risk = Y \times \frac{1}{1000}\left[\sum_{i \in k} C_i S_i + \sum_{i \in u} C_i S_i\right]$$

where:

Y = Tap water intake (L/kg-day)

C_i = Concentration of DBP_i (µg/L)

S_i = Incremental risk for DBP_i $(mg/kg\text{-}d)^{-1}$

1 mg = 1000 µg

k = set of identified DBP

u = set of unidentified DBP

Since *u*, the set of unidentified DBP, will never be completely known, methods must be developed to estimate their potential toxicity (i.e., estimate the summation, $\sum_{i \in u} C_i S_i$) using summary measures, expert judgment, or modeling

techniques. In the case study, it was assumed that the toxicity (or risk) for the unidentified DBP associated with a health endpoint (e.g., developmental effects) is equal to that of the identified DBP for the same health endpoint per unit of organic halide (OX) concentration. That is, the risk from the unidentified components is expressed in terms of the risk of the identified components of DBP, normalized by their respective concentration of organic halides (in µg Cl/L), as shown in Equation 2-3.

(2-3)

$$\frac{\sum_{i \in u} C_i S_i}{C_{uH}^{ox}} = \frac{\sum_{i \in k} C_i S_i}{C_{kH}^{ox}}$$

C_{uH}^{ox} = organic halide (OX) concentration (in μg Cl/L) of all unidentified DBP (H) associated with endpoint h

C_{kH}^{ox} = corresponding concentration (in μg Cl/L) for identified DBP (H) associated with endpoint h

Solving for the toxicity (risk) of the unidentified DBP associated with endpoint h, this quantity can then be expressed as a fraction of the toxicity for the identified DBP, based on their relative OX concentrations (Equation 2-4).

$$\sum_{i \in u} C_i S_i = \frac{C_{uH}^{ox}}{C_{kH}^{ox}} \sum_{i \in k} C_i S_i \qquad (2\text{-}4)$$

C_{uH}^{ox} = organic halide (OX) concentration (in μg Cl/L) of all unidentified DBP (H) associated with endpoint h

C_{kH}^{ox} = corresponding concentration (in μg Cl/L) for identified DBP (H) associated with endpoint h

For the case study, the value of these concentrations, C_{uH}^{ox} and C_{kH}^{ox}, had to represent concentrations of OX in units of Cl/L, as well as represent concentrations that could be associated with endpoint h.

For the identified DBP, C_{kH}^{ox} was calculated as the sum of the individual concentrations, C_i, times their respective OX proportions, ρ_i, in µg Cl/L for each DBP known to be associated with endpoint h:

$$C_{kH}^{ox} = \sum_{i \in k \cap h} \rho_i C_i \qquad (2\text{-}5)$$

ρ_i = Ratio of DBP_i organic halide concentration to DBP_i total concentration

For the unidentified DBP, C_{uH}^{ox} is calculated as the proportion, α_h, of unidentified DBP expressed as a summary measure in OX concentration, in µg Cl/L, associated with endpoint h. As shown in Equation 2-6, the concentration of the unidentified organic

halides is a function of the proportion of the total organic halides, C_u^{ox}, in the DBP mixture, expressed in µg Cl/L:

$$C_{uH}^{ox} = \alpha_h \, C_u^{ox} \tag{2-6}$$

α_h = Proportion of unidentified DBP associated with endpoint h (on the basis of concentration)
C_u^{ox} = Total organic halide concentration (OX) for unidentified DBPs (µg Cl/L)

Therefore, by substituting the relationships shown in Equations 2-4, 2-5, and 2-6 into Equation 2-2, the risk for a given health endpoint h in the case study can be described by the following:

$$risk_h = \frac{1}{1000} \times Y \times \left[\sum_{i \in k} C_i S_i + \frac{\alpha_h \, C_u^{ox}}{\sum_{i \in k \cap h} \rho_i C_i} \sum_{i \in k} C_i S_i \right] \tag{2-7}$$

In the case study, concentration data were used from a pilot plant study by Miltner et al. (1990). Only the measured concentrations of some identified DBP (C_i) expressed in µg/L and the summary value of the total organic halide (TOX) concentration (C_u^{ox}, expressed in µg Cl/L) were available in this data set. Table 2-1 shows the TOX concentrations for the two treatment trains after the water was subjected to a simulated distribution system. Approximately 40% of the TOX was identified in each of these treatment trains. Further, it was assumed that the OX DBP identified by Richardson (1998) represented all OX DBP in water treated by filter-Cl_2 (70

TABLE 2-1 Total Organic Halides (TOX, µg Cl/L) in Simulated Distribution (Stored) Pilot Plant Waters			
O_3 - Filter - Cl_2		Filter - Cl_2	
207.4 ± 35.4[a] (± 17%)		258.8 ± 39.2[a] (± 15%)	
identified = 84.4 (40.7%)[b]	unidentified = 123 (59.3 %)[b]	identified = 110 (42.5 %)[b]	unidentified = 148.8 (57.5 %)[b]

[a] mean ± standard deviation
[b] percentages given in Table 6, Miltner et al., AWWA conference proceedings (June 1990)

DBP) or O_3-filter-Cl_2 (62 DBP). The list of potential unidentified OX DBP for O_3-filter-Cl_2 and filter-Cl_2 were determined by subtracting Miltner et al.'s identified OX DBP from Richardson's OX DBP results for the same treatment. The inorganic halide fraction and other organic fractions (e.g., non-halide) were not addressed in the case study.

A quantitative structure-activity relationship (QSAR) was used to determine which of the unidentified DBP (listed by Richardson, 1998 minus the Miltner et al. identified DBP) could potentially be associated with each health endpoint, and, hence, what fraction of unidentified DBP (i.e., α_h) is associated with each health endpoint h for each treatment type. Tables 2-2 and 2-3 show the QSAR predictions of carcinogenicity and developmental toxicity that were produced by the TOPKAT® software package (Toxicity Prediction by Komputer-assisted Technology), introduced in 1987 by Health Designs, Inc. Since TOPKAT does not have predictive capability for reproductive

TABLE 2-2

Chemical Class	Total Developmental	Total Cancer	Cancer Female	Cancer Male Mouse	Cancer Female Rat	Cancer Male Rat
Aldehydes	0	1	1	0	0	0
Acids	3	5	4	2	3	0
Ketones	7	8	0	7	0	3
Lactones	0	3	1	1	1	0
Alcohols	0	1	0	1	0	0
Esters	1	1	0	0	0	1
Nitriles	4	2	1	0	1	0
Amides	0	0	0	0	0	0
Halo/Nitro Alkanes - Alkenes	3	12	7	5	6	6
Count / Total	18/43	33/57	-	-	-	-
% Associated with Endpoint	42	58	-	-	-	-

TABLE 2-3

TOPKAT® QSAR Predictions by Endpoint for Known DBP Not in the Miltner et al. (1990) Sample, O_3-Filter-Cl_2 Treatment Train; Number Associated with Toxicity

Chemical Class	Total Developmental	Total Cancer	Cancer Female Mouse	Cancer Male Mouse	Cancer Female Rat	Cancer Male Rat
Aldehydes	1	4	3	0	0	2
Acids	5	3	1	0	1	0
Ketones	5	7	1	5	0	2
Lactones	0	1	1	0	0	0
Alcohols	0	1	0	1	0	0
Esters	1	2	1	1	0	1
Nitriles	4	1	0	0	1	0
Amides	1	1	0	1	0	1
Halo/Nitro Alkanes and Alkenes	6	6	1	1	1	3
Count / Total	23/41	26/47	-	-	-	-
% Associated with Endpoint	56	55	-	-	-	-

endpoints, developmental predictions were used as a surrogate for reproductive effects. Several important sources of uncertainty are recognized in this process. These include:

- Statistical models built into the TOPKAT® software may have introduced classification errors.
- The actual number and molecular weights of the chemicals that make up the unidentified DBP are unknown.
- The assumption that the toxicity of the unidentified DBP is the same as it is for the identified DBP when normalized in terms of OX concentration measured as µg Cl/L may be incorrect.

The EPA requested the experts' assistance in: how to optimize use of all available exposure, toxicity, and epidemiologic data to best characterize DBP risks across drinking water treatment systems; how to better incorporate information on the unidentified DBP into the risk assessment; identification of other QSAR models or different toxicity measures than those generated by TOPKAT that could be used; application of risk characterization methods that could be investigated based on assumptions appropriate for the data; and recommendation of ways to characterize uncertainty and variability.

2.2. PRESENTATION: OVERVIEW OF CHEMICAL EXPOSURE CONSIDERATIONS IN THE CASE STUDY OF THE U.S. EPA'S COMPARATIVE RISK FRAMEWORK METHODOLOGY (CRFM): ENGINEERING CONCERNS, SOURCE WATER CHARACTERISTICS, UNIDENTIFIED TOX, TAP WATER CONSUMPTION (G. Rice)

A goal of the illustrative case study in the draft CRFM (U.S. EPA, 1998) was to facilitate a comparison among two hypothetical drinking water treatment systems. This was accomplished by structuring the risk assessment/risk management interface through construction of a transparent, decision analytic approach. Application of the CRFM results in the comparison of cost-effectiveness ratios for each drinking water

treatment system under consideration. The costs incurred through implementation of the interventions form the numerator and the gain in public health associated with the intervention is quantified in the denominator of the cost-effectiveness ratio. The denominators of the cost-effectiveness ratios are based on risks posed by the pathogens and the disinfection byproducts. In the case study of the CRFM, unbiased estimates of the risks were quantified through application of the National Academy of Science Risk Assessment Paradigm (NAS, 1983). For convenience, the risks analyzed were limited to those posed by the disinfection by products and oocysts of the protozoal parasite, *Cryptosporidium parvum*. The components of the DBP exposure assessment developed in the limited case study as well as potentially important exposure considerations not developed in the case study are described herein.

Exposure assessment consists of the evaluation of the magnitude, frequency, duration, and route(s) of exposure. The risks posed by chemicals in drinking water can be analyzed by aggregating exposure and effects, as is conducted in epidemiologic investigation, by disaggregating exposure and effect and evaluating the components independently, and then integrating them to assess risks (the approach taken in the illustrative case study in the CRFM and described here). Alternatively, a hybrid approach using both epidemiology (aggregation) and toxicology (disaggregation) can be used.

2.2.1. Characteristics of the Source Water. Levels of DBP-precursors may be variable across water bodies (e.g., bromide levels) or within water bodies (e.g., due to climatological variation or seasonal changes in the patterns of water shed use). The presence of other contaminants (biotic or abiotic) may influence the water treatment

choice. Source water acidity or alkalinity or temperature influence the presence and concentration of DBP in treated water. In the case study, the source water was drawn from the Ohio River (Miltner et al., 1990, 1992). The temporal variability of DBP-precursors in the source water was not analyzed and the impact of this variability on the *differences* in the distribution of quantities and types of DBP formed between the treatment systems being analyzed was not characterized.

2.2.2. Alternative Treatment Systems. The drinking water treatment system alternatives impact the DBP levels in the treated drinking water. Factors that are important in the selection of alternative drinking water treatment may include:

- feasibility,
- regulatory requirements,
- acceptability of the intervention for legal or ethical reasons (e.g., a community-based program mandating installation of in-home water filters in the homes of a sensitive subpopulations may be unacceptable),
- intervention cost, and
- anticipated benefits.

In the case study, two drinking water treatment systems were compared. The baseline system consisted of coagulation, sedimentation, sand filtration, and chlorine disinfection and the alternative system consisted of the baseline system supplemented by a pre-ozonation step (Miltner et al., 1990; U.S. EPA, 1998).

2.2.3. Concentrations of DBP in Treated Waters: Distributions. Unbiased estimates of the distributions of the quantities and types of DBP that form in the drinking water treatment system are needed to characterize exposure. Ideally, these concentrations will be measured at the taps over time. Data from Miltner et al. (1990, 1992) were used in the analysis (see Tables 2-4 and 2-5). The DBP were divided into

TABLE 2-4

DBP Measured Concentrations and Fractional Halogen Contribution in Water Treated Using the Baseline Treatment Technology[a,b]

Chemical	Meal (mg/L)	Standard Deviation (mg/L)	Ratio of the OX Concentration Value to the Total Concentration
$CHCl_3$	55.50	2.01	0.891
BDCM	24.40	1.52	0.649
CDBM	10.20	0.85	0.511
$CHBr_3$	0.35	0.30	0.421
CH	4.20	0.30	0.643
MCA	1.44	0.10	0.375
DCA	30.85	1.49	0.550
TCS	20.10	0.97	0.651
MBA	0.29	0.02	0.255
DBA	1.50	0.12	0.326
BCA	8.50	0.06	0.409
DCAN	3.50	0.43	0.645
TCAN	0.20	0.06	0.737
BCAN	1.90	0.24	0.459
DBAN	0.15	0.07	0.357
BrO_3	0.00	0.00	0[c]

[a] The concentration of each DBP is assumed to be normally-distributed.

[b] The standard deviation was calculated using mean and 95th percentile values developed from Miltner et al. (1990, 1992), assuming normality.

[c] Bromate is not an organic halogen, and therefore, this fraction is zero.

TABLE 2-5

DBP Measured Concentrations in Water Subjected to the Ozone Pretreatment Technology[a,b]

Chemical	Meal (mg/L)	Standard Deviation (mg/L)	Ratio of the OX Concentration Value to the Total Concentration
$CHCl_3$	39.55	2.95	0.891
BDCM	21.10	0.18	0.649
CDBM	13.00	0.49	0.511
$CHBr_3$	1.50	0.18	0.421
CH	5.80	0.61	0.643
MCA	1.46	0.05	0.375
DCA	19.30	0.79	0.550
TCS	10.00	0.73	0.651
MBA	0.28	0.04	0.255
DBA	1.98	0.13	0.326
BCA	6.70	0.12	0.409
DCAN	2.60	0.24	0.645
TCAN	0.05	0.00	0.737
BCAN	1.65	0.12	0.459
DBAN	0.55	0.14	0.357
BrO_3	4.00	0.36	0[c]

[a] The concentration of each DBP is assumed to be normally-distributed.

[b] The baseline technology values (filter-Cl_2) also apply to the point of use filter technology since this supplemental technology is assumed not to affect DBP concentrations.

[c] Bromate is not an organic halogen, and therefore, this fraction is zero.

two groups. The first group included 16 DBP concentrations that had been individually measured. The second group included all other halogenated DBP (referred to as the "unmeasured DBP"). Although their concentrations have not been measured individually, the total halogen (OX) portion of their collective concentration can be calculated (details provided in U.S. EPA, 1999; see Appendix A of this report). Experimental non-detects were set to one half of the detection limit.

2.2.4. Contact. Human exposure only occurs when an agent comes into contact with the human membranes. As shown in Figure 2-3, population demographics, activity, mobility, and mortality as well as water source and structural characteristics (e.g., room dimensions, air flow patterns, etc.) influence the pathways for contact with the chemicals in the treated water. For example, DBP levels are known to vary depending on the type of distribution system and with distance from the chemical-treatment facility. These pathways may be chemical-specific (e.g., may depend on volatility of the chemical) and involve direct or indirect pathways of exposure. Chemicals may be present in vapor, aerosol, or liquid form(s), enter the body via respiration, ingestion, or dermal penetration, and may be metabolized before distribution to the target organ(s).

In the CRFM case study, the goal was to develop unbiased estimates (of dose, exposure, and risk) for risk comparisons. A disaggregated approach to exposure assessment was chosen. Exposure was limited to drinking water consumption; other pathways such as dermal exposure were not considered. A limited number of compounds was assessed with exposure to unidentified TOX included, but unidentified total inorganic halides (TIX) were not considered. DBP exposure was assumed to be a

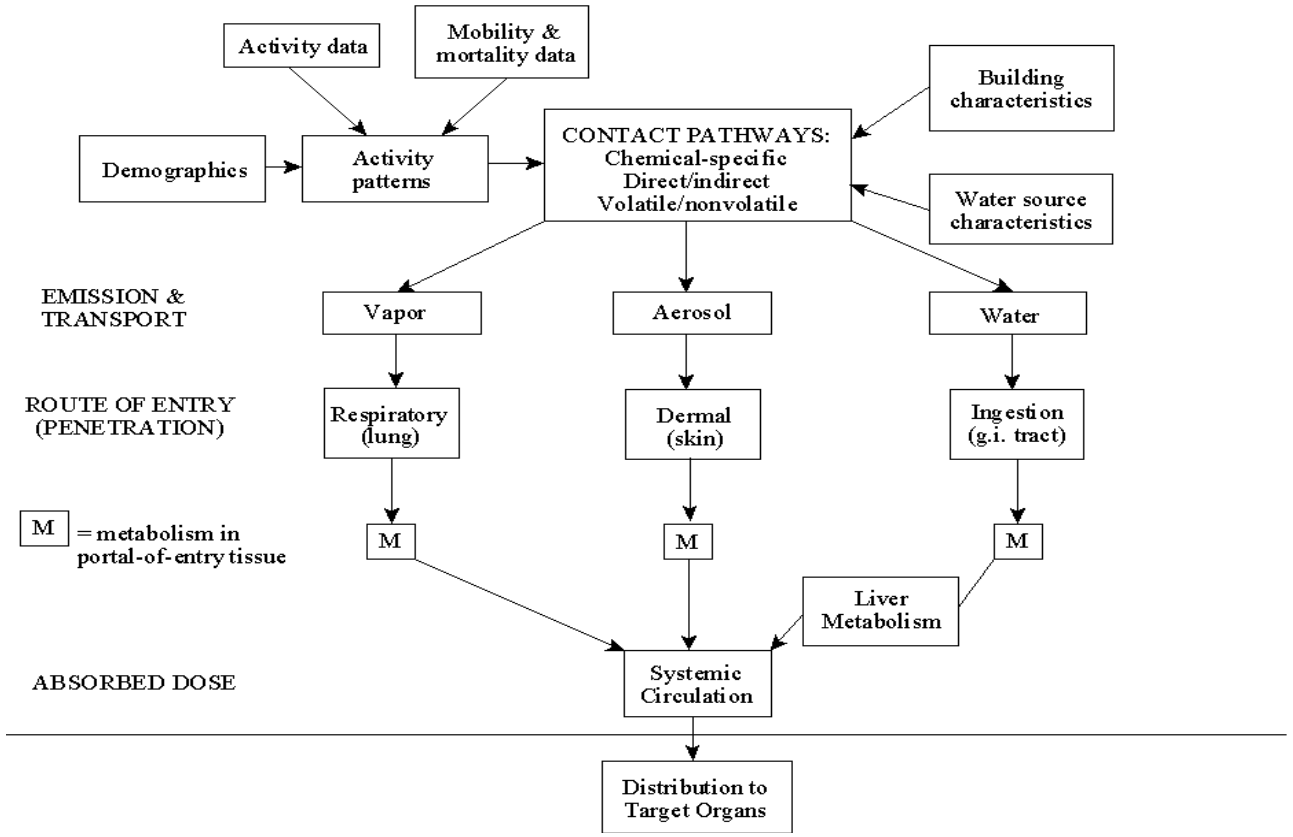


FIGURE 2-3

Human Exposure Pathways

Source: Adapted from Weisel et al., 1999a. Developing Exposure Estimates. In: Exposure to Contaminants in Drinking Water. Stephen Olin, Ed.

function of total tap water consumed (L/kg-day). All water from the household tap consumed directly as a beverage or used to prepare foods and beverages was considered tap water. The studies of Ershow and Cantor (1989) of the U.S. population and the Canadian Ministry of National Health and Welfare (1981), presented in U.S. EPA (1997, Exposure Factors Handbook) were used to derive consumption estimates. In addition, the Continuous Survey of Food Intake by Individuals (CSFII) data (1994-1996) is currently undergoing evaluation within the EPA. The CRFM case study quantified tap water consumption by fitting lognormal distributions to age-specific intake data for the U.S. population developed by U.S. EPA (1997) based on Ershow and Cantor (1989) and shown in Table 2-6. The water consumption of some subpopulations was evaluated and found not to differ from the general population estimates. Because reproductive and developmental effects induced by DBP are of concern, the water consumption of pregnant women was evaluated. However, according to the data of Ershow and Cantor (1989), the water consumption of pregnant women does not differ from general population values. Therefore, no adjustment to consumption rates for this subgroup in the CRFM was made. The AIDS population, however, has been reported to drink significantly less tap water (Perz et al., 1998) than the general population. The water consumption of this subgroup was adjusted downward in the case study. The case study did not, however, evaluate exposure routes other than oral, compare differences in DBP exposures from heated vs. unheated tap water, or account for potential changes in consumption patterns (e.g., in CSFII increased use of bottled water) since the time of data collection by Ershow and Cantor (1989).

TABLE 2-6

Tap Water Consumption in the General Population (ml/kg-day) by 5-Year Age Groups[a]

Age (Years)	Population Percentile							
	5	10	25	50	75	90	95	Arithmetic Mean[b]
0 to 4	9.14	13.66	23.71	38.5	57.4	82.89	103.03	44.4
5 to 9	8.56	12.14	18.36	27.72	40.78	56.1	65.56	31.2
10 to 14	5.4	8.06	12.72	19.28	28.06	38.02	44.56	21.3
15 to 19	3.9	5.7	9.6	14.8	21.5	29	35	16.3
20 to 24	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
25 to 29	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
30 to 34	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
35 to 39	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
40 to 44	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
45 to 49	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
50 to 54	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
55 to 59	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
60 to 64	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
65 to 69	8.7	10.9	15.1	20.2	27.2	35.2	40.6	21.9
70 to 74	8.7	10.9	15.1	20.2	27.2	35.2	40.6	21.9
75 to 79	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4
80 to 84	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4
85 +	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4

[a] Ershow et al. (1991) cited in U.S. EPA (1997)

[b] The arithmetic mean value for each age group was computed by fitting a lognormal to the percentile values listed and computing the arithmetic mean corresponding to that distribution's geometric mean and geometric standard deviation.

A central question posed to the experts was how the exposure assessment approach used in the CRFM case study can be improved.

2.3. PRESENTATION: OVERVIEW OF TOXICOLOGY/CARCINOGENICITY ANIMAL DATA FOR USE IN QUANTITATIVE RISK ESTIMATION (J. Lipscomb)

The goal of extrapolating animal toxicity dose-response data to predict the likelihood of adverse effects in humans is to use the best available toxicity data in the risk assessment. For the DBP, this is complicated by many factors, including the human exposure to low concentrations of these chemicals in treated drinking water and the conducting of animals experiments at high doses of the same or closely related chemicals. In addition, the question arises as to whether the critical effects observed in animals are likely to be the same as the effects which are predicted to occur in the humans.

Epidemiologic data for DBP have identified potential health outcomes of concern (i.e., cancer, reproductive and developmental effects). A weak to moderate association has been demonstrated between:

- low birth weight and consumption of chlorinated water,
- spontaneous abortions and bromodichloromethane (BDCM) exposure, and
- neural tube defects and exposure to trihalomethanes (THM).

Because the human data are uncertain and sparse, reproductive and developmental toxicity and carcinogenicity data from peer-reviewed, published animal studies were used to estimate health risks for the DBP. While hundreds of chemicals have been identified as DBP in drinking water, chemicals applied in the case study were restricted to those identified in the two treatment trains of interest and with available

toxicity data for the human health points of concern. Other DBP that have toxicity data, but were not shown to occur in the studies of Richardson (1998) or Miltner et al. (1990) were excluded. The DBP that were identified in drinking water and met the above criteria for inclusion in the case study are listed in Table 2-7.

2.3.1. Developmental and Reproductive Effects. The available animal developmental toxicity data demonstrate multiple endpoints, primarily resorptions, decreased live births, decreased crown-rump length, decreased body weight, heart malformations, and eye malformations. Data availability restricted the consideration of reproductive toxicity to that of direct effects on male reproductive endpoints. The available studies for developmental and reproductive toxicity of the DBP comprise primarily studies in rats treated by gavage, some with limitations in study design (e.g., maternal toxicity) or reporting of results.

In estimating risk for developmental and reproductive toxicity, a dose-response model with a threshold parameter was applied to each endpoint within a study that measured multiple endpoints (see Appendix A). Identified DBP toxicity data sets were excluded when the model could not make reliable predictions or when the data sets indicated a threshold effect for reproductive or developmental endpoints. The Linearized Multi-Stage model was applied to available animal bioassay data to determine “slope factors” or estimates of the potency for a given chemical. To avoid the generation of point estimates of toxicity, a log normal distribution for the slope factors was assumed. A surrogate approach was used to address the developmental toxicity data gaps for dibromoacetic acid (DBA), bromochloroacetic acid (BCA), and dibromoacetonitrile (DBAN) because available data indicated that developmental

TABLE 2-7

Disinfection Byproducts Considered in CRFM Case Study

DBP with Reproductive/Developmental Data	DBP with Carcinogenicity Data
Monochloroacetic Acid (MCA)[a]	Bromodichloromethane
Dichloroacetic Acid (DCA)	Chlorodibromomethane
Trichloroacetic Acid (TCA)	Bromoform
Monobromoacetic Acid (MBA)	Chloral Hydrate
Dibromoacetic Acid (DBA)	Dichloroacetic Acid
Bromochloroacetic Acid (BCA)	Trichloroacetic Acid
Dichloroacetonitrile (DCAN)	Bromate
Trichloroacetonitrile (TCAN)	Chloroform[b]
Bromochloroacetonitrile (BCAN)	
Dibromoacetonitrile (DBAN)	
Bromodichloromethane (BDCM)[a]	

[a] MCA and BDCM were excluded from the reproductive and developmental risk assessments because threshold parameters were modeled for all endpoints.

[b] Chloroform has been excluded from the risk assessment because it is thought to be a threshold carcinogen, and its concentration for either treatment train considered is less than chloroform's estimated threshold.

toxicity may be common for the haloacetic acid and haloacetonitrile DBP. The toxicity and potency of dichloroacetic acid (DCA) was used as a surrogate for the toxicity and potency of the haloacetic acids (HAA). Likewise, data for trichloroacetonitrile (TCAN) were used as a surrogate for the haloacetonitriles (HAN). Tables 2-8 and 2-9 show the incremental developmental toxicity risk for the identified DBP and the non-cancer dose-response modeling results for DCA and trichloroacetic acid (TCA), respectively.

The incremental risk for reproductive toxicity for the three identified DBP for which adequate data are available and the non-cancer dose-response modeling results for DCA and DBA are shown in Tables 2-10 and 2-11, respectively.

2.3.2. Cancer. Epidemiologic studies have identified an association between the ingestion of disinfected water and colorectal and bladder cancer in humans. Animal bioassay data have shown evidence that several of the identified DBP are possible human carcinogens (see Table 2-12). Site concordance between the human studies and animal data is recognized as an issue for further deliberation. For the case study, it was assumed that cancer risk in animals can be extrapolated to humans and that site concordance was not a prerequisite. Slope factors were taken from EPA documents, or verified by EPA Work Groups, except for those for TCA and DCA, which were classified by EPA as C (possible human carcinogen) or B2 (probable human carcinogen), respectively. Slope factors for DCA and TCA were calculated from the risk levels given in Bull and Kopfler (1991). A lognormal distribution for the slope factors was assumed. Unit risk values were recalculated using exposures as calculated in the case study (see Section 2.2) and not using standard default values. Risk estimates for individual

TABLE 2-8

Incremental Developmental Toxicity Risk for Identified DBP

	Slope Factor $(mg/kg\text{-}d)^{-1}$				
Chemical	MLE	95th percentile UCL	GM	GSD	Observed Effect
DCA	8.6×10^{-3}	1.3×10^{-2}	8.6×10^{-3}	1.3	Visceral malformations – Total
TCA	2.0×10^{-2}	3.0×10^{-2}	2.0×10^{-2}	1.3	Fetal body weight – male
MBA	8.4×10^{-3}	2.3×10^{-2}	8.4×10^{-3}	1.8	Fetal crown rump length
DBA	8.6×10^{-3}	1.3×10^{-2}	8.6×10^{-3}	1.3	Estimated using DCA as a surrogate
BCA	8.6×10^{-3}	1.3×10^{-2}	8.6×10^{-3}	1.3	Estimated using DCA as a surrogate
DCAN	5.4×10^{-2}	1.6×10^{-1}	5.4×10^{-2}	1.9	Visceral malformations – cardiovascular
TCAN	2.1×10^{-1}	3.4×10^{-1}	2.1×10^{-1}	1.3	Visceral malformations – Total
BCAN	1.6×10^{-1}	2.4×10^{-1}	1.6×10^{-1}	1.3	Visceral malformations – Total
DBAN	2.1×10^{-1}	3.4×10^{-1}	2.1×10^{-1}	1.3	Estimated using TCAN as a surrogate
BDCM	4.0×10^{-2}	3.1×10^{-2}	4.0×10^{-2}	-	Complete litter resorption[a]
MCA	9.0×10^{-5}	6.0×10^{-3}	9.0×10^{-5}	2.6	Crown rump length[a]

[a] BDCM and MCA not evaluated due to the model's estimation of a threshold effect.

MLE = maximum likelihood estimate

UCL = upper confidence limit

GM = geometric mean

GSD = geometric standard deviation

TABLE 2-9

Dose-Response Modeling for Developmental Toxicity[a]

Data Set	Equivalent Human Dose ED_{01} (mg/kg-d)[b]	Equivalent Human Dose ED_{10} (mg/kg-d)[b]	Threshold (mg/kg-d)[b]
DCA Smith et al., Fetal body weight - male	4.7	27.3	2.2
DCA Smith et al., Fetal body weight - female	18.6	40.4	16.3
DCA Smith et al., Crown-rump length - male	5.1	36.2	1.0
DCA Smith et al., Crown-rump length - female	5.1	36.2	1.0
DCA Smith et al., Visceral malformations Total	1.2	12.2	0
DCA Smith et al., Visceral malformations Cardiovascular	1.7	17.6	0
TCA Smith et al., Complete litter resorption	110.5	143.2	106.3
TCA Smith et al., % Postimplantation loss/litter	51.1	88.9	46.8
TCA Smith et al., Fetal body weight - male	0.5	5.2	0
TCA Smith et al., Fetal body weight - female	0.6	6.0	0
TCA Smith et al., Fetal crown-rump length - male	16.2	26.8	15.0
TCA Smith et al., Fetal crown-rump length - female	22.9	37.9	21.4
TCA Smith et al., Visceral malformations Total	25.7	32.2	25.0
TCA Smith et al., Visceral malformations Cardiovascular, Total	11.9	23.4	10.7
TCA Smith et al., Visceral malformations Levacardia	1.3	13.8	0

[a] Table is modified from Table 4-9 in U.S. EPA (1999)

[b] Doses calculated using $BW^{2/3}$ scaling factor

ED = effective dose

TABLE 2-10

Incremental Reproductive Toxicity Risk for Identified DBP

	Slope Factor $(mg/kg\text{-}d)^{-1}$				
Chemical	MLE	95th percentile UCL	GM	GSD	Observed Effect
DBA	2.5×10^{-2}	6.0×10^{-2}	2.5×10^{-2}	1.7	Number of cauda sperm
DCA	2.5×10^{-2}	6.0×10^{-2}	2.5×10^{-2}	1.7	Estimated using DBA as a surrogate
BCA	2.5×10^{-2}	6.0×10^{-2}	2.5×10^{-2}	1.7	Estimated using DBA as a surrogate

MLE = maximum likelihood estimate

UCL = upper confidence limit

GM = geometric mean

GSD = geometric standard deviation

TABLE 2-11

Dose-Response Modeling for Reproductive Toxicity[a]

Data Set[b]	Equivalent Human Dose ED_{10} (mg/kg-d)[c]	Equivalent Human Dose ED_{10} (mg/kg-d)[c]	Threshold (mg/kg-d)[c]
DCA Cicmanec et al., Testicular degeneration	Failed to converge		
DCA Linder et al., Number caput sperm	33.3	74.6	28.8
DCA Linder et al., Number cauda sperm	Failed to converge		
DCA Linder et al., % Motile sperm	12.6	16.5	9.7
DCA Linder et al., Progressive motility	10.8	15.4	9.7
DCA Linder et al., Testicular histopathology: Faulty spermiation	Failed to converge		
DBA Linder et al., Number caput sperm	5.6	7.7	5.4
DBA Linder et al., Number cauda sperm	0.4	4.2	0
DBA Linder et al., % Motile sperm	9.4	13.9	5.4
DBA Linder et al., Progressive motility	9.4	13.9	5.4
DBA Linder et al., Retention Stage IX spermatids per tubule	0.1	1.1	0

[a] Table is modified from Table 4-9 in U.S. EPA (1999)

[b] All data are for rats except for that of Cicmanec et al. which are for dogs.

[c] Using $BW^{2/3}$ scaling factor

ED = effective dose

TABLE 2-12

Incremental Cancer Risk for Identified DBP

Slope Factor $(mg/kg\text{-}d)^{-1}$						
Chemical	Weight of Evidence Classification[a]	MLE	95th percentile UCL	GM	GSD	Observed Effect
BDCM	B2	5.7×10^{-3}	6.2×10^{-2}	5.7×10^{-3}	4.3	Renal adenomas and adenocarcinomas
CDBM	C	7.2×10^{-4}	8.4×10^{-2}	7.2×10^{-4}	18.0	Hepatocellular adenomas and adenocarcinomas
$CHBr_3$	B2	3.4×10^{-4}	7.9×10^{-3}	3.4×10^{-4}	6.8	Neoplastic lesions in large intestine
CH	C	4.1×10^{-2}	1.3×10^{-1}	4.1×10^{-2}	2.0	Hepatocellular adenomas and adenocarcinomas
DCA	B2	1.4×10^{-3}	1.0×10^{-1}	1.4×10^{-3}	13.4	Hepatocellular adenomas and adenocarcinomas
TCA	C	4.9×10^{-2}	8.4×10^{-2}	4.9×10^{-2}	1.4	Liver neoplasms
Bromate	B2	3.2×10^{-1}	4.9×10^{-1}	3.2×10^{-1}	1.3	Renal adenomas and adenocarcinomas
$CHCl_3$[b]	B2	3.1×10^{-3}	6.1×10^{-3}	3.1×10^{-3}	1.5	Renal tumors

[a] Chemicals classified as B2 have sufficient evidence of carcinogenicity in animals with inadequate or a lack of evidence in humans. For chemicals classified as C, there is limited evidence of carcinogenicity in animals and inadequate or a lack of evidence in humans.

[b] Chloroform has been excluded from the risk assessment because it is thought to be a threshold carcinogen, and its concentration for either treatment train considered is less than chloroform's estimated threshold.

MLE = maximum likelihood estimate

UCL = upper confidence limit

GM = geometric mean

GSD = geometric standard deviation

chemicals were determined by multiplication of slope factors by the predicted intake rates. Chloroform was excluded from the risk assessment because it is thought to have a practical threshold and its concentration for either treatment train is less than chloroform's estimated threshold.

Issues for discussion by the experts were posed:

- Are there other DBP compounds that should be addressed?
- With respect to the data sets available, has the focus been on the critical health endpoints (toxicity) relevant to human health risk?
- Can multiple data sets be used quantitatively to producing the estimates of risk?
- Have reversibility and/or latency of effects been appropriately considered?
- Of what value would other approaches to quantifying rat reproductive effects be in this type assessment?
- Should epidemiologic findings be considered in a more quantitative fashion?
- Is the reliance upon the dose-response for effects produced by "surrogate" compounds appropriate?
- Is the assumption of a log normal distribution of slope factors appropriate?
- Should body weight be scaled to the 3/4 power instead of to the 2/3 power?

2.4. PRESENTATION: OVERVIEW OF AVAILABLE QUANTITATIVE EPIDEMIOLOGIC DATA: CANCER, DEVELOPMENTAL, REPRODUCTIVE ENDPOINTS (P. Murphy)

Some epidemiologic studies of chlorinated water and/or DBP, such as THM, have suggested a weak to moderate association with various site-specific cancers including bladder, colon, and rectum. The epidemiologic literature on adverse reproductive and developmental outcomes is still very sparse and must be increased in

both number and quality before quantitative use of the results can be entertained. The reproductive and developmental endpoints evaluated in these studies are shown in Table 2-13. The studies are described further in U.S. EPA (1998). In the CRFM, the results from these studies could not be used quantitatively in the case study because most of the exposure contrasts were confounded by water source and none of the designs allowed for a comparison of the drinking water treatment practices of interest to the current problem.

Each epidemiologic study was evaluated as to its internal validity (i.e., control for confounding, selection bias, measurement error, and analytic errors and oversight) and then in the context of the body of epidemiologic literature on chlorinated drinking water/DBP. Following a determination of the validity of the individual studies, an evaluation of both causal and noncausal explanations for the observed associations was considered. General guidance for assessing causality in epidemiologic studies includes evaluating the strength of the association, consistency, specificity, temporal association, dose-response or biological gradient, biological plausibility, coherence of findings, experimental evidence of preventability, and analogy. There are a number of problems with the DBP epidemiological literature that make the studies difficult to compare with one another. For example, in many of the reproductive and developmental studies, the investigators have not always used the same operational definitions for endpoints (such as low birth weight and spontaneous abortion) and important confounding variables (occupational exposure, smoking, other risk factors) have not been well-controlled.

TABLE 2-13

Reproductive and Developmental Endpoints Studies in Human Epidemiologic Studies of DBP

Study	Spontaneous abortion	Stillbirth	Pre-term delivery	Low birth weight	Intrauterine growth retardation	All defects	CNS defects	Neural tube defects	Oral cleft defects	Cardiac defects
Kramer et al. (1992)			X	X	X					
Aschengrau et al. (1993)		X				X				
Bove et al. (1992a, 1992b, 1995)		X	X	X	X	X	X	X	X	X
Savitz et al. (1995)	X		X	X						
Kanitz et al. (1996)			X	X						
Swan et al. (1998)	X									
Waller et al. (1998)	X									
Gallagher et al. (1998)			X	X	X					

The epidemiologic studies differ with respect to designs, endpoints evaluated, methods of exposure assessment, exposure contrasts reported, consistency of findings (both within and across studies), and compatibility with existing endpoint-specific epidemiology (e.g., consistency with risk factors such as smoking and fluid consumption), making clear interpretation of the results difficult. These inconsistencies limit their usefulness for quantitative risk assessment. In addition, recent research has demonstrated evidence of publication bias, a form of selection bias, in the cancer literature, where studies with inverse or null associations may not have been published or submitted for publication by the investigators.

The identified need for valid, unconfounded exposure measures in this literature has remained unmet for at least 20 years. Most of the existing studies are confounded by water source (e.g., chlorinated surface waters are compared with untreated ground water), have examined only one class of chemical DBP (i.e., total THM), and have not considered multiple exposure routes. Lack of historical chemical occurrence data is also a problem. In addition, there is the need for more meaningful public health exposure contrasts such as examining the outcomes of interest in the relationship to different water treatment practices.

There have been numerous expert evaluations over the past 20 years of the epidemiological data for chlorinated drinking water and DBP. In general, there is a consensus that the data have limitations and that a conclusion as to a causal relationship cannot be drawn. These evaluation groups include the National Academy of Science (NAS), International Association for Research on Cancer (IARC), EPA, International Society for Environmental Epidemiology (ISEE), International Life Sciences

Institute (ILSI), Health Canada, and the World Health Organization International Programme on Chemical Substance (WHO-IPCS).

To help improve this body of literature, EPA has an ongoing project to develop models for predicting the historic levels of occurrence of THM (and in some cases, haloacetic acids) in specific geographic areas where epidemiologic studies have been performed. The models, developed with historical data from water utilities, will be used to re-evaluate the exposure assessment component of certain recently completed studies, which will then be appropriately reanalyzed. This research should help to reduce some of the uncertainties and problems that were outlined above.

2.5. PRESENTATION: MONTE CARLO RESULTS OF DBP MIXTURES RISK ESTIMATES (J. Cohen)

In the CRFM case study, Monte Carlo analysis was used as a tool to quantify variability (heterogeneity) in the population, (i.e., the range of plausible risks due to differences among members of the population) and to quantify uncertainty (i.e., the range of plausible risks for each individual corresponding to alternative plausible assumptions). The assumptions that contributed the most uncertainty to the estimate for DBP risks were identified.

Variability was quantified by holding uncertain assumptions fixed and computing risk estimates corresponding to different values for parameters that vary among members of the population. Uncertainty was quantified by computing risk for several "representative" members of the population, such as the median individual and the 95th percentile individual.

A two-stage Monte Carlo analysis was conducted as shown in Figure 2-4. Values for uncertain parameters (e.g., cancer slope factors and concentration of DBP)

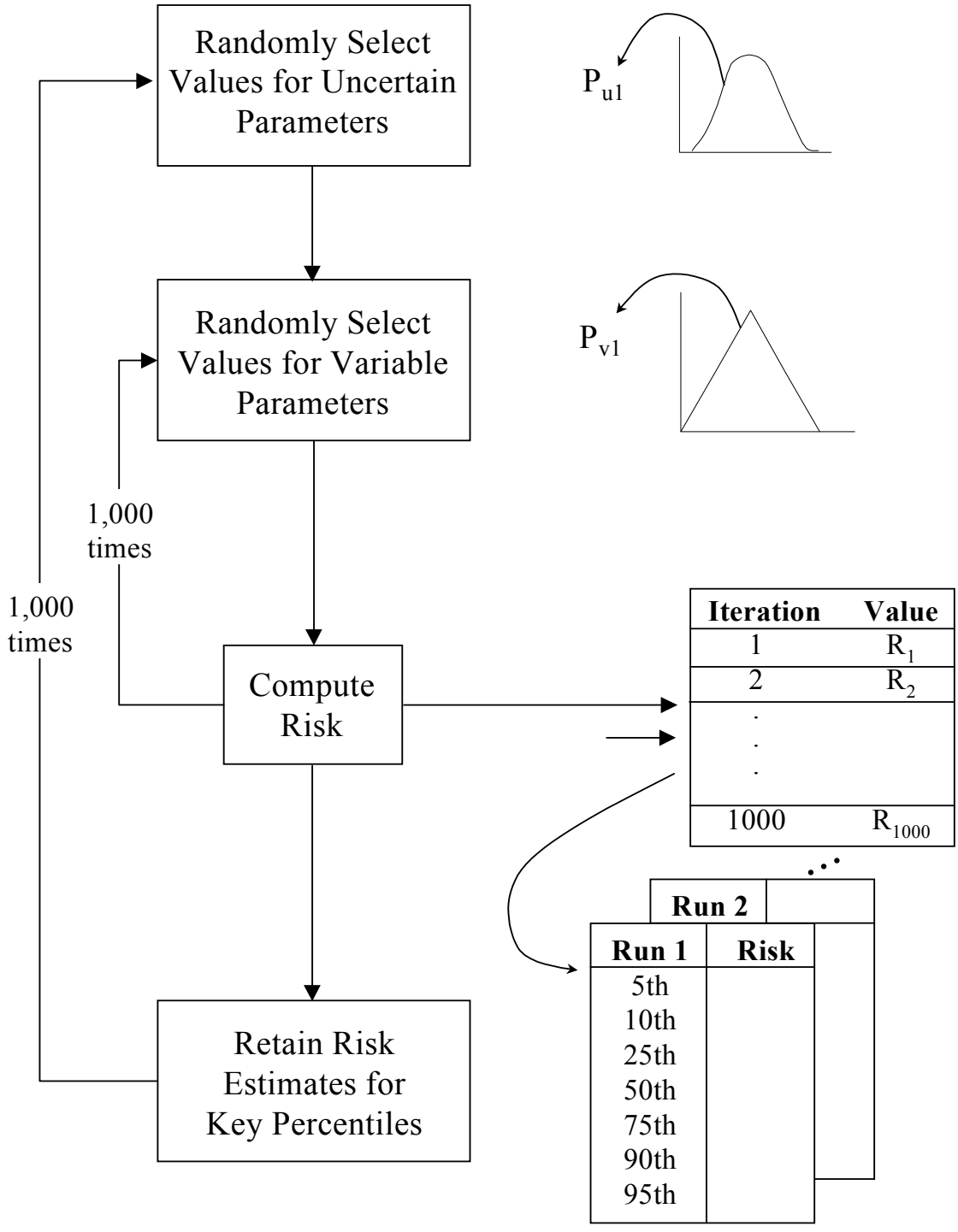


FIGURE 2-4

Two Stage Monte Carlo used in CRFM Case Study

were randomly selected and held constant, and then 1000 sets of values for the variable parameters (e.g., water consumption, L-kg/day) were randomly drawn (corresponding to 1000 iterations of the inner loop) and used to compute 1000 estimates of risk. After ranking the 1000 risk estimates from the inner loop, some key population summary statistics estimates (i.e., 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles) were retained (Figure 2-5). The simulation then proceeded to the next iteration of the outer loop, selecting new random values for the uncertain parameters and then executing 1000 new iterations of the inner loop. The outer loop was ultimately executed 1000 times, yielding 1000 estimates of each of the key population summary statistic risk estimates. For each health condition (cancer, developmental toxicity, and reproductive toxicity), the set of parameters having the greatest influence on the determination of risk was determined by modeling the population mean risk as a function of the uncertain parameters using the following linear regression model:

$$R_{i,50} = a + b_1 V_{i1} + b_2 V_{i2} + b_3 V_{i3} + b_4 V_{i4} + \in_i \qquad (2\text{-}8)$$

where:

V_{ij} = value for the jth parameter for simulation i,

R_{ij} = risk for jth percentile of the population estimated for simulation i,

ϵ = normally-distributed regression model

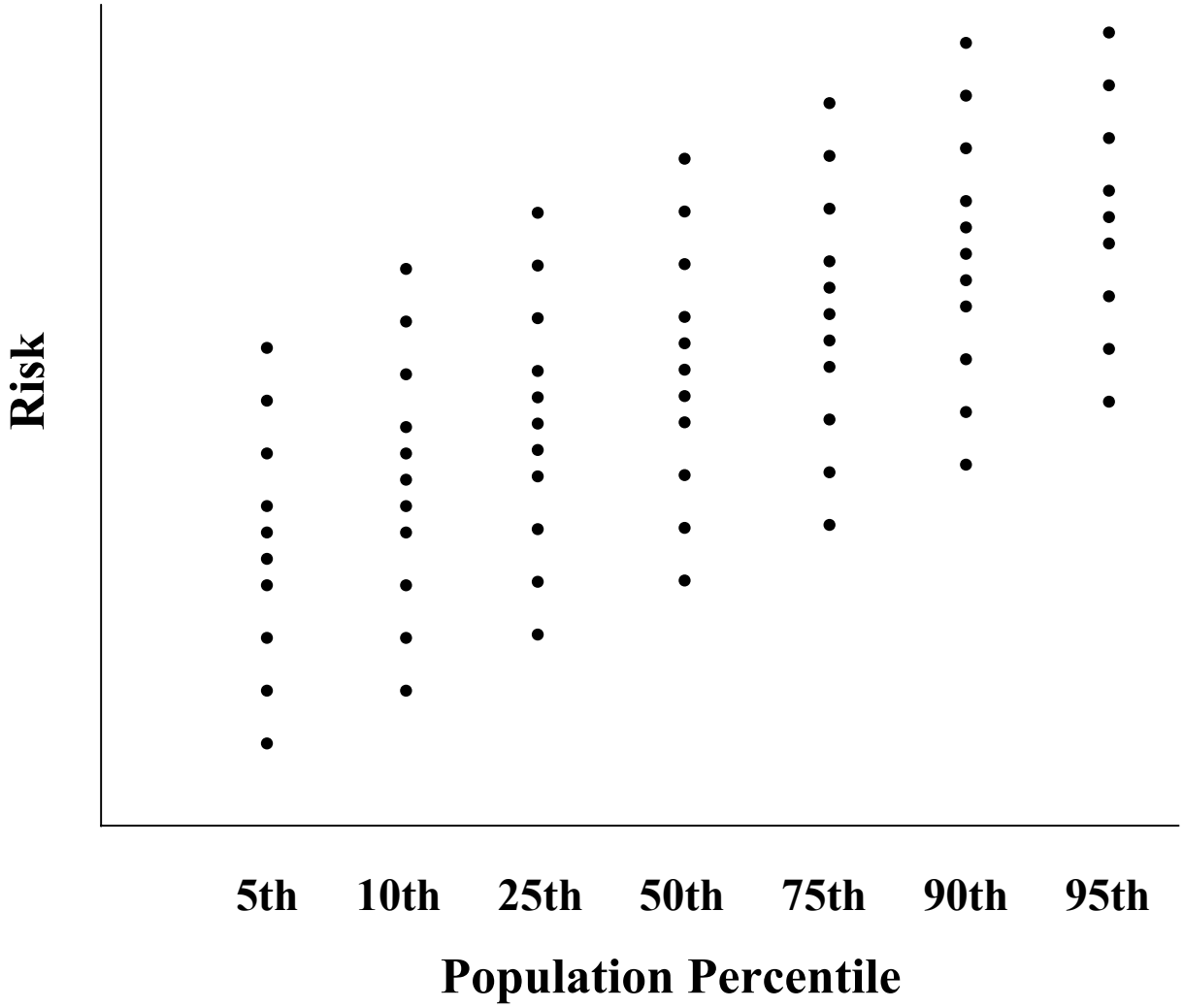


FIGURE 2-5

Quantification of Uncertainty and Variability using Two-Stage Monte Carlo Analysis. Y-axis shows variability in risk estimates for key population percentiles and X-axis shows uncertain parameters.

The plausible range of population average risk values for cancer, developmental toxicity and reproductive toxicity for the two treatment trains (filter-Cl_2, O_3-filter-Cl_2), as well as the reduction in lifetime risk by adding the O_3 pre-treatment are shown in Table 2-14. This table reports key percentiles from the uncertainty distribution describing the range of plausible values for the population average risk. It also reports the ratio of the 95^{th} and 5^{th} percentiles from these distributions, a quantity that serves as a useful benchmark for the purpose of characterizing the range of plausible risk values. The range of uncertainty for the cancer risks for the filter-Cl_2 treatment train is greater (7.1, see Table 2-14) than that for other risks from the same treatment train (e.g., developmental risks, 2.2) or for risks from the O_3-filter treatment train (e.g., 4.3, cancer risks).

Figures 2-6, 2-7, and 2-8 graphically illustrate these results for cancer. Figures 2-9, 2-10, and 2-11 depict these results for developmental toxicity. Finally, Figures 2-12, 2-13, and 2-14 illustrate these results for reproductive toxicity. Uncertainty in the slope factor estimates accounts for the largest portion of the parametric uncertainty in risk estimates for the cancer endpoints. Whereas, the concentration of unidentified total organic halide (TOX) DBP contributes the largest portion of the parametric uncertainty in the developmental and reproductive toxicity endpoints (see Tables 2-15, 2-16, and 2-17).

Not all of the sources of uncertainty could be quantified. Several potential sources of uncertainty not evaluated include:

- exposure
    - the assumption that tap water ingestion dominates intake,

TABLE 2-14

Plausible Range of Population Average Risk Values

Summary Statistic	Filter-Cl_2	O_3-Filter Cl_2	Ozone Pre-Treatment Risk Reduction
	Cancer		
Mean	1.4E-4	1.8E-4	-4.0E-5
5th percentile	5.2E-5	8.4E-5	-1.2E-4
10th percentile	5.9E-5	9.8E-5	-1.0E-4
25th percentile	7.6E-5	1.2E-4	-7.2E-5
50th percentile	1.0E-4	1.5E-4	-4.6E-5
75th percentile	1.4E-4	2.0E-4	-1.7E-5
90th percentile	2.3E-4	2.6E-4	1.2E-5
95th percentile	3.7E-4	3.6E-4	4.5E-5
95th pctl¸ 5th pctl	7.1	4.3	
	Developmental Toxicity		
Summary Statistic	Filter-Cl_2	O_3-Filter Cl_2	Ozone Pre-Treatment Risk Reduction
Mean	9.9E-7	1.1E-6	-9.9E-8
5th percentile	6.5E-7	6.2E-7	-6.0E-7
10th percentile	7.1E-7	7.2E-7	-4.7E-7
25th percentile	8.3E-7	8.8E-7	-3.0E-7
50th percentile	9.6E-7	1.1E-6	-1.1E-7
75th percentile	1.1E-6	1.3E-6	9.6E-8
90th percentile	1.3E-6	1.5E-6	2.8E-7
95th percentile	1.4E-6	1.6E-6	3.9E-7
95th pctl¸ 5th pctl	2.2	2.6	
	Reproductive Toxicity		
Summary Statistic	Filter-Cl_2	O_3-Filter Cl_2	Ozone Pre-Treatment Risk Reduction
Mean	2.5E-6	2.6E-6	-7.7E-8
5th percentile	1.1E-6	1.1E-6	-1.4E-6
10th percentile	1.3E-6	1.2E-6	-1.1E-6
25th percentile	1.7E-6	1.7E-6	-5.4E-7
50th percentile	2.3E-6	2.4E-6	-8.9E-8
75th percentile	3.1E-6	3.1E-6	3.9E-7
90th percentile	4.0E-6	4.3E-6	9.8E-7
95th percentile	4.8E-6	5.1E-6	1.3E-6
95th pctl ¸ 5th pctl	4.4	4.6	

pctl = percentile

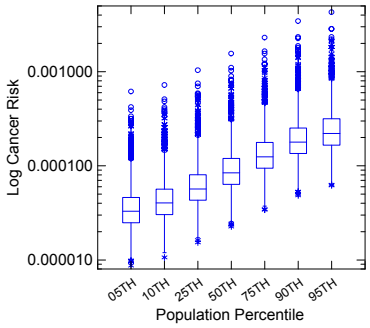


FIGURE 2-6. Lifetime Cancer Risk: Filter-Cl_2 Treatment

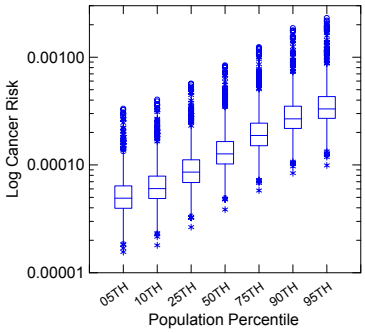


FIGURE 2-7. Lifetime Cancer Risk: O_3-Filter-Cl_2 Treatment

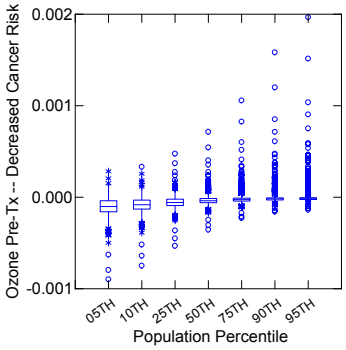


FIGURE 2-8. Reduction in Lifetime Cancer Risk Achieved by Adding Ozone Pretreatment

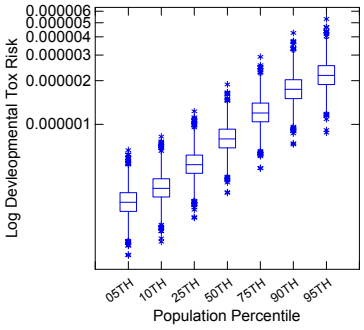


FIGURE 2-9. Lifetime Developmental Toxicity Risk: Filter-Cl_2 Treatment

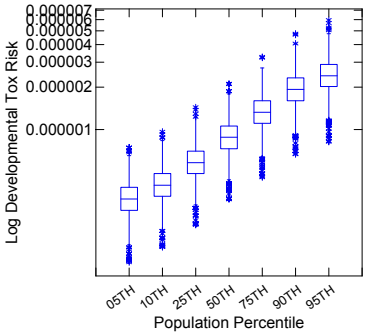


FIGURE 2-10. Lifetime Developmental Toxicity Risk: O_3-Filter-Cl_2 Treatment

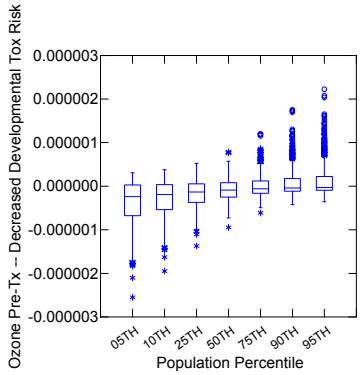


FIGURE 2-11. Reduction in Lifetime Developmental Toxicity Risk Achieved by Adding Ozone Pretreatment

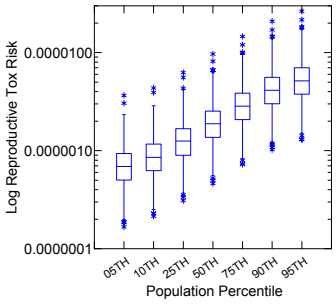


FIGURE 2-12. Lifetime Reproductive Toxicity Risk: Filter-Cl_2 Treatment

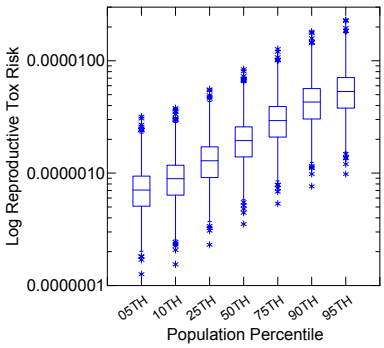


FIGURE 2-13. Lifetime Reproductive Toxicity Risk: O_3-Filter-Cl_2 Treatment

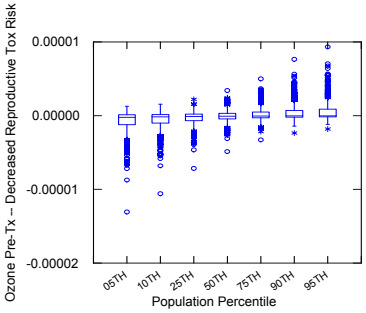


FIGURE 2-14. Reduction in Lifetime Reproductive Toxicity Risk Achieved by Adding Ozone Pretreatment

TABLE 2-15

Proportion of Parametric Uncertainty in Cancer Risk Explained[a,b]

	Disinfection Technology		
Concentration Filter-Cl_2	Filter-Cl_2	O_3-Filter-Cl_2	Filter-Cl_2 - O_3-Filter-Cl_2
BDCM			
CDBM			
$CHBr_3$			
CH			
DCA			
TCA			
Bromate			
Unidentified TOX	3%		13%
Concentration O_3-Filter-Cl_2	Filter-Cl_2	O_3-Filter-Cl_2	Filter-Cl_2 - O_3-Filter-Cl_2
BDCM			
CDBM			
$CHBr_3$			
CH			
DCA			
TCA			
Bromate			1%
Unidentified TOX		9%	26%
Slope Factor	Filter-Cl_2	O_3-Filter-Cl_2	Filter-Cl_2 - O_3-Filter-Cl_2
BDCM	10%	13%	
CDBM	10%	24%	2%
$CHBr_3$			
CH		1%	
DCA	72%	46%	44%
TCA	2%		2%
Bromate		3%	10%

[a] The proportion of variance explained is equal to incremental sums of squares after all other parameters have been added to the regression model (see Equation 2-8) divided by the total model sums of squares.

[b] For clarity, only values exceeding 1% are displayed.

TABLE 2-16

Proportion of Parametric Uncertainty in Developmental Toxicity Risk Explained[a, b]

Concentration Filter-Cl_2	Disinfection Technology		
	Filter-Cl_2	O_3-Filter-Cl_2	Filter-Cl_2 - O_3-Filter-Cl_2
DCA			
TCA			
MBA			
DBA			
BCA			
DCAN			
TCAN			
BCAN	1%		
DBAN			
Unidentified TOX	48%		32%
Concentration O_3-Filter-Cl_2	**Filter-Cl_2**	**O_3-Filter-Cl_2**	**Filter-Cl_2 - O_3-Filter-Cl_2**
DCA			
TCA			
MBA			
DBA			
BCA			
DCAN			
TCAN			
BCAN			
DBAN			1%
Unidentified TOX		60%	62%
Slope Factor	**Filter-Cl_2**	**O_3-Filter-Cl_2**	**Filter-Cl_2 - O_3-Filter-Cl_2**
DCA	5%	2%	
TCA	8%	3%	
MBA			
DBA			
BCA			
DCAN	29%	22%	
TCAN			
BCAN	6%	6%	
DBAN		1%	1%

[a] The proportion of variance explained is equal to incremental sums of squares after all other parameters have been added to the regression model (see Equation 2-8) divided by the total model sums of squares.

[b] For clarity, only values exceeding 1% are displayed.

TABLE 2-17

Proportion of Parametric Uncertainty in Reproductive Toxicity Risk Explained[a, b]

Concentration Filter-Cl_2	Disinfection Technology: Filter-Cl_2	Disinfection Technology: O_3-Filter-Cl_2	Disinfection Technology: Filter-Cl_2 - O_3-Filter-Cl_2
DCA			
DBA			
BCA			
Unidentified TOX	93%		34%
Concentration O_3-Filter-Cl_2	**Filter-Cl_2**	**O_3-Filter-Cl_2**	**Filter-Cl_2 - O_3-Filter-Cl_2**
DCA			
DBA			
BCA			
Unidentified TOX		97%	68%
Slope Factor	**Filter-Cl_2**	**O_3-Filter-Cl_2**	**Filter-Cl_2 - O_3-Filter-Cl_2**
DCA	7%	3%	
DBA			
BCA			

[a] The proportion of variance explained is equal to incremental sums of squares after all other parameters have been added to the regression model (see Equation 2-8) divided by the total model sums of squares.

[b] For clarity, only values exceeding 1% are displayed.

    - the use of *total* tap water intake value (rather than another estimate of tap water intake such as unheated tap water),

- toxicity
    - use of QSAR to quantify the proportion of unidentified DBP associated with health endpoint, h (α_h),
    - the assumption that the unidentified DBP pose the same risk as the identified DBP on a µg OX/L basis,
    - the assumption that chloroform is a threshold carcinogen,
    - use of animal toxicity data to quantify the potency or slope factor (S_i), and
    - the assumption that the slope factors (S_i) are statistically independent.

The exposure assumption that ingestion dominates intake could be important if other routes of exposure result in much more efficient uptake or metabolism of the DBP. Total tap water intake as the relevant measure of exposure is unlikely to be important as shown by the uncertainty analysis. While there is some speculation that heating tap water may remove some of the volatile DBP, restricting attention to the intake of only unheated water affects the estimate of risk by at most a factor of 2, indicating that this assumption is not a relatively important source of uncertainty.

The proportion of unidentified DBP associated with health endpoint, h ($\alpha_{h,}$) was quantified using QSAR. Table 2-18 summarizes the impact of these extreme alternative assumptions on the expected value of the population average risk. The range of risks associated with the extreme alternative assumptions of 0% or 100% generally spanned a factor of approximately 5 to 10, suggesting that this assumption does not substantially contribute to uncertainty.

TABLE 2-18

Impact of Alternative Assumptions for α_h on Estimated Risk
(Expected Value of the Population Mean Risk)

Health Endpoint	Base Analysis	Alternative Analyses α = 0%	Alternative Analyses α = 100%
Filter-Cl_2			
Cancer	1.4E-4	5.2E-5	2.1E-4
Developmental Toxicity	9.9E-7	3.7E-7	1.8E-6
Reproductive Toxicity	2.5E-6	6.3E-7	5.1E-6
O_3-Filter-Cl_2			
Cancer	1.8E-4	6.6E-5	2.7E-4
Developmental Toxicity	1.1E-6	2.7E-7	1.7E-6
Reproductive Toxicity	2.6E-6	4.3E-7	4.3E-6

The assumption that the unidentified DBP pose the same risk as the identified DBP was evaluated by assuming alternatively that the unidentified DBP pose only 50% the risk as the identified DBP (on a mg OX/L basis), and that the unidentified DBP pose twice the risk as the identified DBP (on a mg OX/L basis) (Table 2-19). The results indicate that this range of assumptions corresponds to a range of risk estimates spanning a factor of approximately 5 to 10.

The assumption that chloroform is a threshold carcinogen affects the overall risks by approximately 1.2 to 1.4, despite the assumption that the concentration of chloroform is large and exceeds that of many of the other DBP. Whether or not chloroform is a carcinogen at environmentally relevant exposure levels affects the cancer risk estimates for two reasons. First, because the concentration of chloroform exceeds that of many other DBP, its potential contribution to carcinogenicity is substantial. The assumption of a threshold dose-response for carcinogenicity removes its contribution from the risk estimate. Second, because chloroform's concentration is large compared to that of other DBP, its classification as a carcinogen affects the estimated risk associated with exposure to unidentified DBP. Specifically, if it is not classified as a carcinogen, its potency is removed from the weighted average used as an estimate of the typical potency of an unidentified DBP. Since chloroform's assumed potency is less than the weighted average potency of the other identified DBP, removing it from consideration (by assuming it does not behave as a carcinogen at environmentally relevant doses) increases the weighted average potency of the set of identified DBP. These two influences on risk work in the opposite direction and hence,

TABLE 2-19

Impact of Alternative Assumptions for the Relative Toxicity of Unidentified DBP *vs.* Known DBP on Estimated Risk
(Expected Value of the Population Mean Risk)

Health Endpoint	Base Analysis	Alternative Analyses	
		Relative Tox = 50%	Relative Tox = 200%
Filter-Cl_2			
Cancer	1.9E-4	52.E-5	2.4E-4
Developmental Toxicity	9.9E-7	3.7E-7	1.6E-6
Reproductive Toxicity	2.5E-6	6.3E-7	4.4E-6
O_3-Filter-Cl_2			
Cancer	1.8E-4	6.6E-5	2.9E-4
Developmental Toxicity	1.1E-6	2.7E-7	1.9E-6
Reproductive Toxicity	2.6E-6	4.3E-7	4.8E-6

partially cancel each other out. Assuming chloroform is a threshold carcinogen decreases the total cancer potency of the identified DBP, but increases their potency on a per mg OX/Cl basis, increasing the assumed potency of the unidentified DBP.

Risk estimates computed using the assumption that for each health endpoint, the slope factors are perfectly correlated and do not differ substantially from the risk estimates computed, with the assumption (used in the CRFM document) that these quantities are statistically independent. This finding indicates that the assumption of statistical independence is not an important source of uncertainty.

In place of the animal bioassay data used to quantify DBP carcinogenicity, the epidemiology literature could be used. The following discussion estimates the approximate degree to which the use of the epidemiology results would affect the results of the risk assessment.

For the purpose of this analysis, attention is restricted to bladder and rectal cancer. The SEER statistics data base reports the lifetime risk of disease for these types of cancer:

- For bladder cancer, the lifetime risk is 2.27% (Ries et al., 1998, Table XXVI-8), although the risk for males is much higher (3.37%) than it is for females (1.17%);
- For colon and rectal cancer [get rectal only], the lifetime risk is 5.56% (Ries et al., 1998, Table VI-13).

Since the odds ratios for these diseases are not much greater than unity, the incremental risk of disease can be estimated as the product of the population lifetime risk and 1 minus the odds ratio. Dividing this incremental risk by total daily TOX intake yields an estimate of the slope factor in $(mg/kg\text{-}day)^{-1}$. In place of a measured dose level, daily TOX intake is estimated here as the product of the average concentration for

the Cl-filter treatment train (approximately 0.25 mg/L, Table 3.1-2, U.S. EPA, 1999) and the arithmetic average daily tap water intake rate (0.022 L/kg-day[1]). Table 2-20 summarizes the calculation of the slope factor for bladder cancer and rectal cancer. Assuming that these types of cancer represent the vast majority of the cancers caused by exposure to disinfected drinking water, the slope factor for total TOX in disinfected drinking water is the sum of the slope factors for these individual cancers. This slope of 4.7 $(mg/kg\text{-}day)^{-1}$ can be compared to the animal bioassay-derived concentration-weighted average slope factors for identified DBP. Using the mean DBP concentration values as the weights, along with the slope values estimated from animal bioassay data (Table 4-2, U.S. EPA, 1999) yields an average slope factor of 9×10^{-3} $(mg/kg\text{-}day)^{-1}$ for the filtration-chlorine train, and 1.8×10^{-2} $(mg/kg\text{-}day)^{-1}$ for the ozone-filtration-chlorine treatment train. Therefore, the epidemiologically-derived slope factor exceeds the animal bioassay derived averages by more than 2 orders of magnitude. The risk calculated using the epidemiologic information is approximately 500 times larger than the risk determined from the animal data, supporting that the "suggestive" findings for cancer from the epidemiologic data may be considered important and that the risk estimated from the animal studies could be an underestimate.

2.6. PARTICIPANT DISCUSSION: CURRENT DATA AND METHODOLOGIES

The participants noted that the context of use of the epidemiologic data in the CRFM case study differs from the usual epidemiologic context. In the case study, the question is not whether there is solid evidence for causality, but whether the

[1] The arithmetic mean is the proper summary statistic to use. Since risk is hypothesized to be linear in dose, the average risk for the population as a whole is equal to the risk for an individual whose consumption is equal to that of the average for the population. The average intake rate was calculated by averaging the arithmetic means of the lognormal intake rates calculated in U.S. EPA (1999, Section 3.2).

TABLE 2-20

Calculation of Total TOX Cancer Slope Factor Using Morris et al. (1992) Meta Analysis Results

Cancer Type	Population Lifetime Risk	Odds Ratio Minus 1	Tox Concentration (mg/L)	Tap Water Intake (L/kg-day)	Total TOX Dose (mg/kg-day)	Slope $(mg/kg\text{-}day)^{-1}$
Bladder	2.27%	0.21	0.25	0.022	$5.5x10^{-3}$	$8.7x10^{-1}$
Rectal	5.56%	0.38	0.25	0.022	$5.5x10^{-3}$	$3.8x10^{0}$
Total						4.7

epidemiologic studies point to some probability, or a likely outcome. The indication of adverse reproductive or developmental effects from epidemiologic data should not be excluded.

The participants acknowledged the data gaps in research on DBP. It was noted that there are a number of studies underway in animals regarding pharmacokinetics of DBP. In addition, it was acknowledged that there are limitations in using gavage animals studies (a bolus dose of a chemical in a vehicle which may also have an effect) for predicting response in humans consuming tap water throughout the day. The participants questioned why, in the comparison of risks with animal and epidemiologic data, bladder cancer was chosen as there has been no comparable tumor seen in animals studies. Kidney tumors in animal studies of the DBP may not be the most relevant tumors for extrapolation to humans. It was suggested that gastrointestinal tumors (i.e., colo-rectal tumors from the human studies and large intestine in animal studies) might be more appropriate. The participants thought the question of the necessity (or not) of site-concordance required further discussion during the breakout sessions (Refer to Section 4).

The participants addressed the question of how the exposure assessment approach in the CRFM could be improved. It was stated that examination of central tendency and distribution of the whole population does not always provide information on the subpopulation. For example, more recent information on pregnant women suggests that consumption may increase during pregnancy. Consumption also varies based on activity (e.g., recreation, exercise) and time at residence (consumption at home vs. at work). It was noted that CSFII addresses some concerns about

consumption information for subpopulations. For example, consumption data are segregated by age, geography, race, pregnancy, lactating women, and socio-economic status in the survey. The CSFII also reports consumption data for bottled water, soda, tea, and coffee. It was noted that chemical constituents present in bottled water are often not known; some bottled water is treated. The participants reiterated that the presence and concentration of DBP varies based on numerous factors including the source, storage and distribution systems and the influence of biota (may breakdown organic halides). There are daily and seasonal changes in the concentration of DBP both at the tap and throughout the treatment train. There are some studies in progress on the effect of heating water on the concentrations of DBP. Additional research needs be designed to look at chemical constituents, exposure differences and to make comparisons at points throughout the water distribution system (Section 4.1 discusses these points in more depth).

In response to the question posed by EPA as to how to incorporate information on the unidentified DBP into the risk assessment, the participants felt that the assumption that the unidentified DBP pose the same risk as the identified DBP is a big assumption. There is also uncertainty in that there may be a correlation between concentration of constituents and daily intake (e.g., a high concentration may reduce the intake due to taste, odor aversion). It was noted that Richardson (1998) did not identify all the chemicals in drinking water. The TIX may be closer in approximating the toxicity of the DBP than the TOX. The unidentified DBP may be high molecular weight, polar compounds such as pesticides or solvents, that could be more toxic than the TOX. The mean of the TOX should be included as well as the median when showing results as it

is a useful descriptor. Section 4.2 presents the breakout group discussion of the unidentified constituents.

It was noted that it is the assumptions that are driving the sensitivity analysis in the CRFM (i.e., the results may be an artifact of the assumptions). The model used to determine parameters having the greatest influence on the determination of risk (Equation 2-8) is very strongly linear and may overlook nonlinear components that explain the risk. The point was made that one needs a better understanding of the epidemiology data to better explain the variance. It was acknowledged that there is a lot of uncertainty not being captured by the Monte Carlo analysis. These points are further discussed in Section 4.

3. NOVEL METHODS FOR MIXTURES

3.1. PRESENTATION: DOSE-RESPONSE MODELING IMPROVEMENTS: CANCER (D. Hattis)

Knowledge of the process of cancer, defined here as the end result of a sequence of heritable changes in somatic cells, provides support for the assumption of low-dose linearity in risk assessment. Genetic modes of action where the chemical or agent reacts directly with DNA is based on bimolecular reaction kinetics as well as pharmacokinetic processes (i.e., Michaelis-Menten enzyme kinetics and transport) that are linear at low doses. Pharmacodynamics, that is the events between DNA reaction and the appearance of tumors, are also linear. One caveat is the possible induction of repair or defensive metabolizing enzymes that, in some low-moderate dose range, result in "fixing" more background damage from other agents/cancer processes than the direct damage induced by the compound under study. When a low-dose linear process is combined with a process that is highly nonlinear at low doses, or with a nonlinear process at high doses, the linear process is the determinant of the overall response.

How should uncertainty/confidence distributions for cancer potency estimates for chemicals where there are bioassay data be derived? There are approaches to determining minimal estimates of uncertainty from the biological literature. Estimates using log-normal distributions of three types of activities (Table 3-1), showed a geometric standard deviation (GSD) of approximately 5. Uncertainty can be inferred from three cases of PBPK-based risk analysis with ethylene oxide, butadiene, and perchloroethylene (Table 3-2 and Figures 3-1 and 3-2). Using the PEA upper confidence limit (UCL) estimate of risk as approximately a 95^{th} percentile value (1.6449

TABLE 3-1

Indicated Variability for Non-Redundant Data Sets By Activity Category

Activity Category	Total Number of Data Sets Number of Non-Redundant Data Sets[a]	Geometric Mean of Log_{10} (GSD)	(5%-95% Range)
Metabolic Activation	24	22	.253 (.132-.482)[b]
Detoxification	27	19	.243 (.087-.681)
DNA Repair	20	18	.295 (.134-.650)
Complex	7	5	.375 (.167-.843)
Total	78	61	

[a] In some cases, the data for a particular data set were analyzed in two ways: (1) as a whole-population aggregate, and (2) broken-down into separate subcategories by genotype, gender, cancer cases vs. controls, etc. The numbers in this column and the calculations in the final column represent distinct whole-population, non-redundant data sets.

[b] These ranges were calculated assuming that the distribution of the Log_{10}(GSD) values for variability for different data sets is itself log-normally distributed. These ranges therefore represent an estimate of the variability measurements among different specific kinds of activities, tissues, etc.

GSD = geometric standard deviation

TABLE 3-2

Uncertainties in Carcinogenic Risk Estimates For Genetically-Acting Agents, as Inferred from Three Case Studies of PBPK-Based Risk Analyses

Compound	Hattis "Best Estimate"	Hattis "Plausible Upper Limit"	EPA UCL CPF	Hattis Best/ Hattis UCL Ratio	Hattis Best/ EPA UCL Ratio
Ethylene Oxide	0.0065	0.019	2.80E-02	0.342	0.232
Butadiene	0.00079	0.032	9.80E-02	0.025	0.008
Perchloroethylene	0.00067	0.013	3.30E-03 Geom. Mean Geom. Std Deviation. Geometric Std. Err.	0.052 0.076 3.881 2.188	0.2093 0.072 6.703 2.999

UCL = upper confidence limit

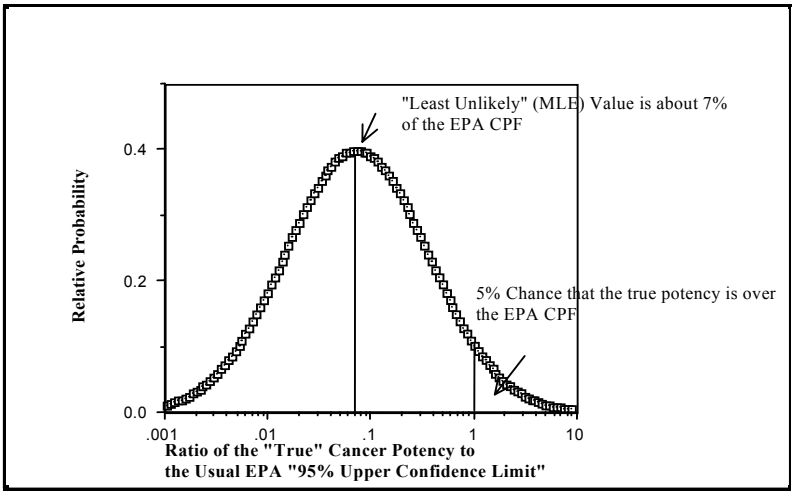


FIGURE 3-1

Estimated Likelihood Distribution for Cancer Potencies for Genetically-Acting Carcinogens – Log Plot

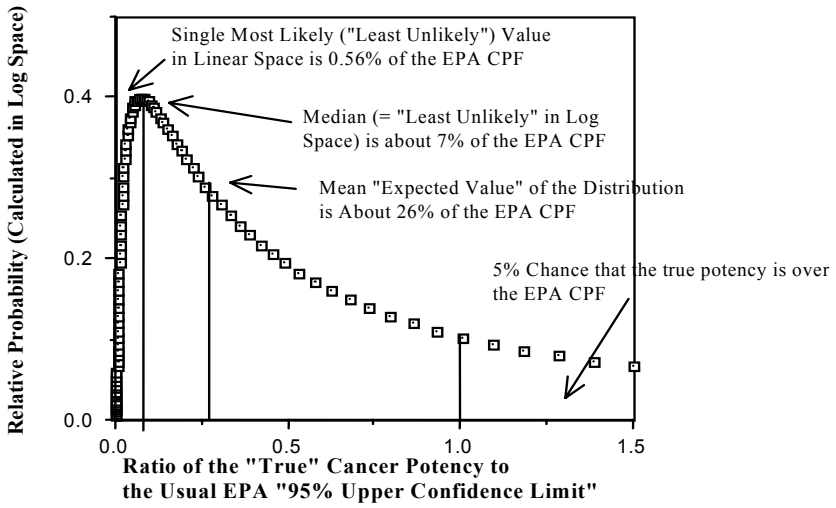


FIGURE 3-2

Estimated Probability Distribution for Cancer Potencies for Genetically-Acting Carcinogens – Linear Plot

standard deviations above the median) and representing uncertainties as log-normally distributed about a median estimate at about 0.072 times the EPA UCL, then the geometric standard deviation of the lognormal distribution representing uncertainties is $10^{[\log(.0724)/1.6449]} = 4.93$ (Hattis and Goble, 1991; Hattis and Barlow, 1996; Hattis and Minkowitz, 1996). Work by Crouch (1996) and by Kodell et al. (1996) showed a GSD of 10.5-11. Table 3-3 shows a scale for understanding the differences between particular percentile of log normal distributions. For example, a GSD of 5 shows a 200-fold difference between the 5th and 95th percentile. This is one approach to showing central tendency and the range of variability. Another way of expressing risk in terms of both variability and uncertainty is shown in Table 3-4. The intersection of the arithmetic mean of the uncertainty distribution and the arithmetic mean of the variability distribution (8.2×10^{-7}) is the expected risk for an individual of unknown susceptibility.

3.2. PRESENTATION: MODELING IMPROVEMENTS - DEVELOPMENTAL DATA (B. Allen)

Developmental risk assessment has traditionally been conducted by determining the NOAELs (no-observed-adverse effect levels) and LOAELs (lowest-observed-adverse effect levels) in animal studies; these determinations are based on a comparison of statistical or biological differences between groups. Uncertainty factors are applied to the LOAELs or NOAELs for derivation of an RfD (chronic oral reference dose) or RfC (chronic inhalation reference concentration).

Dose-response modeling as a feasible alternative to NOAEL-based approaches is a relatively new concept in developmental toxicology. Benchmark doses (BMD) or concentrations (BMC) can be estimated for a pre-determined response, typically one not far from the range of observation.

TABLE 3-3

A Scale For Understanding Lognormal Variability Fold Differences Between Particular Percentiles of Lognormal Distributions

Log_{10}(GSD)	Geometric Standard Deviation	5%-95% Range (3.3 stand deviations)	2.5%-97.5% Range (3.9 standard deviations)	1%-99% Range (4.6 standard deviations)
0.1	1.26	2.1 fold	2.5 fold	2.9 fold
0.2	1.58	4.5 fold	6.1 fold	8.5 fold
0.3	2.0	10 fold	15 fold	25 fold
0.4	2.5	21 fold	37 fold	73 fold
0.5	3.2	44 fold	91 fold	210 fold
0.6	4.0	94 fold	220 fold	620 fold
0.7	5.0	200 fold	560 fold	1,800 fold
0.8	6.3	430 fold	1,400 fold	5,300 fold
0.9	7.9	910 fold	3,400 fold	15,000 fold
1	10.0	1,900 fold	8,300 fold	45,000 fold

TABLE 3-4

Example of a Combined Presentation of Variability and Uncertainty Variability and Uncertainty for a Conventionally Assessed 10^{-6}/Lifetime 95% Upper-Confidence-Limit Individual Cancer Risk--260 Million People Exposed -Uncertainty Dimension (Z)-

Variability Dimension (Y)	50% Confidence Level	Arithmetic Mean ("Expected Value")	90% Confidence Level	95% Confidence Level
Median Sensitivity Individual (50th percentile)	7.2E-08	2.6E-07	5.8E-07	1.0E-06
Arithmetic Mean Sensitive Individual	1.8E-07	8.2E-07	1.7E-06	3.1E-06
1/10 Most Sensitive Individual (90th percentile)	4.2E-07	1.7E-06	3.6E-06	6.5E-06
1/20 Most Sensitive Individual (95th percentile)	6.8E-07	3.1E-06	6.2E-06	1.2E-05
1/100 Most Sensitive Individual (99th percentile)	1.7E-06	1.0E-05	1.9E-05	3.8E-05
1/1,000 Most Sensitive Individual (99.9th percentile)	4.6E-06	4.6E-05	6.7E-05	1.6E-04
1/100,000 Most Sensitive Individual (99.99th percentile)	1.0E-05	1.8E-04	1.9E-04	5.2E-04
1/Million Most Sensitive Individual (99.9999th percentile)	4.1E-05	1.6E-03	1.1E-03	3.8E-03
Number of People Expected to Be Affected/Year – 260 Million Exposed	0.68	3.0	6.1	11

Uncertainty factors are still applied, in this case to the BMD or BMC, to derive a regulatory limit such as an RfD or RfC.

A clear understanding of the mechanism of action is not a prerequisite for the BMD approach. However, there are several features unique to developmental toxicity data that must be considered in any dose-response modeling. While the dam is considered the experimental unit, as she receives the treatment, it is the risk to the embryo or fetus that is desired. Moreover, there may be a mixture of continuous and quantal endpoints within and among fetuses that are measured in a developmental study. Response may depend on a number of covariates other than dose, such as the size of the litter. Intralitter correlation is very likely (although its magnitude is not known with certainty and may vary depending on the endpoint(s) and mechanism of action of the chemical insult).

Quantal endpoints (i.e., those responses for which one counts the presence or absence of the effect) include resorption, death, malformation, or anomaly. Such endpoints have been modeled as follows.

First, to account for intralitter correlation, one can assume that each litter has an independent underlying probability that a fetus will be affected (for any endpoint). There is a mean probability of response depending on dose (and litter size); the litter-specific probabilities of response vary around the mean according to a beta distribution. Figure 3-3 shows the variety of shapes (for the probability density function) that can be obtained with a beta distribution.

Second, one assumes that within litters, fetuses respond independently according to a binomial model. Overall, a beta-binomial model is obtained. Responses

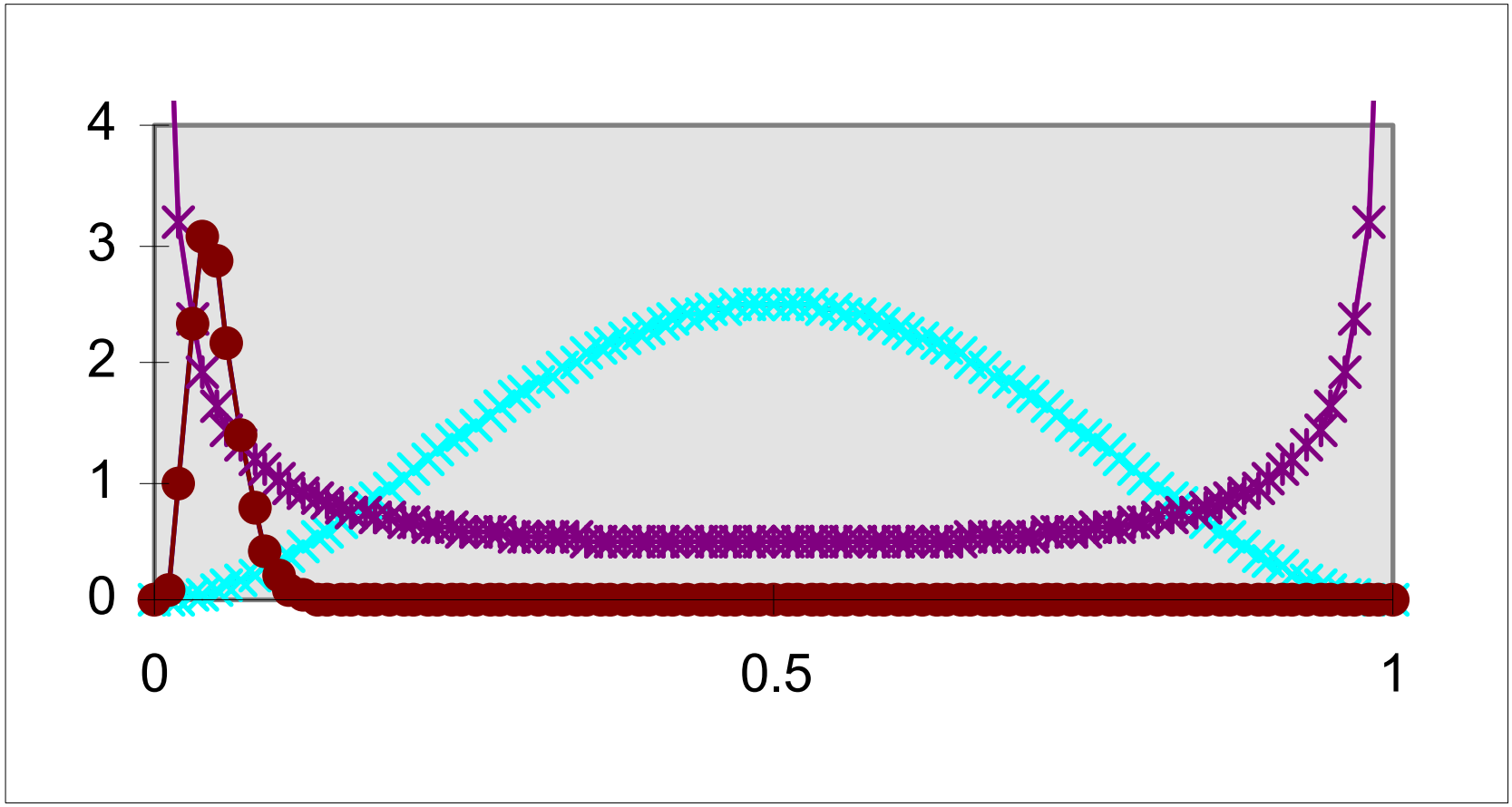


FIGURE 3-3

Beta Distributions

are correlated because fetuses in the same litter (with the same underlying probability of response) respond more similarly to one another than they do to other fetuses from other litters.

The work of Allen et al. (1994) suggests a log-logistic model, shown below in Equation 3-1, works well for quantal endpoints in developmental studies,

$$P(d,s) = a + r_1 s + (1 - a - r_1 s)/[1 + \exp\{B + r_2 s - g*\log(d-d_0)\}] \qquad (3\text{-}1)$$

where d is dose, s is litter size, and d_0 is the threshold dose parameter. The threshold dose parameter as well as the parameters a, r_1, r_2, B, and g are estimated by the maximum likelihood method. The log logistic model represents the relationship between dose (and litter size) and the mean of the beta distribution of probabilities of response discussed above.

A large-scale study of the log-logistic model (among several others) was reported by Allen et al. (1994). The log-logistic model was compared to litter-based estimates (estimating the probability of one or more affected fetuses within any given litter), generic models of fetal effect probabilities (using the overall proportion of affected fetuses without regard to grouping within litter), and two other fetal-based models specific to developmental toxicity (the so-called Rai and Van Ryzin and NCTR models). It was found that the log-logistic model can describe the results from a wide variety of actual, observed developmental toxicity studies. Moreover, the comparison of the log-logistic model to the Rai and Van Ryzin and NCTR models revealed that the log-logistic model was more flexible in dealing with litter size effects on probability of response. In the majority of cases studied by Allen et al. (1994), litter size was an important explanatory variable. BMD levels were determined that, on average, afforded the same

degree of protection as the NOAEL-based approach. When based on the log-logistic model predictions, a 95% lower bound on the dose associated with 5% additional risk provided that same level of protection.

Continuous endpoints, such as fetal weight or crown-rump length, are also observed in developmental toxicity studies and can be modeled, individually, with dose-response models. Two modeling approaches have been used. First, the "mean of means" model, shown in Equation 3-2, estimates changes in litter means and provides estimates of the dose-dependency of the mean of means. For any dose level, the litter specific means are assumed to vary normally around the mean predicted by Equation 3-2 (with, typically, each group allowed to have a variance independent of that in other groups). A disadvantage to this approach is that there is no direct link to the calculation of risk.

$$M(d) = a + b*d^r \qquad (3\text{-}2)$$

where: a is the intercept, b is the slope, and d is dose.

A second approach to modeling continuous endpoints is to convert the continuous response to a quantal response. For example, the probabilities of abnormally-low fetal weight could be modeled using the log-logistic model (Equation 3-1). This model can estimate risk, but "normal" and "abnormal" response needs to be explicitly defined by the toxicologist. The two models yield different answers sometimes; it is not clear which model is preferable.

The multinomial modeling approach is a way to consider more than one endpoint at a time and a means by which both quantal and continuous effects can be treated together. Multinomial models are based on a sequence of biological events and attempt

to represent the probability of the induction of one or more endpoints (e.g., fetal death), as shown in Figure 3-4. These models are more complicated than the preceding quantal or continuous models, but may be more biologically-based and may address the issue of multiple endpoints. Developed by Chen and colleagues at NCTR and by Ryan and colleagues at Harvard (Catalano et al., 1993), the main features of these models are that:

- latent variables underlying the observation of malformations are considered,
- conditional probability models for malformations are dependent on fetal weight (individual and litter average), and
- the GEE (generalized estimation equation) approach is used for parameter estimation (rather than the maximum likelihood estimation).

Biologically-based models have also been considered in the context of developmental toxicity risk assessment. Such models tend to be highly chemical-specific, and their main advantages are associated with the fact that they incorporate chemical-specific pharmacokinetics and pharmacodynamics and that they consider mechanism of action information. The models of EPA's NHERL Laboratories (Shuey et al., 1994), David Gaylor and colleagues at NCTR (Gaylor and Razzaghi, 1992), and Leroux and colleagues at the University of Washington (Leroux et al., 1996) are three examples of biologically-based models.

The most complete model is that of Shuey et al., shown in Figure 3-5, wherein the mechanism of induction of malformations and/or fetal weight reduction is modeled based on inhibition of thymidine synthetase and subsequent effects on alteration in cell cycling and dysmorphology. The model of Gaylor and Razzaghi considers the

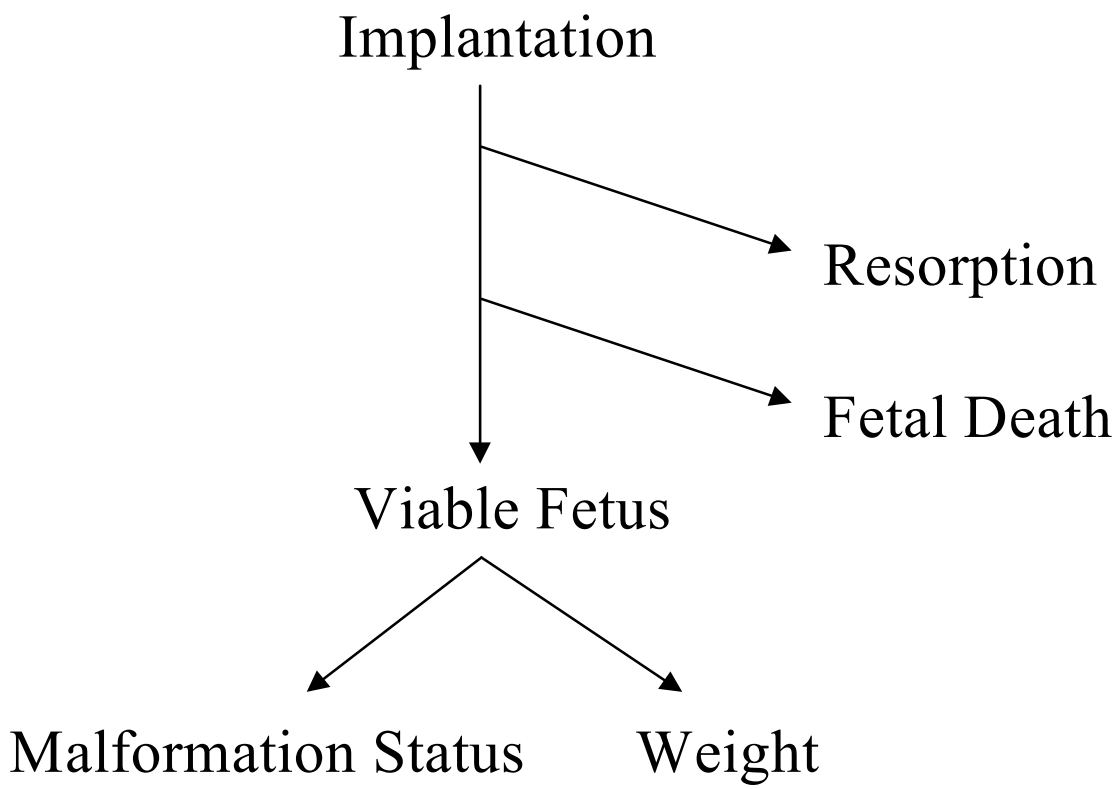


FIGURE 3-4

Multinomial Models

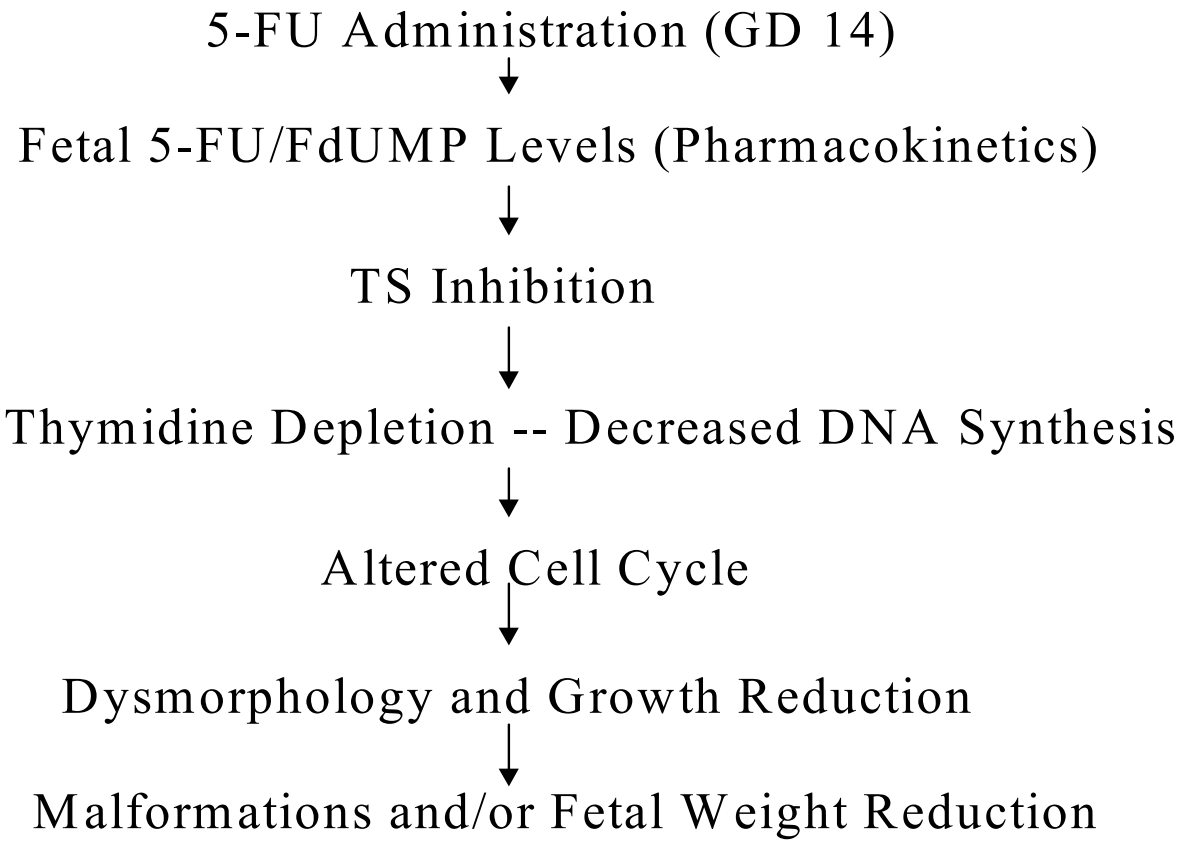


FIGURE 3-5

BBDR of 5-Fluorouracil: Shuey et al., 1994

development of an n-stage process. These researchers have examined the dose-dependent effect of chemicals on critical cell populations (see, for example, Equation 3-3). In the case of cleft palate formation, for instance, there is a stage of cell population growth with a critical number of cells needed for normal palatal development. Equation 3-3 could be the basis for modeling a chemical's potential for interference in normal population growth to that critical number. The model of Leroux et al. is similar to multistage cancer modeling (Figure 3-6). It focuses on cell differential as one critical factor.

$$N(t,d) = N_0 \exp\{B_0 * t * \{-a * d^r\}\} \quad (3\text{-}3)$$

The biologically-based modeling approaches to developmental toxicity risk assessment are relatively new and will take time to progress. In the meantime, BMD approaches are available and likely can be applied successfully to risk assessment of the developmental toxicity associated with exposure to the DBP. In many cases, that would entail estimating a BMD corresponding to 5% or 10% risk followed by use of a toxicologically based uncertainty factor (or, in those rare instances where no threshold was assumed and where low-dose linearity was thought to be appropriate, use of linear extrapolation). Such procedures might be recommended for the CRFM case study.

3.3. PRESENTATION: DOSE-RESPONSE MODELING IMPROVEMENTS: REPRODUCTIVE TOXICITY (D. Hattis)

Two reproductive effects will be the focus of this section: male fertility effects (i.e., the use of sperm counts and other sperm quality parameters as predictors of male fertility) and infant mortality as a consequence of low birth weight and decreased gestational age. These endpoints will be used to demonstrate some approaches to modeling dose-response data for reproductive endpoints.

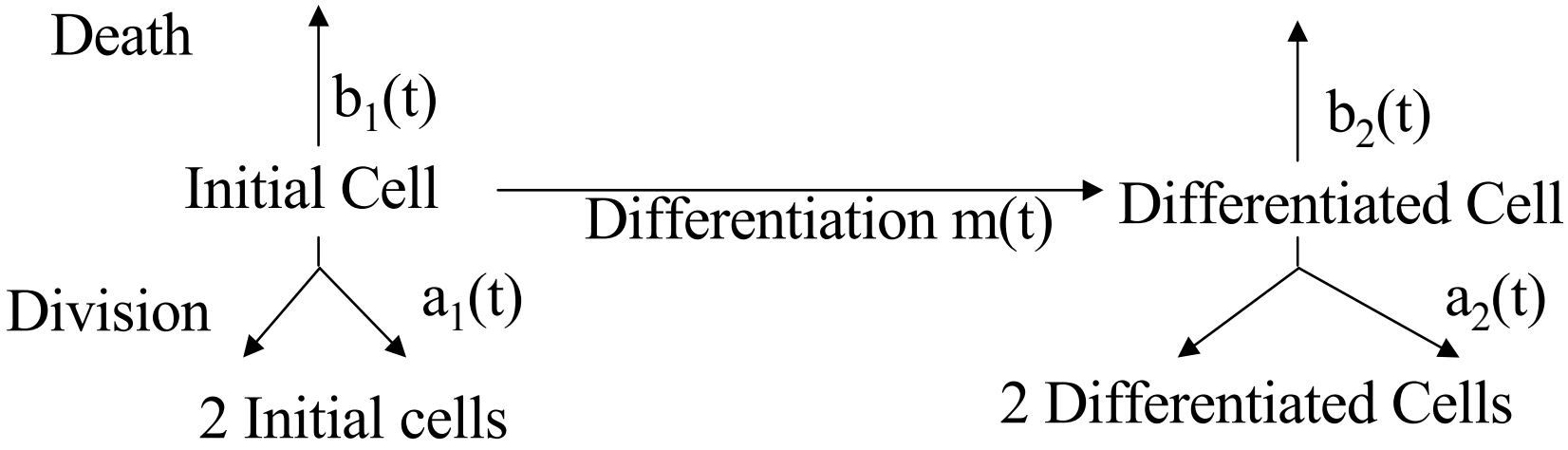
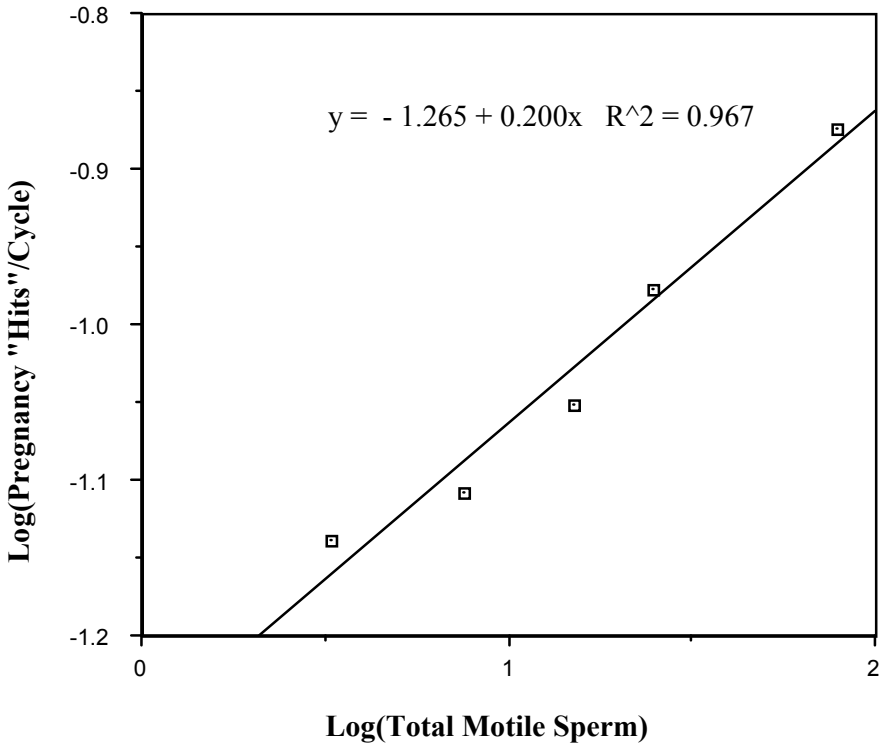


FIGURE 3-6

BBDR Modeling: Leroux et al., 1996

Sperm count and other sperm quality parameters are used as predictors of male fertility. One approach is to evaluate the incidence of infertility. For example, Meistrich and Brown (1983) defined the increase in "% infertility" as the fraction of couples presenting themselves for evaluation and treatment after at least a year of unprotected intercourse. Another approach is to model the effect of sperm counts on the per-cycle conception probability and the distribution of conception times. Data supporting this approach include couples presenting themselves for treatment of infertility (Steinberger and Rodrigues-Rigau, 1983); data from artificial insemination (Hattis, 1998); and data from prospective studies of "unselected" couples (Clegg, 1999). Hattis (1998) analyzed the data of Brasch et al. (1994), which provided the frequency of conception per cycle for intrauterine insemination as a function of the total number of motile sperm that are available for use. The relationship was far less than linear; that is, increasing numbers of sperm increase the probability of conception, but not proportionately (Figure 3-7). If 80 million sperm are available, then the conception probability is a little less than double what it would be with only 3-8 million sperm. Clegg (1999) found that the most important parameters are the total number of sperm and the percentage of strictly normal sperm; each parameter has high-dose saturating behavior. That is, there is a point at which increases in sperm count are not linearly-related to increased fertility.

Over many orders of magnitude, there is a strong relationship between infant mortality and birth weight (Figure 3-8). Birth weight is likely a marker for incomplete development. Hattis and coworkers (Ballew and Hattis, 1989; Rees and Hattis, 1994; Hattis, 1998) conducted an analysis of the implications of reduced fetal weights in relation to glycol ether exposures in animals. Fetal weight was used as a predictor for



*The "hits/cycle" data that form the basis of the y axis are derived with the aid of a "one-hit" transformation of the original observations of the frequency with which couples in different groups conceived during the period of observation:

Observed fraction of couples who conceive = 1 - Poisson Probability of 0 "Hits"/Couple = 1 - $c^{-\text{conception "hits"/couple}}$, therefore
conception "hits"/couple = -ln(1-observed fraction of couples who conceive)

FIGURE 3-7

Log Log Plot of the Relationship Between Total Motile Sperm Count and Pregnancy "Hits" Per Menstrual Cycle (Data of Brasch et al., 1994)

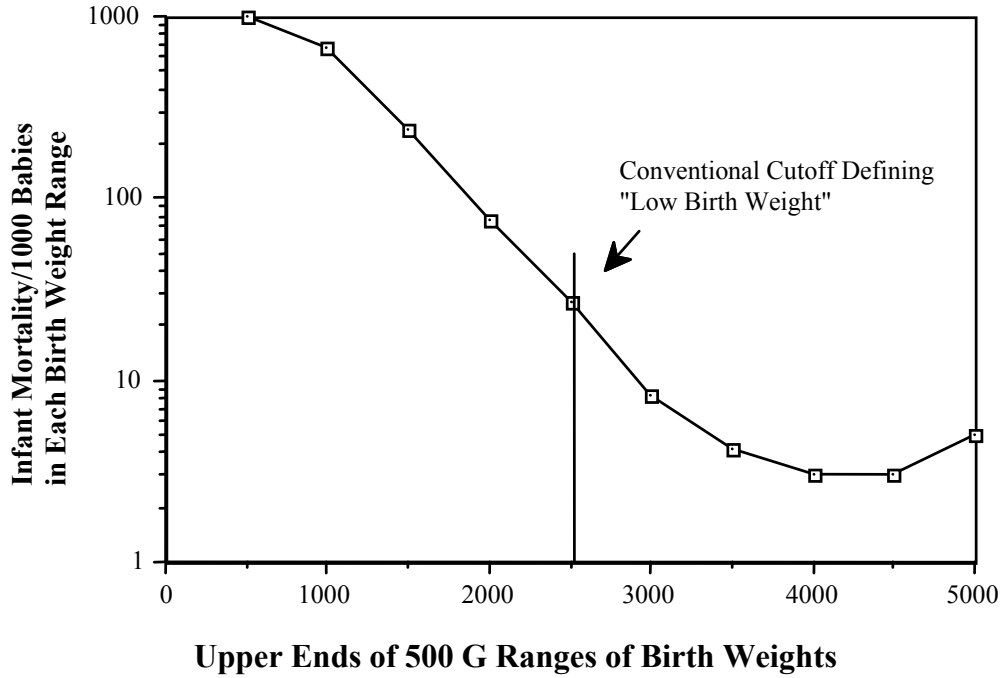


FIGURE 3-8

Relationship Between Weight at Birth and Infant Mortality

fetal mortality (see Figure 3-9). Recent tests of the predictive accuracy of the relationship between birth weight and infant mortality have included the effect of smoking on birth weight and the incidence of premature births (<37 weeks of gestation). The effects of smoking on birth weights and prematurity predict the magnitude of the effect of various amounts of smoking on infant mortality. Advantages to using birth weight are that it:

- is a continuous variable and statistically powerful,
- is an important predictor of responses that are not easily measured directly (e.g., infant mortality), and
- responds to modest degrees of environmental exposure.

The latter is supported by data on cigarette smoking from the 1990 Birth Cohort Linked Birth/Infant Death Data Set (NCHS, 1996), where 6 cigarettes/day produces a 180 g reduction in birth weight (Figure 3-10), and by data on altitude (Cogswell and Yip, 1995), where 4000 feet elevation results in a 70 g reduction in birth weight (Figure 3-11). Disadvantages to using birth weight as a biomarker for potential adverse effects, are that it:

- is affected by many “confounders”, many of which are not recorded on birth certificates and cannot be controlled, and
- is a non-specific indicator (i.e., it does not provide information on distinctive exposures).

One approach would be to use sperm count, fetal weights, or another endpoint as a biomarker for potential human effects. After dose-response modeling, the results would be extrapolated to humans (e.g., using $BW^{3/4}$ power). The significance of these markers would be interpreted from human information. This approach was applied to the animal fetal weight data of Smith et al. (1988) after exposure to trichloroacetonitrile

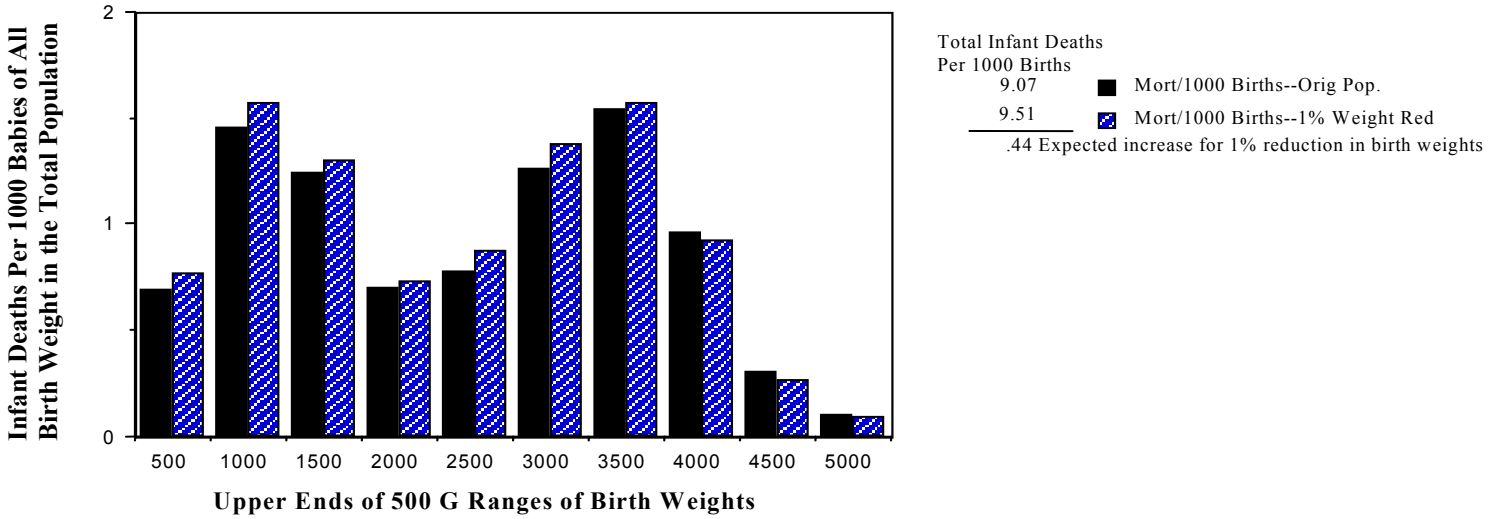


FIGURE 3-9

Expected Effect of a 1% Reduction in Birth Weights on the Distribution of Overall Infant Deaths Per 1000 Babies Born in the Total Population

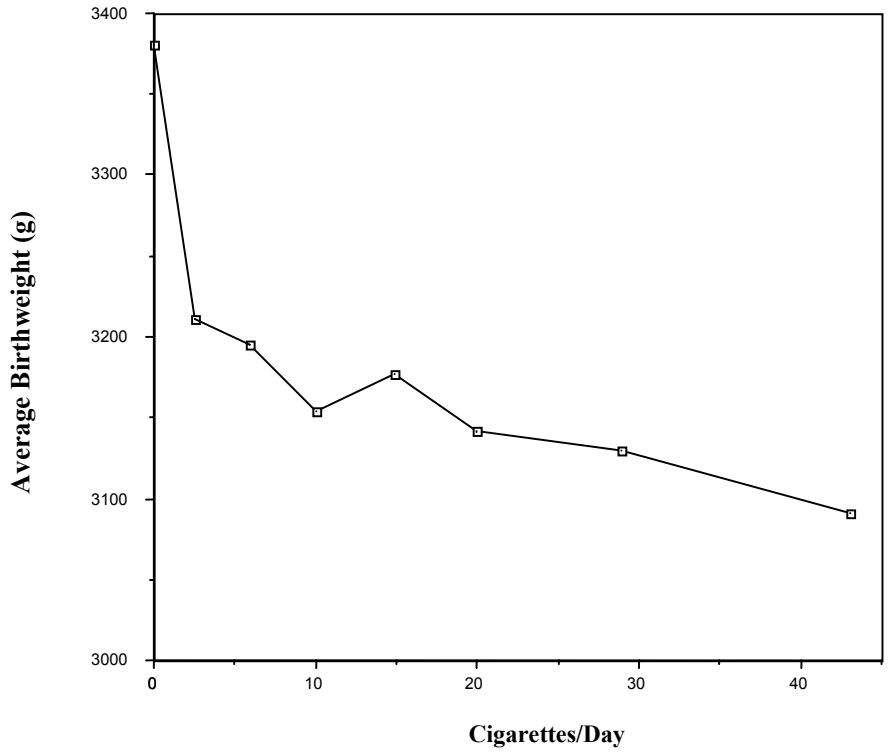


FIGURE 3-10

Effect of Cigarette Smoking on Birthweight; 1990 Data for All Races, All Gestational Ages

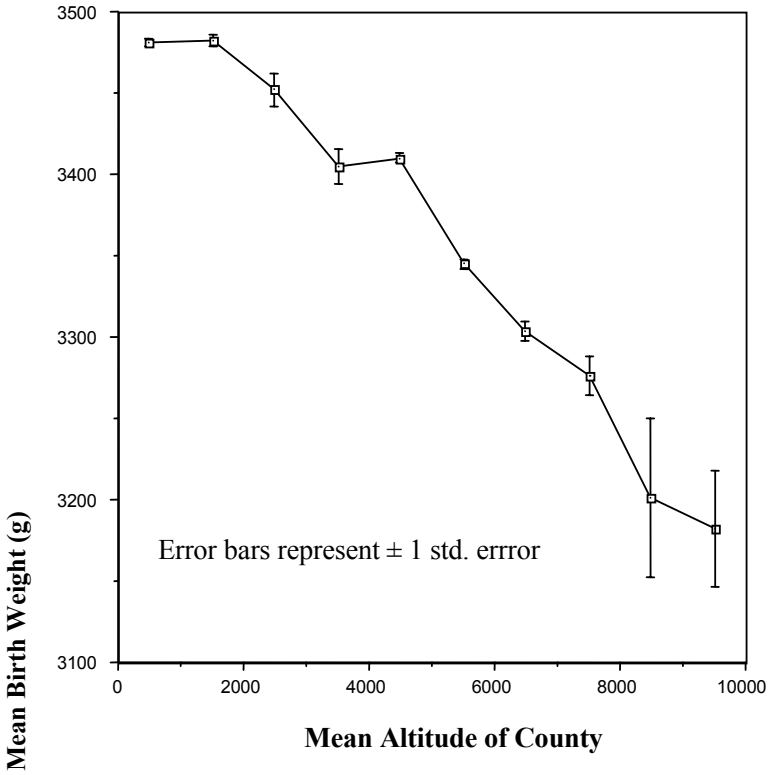


FIGURE 3-11

Effect of Maternal Residence on Mean Birth Weight

(TCAN), the data of Christ et al. (1995) after exposure to bromochloroacetonitrile (BCAN), and the data of Smith et al. (1989) after exposure to trichloroacetic acid (TCA) as shown in Figures 3-12, 3-13, and 3-14, respectively. As an alternative approach, a TEF approach was taken using TCA equivalents from the data of Christ et al. (1995), Smith et al. (1988, 1989a, 1992), Randall et al. (1991), and Smith et al. (1989b), as shown in Table 3-5. Three different fits (linear, simple quadratic, cubic) were made to the fetal weight and TCA equivalent (mg/kg); the cubic fit is shown in Figure 3-15.

These types of approaches could be applied to the current problems for reproductive effects of the DBP and in the CRFM case study.

3.4. PRESENTATION: DBP HUMAN EXPOSURE ESTIMATES: MULTI-ROUTE (C. Weisel)

Exposure is any contact with a chemical, biological, or physical agent at the boundary of the body over a specified period of time. How the substance contacts the body resulting in a dose is the exposure route; these include inhalation, ingestion and dermal penetration. The exposure pathway is how the substance moves from the source to the receptor. For DBP, exposure pathways start with their formation in the treatment plant and go throughout the distribution system to the tap in the home, at work, or other locations where people drink or use the water.

Exposure to DBP in drinking water has been studied by linking the concentration at the point of contact with the route, amount, and duration of that contact. In addition to the ingestion route considered in the CRFM, inhalation and dermal exposures need to be considered (U.S. EPA, 1994). Figure 3-16, adapted from the National Research Council (1991), provides an overall framework to look at exposure. Figure 3-17 shows

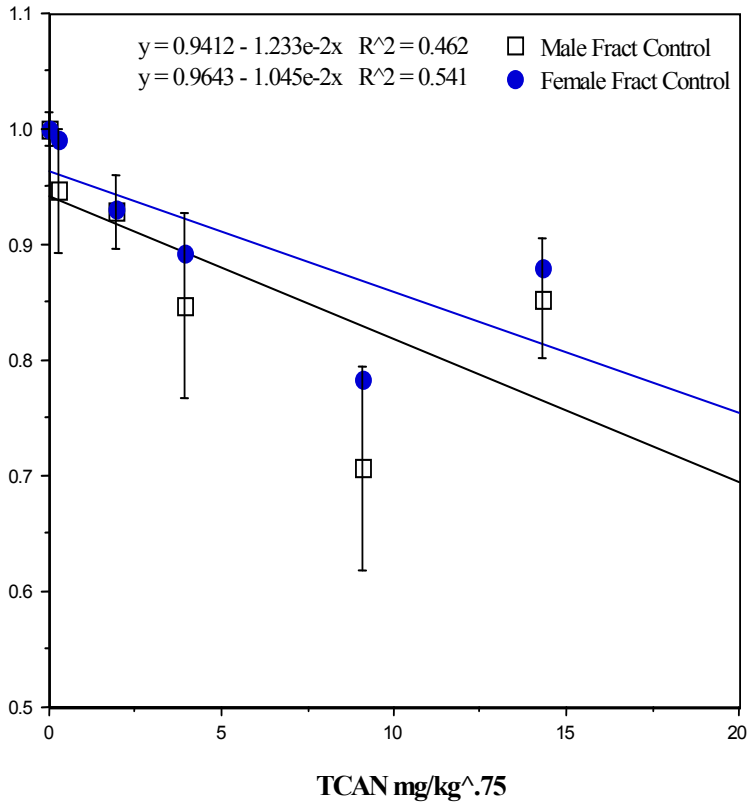


FIGURE 3-12

Data of Smith et al. (1988) on the Fetal Weight Response to Trichloroacetonitrile

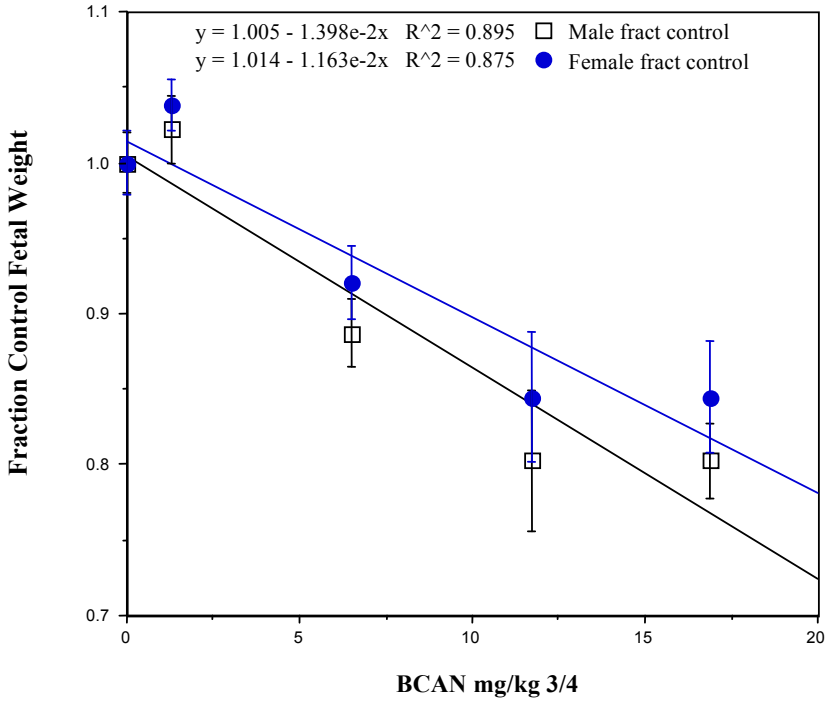


FIGURE 3-13

Data of Christ et al. (1995) on the Fetal Weight Response to Bromochloroacetonitrile

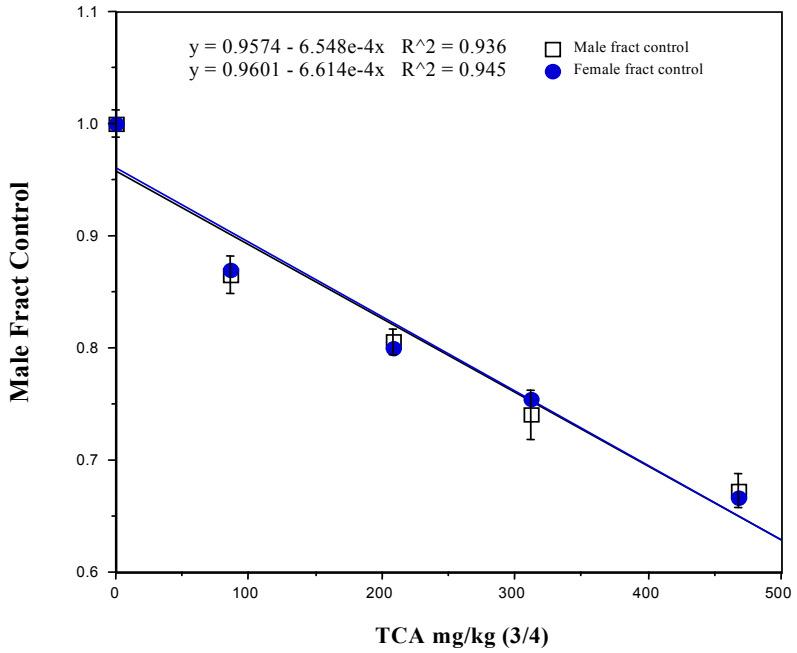


FIGURE 3-14

Data of Smith et al. (1989a) on the Fetal Weight Response to Trichloroacetic Acid

TABLE 3-5

Calculated Toxic Equivalency Factors (TCA Dose Equivalents) for the Potency of Various DBP for Reducing Fetal Weights in Animals

	TEF fitted	(mg TCA equiv/mg chemical)
TCA	1	(defined)
DCA	0.74	
MBA	2.3	
DCAN	28.3	
TCAN	12.1	
BCAN	7.5	
fetal weight/TCA dose-equivalent slope	7.86E-04	Fractional change in fetal weight/ ($mg/kg^{3/4}$ TCA human equivalents)

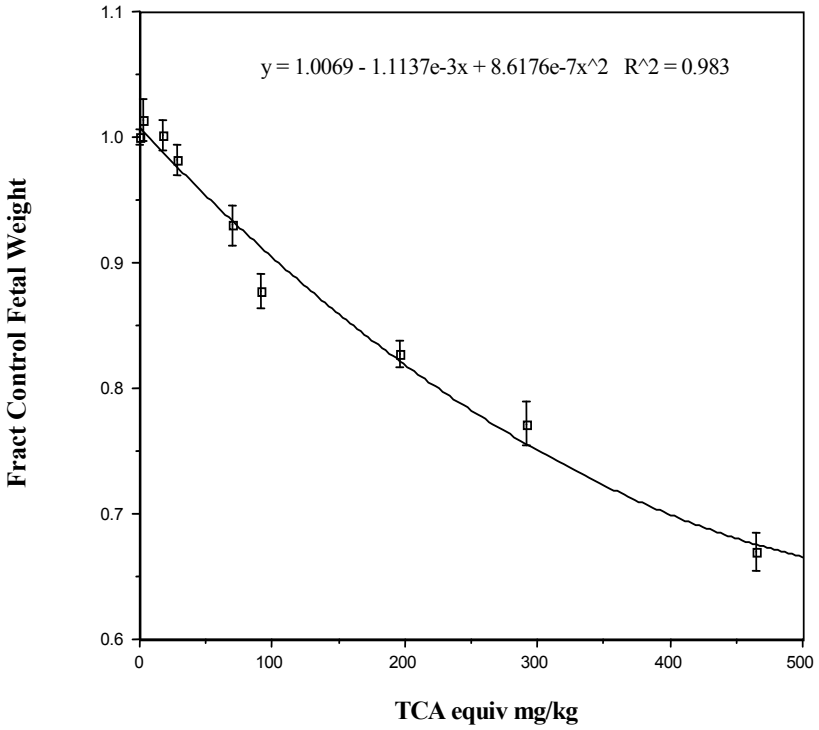


FIGURE 3-15

Results of Regression Analysis of the Fraction of Control Fetal Weight Response in Grouped Categories of TCA Equivalents

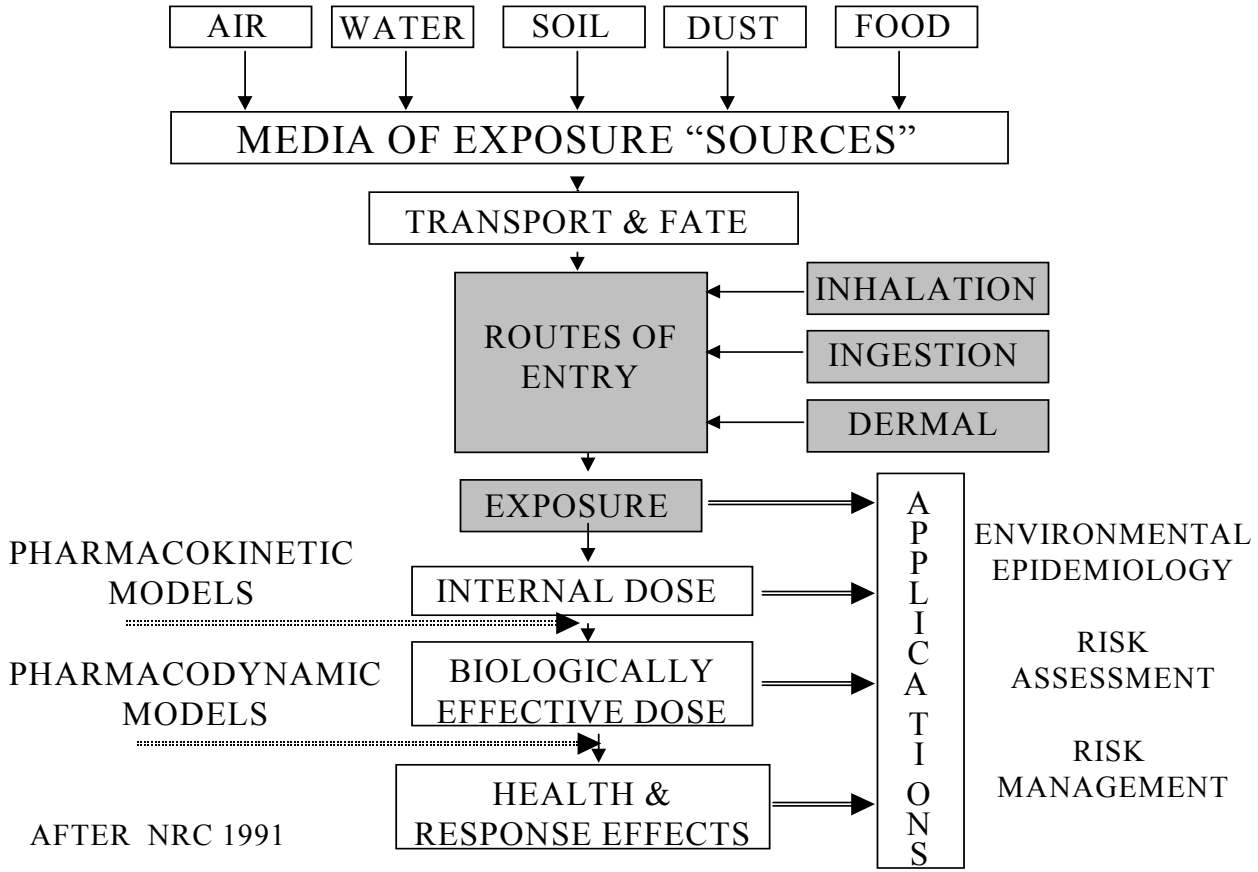


FIGURE 3-16

Exposure Framework

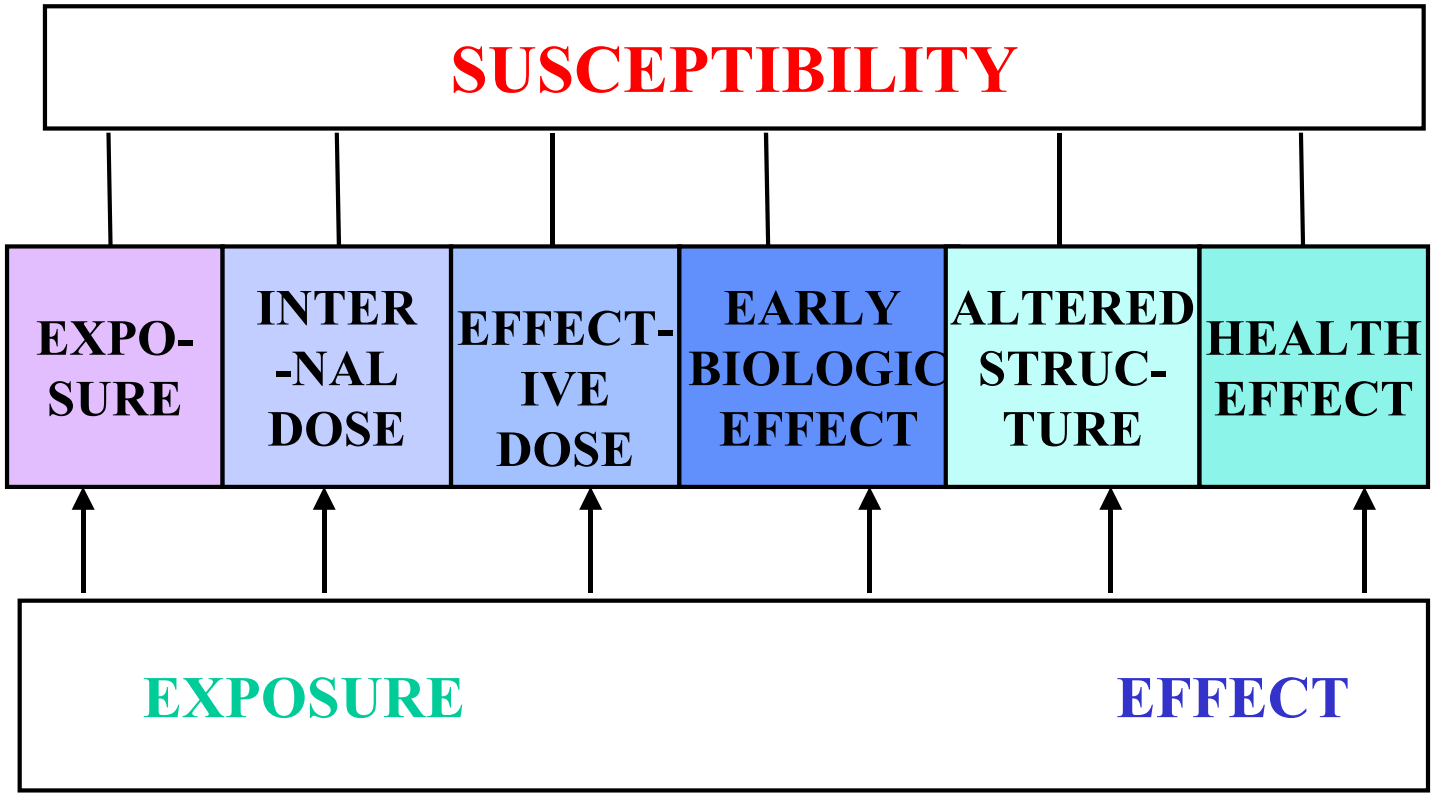


FIGURE 3-17

Biomarker Continuum

the continuum of biomarkers from exposure to internal dose of the agent and, effective dose at the target tissue, through induction of an early biologic effect (related to sensitivity and susceptibility of individuals and subpopulations), through alteration of structure (such as RNA and DNA) and adverse health effect(s). Approaches to evaluating DBP include conducting:

- individual exposure assessment,
- ecological epidemiological study, and /or,
- case control or cohort studies.

Each of these approaches uses a variety of tools, such as:

- questionnaires,
- multimedia measurements (e.g., in air, water)
- biomarker measurements,
- modeling (for population exposure assessments), and
- historic reconstruction (to understand what happened in the past).

Studies of DBP in water indicate multiple exposure routes; looking only at ingestion of DBP is not sufficient for estimating exposure. Shower stall and indoor air concentrations are elevated with respect to volatile DBP after showers and other water uses. As shown by measurement of biomarkers in studies of aqueous solutions in animals and in *in vitro* studies, some DBP cross the skin. Blood, breath, and urine DBP levels are elevated after showering, bathing, and swimming; as the concentration of volatile DBP increase, so do the levels of the biomarkers.

The shower studies of Weisel et al. (1990; Jo et al., 1990a, 1990b) evaluated the influence of inhalation and dermal exposure to DBP, specifically chloroform,

dibromochloromethane (DBCM), and bromodichloromethane (BDCM), during showers. Exposure to subjects was measured during a 10-minute shower (mean shower time), 10 minutes standing next to the shower (to measure only inhalation exposure), and 10 minutes showering while breathing filtered air (to measure only dermal exposure). Chloroform concentration was measured in the water, air, and exhaled breath of subjects during and following the shower. There was a linear relation between shower air and water concentrations of chloroform (Figure 3-18). After showering, chloroform breath concentrations of showering subjects were increased in a concentration-dependent manner with water chloroform concentrations, and decreased with cessation of exposure (Figure 3-19). As shown in Figure 3-20, comparison of chloroform breath concentration between normal and inhalation only showers, inhalation of chloroform is a significant exposure route. Further, the difference in breath concentrations between the two exposures can be attributed to the contribution of dermal exposure. This is also exemplified in Table 3-6. The duration of the shower increases chloroform breath concentrations, as does increasing the water temperature (Figure 3-21). Using assumptions about exposure parameters (e.g., breathing rate, absorption, chloroform concentration [25 µg/L], daily water consumption, etc.), dose contributions from the inhalation and dermal routes while showering were calculated and compared with chloroform exposure from water ingestion. As Table 3-7 shows, contributions from these routes can exceed the contribution from water ingestion.

Drinking of hot beverages (e.g., coffee, tea, soup) and cold beverages (e.g., water, reconstituted beverages, ice) contribute to exposure from ingestion. Water ingestion, an important exposure variable for the DBP, is affected by an individual's

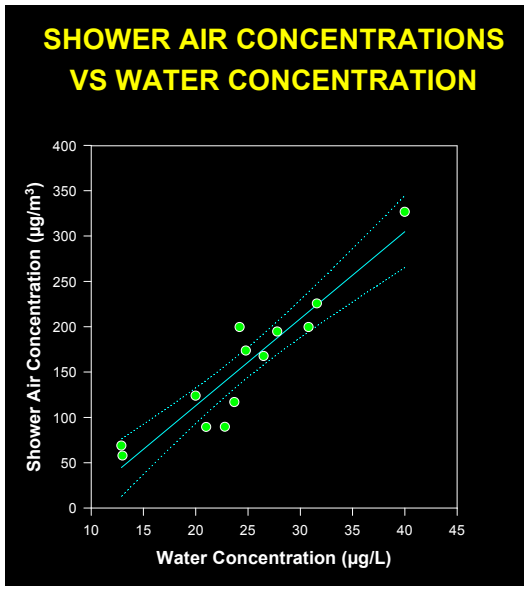


Figure 3-18. Shower Air Concentrations vs. Water Concentration

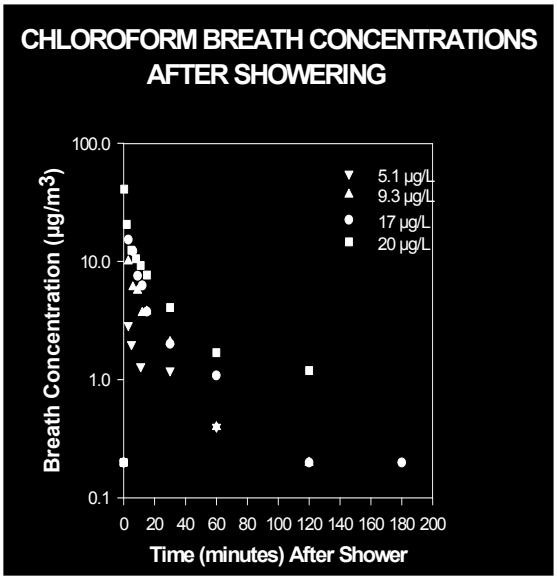


Figure 3-19. Chloroform Breath Concentrations After Showering

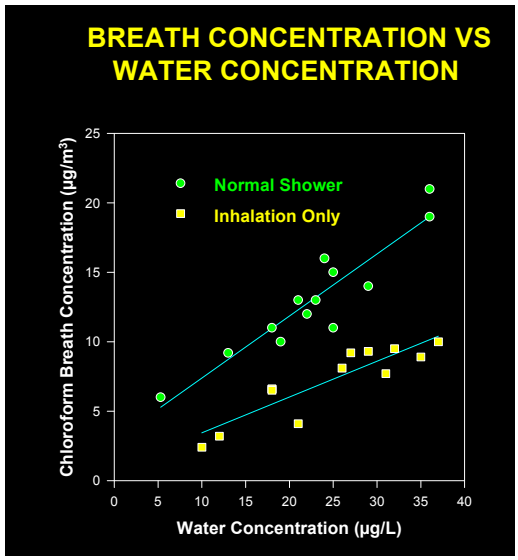


Figure 3-20. Breath Concentration vs. Water Concentration

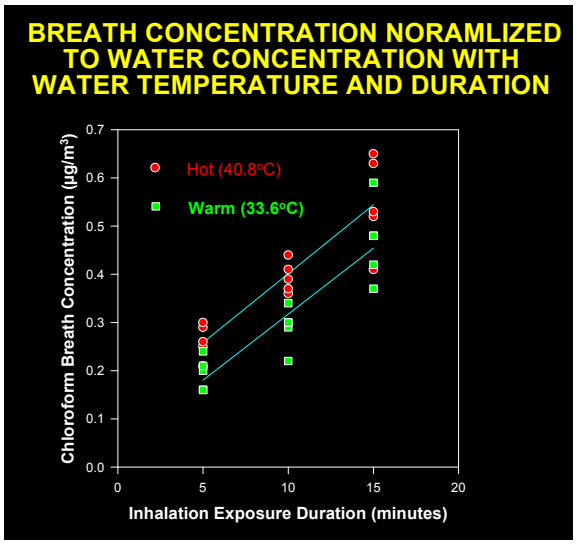


Figure 3-21. Breath Concentration Normalized to Water Concentration with Water Temperature and Duration

TABLE 3-6

Chloroform Breath Concentrations by Exposure Route[a]

Water Concentration 20-40 µg/L	Amount Expired After Exposure
Ingestion (0.5 L)	Not detected
Inhalation 10 minutes	0.02-0.05 µg
Dermal shower 10 minutes	0.02-0.13 µg
Dermal bath 10 minutes	0.33-0.56 µg

[a] Weisel and Jo (1996)

TABLE 3-7 Chloroform Dose for Shower Study[a]	
	Estimated Dose (µg/kg-day)
Normal Shower (10 minutes)	
Inhalation	0.24
Dermal	0.23
Total shower	0.47
Water Ingestion	
2 L	0.7
0.15 L	0.05

[a] Jo et al. (1990a)

habits (such as exercise), season/climate, and location/region. Median tap water ingestion is approximately 1.61 L/day (0.77-2.6 L/day is the range for the 10^{th}- 90^{th} percentiles). The temperature of the water affects the concentrations of some chemicals and may decompose other chemicals. For example, boiling of the water increases the concentration of nonvolatile chemicals. In contrast, heating of water volatilizes some chemicals (such as THM), decreasing their concentration in the water, but increasing their concentration in the air. These volatile species are released into the air based on Henry's Law and can be measured within shower stalls, over sinks, and in indoor air. Aerosol formation of non-volatile species occurs during spray of the water; aerosol spray undergoes size redistribution within the home. In addition to showering, vapors and aerosols are generated during humidifier use (likely a very important source), washing, bathing and other activities in the home contributing to levels of chemicals in indoor air. For showering/bathing, U.S. EPA (1997) uses defaults of 10 minutes (the median is closer to 7 minutes), 1 shower/day (although 5% of the population shower more than once per day), 350 days/year. The 50^{th}, 75^{th}, and 90^{th} percentiles for shower duration are 7, 9, and 12 minutes/day, respectively.

Inhalation exposure through distribution of vapors and aerosols within a home can be modeled. Air exchange processes are described to establish spatial and temporal changes in air concentrations. Use of water filters and hot water heaters are evaluated to determine whether a constant or variable water concentration is to be used for modeling. Breathing rate is a variable considered in estimating dose (Wilkes et al., 1996; Wilkes, 1999).

Direct dermal contact with DBP in water occurs during showering and bathing and also with washing and swimming. For small children (e.g., 3-7 years old), playing in wading pools may be a significant source of contact with these chemicals during the summer months. Two approaches have generally been used for modeling dermal exposures: steady state transference using permeability coefficients across the stratum corneum, and membrane flux, which considers skin structure, flux across the skin by skin type, and permeability coefficients (Roy et al., 1996; Bunge and McDougal, 1999).

Estimates of exposure concentrations from air or water are overlaid with "allowable" or reasonable scenarios and activity patterns to generate exposure distributions for the population. Activity patterns and other variables for the specific region are investigated so that water use patterns and other characteristics of the population can be established. Often, simulation routines (e.g., Monte Carlo techniques) are used to describe distributions of air and water uses, frequency, and duration. Consideration of age and years in residences (transient population groups), and changes in water concentrations over time are considered when examining chronic exposures. For acute exposures, the time of year for peak concentrations or other events are factored into predicting acute health outcomes (e.g., birth-related effects). A summary of the relative importance of various media in contributing to population dose is shown in Table 3-8 for chloroform and a non-volatile species (i.e., chromium).

Approaches to estimating exposure in epidemiological studies have focused on areas using chlorinated water based on chlorine use at the treatment plant over time. Measured or predicted concentrations of THM at the treatment plant are combined with

TABLE 3-8

Summary of Population Dose - mg[a]
(Assuming Unity Water Concentration)

	Route	50th	95th
Chloroform	Ingestion	1.3	2.6
	Inhalation	1.3	3.9
	Dermal	0.6	1.5
Non-volatile	Ingestion	1.3	2.6
	Inhalation[b]	<0.001	<0.001
	Dermal	0.005	0.011

[a] Wilkes (1999)

[b] Did not consider humidifiers

responses from residents to questionnaires. Questionnaires attempt to obtain information on:

- source of water and use of filtration systems,
- types and amounts of water used for cooking, bottled water use, and hot and cold water use,
- frequency, duration, and water temperature for showering and bathing,
- other water uses, such as humidifiers, washing, dishwasher, and washing machines,
- target populations, i.e., their location, activities, seasonality, children, pregnant and lactating women, time spent away from home (e.g., at work), and
- potential confounders, such as swimming and non-residential use.

Because water concentrations vary spatially and temporally, there are continued reactions with chlorine residuals and microbial degradation within the distribution system. THM may not be the biologically-active agent. Estimating exposure using only the ingestion route may not be accurate. Therefore, exposure may be misclassified in epidemiological studies due to these factors.

The Total Exposure Assessment Methodology (TEAM) study (Wallace et al., 1985, 1986, 1987) and more recent studies by Weisel et al. (1999b) are examples of population-based studies. These studies measured THM in indoor air. Median indoor chloroform levels were four times higher than outdoor levels in New Jersey, suggesting to the authors that water use was the source of chloroform (Wallace et al., 1987). THM breath concentrations, unlike some other volatile organic compounds, were related to water concentration, not indoor air concentration. More recent THM breath concentrations in New Jersey (Weisel et al., 1999b) showed lower levels than those

found by TEAM. Although associations were still found, the authors attributed the lower breath levels to lower water concentrations of these chemicals. Post-shower breath concentrations documented the strong association for THM with water concentration (Tables 3-9, 3-10, and 3-11). The concentration and ingestion of trichloroacetic acid (TCAA) and dichloroacetic acid (DCAA) in water were compared with their urinary excretion in a population of 48 subjects and a subset of the population comprised of 25 subjects who ingested water only at home where the drinking water was analyzed (Weisel et al., 1999b). An association between the amount of TCAA ingested calculated as the product of water concentration and amount of water ingested was identified across all subjects. That association was stronger in the subset of individuals who only ingested water at home, when misclassification was reduced. These associations suggest a dose-response relationship for urinary TCAA as biomarker. In addition, while the excretion rate of TCAA was associated with ingestion for those subjects who drank water only at home (Figure 3-22), it was not related to water concentration of TCAA (Figure 3-23), indicating that water concentration is not a good measure of exposure to TCAA since it does not account for the variability in the amount of water ingested by the population. No associations were found between DCAA water concentration and DCAA excretion rate or for water ingestion and excretion of DCAA. This suggests that urinary DCAA is not good biomarker of exposure to DCAA, with its rapid metabolism rate being the likely cause.

In conclusion, both breath and urinary biomarkers can be developed for DBP and can be used in epidemiological studies; however, knowledge of residence time is

TABLE 3-9

Comparison of Air THM Concentration ($\mu g/m^3$) for Low and High Water Groups

	$CHCl_3$	BDCM	CBDM
Low water concentration homes (n=25)			
Mean±SD	0.44±0.55[a]	0.38±0.82	0.44±0.95
Median	0.20	0.05	0.17
>DL[2]	16	12	5
High water concentration homes (n=23)			
Mean±SD	4.46±6.54	0.75±0.96	0.53±0.84
Median	1.25	0.32	0.16
>DL[2]	23	16	7

[a] The difference between the low and high water concentrations are statistically significant at $p<.05$.

TABLE 3-10

Mean (Median) THM Breath Concentrations (μg/m^3) After a Shower

Collection Time	Water Group	N	$CHCl_3$	BDCM	CBDM
<5 minutes	Low	6	4.0 (1.3)[a]	1.4 (nd)[a]	1 (nd)[a]
	High	7	54 (59)	10 (11)	4.8 (3.6)
5 to 20 minutes	Low	7	1.5 (1.5)[a]	0.3 (nd)[a]	1 (nd)
	High	7	130 (20)	13 (5.9)	2.8 (0.84)
>20 minutes	Low	4	1 (nd)	0.3 (nd)	1 (nd)
	High	2	20 (-)	0.3 (nd)	1 (nd)

[a] The difference between the low and high water concentrations are statistically significant at $p<.05$.

TABLE 3-11

Pearson/Spearman Correlation Coefficients (r^2): THM Water Concentration or THM Exposure with Exhaled Breath

	Water	Exposure
	Immediately after shower	
$CHCl_3$	0.78[a]/0.69[a]	0.82[a]/0.77[a]
BDCM	0.74[a]/0.84[a]	0.67[a]/0.79[a]
CDBM	0.66[a]/0.74	0.40/0.65
$CHBr_3$	0.97[a]/0.89[a]	0.93[a]/0.90[a]
	5-20 minutes after shower	
$CHCl_3$	0.69[a]/0.79[a]	0.73[a]/0.80[a]
BDCM	0.27/0.79[a]	0.16/0.76[a]
CDBM	0.02/0.37	0.12/0.24
$CHBr_3$	0.12/-0.17	0.19/-0.26

[a] The difference between the low and high water concentrations are statistically significant at $p<.05$.

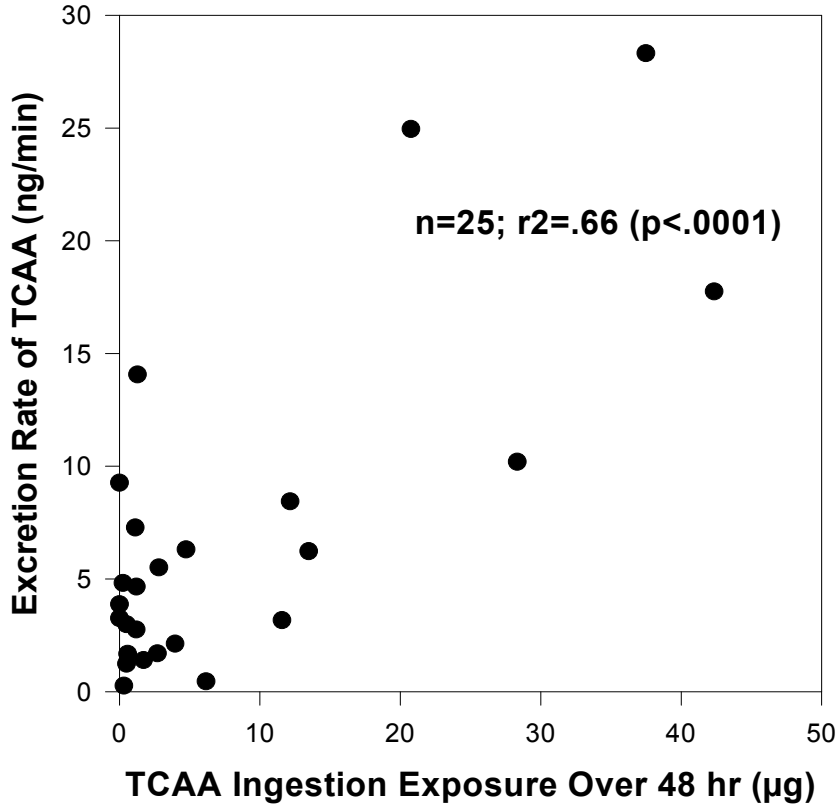


FIGURE 3-22

TCAA Ingestion Exposure vs. Urinary Excretion

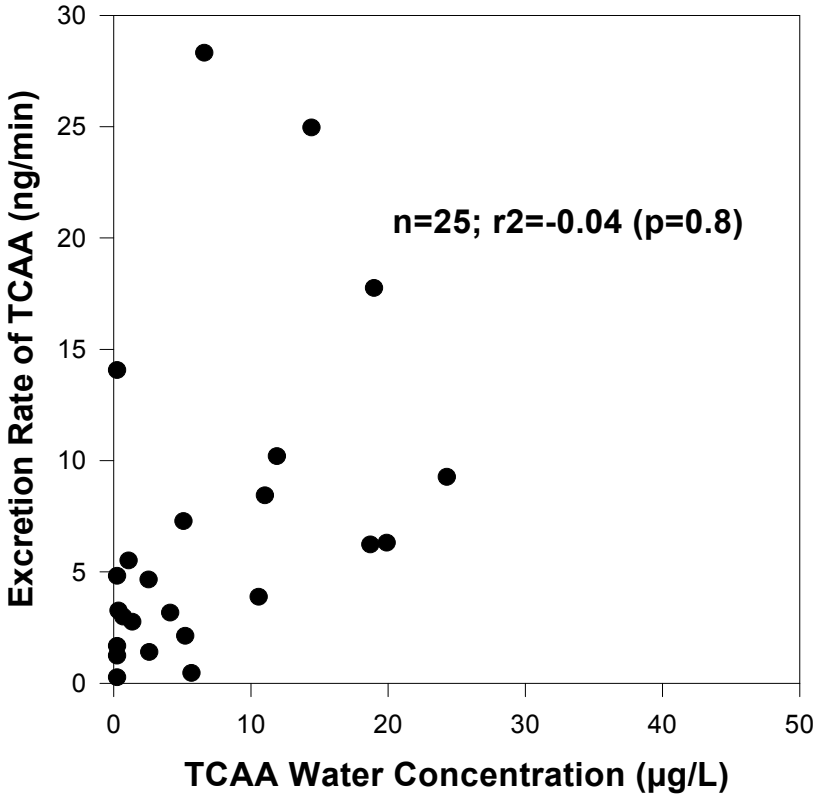


FIGURE 3-23

TCAA Urinary Excretion Exposure and Water Concentration

critical. Large variations in ingestion amounts can cause misclassification of exposure when water concentration is used as a surrogate for exposure if ingestion is the primary route. For some DBP, inhalation and dermal exposures contribute to the overall dose, with the relative importance of each route dependent on properties of the particular DBP (e.g., volatility). Biomarker and exposure/dose models can be used to determine total exposure in epidemiological studies to reduce misclassification and define routes. The route of exposure is an important determinant of the kinetics of the DBP (absorption, distribution, metabolism). The use of water concentration of a specific DBP (e.g., THM) as an exposure surrogate for all DBP may cause misclassification since the importance of different exposure routes can vary across compounds. Exposure for selected agent(s) or DBP(s) may be under-predicted or may not be proportional to the biologically-active agent.

3.5. PRESENTATION: DBP CONCENTRATION DATA VARIABILITY, ICR DATA (P. Fair)

Disinfectant(s) added to water react with organic material and bromide present in the source water to form DBP, a wide range of compounds for which only the major components have been analytically identified. Numerous factors influence DBP formation, including:

- the disinfectant (what disinfectant is used and its concentration),
- organic material (its chemical nature),
- temperature (affects reaction kinetics, determined by season of the year),
- time (location of sampling, how long the disinfectant has been in contact with organics in the water),

- pH (influences the types of by-products), and
- bromide (presence, concentration).

The nature of the organic material that reacts with the disinfectants may vary with season of the year and the watershed, leading to variability within and between the water systems. In general, the greater the concentration of organic material, the greater the formation of by-products.

DBP formed from chlorination include halogenation products (total organic halides, TOX) and oxidation products because chlorine is a strong oxidizer. Approximately 20% of the chlorine reacts to form halogenation products while the remainder goes to oxidizing organic materials. Among the halogenation products are: THM, HAA, HAN, haloketones (HK), chloral hydrate (CH), and chloropicrin (CP). Depending on the water, one can account for 10-50% of the TOX following chlorination, although TOX are highly variable. As there is continued formation of TOX within the distribution system, TOX and the individual by-product concentrations change with time. Concentrations are variable, some reactions occur rapidly, and concentrations may increase with distance (and time) from the treatment facility. Some by-products are also subject to chemical or microbial degradation and their concentrations may decrease with distance from the treatment facility. The pH of the water influences the types of by-products formed following chlorination. With increasing alkalinity, formation of TOX and haloacetic acids (e.g., TCAA [trichloroacetic acid]) are decreased, but THM formation is increased. The pH of the water may change during the treatment process, so where the chlorine is added in the process can greatly influence the types of by-products formed. The Stage 1 D/DBP Rule will require water systems treating surface water to practice

enhanced coagulation which involves lowering the pH during the coagulation process. Many water systems will need to raise the pH before the water is sent into the distribution system in order to prevent corrosion and comply with the Lead and Copper Rule. Bromide concentrations also influence the halogenation reactions. High bromide concentrations favor the formation of brominated species, whereas at low bromide concentrations, primarily chlorine substituted by-products are formed. If hypochlorite solutions instead of gaseous chlorine are used for water treatment, chlorate is added to the water as a decomposition product present in the hypochlorite solutions.

Alternate disinfectants also lead to the formation of by-products. Chloramination produces halogenated by products (TOX), cyanogen chloride, cyanogen bromide (in bromide rich water), oxidation by products, and organic chloramines. Chlorine dioxide is a strong oxidizer and its use leads to the formation of oxidation products in addition to the major by-products of chlorite and chlorate. A small amount of halogenated by products (TOX) may are also be formed. Oxidation products are formed when ozone, a strong oxidizer, is used for water treatment. If the water source also contains bromide, then bromine substituted by products and bromate are formed with ozonation.

A study is underway in the U.S. EPA's Office of Water under the Information Collection Rule (ICR). The ICR is a data-gathering and evaluation effort wherein data from all treatment systems serving populations of 100,000 or more persons were collected. Information on source water characteristics, microbial contamination (in surface water supplies), DBP and precursor identity and concentration, and treatment plant design and operation are being compiled and evaluated. In addition, studies are being conducted to evaluate treatment technologies (e.g., membranes and granulated

activated carbon) for precursor removal. The ICR monitored 296 water systems for 18 months (July 1997- December 1998). Monthly data on the treatment plant operation, water quality parameters and DBP precursors (bromide, UV_{254}, and total organic carbon [TOC]), and quarterly data on DBP at the entry and terminal points, as well as three other points, within the distribution system were collected. All plants monitored for concentrations of THM, HAA, HAN, HK, CP, CH, and TOX. The TOX measurements provided information on unidentified halogenated products. Specialized data for alternate disinfection processes were monitored, including: aldehyde and bromate formation following ozonation (20 plants), cyanogen chloride following chloramination (184 plants), and aldehydes, bromate, chorite, and chlorate following chlorine dioxide treatment (32 plants). The monitoring data from the ICR will provide baseline occurrence data for approximately 500 water treatment plants, refine existing models used to predict DBP formation, and evaluate how DBP concentrations will change as treatment changes are implemented.

3.6. PRESENTATION: HUMAN EXPOSURE ESTIMATES: WATER CONSUMPTION (R. Schoeny)

A mandate of the Safe Drinking Water Act (SDWA) Amendments of 1996 requires EPA to identify subpopulations at elevated risk and to conduct studies characterizing health risk to sensitive populations from contaminants in drinking water. A population can be considered “sensitive” by virtue of its high exposure (e.g., high water consumption) or by virtue of its innate or intrinsic sensitivity, due to genotype or phenotypic characteristics (e.g., immune status).

Consumption of 2 liters/day as a default value for individual water intake is used widely by federal agencies, including the EPA and the World Health Organization

(WHO). This consumption value was based on an analysis of USDA's 1977-1978 National Food Consumption Study published by Ershow and Cantor (1989). This report for the National Cancer Institute identified the 90th percentile consumption level to be about 2 liters of water per day for an adult. However, tap water consumption patterns have presumably changed during the past 20 years, and the SDWA Amendments require up-to-date information on water consumption. For example, bottled water was seldom used in the late 1970's, but now may represent a substantial portion of fluid intake.

The EPA's Office of Water has conducted a new analysis of drinking water consumption which considers multiple water sources. Estimates are stratified by age, gender, race, socioeconomic status, geographic region, and separately for pregnant and lactating women. The data source is the USDA's 1994-1996 Continuing Survey of Food Intake by Individuals (CSFII). It is expected that the analyses will be applied in both risk assessment and in the determination of benefits and costs required by the SDWA amendments. The generation of risk or benefits for specific populations will be facilitated by use of specific drinking water estimates.

USDA's 1994-1996 Continuing Survey of Food Intake by Individuals (CSFII) is a 2-day (2 non-consecutive days) dietary intake recall survey of 15,303 respondents. It is a complex, stratified, multistage, area probability sample of the U.S. population that includes (by design) over-sampling of low-income population, young children, and the elderly. In addition to dietary information, some demographic and physical data (e.g., body weight) were collected. The CSFII has a response rate of 76%. Surveys are

conducted by trained interviewers who use a variety of visual props to assist in recording of accurate portion sizes.

Specific questions were included in the survey to gather information on the sources of water consumed by the respondents. Water sources identified in the analysis included community water supplies (e.g., municipal tap water), bottled water, and other sources (e.g., well, cistern, spring, etc.). The analyses differentiated between direct water (plain water consumed directly as a beverage) and indirect water which was added to foods and beverages during final home or restaurant preparation (e.g., coffee, tea, reconstituted fruit juice). This analysis did not quantify what was defined as intrinsic water; that is, water contained in foods and beverages at the time of market purchase (e.g., canned soup).

There is uncertainty in the analysis. Dietary recall is subjective (e.g., quantity of food consumed), and it is not known if 2 days is the most appropriate period. Another source of uncertainty is grounded in the calculation of indirect water from food codes and the amount of water in foods based on USDA's standard recipes. In calculating the amount of water consumed from various sources from questionnaire responses, assumptions had to be made. The EPA analysis used the following assumptions for water consumption: all = 100%, most = 75%, some = 25%.

Estimates of water consumption for all age groups and males and females combined support for the use of a 2 liters/person day default (Table 3-12). The 90^{th} percentile of community tap water intake is 2.02 liters (across all age groups). In addition, the preliminary analysis supports the use of 1 liter/day for a 10-kg child. The

TABLE 3-12

Community Water Ingestion (L/person/day)
(Consumers and Non-Consumers)

Age	Mean	90th percentile	95th percentile
<1 yr	0.34	0.88	1.04
1-10 yr	0.40	0.90	1.12
11-19 yr	0.68	1.53	1.95
20-64 yr	1.09	2.25	2.86
65+ yr	1.13	2.14	2.55
General Population	0.93	2.02	2.54

estimated 95th percentile of community/tap water intake is 1.12 liters for a child 1-10 years old.

Bottled water represents a substantial proportion (13.4%) of combined direct and indirect water intake. When comparisons were made base on "poverty" or "non-poverty" status, respondents did not differ substantially in mean intake of tap or bottled water. In general, males drink more than females, with adolescent males drinking approximately 3 liters/day. Based on per kg body weight, infants (< 1 year old) drink approximately 3 times as much tap water as adults. Lactating women consume, on average, considerably more tap water than women of child-bearing age. Residents of rural areas consume, on average, less bottled water and more water from "other" sources, and residents in the western United States consume more bottled water than other regions.

A report on the analyses has recently been reviewed by the Science Advisory Board (SAB) to the U.S. EPA. Their preliminary comments indicate that the CSFII data are an appropriate choice and that the analytic methods used are sound. The report will be revised and released early in calendar 2000.

3.7. PRESENTATION: PROBABILISTIC APPROACHES TO DEVELOPING DISTRIBUTIONS OF RISKS (W. Huber)

3.7.1. Variability and Uncertainty. Variability is diversity or heterogeneity in a well-defined population of individuals or series of observations. In risk assessment, the individuals or observations are usually indexed by time or spatial location or both. For example, the population exposed to DBP is 170 million people drinking treated water across the United States within a future (as yet unspecified) time frame. The DBP concentrations in the treated water also vary with time and location. In the CRFM case

study, the concentrations used in the risk assessment are those observed for one week from one sampling point serving no people (pilot plant).

Variability is related to the experimental situation or question. In general, there are three different types of variability in risk assessment: population, temporal, and spatial. There is a "target" population of individuals for whom the risk is being assessed. The population must be *well-defined*, i.e., who, what, and when must be known. Temporal variability is manifested in the variation of concentration or dose over time (such as DBP concentration at different sampling times). For acute effects, temporal variation can be very important. Some of the variation within a spatially-distributed population of individuals can be attributed to spatial locations. Other factors, such as the concentration term, usually vary with spatial location. (Spatial and temporal variation often exhibit autocorrelation. Properties of individuals are, however, usually considered to vary independently of each other.)

Uncertainty, or imperfect knowledge, arises from ignorance or incomplete information. There are many forms of uncertainty. Some uncertainty is probabilistic, some uncertainty is in the model, and other uncertainty is "unquantifiable". The CRFM divides probabilistic uncertainty into random error and "inherent randomness". Random error can be treated statistically. As for inherent randomness, one elects to ignore it and treats it as a random term in the model (Morgan and Henrion, 1992).

Model uncertainty has many forms that should not or cannot be assessed with probabilistic approaches, including:

- simplifying assumptions,
- approximations,

- degree of empirical validation,
- amount of extrapolation, and
- amount of detail.

Forms of unquantifiable uncertainty, which cannot be assessed numerically, are:

- "lack of empirical basis",
- subjective judgment,
- linguistic imprecision (such as data from an ambiguous report),
- disagreement (such as to which model to apply),
- systematic error, and
- "data uncertainty".

All of the components of uncertainty need to be identified before bounds can be placed on the total uncertainty.

The concepts of variability and uncertainty overlap and are frequently a function of the choice of models.

Probabilistic techniques use distributions. Frequency distributions and probability distributions are the same mathematical object. Almost all variability can be represented by frequency distributions. Only "random" forms of uncertainty can be represented by probability distributions. In many cases, the uncertainty that can be probabilistically quantified is dwarfed by the other kinds of uncertainty. Every effort should be made to identify numerical bounds on the magnitude of the "unquantifiable" components. Many of the "unquantifiable" uncertainties may cancel out (through negative covariation or by sharing a common additive component) in a comparative risk assessment. For example, the comparison of chlorination-filtration with ozonation-

chlorination-filtration subtracts many components of uncertainty common to both treatment methods. Thus, using some models, one may be able to factor out some uncertainty.

3.7.2. Maximum Likelihood Estimation. When one has data and needs to make decisions based on those data, a rational decision theory framework can be applied. In this framework, there is a state space of possible outcomes of a random variable. There is a set of distributions representing realistic states of nature. The set of possible decisions is specified. A loss function specifying the costs for a bad decisions must be known. Optionally, one may also specify an *a priori* probability distribution of the states of nature.

Within this framework, and independent of it, there are many criteria for choosing or evaluating a decision procedure. Among them are:

- maximum likelihood and likelihood ratio,
- Bayes,
- minimax,
- invariance,
- unbiasedness,
- sufficiency,
- robustness,
- method of moments, and
- asymptotic efficiency.

In Maximum Likelihood Estimation (MLE), the states of nature are parameterized by real parameters (or vector of parameters), θ. The decision is to determine what is the "true" state of nature. The loss function is not considered at all. Nevertheless, MLE can be useful for identifying appropriate distributions for modeling or simulating populations and observations. It is discussed because it is one of the few practical approaches available for identifying mixtures of distributions.

In an experiment (or series of experiments) yielding a set of outcomes $\{x_1, x_2, ..., x_n\}$, the likelihood function $L(\theta)$ is simply the probability of $\{x_1, x_2, ..., x_n\}$ given θ, $p_\theta(\{x_i\})$. The MLE is the set of values of θ which maximize $p_\theta(\{x_i\})$. In many cases, the MLE is unique and it is almost normally-distributed with covariance matrix equal to the inverse of $-\nabla_\theta \nabla_\theta \ln(L)|_{\theta = MLE}$. From this, one can figure out the uncertainty of the results. For example, let X be the concentration of a DBP, assumed to be normally-distributed. Suppose that independent random observations of X are available as $\{x_1, x_2, ..., x_n\}$. The possible states of nature are normally-distributed as shown in Equation 3-4:

$$f(x) = \frac{\exp\left(-\left[\frac{(x-\mu)^2}{2\sigma^2}\right]\right)}{\sqrt{\sigma^2 2\pi}} dx; \theta = (\mu, \sigma); \sigma > 0 \qquad (3\text{-}4)$$

The log likelihood function -ln(L), which must be minimized to maximize L, is therefore:

$$\sum_{i=1}^{n} \left[(x_i - \mu)^2 / 2\sigma^2 + \ln(2\sigma^2\pi)/2 \right] \qquad (3\text{-}5)$$

A unique minimum occurs where μ = arithmetic mean of $\{x_i\}$ and σ = standard deviation of $\{x_i\}$ (provided this is nonzero).

One can also find the so-called "second order uncertainty" with MLE. The estimated values of μ and σ are independent with variances of σ^2/n and $2\sigma^2/n$, respectively. When n is large enough, these variances approximately characterize the *uncertainty* distributions of μ and σ. Thus, MLE simultaneously yields estimates of variability (in the form of σ^2) and uncertainty (in the form of the uncertainty distribution of μ and σ).

Some advantages and disadvantages of MLE are listed in Table 3-13. Maximum likelihood works well with lots of data and serves to complement Monte Carlo techniques as a means to separate uncertainty and variability.

3.7.3. Mixtures of Distributions. Mixtures of parameterized distributions can be used as an alternative to assuming one nice mathematical distribution (such as normal or lognormal). Mixtures of distributions arise in nature, such as the National Inorganic and Radionuclides Survey (NIRS) data base of radon measurements in drinking water. The probability plots suggest that these data are only approximately characterized by a lognormal distribution. The approximation is poorest where it often matters the most- in the high-concentration "tail" of the distribution (See Figures 3-24, 3-25, and 3-26.).

The definition of a mixed distribution is as follows:

- Let $f_1(X; \theta_1),..., f_k(X; \theta_k)$, be a sequence of probability distribution functions. X is the variate and the $\{\theta_k\}$ are the parameters.
- Let $\pi_1, ...,\pi_k$ be a sequence of strictly positive real numbers with $\pi_1 + ... + \pi_k + 1$. Then $\pi_1 f_1(X; \theta_1) + ... + \pi_k f_k (X;\theta_k)$ is a finite mixture distribution.

TABLE 3-13

Advantages and Disadvantages of Maximum Likelihood Estimation (MLE)

Advantages	Disadvantages
• MLE quantifies uncertainty in the distribution parameters	• It may produce misleading results with small data sets
• It works with censored data (such as NDs), even with varying censoring limits	• It can produce biased estimators
• It is well know	• It pays no attention to the loss function
• It is asymtotically efficient	• Obtaining MLE results can be computationally trickly
• It easily accommodates changes in variable (such as Box-Cox transformations)	

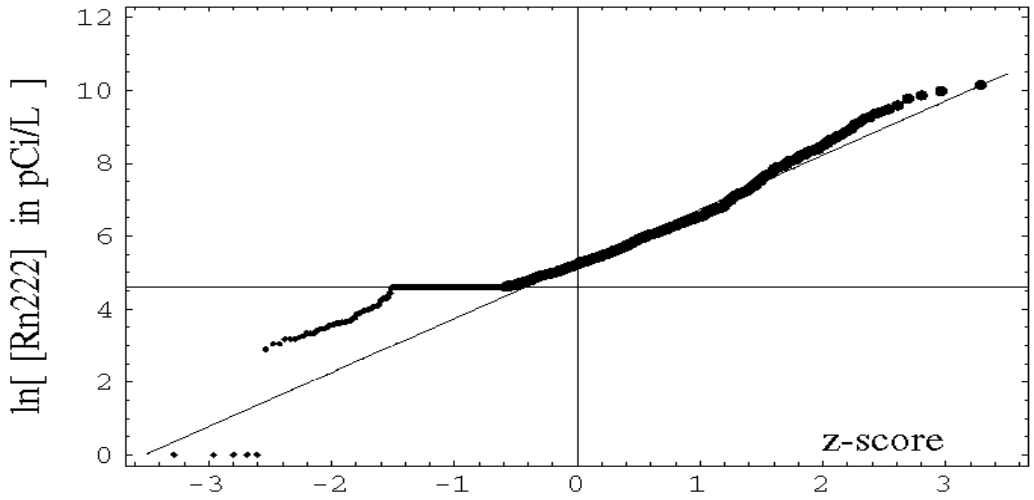


Figure 1: LogNormal probability plot showing the 707 values > 100 pCi/L as larger dots and the 275 values ≤ 100 pCi/L as smaller dots

FIGURE 3-24

Example: NIRS Radon Data. LogNormal Probability Plot Showing the 707 Values > 100 pCi/L (Thick, Black Line) and the 275 Values ≤ 100 pCi/L (Smaller Dots).

Source: Burmaster and Wilson, *Risk Analysis* (submitted);
http/www.alceon.com/FitMixfini.pdf

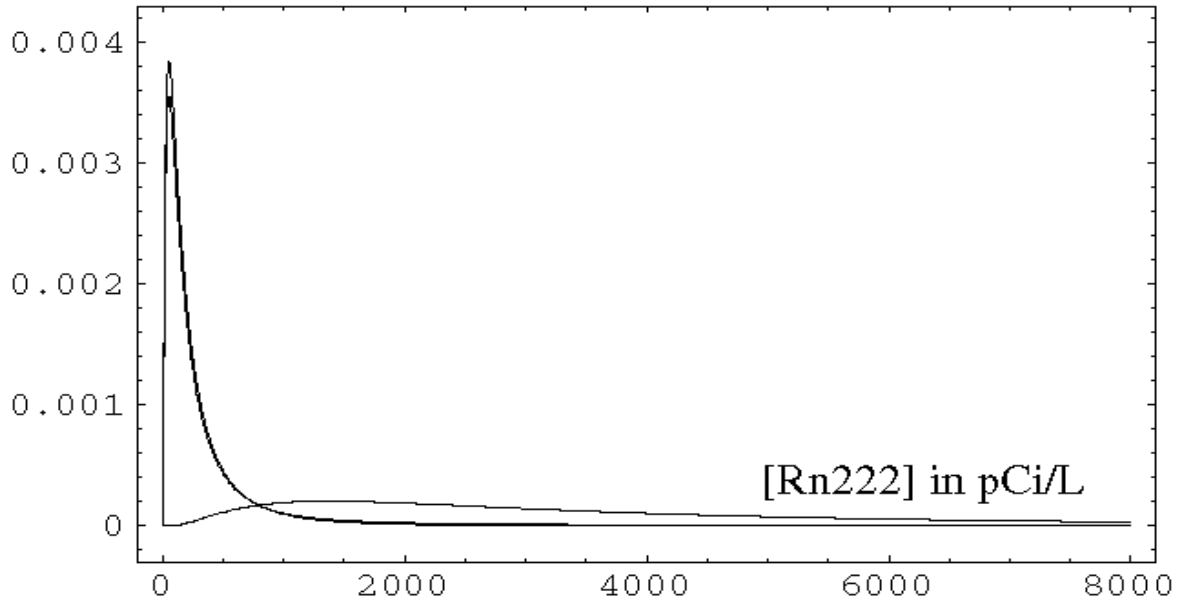


Figure 4B: PDF for Model 2 fit by MLE (black line) and the PDFs for the pure components (gray lines)

FIGURE 3-25

Burmaster and Wilson's Fit. PDF for Model 2 Fit by MLE (Darker Line that Peaks Near Zero) and the PDFs for the Pure Components (Thinner, Flat Line).

Source: Burmaster and Wilson, *op. cit.*

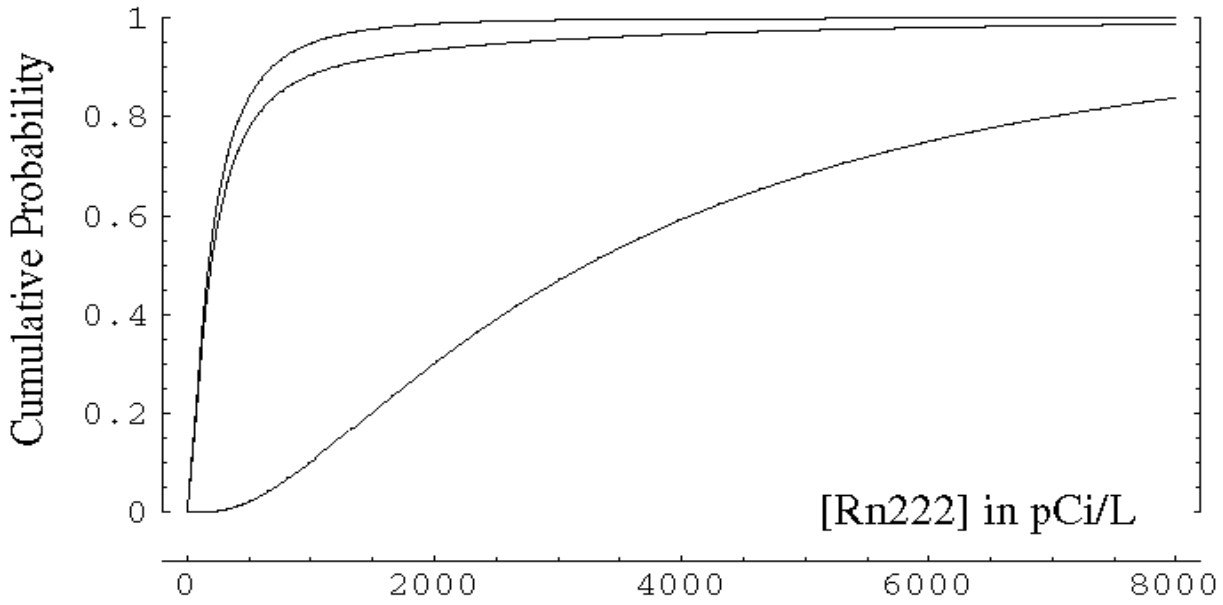


Figure 4A: CDF for Model 2 fit by MLE (black line), flanked by the CDFs for the pure components (gray lines)

FIGURE 3-26

Burmaster and Wilson's fit as PDFs. CDF for Model 2 Fit by MLE (Middle Line), Flanked (on the Top and Bottom) by the CDFs for the Pure Components.

Source: Burmaster and Wilson, *op. cit.*

Mixture distributions have advantages over mathematically simpler distributions: they expand the range of available distributions for fitting data; they often correspond better to real phenomena; and they can model “surprise” and rare events. Use of mixture distributions and MLE offer advantages in that uncertainty in the mixing parameters $\pi_1, ...,\pi_k$ is quantified, the MLE can assess whether a component is statistically significant, and the MLE is one of the few ways to make estimates with general mixture models.

However, there are several difficulties in using MLE for estimates in a mixture model framework. Deciding how many mixture components should be used is an issue with this approach. Another issue is that solutions to the MLE equations can be difficult to find or may be numerically unstable since ln(L) is almost parabolic near its maxima.

One way to determine the number of components is a graphical technique, the mixture diagnostic plot (MDP), developed by Roeder (1994), as depicted in Figure 3-27. The MDP is a graphical expression of a formal hypothesis test of whether the number of normal components in a mixture is k ($k \geq 1$) or k + 1. (It assumes each component of the mixture has the same spread.) The test is based on the number of sign changes found in comparing a nonparametric smooth of the empirical density function to a k-component fit to the data.

In the figures (Figures 3-24, 3-25, and 3-26) of the NIRS data, the smoothed (empirical) distribution appears to depart somewhat from the best-fitting lognormal distribution. The smooth may have some “bumps”, but they are small. Roeder’s MDP, in both the graphical form (shown in Figure 3-27) and as a statistical test, support the alternative hypothesis of (at least) two components to the data and reject the null

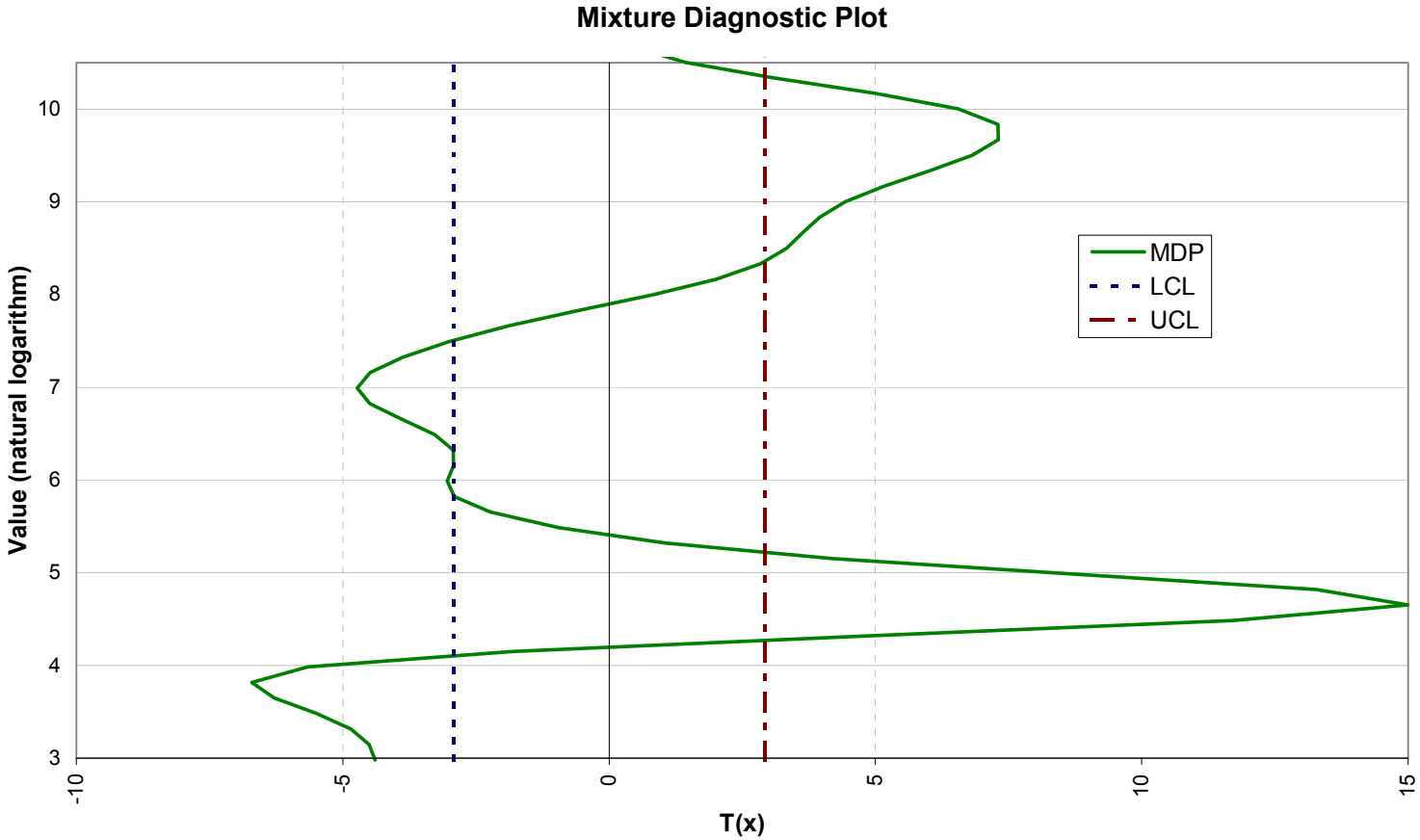


FIGURE 3-27

Roeder's MDP for k=1 Supports Burmaster and Wilson

hypothesis of just one component (k=1). This supports conclusions reached by Burmaster and Wilson independently using other techniques (to appear in *Risk Analysis*).

The MDP is more general than indicated here. It can be developed for any number of components. It does not require that the empirical distribution have any multiple "bumps" at all; in other words, it can detect mixtures of distributions that are so close they are not multimodal. The MDP works directly for mixtures of lognormals (just take logarithms). Unfortunately, computing the significance levels for the corresponding statistical test (the mixtures diagnostic test, MDT) requires Monte Carlo simulation.

3.7.4. Summary. In conclusion, not all uncertainty can be quantified probabilistically. Indeed, perhaps very little of it can be. MLE and mixtures of distributions can enhance the ability to capture more uncertainty quantitatively. The results are directly useful for two-dimensional Monte Carlo simulations. Mixtures of distributions enable better characterization of important tails of empirical distributions. This approach to characterizing distributions looks particularly promising for characterizing risks from DBP in drinking water.

3.8. PRESENTATION: PROPORTIONAL RESPONSE ADDITION (W. Stiteler)

3.8.1. Introduction. Quantification of the risk associated with the low level of exposure to individual components in a complex mixture of DBP (i.e., a mixture with a large number of DBP) presents a difficult challenge. For some components, there may not be toxicity information available. For a particular (noncancer) endpoint, the exposure may be well below threshold for each of the individual components. Adding these

components together, however, may result in a total mixture dose that is in the range where there may be concern about appreciable risk for an adverse effect.

A definition of additive is based on the idea that the response resulting from exposure to a mixture of chemicals is the response that would be "expected" based on what is known about the response to the individual components of the mixture. This "expectation" may vary, however, depending on the way in which the components of a mixture act to produce an effect.

A type of additivity resulting when two or more chemicals cause the same effect by the same (or similar) mechanism (similar joint action) is known as dose additivity. If the components produce the same effect by entirely different mechanisms (independent joint action), the result is known as response additivity.

Under the assumption of dose addition, both of the components are causing the same effect by the same mechanism, and thus, one of the chemicals can be treated as a dilution or concentration of the other. An adjustment factor describing the relative potency of the two chemicals is used to adjust the dose of one chemicals to scale it to an equivalent level of the second chemical. Note that to employ this definition to a large mixture, it would be necessary to have relative potency values to adjust the doses of all components to some reference chemical.

Under response addition, all of the components cause the same effect, but by different and independent mechanisms. Thus, an individual may show a response to exposure to a binary mixture that results from chemical 1, chemical 2, or both chemicals. A Venn diagram is a convenient way to illustrate. If we let A represent the event that an individual responds to chemical 1 and B represent the event that an

individual responds to chemical 2, then the event of interest under exposure to the mixture would be the union A∪B. The union of A and B is illustrated in Figure 3-28.

If A and B are independent events, the probability of the union (the probability of response to the mixture) is given by:

$$P(A \cup B) = P(A) + P(B)\,[1 - P(A)] \qquad (3\text{-}6)$$

This expression takes into account the fact that the individuals responding to chemical 1 cannot respond to chemical 2 as well.

By symmetry, this could also be expressed as:

$$P(A \cup B) = P(B) + P(A)[1 - P(B)] \qquad (3\text{-}7)$$

Both Equations 3-6 and 3-7 reduce to:

$$P(A \cup B) = P(A) + P(B) - P(A)P(B) \qquad (3\text{-}8)$$

Note that the responses add only if the last term in Equation 3-8 is ignored. This might be justified in the low dose region where both P(A) and P(B) would be small, making their product even smaller.

There is a special case, however, where the products P(A)P(B) will disappear from Equation 3-8. This occurs when A and B are mutually exclusive. This is sometimes referred to as complete negative correlation and occurs when an individual susceptible to chemical 1 is not susceptible to chemical 2 and vice versa. Figure 3-29 illustrates this situation.

Complete negative correlation results in true addition of the responses as:

$$P(A \cup B) - P(A) + P(B) \qquad (3\text{-}9)$$

Yet another variation on response addition occurs when individuals susceptible to one chemical are also susceptible to the other. This is sometimes referred to as complete positive correlation. The Venn diagram in Figure 3-30 illustrates this situation.

In this case, $P(A \cup B) = P(A)$, assuming that A is the more toxic chemical.

Dose addition and response addition are both based on mechanisms of action. This is a desirable property when, as will sometimes be true for a binary mixture, something is known about mechanisms. However, mixtures consisting of a large number of components present a problem in that it is unlikely that sufficient information will be available to identify the mechanisms of action for all of the possible pairwise combinations of binary subsets of the components. Even if the information is sufficient to distinguish between dose addition and response addition for each of the binary subsets, it is unlikely, for a large number of components, that there will concordance; some pairs may suggest dose addition while other pairs suggest response addition. Thus, a mechanism-based definition of addition may not be the best way to approach complex mixtures composed of a large number of components. It may be better to use a "generic" definition of additivity that is not tied to any specific information about mechanism of action.

3.8.2. Methods. A method for estimating the risk associated with a mixture based on the proportion of the components in the mixture is being proposed. This method is based on a generic definition of additivity described by Chen et al. (1989), which is referred to here as "proportional response addition". This definition of additivity does

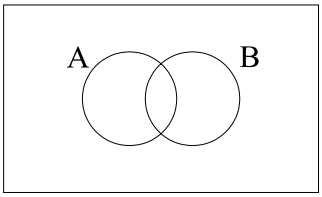


Figure 3-28. A∪B

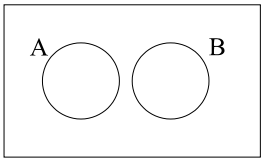


Figure 3-29. Complete Negative Correlation

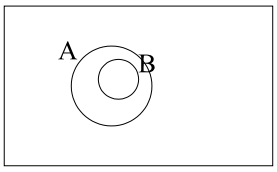


Figure 3-30. Complete Positive Correlation

not rely on any specific knowledge of the mechanism of action of each component in inducing the response. The total dose of the mixture can be held fixed and the expected response to various mixture blends can be estimated based on the known response of the chemical components. Figure 3-31 depicts proportional response addition for a binary mixture.

Suppose that a mixture is composed of n components and that the dose-response relationship for the i^{th} component is represented by P_i(dose). Let the individual doses of the n components be represented by d_1, d_2, d_3, ... d_n. The total amount or dose of the mixture is then $D = d_1 + d_2 + ... + d_n$. The proportion of that total amount that is represented by component i is then given by $\pi_i = d_i / D$.

Then under proportional response addition, the response to the total dose D of the mixture would be:

$$P_{mix}(D) = \Pi_1 \cdot P_1(D) + \Pi_2 \cdot P_2(D) + \cdots + \Pi_n \cdot P_n \qquad (3\text{-}10)$$

Figure 3-32 shows the dose-response surface for a hypothetical binary mixture at varying mixture total doses and mixture blends. As another example, suppose there are four components in a mixture and that the amounts are 10, 15, 25, and 50 ppm, respectively. Then the total amount of the mixture would be D = 100 ppm and the relative proportions of the four components would be 0.1, 0.15, 0.25, and 0.5, respectively. Assuming that individual dose response curves P_1, P_2, P_3, and P_4 are available, the response to the mixture under proportional response addition would be calculated as:

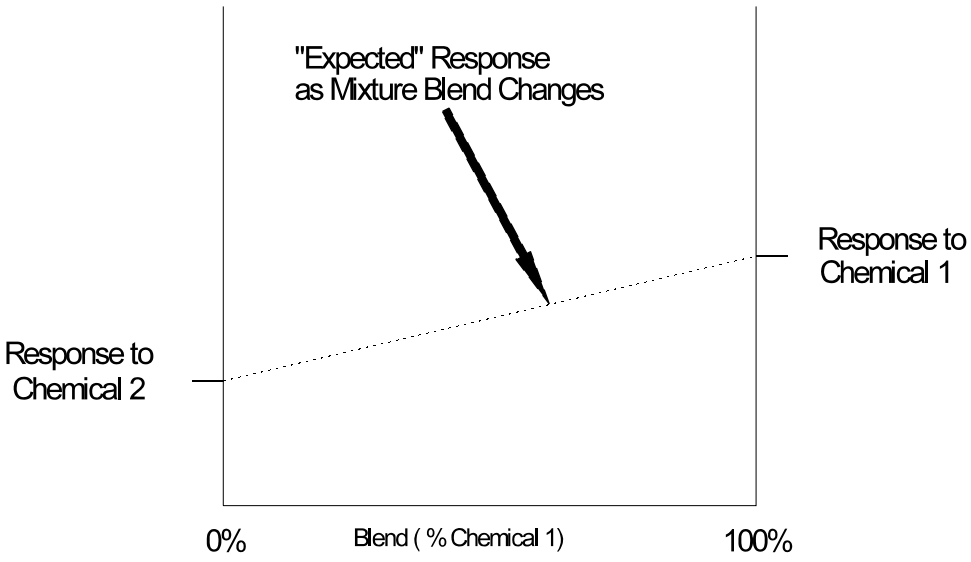


Figure 3-31. Proportional Response Addition (Total Dose Held Fixed)

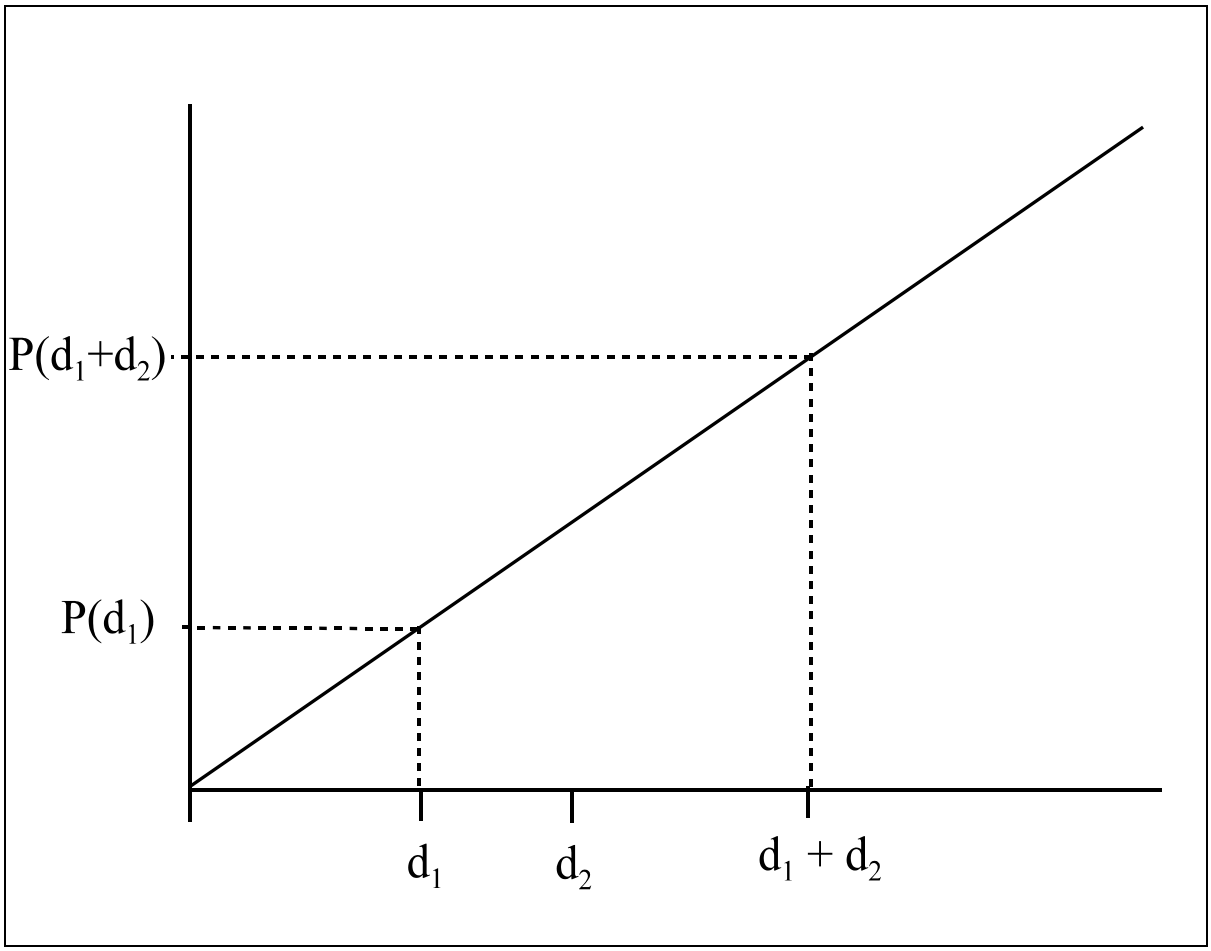


FIGURE 3-32

Linear Model Evaluated at d_1 and at $d_1 + d_2$

$$P_{mix}(D) = 0.1 \times P_1(100) + 0.15 \times P_2(100) + 0.25 \times P_3(100) + 0.5 \times P_4 \quad (3\text{-}11)$$

This approach involves estimating the risk for each individual component at the level of the whole mixture. This gives an estimate of the risk for each of the components as if it were present at a level equal to the whole mixture. These risks are then apportioned according to the percentage of the total mixture that each component represents. Thus, extrapolation into the low dose region is avoided; this is especially important for those effects that may have thresholds.

It is interesting to note that if (1) the dose response relationship is linear, and (2) there are no thresholds, then calculating the mixture risk from proportional response addition is equivalent to calculating that risk under the assumption of ordinary response addition. For example, take a binary mixture with doses d_1 and d_2. The contribution of chemical 1 to the total risk under proportional response addition would be $[d_1 /(d_1 + d_2)]\cdot P_1(d_1 + d_2)$ while under response addition, the contribution of chemical 1 to the total risk would be $P_1(d_1)$. These are equal, however, if the dose-response relationship is linear and has no threshold as Figure 3-33 illustrates. The slope of the line would be given by:

$$Slope = \frac{P_1(d_1)}{d_1} = \frac{P_1(d_1 + d_2)}{d_1 + d_2} \quad (3\text{-}12)$$

Then multiplying by d_1 gives the result. The contribution of chemical 2 would be calculated in a similar manner.

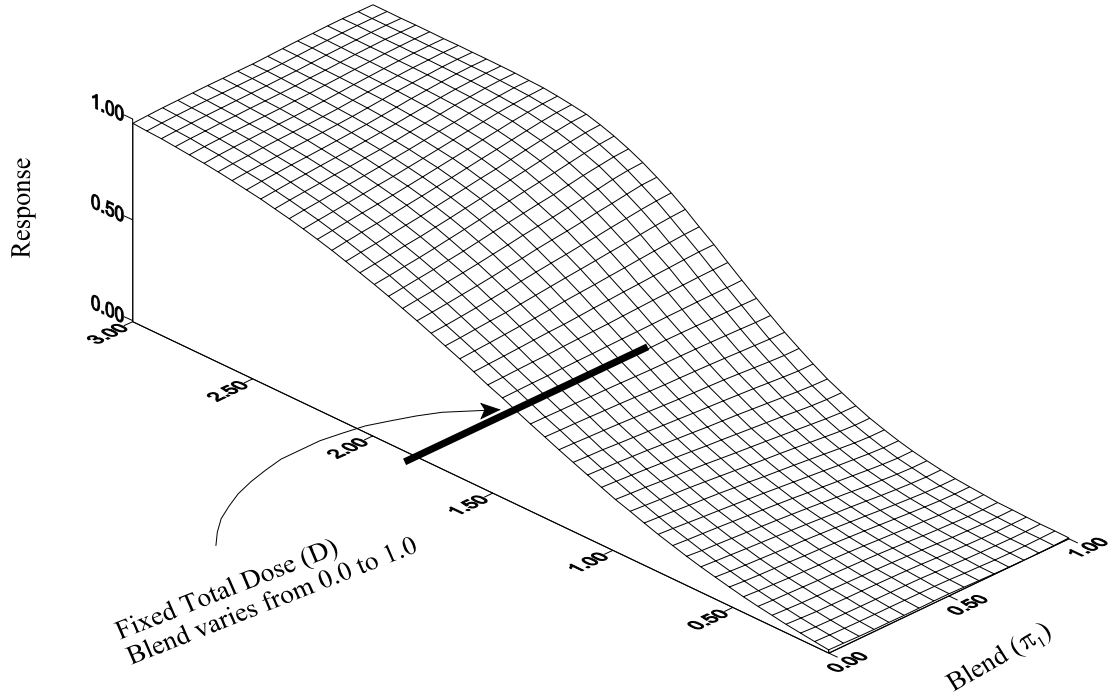


Figure 3-33. Proportional Response Addition for a Binary Mixture

Note that if the dose-response function for the first component has a threshold, then it is possible that $P_1(d_1) = 0.0$ while $P_1(d_1 + d_2) > 0.0$. In that case, the two methods would lead to different estimates of risk.

Thus, under conditions that might be encountered with a non-threshold endpoint (e.g., cancer) where exposures are in the linear portion of the dose-response curve, proportional response addition and response addition would result in identical risk estimates.

The developmental and reproductive health risks for two classes of DBP, the haloacetic acids and the haloacetonitriles, were evaluated to serve as an example for illustration of the proportional response additivity methodology. The haloacetic acids and haloacetonitriles commonly found in drinking water are listed in Table 3-14. The table shows the chemical name, formula, and acronyms used in this presentation. In addition, the table presents a indication of the availability of developmental and reproductive toxicity data. Seven of the eleven haloacetic acids (MCA, DCA, TCA, MCA) and haloacetonitriles (DCAN, TCAN, BCAN) have been subjects of developmental toxicity studies by a single group of investigators, and three of the haloacetic acids (DCA, MBA, DBA) have been the subjects of male reproductive studies by another group of investigators. All of these studies were conducted in rats using gavage administration. The results for developmental toxicity were positive. For reproductive toxicity, the dihalogenated haloacetic acids gave positive results, but the monohalogenated acetic acid (MBA) gave negative results. An additional chemical, the haloacetonitrile DBAN, was tested in a short-term developmental and reproductive toxicity screening study in rats by the NTP (1992), with negative results. DBAN was

TABLE 3-14

Availability of Developmental and Reproductive Dose-Response Data for Haloacetic Acids and Haloacetonitriles Found in Drinking Water

Chemical			Developmental Toxicity[a]	Reproductive Toxicity[a]
Haloacetic Acids				
$ClCH_2COOH$	Monochloroacetic Acid	MCA	y, (+)	
$Cl_2CHCOOH$	Dichloroacetic Acid	DCA	y, +	y, +
Cl_3CCOOH	Trichloroacetic Acid	TCA	y, +	
$BrCH_2COOH$	Monobromoacetic Acid	MBA	y, +	y, -
$Br_2CHCOOH$	Dibromoacetic Acid	DBA		y, +
BrClCHCOOH	Bromochloroacetic Acid	BCA		
Haloacetonitriles				
Cl_2CHCN	Dichloroacetonitrile	DCAN	y, +	
Cl_3CCN	Trichloroacetonitrile	TCAN	y, +	
BrClCHCN	Bromochloroacetonitrile	BCAN	y, +	
Br_2CHCN	Dibromoacetonitrile	DBAN	y,(-)[b]	y, (-)[b]
Br_2ClCCN	Dibromochloroacetonitrile	DBCAN		

[a] Data are from gavage studies in rats unless otherwise noted.

[b] Data are from a screening-level drinking water study in rats.

y = yes, adequate data available

+ = results were positive for adverse effect

- = results were negative for adverse effect

(+) = results were marginally positive

(-) = results were negative, but a toxicity-based MTD could not be achieved due to taste aversion and consequent refusal to drink higher concentrations of the chemical, and this was a short-term screening study

administered in the drinking water, which is preferable in terms of relevance to human exposure to DBP. The animals, however, refused to drink the DBAN solutions at higher concentrations, so the maximum tolerated dose was defined on the basis of taste aversion rather than actual toxicity. The negative results from that study are present in parentheses, to indicate that this was a screening level study and a toxicity-based MTD was not achieved. In addition, the positive results for MCA were borderline in terms of statistical significance and are therefore shown in parentheses.

In order to employ the proportional response additivity approach, a common sensitive endpoint across chemicals is needed. Data sets were examined with regard to NOAELs and LOAELs in order to select endpoints for each compound that appeared sensitive and were reported across the entire series of compounds. Table 3-15 lists the endpoints that were then further examined using a threshold dose-response model as described subsequently in this section. For the purposes of this illustration, focus was on the developmental toxicity data, because more chemicals were tested, and all the chemicals tested by gavage, including both chlorinated and brominated compounds and both haloacetic acids and haloacetonitrile, gave positive results. Thus, it appeared that developmental toxicity was characteristic of these chemical classes.

Further evaluation of the data sets listed in Table 3-15 by dose-response modeling (discussed in next paragraph) showed that visceral malformations, particularly cardiovascular (interventricular septal defects, defect between ascending aorta and right ventricle, and levocardia) and smaller fetal size (body weight and crown-rump length) appeared to be the most sensitive endpoints in common for these chemicals. An example of these data are shown for DCA in Table 3-16. Note that some of the data

TABLE 3-15

Developmental and Reproductive Toxicity Data Sets for Haloacetic Acids and Haloacetonitriles

Chemical	Study	Endpoint (in rats except as noted)
Haloacetic Acids - Developmental Toxicity		
Monochloroacetic Acid	Smith et al., 1990, Teratology 41: 593	Fetal body weight
		Crown-rump length
		Visceral Malformations, Total (% affected/litter
Dichloroacetic Acid	Smith et al., 1992, Teratology 46: 217-223	Fetal body weight - male
		Fetal body weight - female
		Crown-rump length - male
		Crown-rump length - female
		Visceral malformations, Total
		Visceral malformations, Cardiovascular
Trichloroacetic Acid	Smith et al., 1989, Teratology 40: 445-451	Complete litter resorption
		% Postimplantation loss/litter
		Fetal body weight - male
		Fetal body weight - female
		Fetal crown-rump length - male
		Fetal crown-rump length - female
		Visceral malformations, Total
		Visceral malformations, cardiovascular
		Visceral malformations, Levocardia
		Skeletal malformations

TABLE 3-15 (cont.)		
Chemical	Study	Endpoint (in rats except as noted)
Monobromoacetic Acid	Randall et al., 1991, Teratology 43:454	Fetal body weight
		Fetal crown-rump length
		Visceral malformations, Total (% affected/litter)
Haloacetic Acids - Male Reproductive Toxicity		
Dichloroacetic Acid	Cicmanec et al., 1991, Fund. Appl. Toxicol. 17: 376-389	Testicular lesions: degeneration, dog
	Linder et al., 1997, Reprod. Toxicol. 11: 681-688	Number caput sperm
		Number cauda sperm
		% Motile sperm
		Progressive motility
		Testicular histopathology: Faulty spermiation
Dibromoacetic Acid	Linder et al., 1994, Reprod. Toxicol. 8: 251-259	Number caput sperm
		Number cauda sperm
		% Motile sperm
		Progressive motility
		Retention Stage IX spermatids per tubule

TABLE 3-15 (cont.)		
Chemical	Study	Endpoint (in rats except as noted)
Haloacetonitriles - Developmental Toxicity		
Dichloroacetonitrile	Smith et al., 1989, Fund. Appl. Toxicol. 12: 765-772	Complete litter resorption
		% Postimplantation loss/litter
		Fetal body weight - male
		Fetal body weight - female
		Fetal Crown-rump length - male
		Fetal Crown-rump length - female
		Visceral malformations, Total
		Visceral malformations, Cardiovascular
		Visceral malformations, Urogenital
		Skeletal malformations
Trichloroacetonitrile	Smith et al., 1988, Teratology 38: 113-120	Complete litter resorption
		% Postimplantation loss/litter
		Fetal body weight - male
		Fetal body weight - female
		Visceral malformations, Total
		Visceral malformations, Cardiovascular
		Visceral malformations, Urogenital

TABLE 3-15 (cont.)		
Chemical	Study	Endpoint (in rats except as noted)
Bromochloroacetonitrile	Christ et al., 1995, Int. J. Environ. Health Res. 5: 175-188	Complete litter resorption
		% Postimplantation loss/litter
		Fetal body weight - male
		Fetal body weight - female
		Fetal crown-rump length - male
		Fetal crown-rump length - female
		Visceral malformations, Total
		Visceral malformations, Cardiovascular
		Visceral malformations, Urogenital
		Skeletal malformations

TABLE 3-16

Example Data Sets: DCA (Smith et al., 1992, Teratology 46: 217-223)

Dose in mg/kg-day on gestation days 6-15				0	14	140	400
Fetal body weight (g) (mean of litter means)							
	# litters examined			19	18	19	19
	male	mean		3.68	3.75	3.6	3.43
		SD		0.2	0.3	0.2	0.3
		statistical significance					*
		estimated # litters affected[a]		1	0	2	5
	female	mean		3.49	3.6	3.46	3.27
		SD		0.2	0.3	0.2	0.3
		statistical significance					*
		estimated # litters affected[a]		1	0	1	4
Fetal crown-rump length (cm) (mean of litter means)							
	# litters examined			19	18	19	19
	male	mean		3.62	3.64	3.56	3.46
		SD		0.1	0.2	0.1	0.2
		statistical significance					*
		estimated # litters affected[a]		1	1	2	5
	female	mean		3.55	3.59	3.49	3.38
		SD		0.1	0.2	0.1	0.2
		statistical significance					*
		estimated # litters affected[a]		1	1	2	5
Visceral malformations:							
	# litters examined[b]			39	18	19	19
	Total visceral						
	# litters affected			0	1	4	7
	% fetuses affected/litter						
		mean		0	0.69	2.6	9.82
		SD			2.95	5.6	17.2
		statistical significance				*	*
	Cardiovascular						
	# litters affected			0	1	2	6
	% fetuses affected/litter						
		mean		0	0.69	1.02	8.07
		SD			2.95	3.1	16.26
		statistical significance					*

[a] Continuous data were converted to quantal form as described in the text

[b] For controls, # of litters examined is from 2 related studies, combined

* $p \leq 0.05$

are quantal, but other data (body weight, crown-rump length) are continuous, and were converted to quantal (*estimated # of litters affected* in the table) prior to modeling.

Conversion of the continuous-response developmental data to quantal form was performed by assuming a normal distribution with a constant variance across dose groups for the response, and 5% background response rate. Because individual animal data were not available, the number of responders in each dose group was estimated by first establishing a critical value representing the point above (or below, depending on the direction of adverse response) which 5% of the control group lies. Then, for each dose group, the proportion exceeding this critical value was estimated. This proportion was applied to the number of animals in the dose group to determine the number of responders. The doses were converted to equivalent human doses using the scaling factor of body weight to the 3/4 power. A threshold dose-response model was then fit to the data sets for the individual DBP.

As shown previously in Table 3-15, adequate developmental toxicity data were lacking for the haloacetic acids DBA and BCA and for the haloacetonitriles DBAN and DBCAN. A surrogate approach seemed appropriate to fill these data gaps, because the available data indicated that developmental toxicity may be common to the haloacetic acid and haloacetonitrile DBP. As a provisional measure, DCA was selected as a surrogate for these haloacetic acids and TCAN was selected as a surrogate for these haloacetonitriles. A search for mechanistic data to support selection of surrogates revealed studies of mechanisms relevant to carcinogenicity, which may not be relevant to developmental toxicity, and some *in vitro* embryo culture studies, which did not appear to give results corresponding to the available *in vivo* testing. Therefore the

selections of surrogates were based partly on structural similarity and partly on quality of the data (such as better dose spacing) for the surrogate.

The proportional response additivity approach was applied to concentration data from two pilot studies of drinking water disinfection processes: one using Mississippi River water at Jefferson Parish, LA (Lykins et al., 1991) and the other using Ohio River water (Miltner et al., 1990; with further analysis by NCEA-CIN EPA). Data sets for water treated with chlorine were chosen because this process results in higher levels of the haloacetic acids and haloacetonitriles relative to other methods, such as pretreatment with ozone prior to disinfection with chlorine, and/or other disinfectants such as chloramine.

3.8.3. Results. Risks of developmental toxicity were estimated for humans ingesting drinking water containing the haloacetic acids and haloacetonitriles at the concentrations determined in the pilot studies described in the previous section. The risk estimates were based on increased total visceral malformations, increased cardiovascular malformations, decreased fetal body weight, and decreased fetal crown-rump length. [Because the reports of the animal data for MCA and MBA did not break out the cardiovascular incidence data from the total visceral malformation data (stated to be mainly cardiovascular), the proportional risk estimates for cardiovascular malformations used total visceral malformations for those two chemicals.] The risk estimates were similar for total visceral malformations, cardiovascular malformations, and decreased fetal weight, and somewhat lower for decreased fetal crown-rump length.

The risk estimates based on total visceral malformations were selected to illustrate the application of proportional response additivity, because these estimates best illustrated the use of surrogates. Details of these estimates are provided in Tables 3-17 and 3-18. The concentration data, in µg/L, were converted to human doses by assuming water consumption of 2 L/day and a body weight of 70 kg. The total combined dose of haloacetic acids and haloacetonitriles was approximately 4 µg/kg-day for Jefferson Parish (Mississippi River) water and 2 µg/kg-day for the Ohio River water. The risk for each DBP was estimated at the total mixture dose (as if the DBP were present at a dose equal to the whole mixture dose) using a threshold dose response model as previously described. The risk for some components was zero because the threshold for these components was higher than the total mixture dose. The proportional risk for each component was then calculated by multiplying risk at the total mixture dose by the proportion of that component in the mixture. The sum of the proportional risks, or total risk, for the two sets of drinking water data was 1.2×10^{-5} for Jefferson Parish/Mississippi River and 8.9×10^{-6} for the Ohio River. These values are virtually identical, and indicate a relatively low risk for developmental toxicity ($\approx$1 in 100,000) during the gestational period.

If proportional risks based on surrogates were omitted, the total risks for the two sets of drinking water data were slightly lower: 7.4×10^{-6} and 7.1×10^{-6} (0.7 in 100,000). Elimination of surrogates from the risk estimates had a similar impact for estimates based on cardiovascular malformations, but virtually no impact on the estimates based on fetal body weight and none on crown-rump length. Risk was also estimated for an alternative disinfection method involving pretreatment of Ohio River water with ozone

TABLE 3-17

Example Risk Estimate for Developmental Toxicity in Humans Exposed to Haloacetic Acids and Haloacetonitriles in Drinking Water at Concentrations Determined in Pilot Study, Jefferson Parish (Mississippi River) Following Chlorine Treatment

Chemical	Water Concentration µg/L	Estimated Dose mg/kg-day	Proportion of Component in Mixture	Risk at Total Mixture Dose[a]	Proportional Risk[a]
MCA	16	4.57E-04	11.93%	0	0
DCA	44.9	1.28E-03	33.48%	2.04E-05	6.8E-06
TCA	39.8	1.14E-03	29.68%	0	0
M BA	1.2	3.43E-05	0.89%	0	0
DBA[b]	0.8	2.29E-05	0.60%	2.04E-05	1.2E-07
BCA[b]	28.7	8.20E-04	21.40%	2.04E-05	4.4E-06
DCAN	1.6	4.57E-05	1.19%	0	0
TCAN	0.1	2.86E-06	0.07%	1.32E-04	9.8E-08
BCAN	0.7	2.00E-05	0.52%	1.01E-04	5.3E-07
DBAN	Not listed	—	—	—	—
DBCAN[c]	0.3	8.57E-06	0.22%	1.32E-04	2.9E-07
Sum	**—**	***3.83E-03***	***100.00%***	**—**	***1.2E-05***

[a] Based on dose-response data for total visceral malformations, using threshold dose-response model
[b] Estimated using the surrogate DCA
[c] Estimated using the surrogate TCAN

TABLE 3-18

Example Risk Estimate for Developmental Toxicity in Humans Exposed to Haloacetic Acids and Haloacetonitriles in Drinking Water at Concentrations Determined in Pilot Study, Ohio River, Following Chlorine Treatment and Simulated Distribution

Chemical	Water Concentration µg/L (95% UCL)	Estimated Dose mg/kg-day	Proportion of Component in Mixture	Risk at Total Mixture Dose[a]	Proportional Risk[a]
MCA	1.57	4.49E-05	2.12%	0	0
DCA	33.26	9.50E-04	44.80%	1.13E-05	5.0E-06
TCA	21.66	6.19E-04	29.17%	0	0
MBA	0.33	9.47E-06	0.45%	0	0
DBA[b]	1.66	4.75E-05	2.24%	1.13E-05	2.5E-07
BCA[b]	8.66	2.48E-04	11.67%	1.13E-05	1.3E-06
DCAN	4.23	1.21E-04	5.70%	0	0
TCAN	0.27	7.75E-06	0.37%	7.30E-05	2.7E-07
BCAN	2.32	6.64E-05	3.13%	5.57E-05	1.7E-06
DBAN[c]	0.27	7.72E-06	0.36%	7.30E-05	2.7E-07
DBCAN	Not listed		—	—	—
Sum	**—**	***2.12E-03***	***100.00%***	**—**	***8.9E-06***

[a] Based on dose-response data for total visceral malformations, using threshold dose-response model
[b] Estimated using the surrogate DCA
[c] Estimated using the surrogate TCAN

followed by chlorine. This treatment produced lower concentrations of most of the haloacetic acids and haloacetonitriles, and lower total doses, but slightly higher concentrations of MCA, DBA, BCAN, and DBAN than did the parallel disinfection without ozone in the same pilot study. The estimated risk of developmental toxicity (based on dose-response for total visceral malformations) for the alternative ozone-chlorine treatment was 6.7×10^{-6}, slightly lower than that for the chlorine treatment shown in Table 3-18.

3.8.4. Future Directions. Several toxicological (biological and statistical) issues were raised during this exercise that will require further analysis. These issues include: the effect of the vehicle, tricaprylin, in the haloacetonitrile studies; the relevance of using the gavage studies for extrapolation to the drinking water exposure scenario; the appropriateness of combining data within a category (such as fetal size—fetal body weight and crown-rump length); and the usefulness and relevance of *in vitro* studies such as whole embryo culture for chemicals with inadequate *in vivo* data.

Further analysis of dose-response assessment of individual fetal data and of male reproductive data for the haloacetic acids and haloacetonitriles may prove fruitful for application of this method. In depth consideration of surrogate chemicals, including pharmacokinetic and pharmacodynamic mechanisms warrants additional attention. Another direction for future statistical efforts includes the exploration of alternative methods for converting continuous response data and the feasibility of applying proportional response addition across all of the mixture components for a continuous endpoint prior to estimating the risk for the mixture.

3.9. PRESENTATION: NEW MIXTURES METHODOLOGIES: RELATIVE POTENCY FACTORS, TOXIC EQUIVALENCY FACTORS WITH RESPONSE ADDITION (R. Hertzberg)

NCEA-Cin has been working on approaches for assessing the toxicity of classes of similar chemicals. These approaches have included the Relative Potency Factor (RPF) method, interactions hazard index, and extension of the RPF to more complex mixtures.

3.9.1. Relative Potency Factors. Use of Toxicity Equivalency Factors (TEF), such as those for dioxins, are the true form of dose-addition wherein the same mechanism of action is assumed. There is one relative potency value per congener and the mixture dose is treated as an equivalent dose of the index congener. Similar structure, the same mechanism for toxicity, and data from several measures of toxicity are needed to show that the relative potency of the congeners are constant across all effects, time frames, species, routes, and assays. Often, there are insufficient data to validate a TEF approach and few groups of chemicals qualify for its use. Therefore, in many site assessments for classes of chemicals with data considered inadequate for TEF development, either zero is assumed as a risk value for a congener with little toxicity data or the toxicity of the most toxic congener is substituted.

Another approach, more general than the TEF approach, but requiring less information and with more restricted application, is the RPF method (Table 3-19). The TEF can be thought of as a specific type of RPF. The RPF approach also assumes dose addition, requires similar structure or toxicity and empirical similarity amongst the chemical class, but can be applied when such information only exists for organ-specific

TABLE 3-19

Differences Between TEF and RPF for Chemical Classes

	TEF Specific Type of RPF	RPF Generalized Case
Data required for health endpoints	All	May be limited
Data for routes	All	May be limited
Precision	Greater precision inferred	Lesser precision inferred

endpoints or for specific routes. More chemical classes will qualify for this approach, which is accompanied by an indication of data quality and an description of uncertainty. The process for the development of an RPF involves the following:

- demonstration of the need,
- initiation of the consensus process (e.g., meeting of stakeholders),
- development of a clear definition of the class of compounds,
- development of the RPF,
- characterization of uncertainty,
- evaluation of the RPF process, and
- identification of research needs.

A hypothetical example RPF is shown in Tables 3-20 and 3-21. This example shows how an RPF was developed for five cholinesterase inhibitors with data from studies ranging in duration from short to long-term, on several species (including humans), and with the amount and quality of data varying from poor to extensive. The risk characterization for RPF identifies the fraction of the mixture that is the index chemical (that is, so data vs. inference is known) and the overall quality of the RPF (i.e., the numerical consistency, knowledge of toxic similarity and relevance of the data).

Unresolved statistical issues raised by the TEF and RPF for which new methods need to be developed revolve around the combination of highly dissimilar types of data (e.g., NOEL, cancer potency, ED10), judgment of similar toxic mechanism (e.g., for dioxins, TEF required international consensus) and judgment of numerical value of each TEF (i.e., consensus on the value). Other ways to improve the current approaches would be to expand the uncertainty analysis to include more endpoints,

TABLE 3-20

Weight-of-Evidence Classification for Mixture Interactions

I. The interaction has been shown to be relevant to human health effects and the direction of the interaction is unequivocal.

II. The direction of the interaction has been demonstrated *in vivo* in an appropriate animal model and relevance to potential human health effects is likely.

III. An interaction in a particular direction is plausible but the evidence supporting the interaction and its relevance to human health effects is weak.

IV. The information is:
- A. Insufficient to determine to direction of any potential interaction
- B. Insufficient to determine whether any interaction would occur
- C. Adequate as evidence that no toxicologic interaction between/among the compounds is plausible

TABLE 3-21

Weight-of-Evidence Scores for Mixture Interactions

WOE Category	Description	Greater than Additive (+)	Less than Additive (-)
I.	Directly relevant to humans	1.0	1.0
II.	Animal studies, but relevant	0.75	0.5
III.	Plausible evidence, relevant?	0.5	0.0
IV.	Additivity demonstrated or accepted because poor data	0.0	0.0

weighted for relevance, or to base the analysis on a different index chemical. However, the use of more endpoints would require more decision criteria and would imply more objectivity and precision. Information for the dose-response curve may differ if the analysis was to be based on a different index chemical. Constraining the RPF method to those classes of chemicals where all chemicals could be assigned RPF values would avoid the current pitfall of having a class where some chemicals have RPFs and others do not. Imposing this constraint would limit the applicability of the method. Another option would be to have RPFs that are tied to the mechanism of action of the chemical. That is, a chemical may act by different mechanisms, and so there may be a need to have a different RPF assigned for each toxicity mechanism.

Arguments supporting dose-addition include toxicologic similarity and receptor models. Criteria for toxicologic similarity are similarity of chemical structure, toxic endpoints, and numerical closeness of toxicity measurements. If chemicals are identical in toxicologic action, then the difference in toxic potency is only in the magnitude of the effective dose. The receptor model is based on Michaelis-Menten kinetics under steady-state conditions. For competitive agonists, high-dose antagonism produces the same S-shaped dose-response curve as for a single chemical and there is dose-additivity at low doses. For noncompetitive agonists, dose-additivity does not occur at low doses and there is a drop in the maximum response at high doses (see Figure 3-34).

3.9.2. Interaction-based Hazard Index. Another approach is the weight-of-evidence (WOE) modification of the hazard index (HI (that explicitly reflects interaction data.). For single chemical exposure, a hazard quotient (HQ) can be determined for noncancer

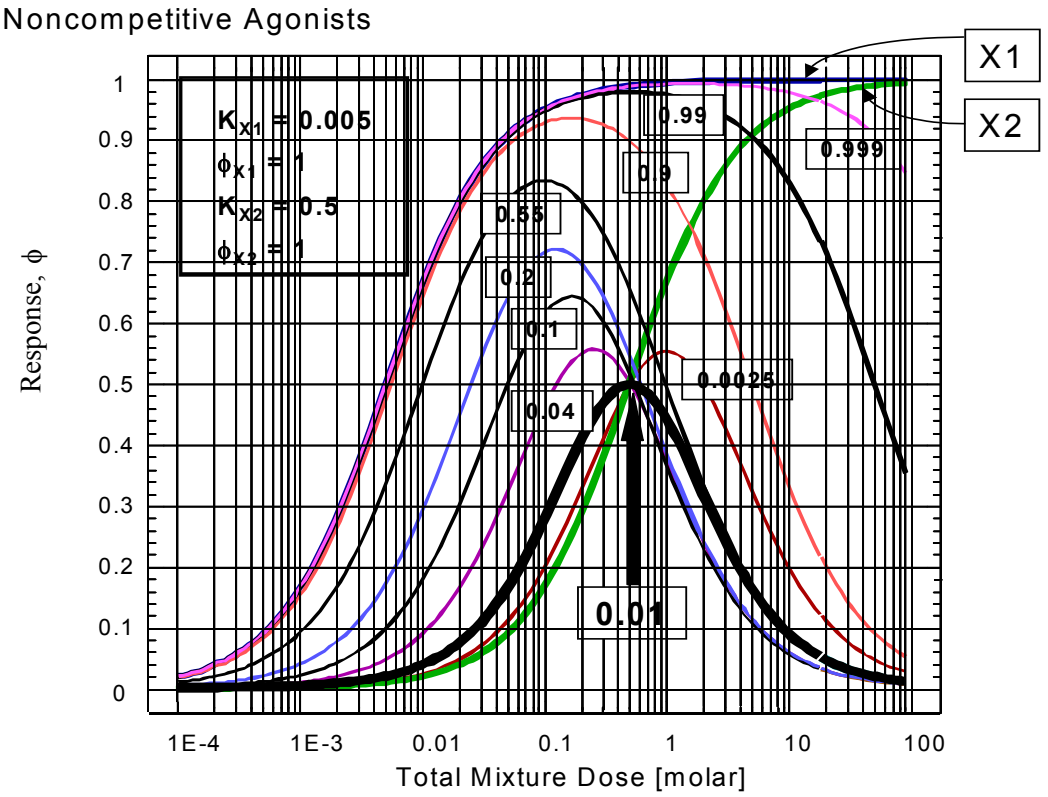


FIGURE 3-34

Hypothetical Dose-Response Curves for Different Mixtures of Two Noncompetitive Agonists with Equal Intrinsic Activities but Differing Affinities for the Receptor. (Ratios are given as proportion of chemical X1, so the curve X1 could have been labelled 1.0 and, similarly, the curve X2 could have been labelled 0.0.)

effects. The HQ, primarily used in Superfund risk assessments, indicates whether intake of the chemical by a particular route (e.g., oral or inhalation) exceeds the reference value (e.g., RfD or RfC) for that chemical for that route. The RfC or RfD is the exposure value for a single chemical for which lifetime daily exposure is expected to be associated with negligible risk of adverse effects, even in sensitive subgroups of the exposed population. The HQ for a chemical for the oral route is:

$$HQ_k = \frac{E_k}{RfD_k} \qquad (3\text{-}13)$$

where:

E = exposure level (or intake)

RfD = oral reference dose

E and RfD are expressed in the same units (e.g., mg/kg-day) and represent the same exposure period (e.g., chronic exposure).

For mixtures, noncancer effects are often assessed by estimating the HI (U.S. EPA, 1986). The HI estimates whether combined exposure (or intake) of the components exceeds the reference value for the mixture (which is the exposure-weighted harmonic mean of reference values for each component). The HI is derived from the concept of dose-addition and is generally calculated for a specific single toxic effect (e.g., reproductive toxicity, hepatic toxicity), because dose-addition requires the assumption of a similar mode of action (or toxicologic effect).

The HI for a mixture of n chemicals is:

$$HI = \sum_{j=1}^{n} HQ_{j_j} \qquad (3\text{-}14)$$

Exposure to the mixture is usually judged acceptable when the HI $\leq$ 1. When HI > 1, toxicity is deemed possible and further investigation is indicated. In practice, separate HIs are determined for each toxic effect of interest, and acceptable exposure is indicated whenever *all* HIs < 1.

The HI approach, however, does not take into consideration the toxicologic interaction of components in the mixture. Existing data on toxicologic interactions are primarily for binary mixtures (i.e., mixtures with two components). In general, toxicologists assume that the magnitude of the interaction decreases with decreasing dose, the magnitude is maximal when the component doses are equitoxic, and the maximum change plausible in the toxicologic effective dose is a factor of about 10. As currently used by EPA, data for the interaction of binary mixtures do not generally change the outcome of the risk assessment, such as clean-up goals at Superfund sites, unless there is strong evidence of a toxicologic interaction.

As a way to take into account interaction information in determining the HI, Mumtaz and Durkin (1992) ranked toxicologic interaction information to estimate confidence in the direction of the interaction (i.e., antagonism, additivity, synergism) and converted that information into a weight-of-evidence (WOE) score. The WOE score was used to convert the HI into an interaction HI (HI_{INT}).

Subsequent to the Mumtaz and Durkin (1992) approach, EPA developed a slightly different approach (Hertzberg et al., 1999) whereby the HI can be modified to account for interactions, as follows:

$$HQ_k = \frac{E_k}{RfD_k} \quad (3\text{-}15)$$

M_{jk} is the estimate of the observed interaction magnitude, synergistic or antagonistic, that chemical k has on the threshold or risk-specific dose (e.g., ED_{10}) of chemical j. The factor f_{jk}, a function of the HQ values, is a normalizing or weighting factor that is a rough measure of the relative toxicity of the k^{th} component compared to all the other chemicals that could interact with the j^{th} chemical. The binary WOE factor, B_{jk}, reflects the strength of studies showing that chemical k influences the toxicity of chemical j and that the influence will be relevant to human health assessment. The WOE classification on which B is based is similar to, but simpler than, the WOE process of Mumtaz and Durkin (1992). It is dependent primarily on data quality factors and relevance of the data to potential human health effects (Table 3-20); in most cases, this related to the extent of any extrapolation. The WOE classification is converted into a numerical weight; positive values indicate synergism and negative values indicate antagonism (Table 3-21). For each pair of component chemicals in the mixture, two WOEs are evaluated: first, for the influence on chemical j on the toxicity of chemical k, and then for the influence of chemical k on the toxicity of chemical j. Factor g_{jk} reflects the degree to which components j and k are present in equitoxic amounts. In practice, equitoxic chemicals are chemicals with equal HQs.

The interaction HI incorporates the actual exposure levels of the components, the estimated magnitude of each pairwise interaction, and the WOE scores. Thus, the influences of all the other interacting chemicals are incorporated into each chemical's modified HQ. The modified HQs are then summed to get the interaction HI for the mixture. For example, assume that there are three chemicals in a mixture, that pairwise there is synergism, and that the observed interaction magnitude is 5 for each pair (M= 5). The HI_{INT} for an equitoxic composition of 1:1:1 is 5 * HI (five times the standard dose-additive HI), for a composition of 8:1:1 is 2.8 * HI, and for a composition of 98:1:1 is 1.4 *HI.

3.9.3. More Complex Mixtures. The Hazard Index and the Relative Potency Factors procedures are applied to groups of toxicologically similar chemicals. A more complicated situation usually occurs, where the exposure is to a collection of chemicals, some that are toxicologically similar, some that interact, and some that are independent. Such a mixture could be assessed by dividing it into separate groups, and then combining the resulting assessments. For example, consider the mixture containing a group (A) of similar chemicals and a group (B) of independent chemicals, where the latter group is also toxicologically independent from the similarity group. First, RPFs are applied to group A, the similarity group, so that group A's exposure is represented by the equivalent exposure to the index chemical (call it X). Second, response addition is applied to the combination of the independent group's exposure with the index chemical's equivalent exposure. The combined risk for these two exposures (group B and the X equivalent) are combined as if they were two independent chemicals.

A more difficult case is when the first group includes some interacting chemicals. A proposed approach might be to characterize that group by the interaction-based HI. The difficulty is that the HI is not a risk estimate and so cannot be directly combined with a risk or response estimated by response addition. One alternative calculation would replace the relative toxicity weighting coefficients (1/RfD in Equation 3-13) by the inverse of the ED10. For similar chemicals where dose addition applies, the resulting HI can be interpreted in a response context: when HI=1, the mixture is at its ED10. Unfortunately, for other values of HI, and for interaction-based HI calculations, no interpretation has yet been proposed in terms of estimated response or risk.

3.10. PRESENTATION: EXPERT JUDGMENT FOR ASSESSING RISK: TOXICOLOGY AND EPIDEMIOLOGY (G. Gray)

3.10.1. Overview of Expert Judgment in Risk Assessment. Expert judgment uses the knowledge and views of experts to characterize the scientific state of knowledge. It is not a quick and easy way to avoid collection of data or analysis. As stated by Morgan and Henrion (1992), “When you need to know the value of an uncertain quantity and limits of data or understanding make standard methods impossible, the remaining option is to ask experts for their best professional judgment”. Expert judgment has a long history in many fields including engineering, finance, medicine, and environmental risk analysis. The field of decision analysis recognizes explicit expert judgment as a legitimate means for characterizing uncertain model parameters with little or no directly applicable data or that require the synthesis of several lines of evidence.

Eliciting expert judgment is a field with its own literature and standards of practice (for general references see Cooke, 1991; Keeney and von Winterfeldt, 1989; Lindley, 1991; Otway and von Winterfeldt, 1992). It requires the analyst (the person trying to get

the information from the experts) to understand the field, work with experts, and document the expert judgments. There are two approaches to eliciting expert judgment: direct elicitation and problem disaggregation and elicitation on individual parts. These approaches may be used together as was the case in the chloroform project (Evans et al., 1994b). Through these processes, expert judgment is made explicit, a quantitative sense of uncertainty is provided, and key sources of uncertainty are identified. In addition, areas of agreement and disagreement among scientists are highlighted, helping to focus future research efforts. Expert judgment facilitates honest communication with decision makers and the public.

Formulation of a protocol for elicitation of expert judgment requires several key elements including:

- clear formulation of questions (clairvoyance test),
- experts must be encouraged to think of a full range of uncertainty,
- several types of expertise may be necessary for complex problems, and
- experts should be trained in calibration.

Who to choose as an expert and how to choose experts are important issues in expert judgment (Graham et al., 1988). Often, experts have bias in their research areas and policy goals, and differ in their breadth and depth of knowledge. Calibration is an important element in that experts often seem to be overconfident on general knowledge questions. However, there is some evidence that experts may be reasonably well-calibrated in their field (Hawkins and Evans, 1989). It must be clear what informs expert judgment as experts in a field often likely read the same or similar body of literature or may have received the same training. The issue of independence of expert judgments

should be considered. Whether to combine, and how to combine, as well as how to present results, are issues for consideration in eliciting expert judgment (for example, Jouini and Clemen, 1996).

3.10.2. Expert Judgment in Epidemiologic Questions. The expert judgment of epidemiologists has been used to characterize the range of risks and uncertainty. These types of studies have primarily been used to resolve confusing data or to synthesize conflicting or uncertain data. The effect of low-level lead exposure on intelligence quotient (IQ) (Whitfield and Wallsten, 1989), the effect of sulfate particles on health (Morgan and Herion, 1992), and the cancer risk of chlorinated drinking water (Evans et al., 1994b) are some examples of expert judgment analysis of epidemiologic questions.

In the study of Evans et al. (1994b), it was found that, due to the limits of data available, experts could only evaluate the risk of chlorinated drinking water. In that protocol, epidemiologic experts were first asked “What is the risk due to lifetime consumption of chlorinated drinking water with a level of trihalomethanes equivalent to 100 ppb of chloroform?”. Many would not answer that question contending that there were not data to answer it. Subsequently, the analysts asked “What are risks of lifetime residential exposure to chlorinated drinking water?”. Epidemiologists who felt comfortable answering the above questions, gave estimates of relative risk of different cancer types or sites and the risks were calculated using SEER background incidence data.

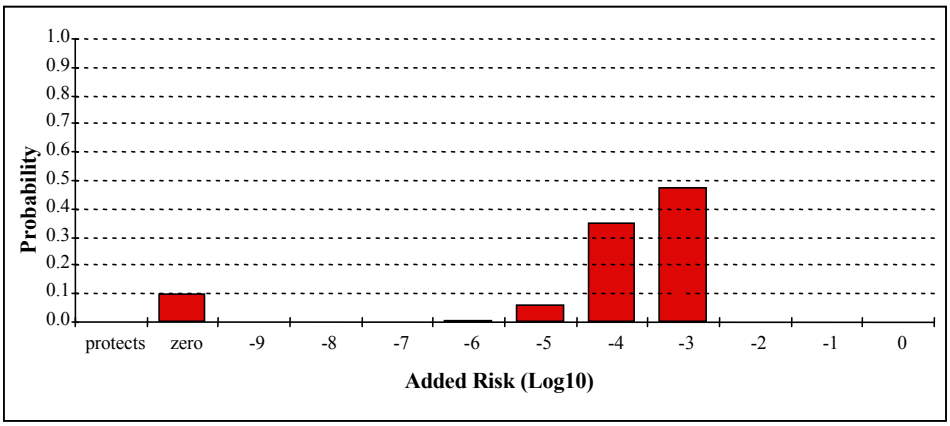
Figure 3-35 shows the probability of added risk predicted by three epidemiologists for the induction of cancer following lifetime residential exposure to

chlorinated drinking water. The epidemiologists were quite uncertain about the risk of chlorinated water. This is reflected in the range of risk values presented. The risk distributions for the different experts were fairly similar, with expected values of risk differing by about a factor of 5, and 95th percentiles differing by a factor of 7. The largest difference was whether the epidemiologists thought the relative risks were less than 1 (i.e., chlorinated water could be protective for cancer). The distributions of the individual epidemiologists tended to be bimodal for uncertainty (i.e., with some probability of zero risk and some probability that the relative risk estimates from some epidemiologic studies are correct). It is notable that the risks above background calculated from the relative risk estimates are fairly high, reflecting the background incidence of the different tumor types.

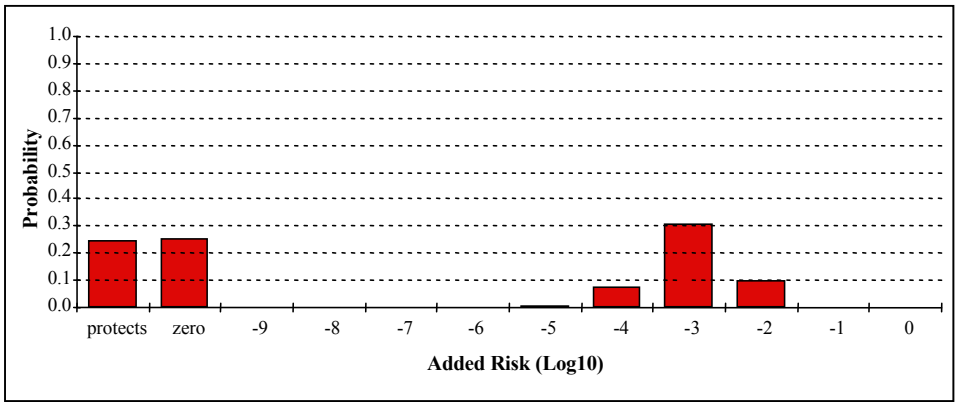
3.10.3. Expert Judgment in Toxicologic Questions. There are fewer examples of the use of expert judgment for toxicologic questions than in epidemiologic issues. Many current approaches to risk assessment are deliberately biased toward conservative estimates, rather than best estimates, of risk. Few attempts have been made to generate best estimates of risk or full uncertainty distributions based on toxicologic data. Two types of uncertainty that can be addressed with expert judgment are parameter uncertainty and model uncertainty.

Parameter uncertainty is usually considered to arise from empirical uncertainty due to statistical variation, inherent randomness, approximation, or other sources. Determination of the speed of light, the rate of growth of populations, or the value of the

Epidemiologist A



Epidemiologist B



Epidemiologist C

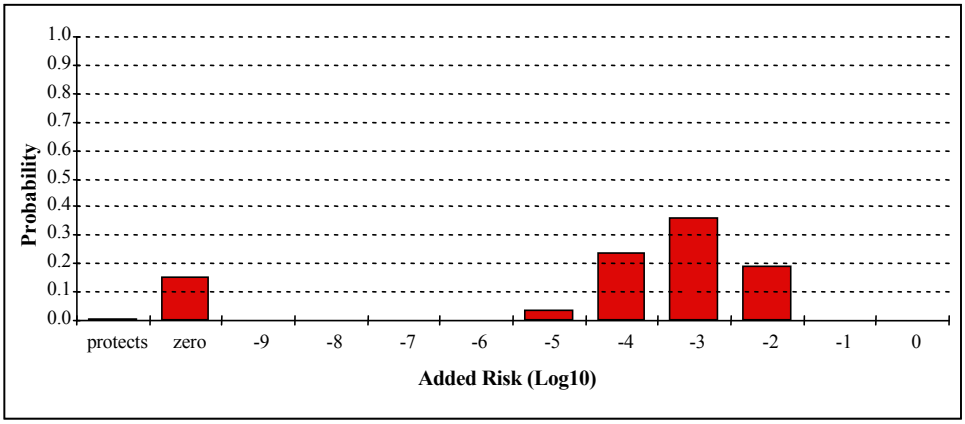


FIGURE 3-35. Probability of Relative Risk for Cancer Predicted by Epidemiologists A, B, and C from a Lifetime of Residential Exposure to Chlorinated Drinking Water

q1 term of the linearized multistage model of carcinogenesis are examples of parameter uncertainty.

Model uncertainty arises when we are unsure how to describe the relationship between two (or more) factors. The relationship between carbon dioxide emissions and global warming, or the shape of the dose-response relationship for a carcinogen at very low doses are examples of model uncertainty. Standard cancer risk assessment methods make conservative choices in the face of uncertainty. For example, standard potency assessment uses the most sensitive species, the most sensitive site, the linearized multistage procedure for dose-response modeling, and dose scaled by surface area for extrapolation to humans, thereby providing a plausible upper limit to the risk that is consistent with some proposed mechanism of carcinogenesis. Derivation of a best estimate of risk requires characterization of uncertainty rather than conservative choices. Some critical sources of uncertainty in potency estimation include: the choice of data set in predicting the human response (e.g., species, tumor site), the measure of dose, dose-response model, and the importance of available mechanistic information.

The chloroform project (Evans et al., 1994b) used expert judgment in evaluating the low dose carcinogenic potency of chloroform (Figure 3-36). What organ was the likely target, the mode of action, how to scale dose, the shape of the dose-response curve, the choice of the data set, and the relative average animal and human sensitivity to chloroform were asked of experts using a probability tree method. This method allows for decomposing the complex problem of estimating potency into scientifically and analytically well-defined questions, for the formation of questions of scientific

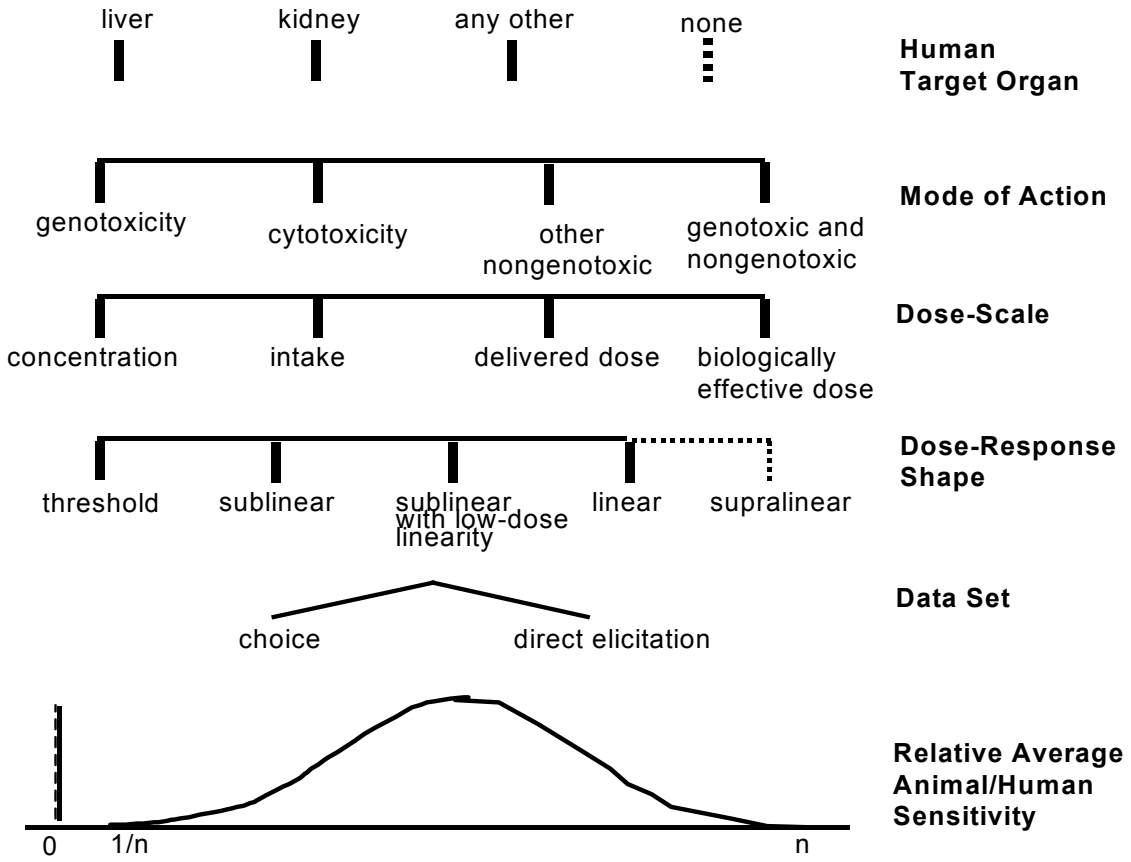


FIGURE 3-36

The Chloroform Probability Tree

Source: Evans et al., 1994b

theory or fact for expert elicitation, and provides structure for expert elicitation. Importantly, the experts were not required to choose one "right" answer, but were encouraged to weight the different alternatives according to scientific plausibility.

The expert judgments were elicited in a give-and-take interview under a structured elicitation protocol. The interviewers acted as "devil's advocate" to focus the discussion, clarify the rationale for a judgment, and highlight data that appeared to be contrary to the expert's stated opinion. The rationale, data, and theory supporting all judgments were elicited and recorded. The experts remained anonymous and were identified only as Experts A-F. Figure 3-37 shows an example of one path through the probability tree by one expert. The experts provided weights for alternative data and analysis methods but did not directly estimate potency. Rather, potency was calculated by the analysts based on the experts' weighting. For example, the path shown in Figure 3-37 produces a risk estimate of 2.2×10^{-7} with a weighting of 0.025 based on 0.20 for genotoxic and nongenotoxic modes of action, 0.25 for delivered dose as the dose-scale, and 0.50 for assumption of the shape of the dose-response curve as sublinear with low-dose linearity ($0.20 \times 0.25 \times 0.50 = 0.025$). Chloroform potency estimates were combined with an estimated exposure from drinking water to estimate risk. Final distributions of risk for induction of tumors at any site from the ingestion of water with 100 ppb of chloroform are a summary of more than 200 paths through the tree weighted by the experts' subjective probability that the path through the tree is correct (see Figure 3-38).

As shown in Figure 3-39, there is heterogeneity in the estimates of risks based on the judgments of the different experts; they tended to think that either there was a

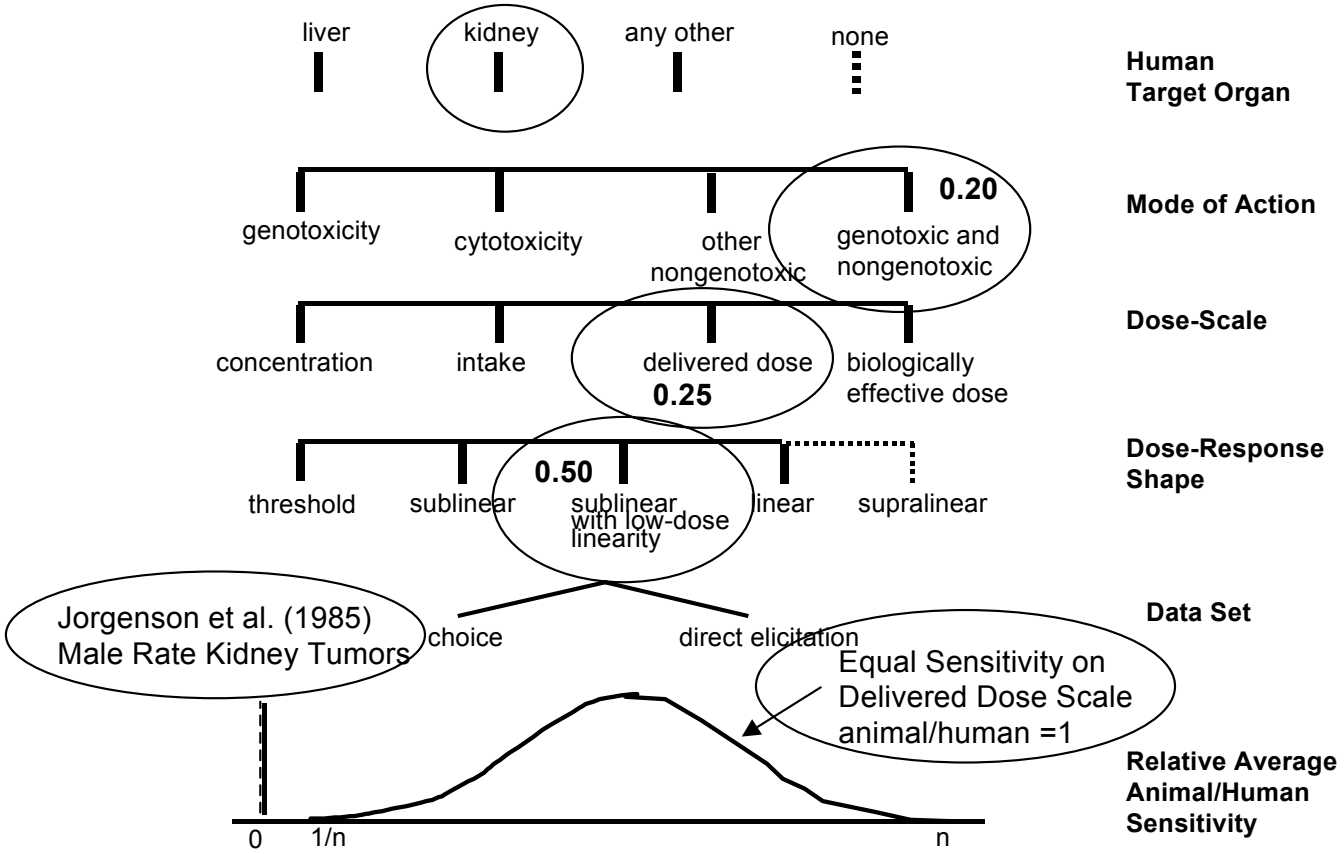


FIGURE 3-37

Constructing Risk Distributions for Chloroform Project. Example of Path by One Expert

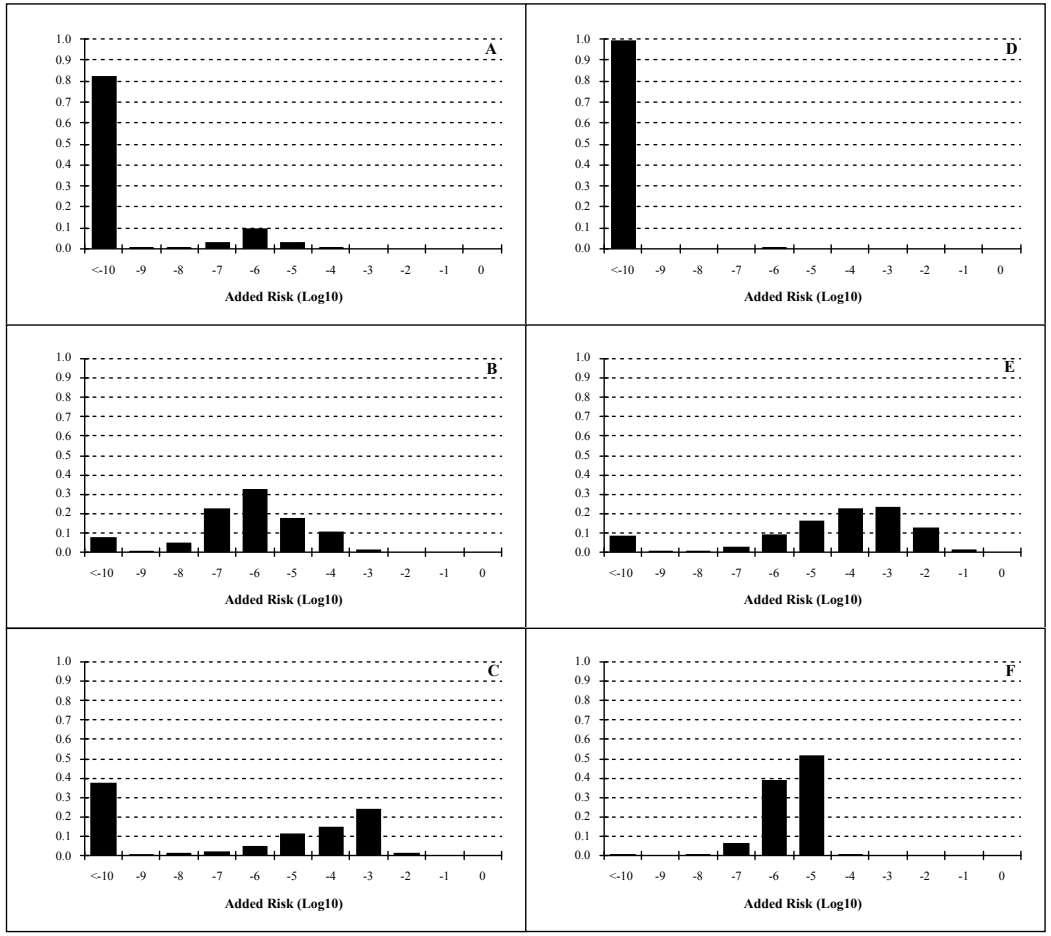


FIGURE 3-38

Results for Individual Experts for 100 ppb Chloroform in Drinking Water Tumor Induction at Any Site

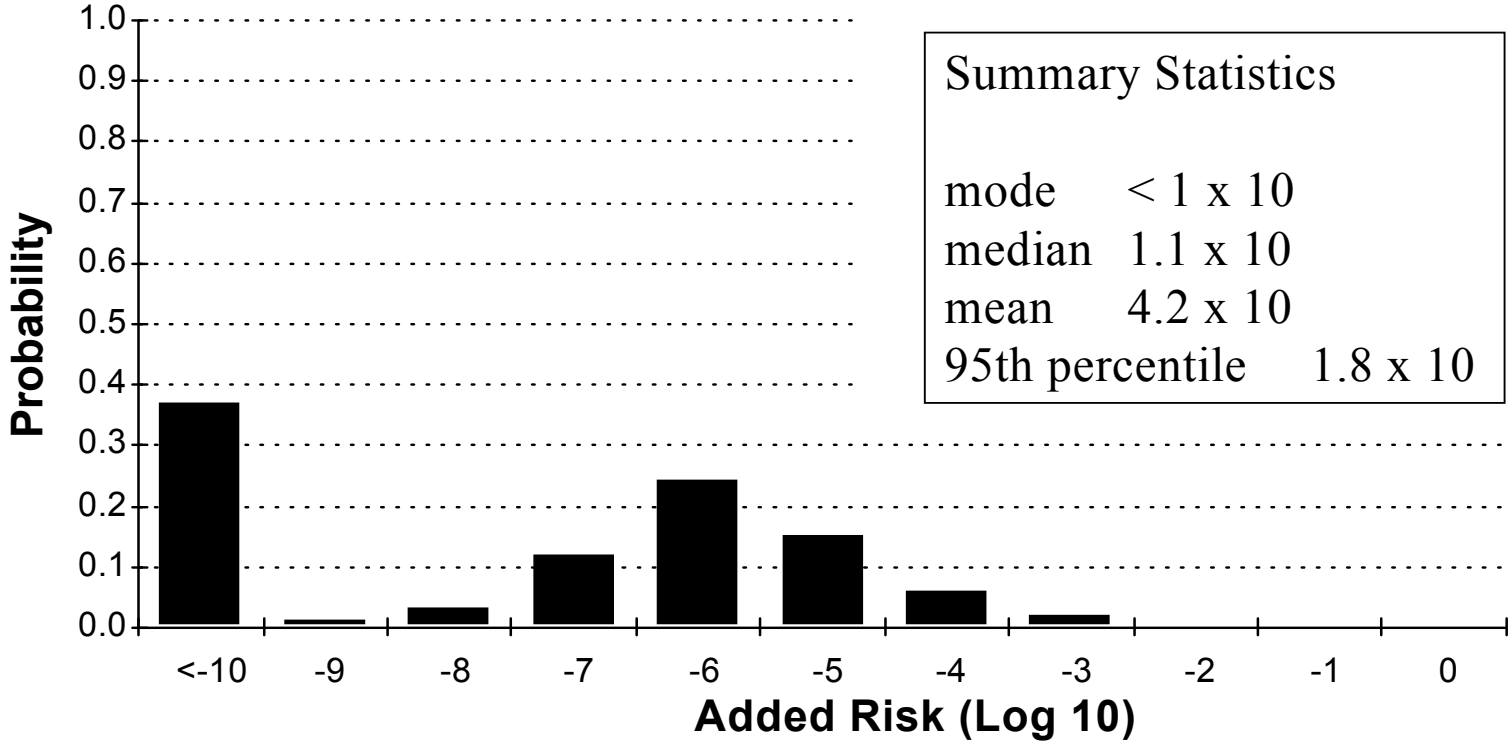


FIGURE 3-39

Lifetime Cancer Risk from Drinking Water with 100 ppb of Chloroform

(Source: Evans et al., 1994b. Regulatory Toxicology and Pharmacology 20:15-36.)

significant health risk for cancer from chloroform in drinking water or there was not. There is considerable controversy about whether to combine expert judgments, and how to do it if it is to be done (Clemen, 1989). As one means of combining estimates, each expert was asked to weight their knowledge on each level of the tree. For example, if an expert thought s/he was equally knowledgeable about all, then the weights would be evenly distributed. The expert could indicate the different levels of expertise with different weights. The trees and the "self-weighted" combined distribution were then calculated; these are shown in Figure 3-40.

The chloroform project demonstrated that expert judgment can be used to quantify model uncertainty in cancer potency estimation. The distributional approach highlighted areas of agreement and disagreement among experts as well as characterized uncertainty and allowed a better understanding of the likelihood of alternative estimates of risk. In addition, the method allowed all relevant scientific evidence about the carcinogenic potential of a chemical to be considered. Table 3-22 shows the strengths and weaknesses of the distributional approach in expert judgment.

3.10.4. Summary. Evaluating epidemiologic and toxicologic information through an expert judgment analysis is no different than eliciting judgment from traditional sources. However, ensuring that both analyses are addressing the same question (e.g., specificity of data, differences in confounding factors) and also uncertainty (e.g., overlapping uncertainty bounds) would be key concerns. For example, in the chloroform project, toxicologists had data on the carcinogenicity (e.g., mechanism, animal bioassay) of chloroform, whereas the epidemiologists reviewed data concerning the differences in cancer rates between populations drinking chlorinated or non-

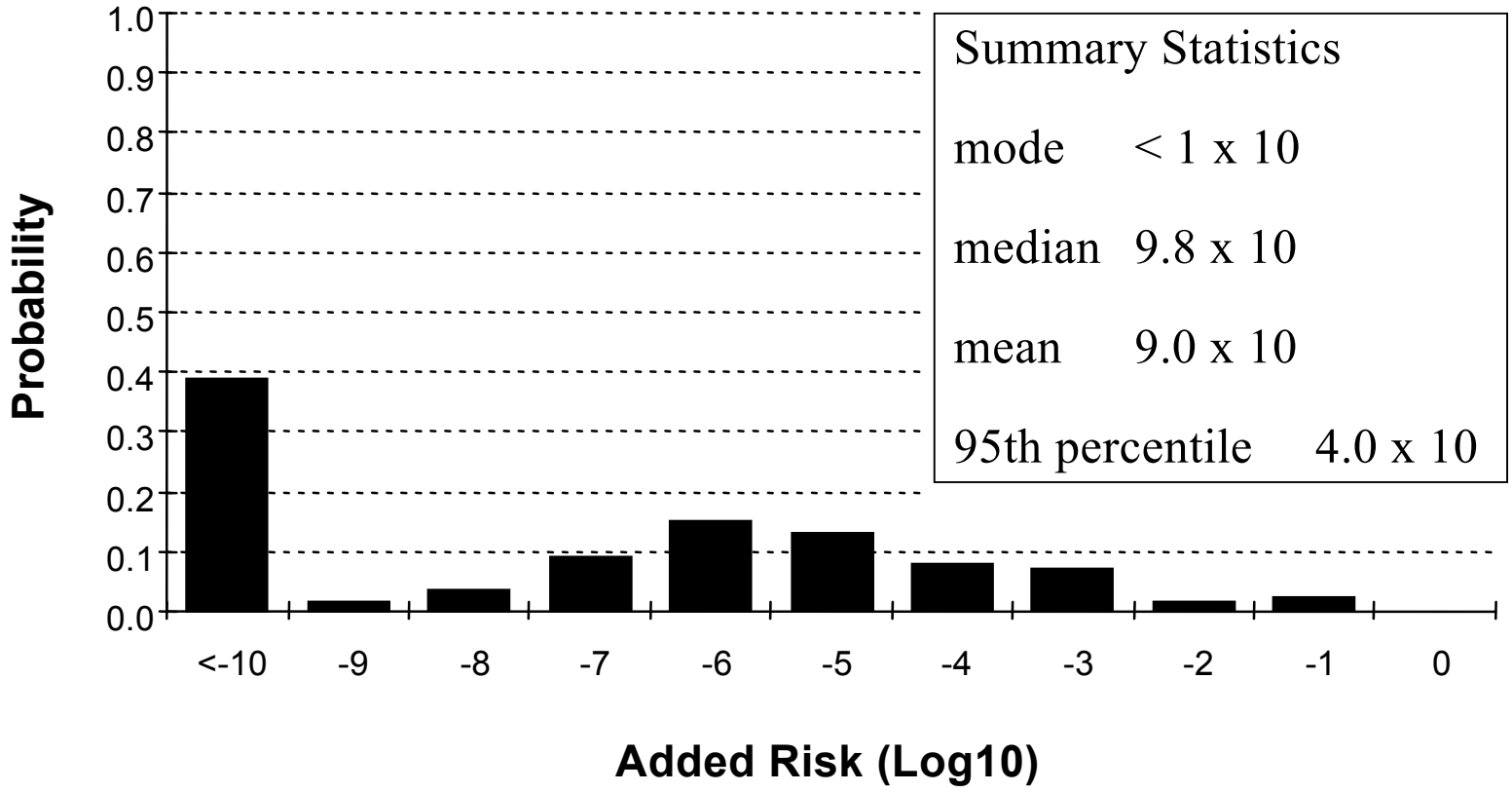


FIGURE 3-40

Combined Results from Experts Considered Self-Weighting

TABLE 3-22

Distributional Approach to Expert Judgment

Weaknesses	Strengths
• Relies on expert judgment which is known to have several problems including “overconfidence” or lack of willingness to answer questions	• Makes expert judement explicit • Provides sense of uncertainty in estimates of potency
• Sensitive to choice of experts	• Rewards advances in scientific knowledge
• Relative costly and analytically intensive	• Identifies key sources of uncertainty • Highlights areas of agreement and disagreement among scientists - focus research efforts • Facilitates honest communication with decision makers and the public

chlorinated water. This meant that, ultimately, different questions were addressed by the two groups of experts. The epidemiologists addressed the relative risk of chlorinated water, while the toxicologists addressed the dose-response relationship of chloroform for cancer. The distribution of risk from the epidemiologists was broad enough so as not to be inconsistent with that of the toxicologists. However, the differences in the distributions raise questions about the level of resolution based on the data considered and the potential for protective effects of the water treatment.

Expert judgment has the potential to help analysis when data are sparse or conflicting. Application of expert judgment must be aware of, and adhere to, norms of the field. Differences in questions, data, and scale make it difficult to directly combine the toxicologic and epidemiologic data. The use of expert judgment in policy-relevant situations should increase its legitimacy. In the future, more attention is expected in the field to combining issues across scientific disciplines, possibly using mechanistic data or expert judgment as an aid in the combination.

3.11. PARTICIPANT DISCUSSION: IDENTIFICATION OF MAJOR ISSUES

Some participants noted that not all cancers are attributable to a heritable genetic mutation, some are induced by epigenetic mechanisms. Cancer is more broadly defined as a derangement or change in cell expression, growth, or death. Recent literature suggests that mutations and other biological events are not random occurrences. Under the proposed new cancer guidelines (U.S. EPA, 1996), EPA is considering mode of action in their quantitative risk assessments (Section 4.3 provides further discussion).

The point was made that the developmental toxicity guidelines (U.S. EPA, 1991) propose a threshold for developmental effects. Questions were raised about the magnitude of intra-litter effects and whether it was appropriate to model individual fetuses. The participants suggested that one way to get a handle on how big intra-litter effects are, is to look at the same developmental toxicants in animals and humans. In the majority of cases studies by Allen et al. (1994), litter size was an important explanatory variable.

A question was raised as to why a log-logistic model was chosen for developmental effects over a log-normal or probit model. As reported in Section 3.2, it was found that the log-logistic model can describe the results from a wide variety of actual, observed developmental toxicity studies. It was suggested that for the CRFM case study, a benchmark dose (BMD), corresponding to 5% or 10% risk followed by use of a toxicologically-based UF, could be likely be applied.

The participants made suggestions for human data sets such as thalidomide and Vitamin A that could be examined for application of various dose-response modeling approaches for developmental and reproductive data. Comparison/correlation of effects in humans and animals could also been made using these data sets.

The ICR and water consumption analyses will fill in some significant gaps in information for exposure assessment of the DBP (see Section 4.1 for more detailed discussion). It was noted that there is a mini-ICR looking primarily at pathogen in finished water.

It was noted that proportional response addition addresses the question of unknowns in the mixture, and that 60-80% of the chemicals in drinking water are

unknown. This approach can be applied with or without information as to mechanism or mode of action and also in cases where dose-addition and response-addition are applied.

The participants noted that the driver for calling chemicals similar or within the same class (i.e., for TEF approaches) is based on a number of factors including mechanism and chemical structure. The dioxin-like PCBs were pointed out as an example. Pairwise data are needed to discern interactions of chemicals, very little of which are available. NCEA-Cin reported that some work is currently being conducted for interactions of chemicals at Superfund sites. In addition, NCEA and NHEERL are conducting studies for pairs of trihalomethanes. One suggestion was to further develop the cholinesterase example through additional testing of cholinesterase inhibitors. All of these approaches are intended to be predictive; predictive approaches incorporate QSAR. It was agreed that further research in this area is needed.

Publication bias in the epidemiologic literature was noted (i.e., negative studies may not be published). This bias would affect the literature reviewed by the experts and likely influence their judgment. The point was raised that epidemiologists may be biased by their training toward a positive interpretation of findings to be protective of public health (refer to Section 2.4 for additional discussion).

It was noted that all areas of a subject under question in an expert judgment exercise need to be represented by a broad range of experts. For example, in the discussion of chloroform carcinogenicity, general cancer experts as well as those conducting research in a particular area need to be included. One participant thought that the latter group may be biased towards their research perspective. To mitigate the

potential for expert bias, analysts try to focus on specific scientific questions rather than broad questions pertaining to risk or policy implications.

A suggestion was made that investigators using expert judgment look at the responses of experts answering questions alone and also within a group (e.g., at a workshop), as there may be differences in response related to input or presence of peers. It was noted that anonymity of the experts may or may not affect the outcome. It was suggested that obtaining the experts' opinions prior to, as well as during a workshop, might provide an indication of bias or the influence of peer presence. For expert judgment to help resolve DBP risk, it was suggested that several mixture risk assessments could conducted and experts queried as to how to weight the different methods. Questions could be asked, that given the current state of the science, would dose-addition, response-addition, proportional response addition or another way be the most appropriate application for this mixture. Experts could also be queried about the most appropriate health endpoint. Expert judgment will not resolve the problems of data gaps or needed research, but may reconcile conflicting data.

4. GROUP DISCUSSION

Seven discussion groups were formed to respond to the questions posed in the workshop charge to the participants. The groups and their participants are shown in Table 4-1. The following sections provide a summary of each breakout group's discussion. The participants were encouraged to think of these questions not just in the context of the Comparative Risk Framework Methodology (CRFM), but more broadly in how to approach risk assessment. These were:

1. Identify approaches that incorporate the observational and experimental data on disinfectant by-product (DBP) health effects (i.e., *in vitro*, *in vivo* and human data) into the risk assessment and still maintain the ability to compare risks across drinking water treatment options.

2. What techniques exist that can incorporate expert judgment into the risk estimates? For example, are there qualitative techniques that could be utilized to influence the process of developing quantitative estimates?

3. How can different aspects of the current approach to estimate the risks posed by DBP exposures be improved? Specifically, address the topics of concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, use of Monte Carlo procedures, handling of uncertainty and variability, and the appropriateness of assumptions and endpoints used for mixtures risk estimation.

4. How should the toxicity of well-studies DBP, or of identified DBP, for which little or no data exist, be handled? Is it appropriate to use data on a similar chemical as surrogate data for another chemical?

5. For developmental, reproductive and non-genotoxic carcinogenicity, how can the concept of thresholds be handled? Is it reasonable to suggest that a mixtures toxicity threshold exists that is possibly well below the thresholds for the individual chemicals?

6. How should dose-response data from individual chemicals be combined and used in a mixtures risk assessment when their specific endpoints differ (e.g., both visceral malformations and crown rump length shortening to estimate developmental risks; or both liver and kidney tumors for cancer risk)?

TABLE 4-1

Workshop Breakout Discussion Group and Participants

Exposure	Unidentified DBP	Cancer	Reproductive/ Developmental Toxicity	Mixtures Risk Characterization	Uncertainty and Variability	Toxicology, Epidemiology and Expert Judgment
Brenda Boutin Gunther Craun Pat Fair Glenn Rice Clifford Weisel	George Gray William Huber Jennifer McLain Chandrika Moudgal Linda Teuschler	Robert Bruce Josh Cohen George Gray Richard Hertzberg Michael Pereira Charles Poole Rita Schoeny William Stiteler	Bruce Allen Joan Colman Dale Hattis John Lipscomb Jeff Swartout	Joan Colman Richard Hertzberg Jennifer McLain Chandrika Moudgal Glenn Rice Rita Schoeny William Stiteler Clifford Weisel	Bruce Allen Brenda Boutin Josh Cohen Dale Hattis William Huber Jeff Swartout Linda Teuschler	Gunther Craun George Gray John Lipscomb Patricia Murphy Charles Poole

7. Human cancer risks, largely based on animal data are interpreted by the EPA as " the lifetime excess cancer risk per the exposure." How should analogous developmental and reproductive risks be interpreted for the mixtures risk estimate?

8. Are there newer data and methods that EPA should be considering in order to improve these risk assessments? Specifically, address advancements in dose-response modeling, analytical chemistry, exposure characterization, mixtures risk assessment methods, probabilistic techniques, quantitative structure activity relationships, and methods for estimating risk for the unidentified DBP.

4.1. EXPOSURE GROUP

Participants in this breakout group discussion were: Brenda Boutin, Gunther Craun, Pat Fair, Glenn Rice, and Clifford Weisel.

4.1.1. Use of Full Exposure Models. One of the components of the risk assessment paradigm is exposure assessment. There are many ways to assess human exposure for risk assessments, and it is important to specifically define exposure as to relevant time frame, routes of exposure, and the contaminants that are included or excluded. Full exposure models include characterization of all relevant DBP contacts through multiple exposure routes over an appropriate time period, including variability of tap water, DBP types and concentrations. Full exposure models may be used in both risk assessment and epidemiologic studies to determine which routes and levels of DBP exposure are important for the evaluation of various health outcomes. Potential population distributions of exposure should be considered rather than point values; this is especially important for susceptible or high-risk subpopulations. Linkage of the exposure estimates to a physiologically-based pharmacokinetic (PBPK) model, if available, should be conducted to estimate human doses.

DBP exposures have been documented (through exposure biomarkers) to occur through multiple exposure routes; consideration of multi-route exposure may be important when conducting risk assessments for DBP. The inhalation exposure for volatile DBP and dermal exposure to highly lipophilic DBP can result in exposures equivalent to ingestion for median water uses. Thus, when comparing risks from different water sources and treatments practices (which may result in different types of DBP and concentrations), it is critical to include all exposure routes. Relative doses of each DBP are dependent upon the contributions by each exposure route; for some DBP, inhalation exposures may be very important. The total risk could change dramatically when inhalation exposures are considered depending on the DBP and the extent of exposure. It is also important that specific DBP be identified and quantified, as the multi-route exposure approach can be problematic for DBP that are not specifically identified and when concentrations are not measured (e.g., compounds identified only as TOX). However, it may be possible to evaluate the overall volatility or lipophilic nature of the mixture to estimate the importance of the inhalation, dermal, and ingestion contributions.

In epidemiologic studies, full exposure models should incorporate the range of water concentrations at both the treatment plant and within the distribution system over the etiologically relevant time period, changes in the mixture of DBP during the exposure period if there have been changes in water sources or treatment practices, water use and consumption patterns that may affect ingestion, inhalation, and dermal exposures, other human behavioral activities or characteristics that may affect exposure, and household/work place characteristics.

This can provide a total exposure across all routes that could be linked to PBPK models to provide dose estimates. The use of such a model will be most effective in epidemiologic studies of adverse reproductive and developmental effects, since information on peak, relatively short-term exposure, rather than the average or integrated exposure over a long time period, is probably (or just use may be) more relevant. DBP concentration information may be combined with questionnaire data such as water use and housing characteristics to quantify exposure for the study population. Short-term temporal peaks in water concentrations should also be modeled since these may be critical for some health outcome (e.g., adverse reproductive and developmental effects). For cohort, case-control, and ecological epidemiologic studies in specific communities, the exposure models can be used to generate retrospective exposure distributions for different parts of the study area and for various time periods of interest, and this can help reduce exposure misclassification. Development and better use of biomarkers of exposure in future analytical epidemiologic studies should be considered, since this can help to further reduce exposure misclassification. In general, the reduction of misclassification bias by exposure models and biomarkers will improve the statistical power of a study, as imprecise exposure measures tend to bias study results toward the null value. Instead of classifying study participants in a broad exposure category (e.g., as being exposed to disinfected or undisinfected water), investigators should measure and identify specific DBP and consider the water usage and consumption patterns to better estimate exposure. Water consumption information can be projected for a particular region of the country and target population. This will also help reduce exposure misclassification. However, more complete water

consumption data are needed, especially to develop distributions of water consumption of various subpopulations. In this regard, the CSFII data should be made available to adequately assess consumption by age and to consider individual variability (e.g., consumption patterns for same person on each of two days).

In general, exposure is a function of the concentrations of DBP in water and patterns of contact (frequency and duration) including consumption, over time. It is important to recognize the etiolotically-relevant exposure period (i.e., the time frame over which exposure should be evaluated). Acute exposures may be more relevant for developmental outcomes and chronic exposures for cancer. It is proposed that the exposure be linked to biokinetic models so that differences in toxicokinetics can aid in interpreting time, route, and cross species extrapolations. To evaluate the appropriate time period, it is also necessary to consider the endpoint of interest: for acute effects (including reproductive or developmental), peak or average daily exposure may be needed, whereas for cancer, annual or integrated longer-term exposure estimates may be required. When considering chronic exposures, it may be useful to build exposure over shorter time periods (e.g., 3-month exposures) to evaluate possible seasonal variation. Annual variations may also be important, and this should be considered when integrating exposure over long time periods. In general, long-term changes that have occurred over the relevant latency (e.g., 30 to 40 years) period for cancer effects will be more important than seasonal variation or even changes within the distribution system. Long-term exposures should consider changes in water treatment practices made since the early 1970s, as these have resulted in a great reduction in the occurrence of DBP for many water systems.

Distribution of exposures and doses, and not just single point values, should be used in the risk assessment. These distributions could be constructed from distributions of water concentrations for the DBP for the particular water treatment combined with population water usage, such as ingestion, showering duration, washing, and housing characteristics. Techniques, such as Monte Carlo, could be used to generate a distribution of exposure for the population of interest and also to determine risk distributions. It needs to be recognized that the distributions should also account for the differences between acute and chronic exposures. There may be short-term peak concentrations that are higher than the chronic exposures, resulting in higher exposures that may be of concern when calculating certain risks (e.g., developmental outcomes).

4.1.2. Exposure Variability Extrapolations. Human exposures are generally less than those used in animal studies (on a per mg/kg BW/day basis). Also, animal studies are often conducted using different routes than those to which the human population is exposed. Route-to-route and high-to-low dose extrapolation from animal data to humans should be carefully evaluated. The extrapolations of data should take into the account differences in how the DBP are metabolized and distributed in the body. One important consideration is the route of exposure. After the ingestion of low concentrations of DBP, there is complete metabolism during the first pass through the liver, while the inhaled and dermally-absorbed compounds are distributed throughout the body prior to hepatic metabolism. Further, due to the high doses in animal studies, there generally is incomplete metabolism of the compounds, even when ingested. An evaluation of how the susceptibility of the animal model fits into the distribution genetics of animals is also needed.

There will be sufficient data on concentrations of THM, HAA, bromate, and aldehydes in water systems throughout the U.S. after the ICR data become available (see Section 3.5). These data can serve as inputs to existing mathematical models that predict concentrations at the tap. However, a large percentage of the DBP in water will still remain unidentified. The extrapolation of the unidentified DBP, based on a surrogate of TOX, is questionable. Expert judgment could possibly be used to help characterize risks posed by TOX and other non-identified DBP in populations. However, to obtain population distribution of exposures, appropriately designed surveys may be better at providing missing data. Volatile DBP may be good surrogates for inhalation exposure to unidentified DBP. Data on skin permeability is needed for better predictions of dermal exposures. The expected reliability of concentration data is about one order of magnitude; however, model systems can improve that uncertainty.

4.1.3. Sampling Location Impact on DBP Concentrations. The following is a summary of data on DBP occurrence from the water treatment plant to human exposure at the residential tap.

At the Water Treatment Plant:

- Exposures are generally classified into groups such as THM, HAA, BrO_3, and TOX (TOX may be a surrogate for halogenated compounds, but should not be used for regulatory purposes). DBP concentration values exist from large systems, but it is not known if small systems have similar values. Data will become available as small systems become part of regulations. When considering the available data on DBP in water to assess human exposures in epidemiological studies, it is important to use information about specific DBP rather than groups of DBP (e.g., each species of THM should be considered rather than total THM).

- Data for TOC, THM, Cl_2 residual, HAA, etc., will be available when ICR data are reported. Good, predictive models can be developed for concentrations of THM and HAA based on TOC, Cl_2, etc. HAA are likely under-predicted by about 25% with current models; newer models with the

ICR data may be better. Models are also available for BDCM, other species, and chlorohydrates.

- When attempting to predict TOX, it should be noted that TOX is measured in moles and converted to mg chloride. The calculation underestimates brominated components because of difference in molecular weight.

- More information exists on chlorinated by-products than for other disinfectants. More data for chloramines, ozone, and chlorine dioxide by-products, as well as predictive models of their concentration at the water treatment plant and/or distribution system, are needed.

In the Distribution System:

- EPA-net model is available to consider hydraulics of water and flow through the system. It can also be used to predict DBP levels throughout the system for use in assessing exposure.

- The upper range of values in distribution systems for THM tend to be 2 to 10 times those at the water treatment plant. Thus, if an exposure assessment is being conducted for the entire population on the distribution system, and a single sample is available from the water treatment plant, additional samples are required from the system to produce more precise estimates (i.e., less than 2- to 10-fold). Single samples may overestimate HAA as they decrease in the distribution system; in other systems, they may increase in the same manner as the THM. Models can also be used to predict distribution system exposures.

- Variability of TOX data in the distribution system is needed.

- Changes in DBP within home plumbing systems are very small because of the relatively short residence times within the home.

- To assess concentration at home taps, predictions of how concentrations vary and the water residence time in the distribution system from the water treatment plant to the home are needed. Distance from the water treatment plant is not enough to determine residence time. Also needed are water data for flow rates and how flow is affected by storage tanks and pressure changes (flow may not always be on a direct route from the plant). It may be difficult and time consuming to obtain these values. However, it may not always be necessary to obtain this level of exposure when conducting epidemiological studies or risk assessments. For example, long-term exposures are relevant for cancer effects, and estimates of the variability of DBP in the distribution system may show that they make little difference in constructing integrated exposures.

4.1.4. Data Considerations for Exposure Routes.

Ingestion:

- At the home or elsewhere, the form in which consumption occurs is important to consider (e.g., if water is heated before consumption, volatile organic compounds will be driven off; thermally unstable compounds decrease; the concentration of non-volatile compounds may be increased due to water evaporation and volume reduction. Additionally, inhalation exposures to the volatile compounds may be increased.)

- Consumption data are needed; several data sets are just becoming available, but they may not provide the information needed for pregnant and lactating women. It is not clear whether water consumption for pregnant and lactating women increases if there are differences amongst various ethnic groups. Data are needed to assess if consumption may be high in certain geographic areas. This is an example of when peak concentration data may be critical in relation to consumption data.

- For beverages made with tap water, concentration values or estimated concentrations at the residential tap can be used. For beverages made with water at the manufacturing/bottling plant, different concentration data are needed. Ingestion away from home (i.e., consumption of coffee, hot and cold tea, bottled water) also needs to be considered.

Inhalation:

- Showering is an important pathway of exposure route. Models exist to estimate inhalation exposures using water temperature, Henry's Law constants for contaminants of concern, and other parameters (air exchange rate). Some people may have much higher inhalation exposures to volatile DBP and may also have higher dermal exposures (e.g., frequent swimmers, users of hot tubs and spas). Identification of these subgroups and estimation of their ranges of exposures should also be considered. Exposure of pregnant women by these routes should also be recognized, as swimming is an exercise available to pregnant women.

- Showering, washing, and dishwashing all contribute to the exposure from the indoor air to all household members.

- Non-volatile compounds may be distributed throughout the home by humidifiers.

- Housing characteristics are important for inhalation exposures and data are needed to validate whole house exposure models.

Dermal:

- Dermal exposures are the predominant exposure route from showering and bathing. However, not as much HAA exposure occurs from dermal absorption (because these are ionized).
- Data are needed on skin permeability, especially for young children.
- Recreational exposures to DBP through chlorinated swimming pools need to be quantified.

4.1.5. Bounding of Exposure Values. The participants in this group thought that some rough bounding could be placed on some DBP classes for the three routes. For THM, median ingestion exposures are about same order of magnitude with a fairly narrow range. Low to high exposures would likely vary by a factor of 5, with exposure by age varying by a factor 2 to 5. Residential inhalation exposure of THM may vary by a factor of 10 depending on ventilation, water temperature, and bathing habits. Higher bathing water temperatures, frequent bathing, longer duration of bathing, and decreased ventilation increase exposures through this route. Dermal exposure to THM depends on duration of bathing (except for swimmers), but varies by a factor of 3 to 4. Primary exposure to HAA is from ingestion unless there is a humidifier in use. The TOX was expected to fall somewhere between HAA and THM in exposure.

4.1.6. Recommendations. The exposure group participants offered the following recommendations:

- Multi-route exposures should be considered.
- Full exposure models linked to PBPK models with appropriate fetal and dermal models to predict source to population dose should be used. These models should be evaluated with experimental and field data.
- Long-term research goals should be to continue to invest time and efforts into identifying chemicals in TOX and further identifying DBP that make-up the unknown fraction. Identification of DBP from ozone, chloramine, and

chlorine dioxide treatment processes should also be long-term research goals.

- Actual exposure data should be used to help define ratios of mixtures for toxicology studies (i.e., brominated/non-brominated species). Ratios of mixtures should also be considered when evaluating exposures in epidemiological studies.

- More attention should be paid to the potential value of whole mixture testing. Consideration should be given as to whether whole mixture testing will assist in estimating risks.

4.2. UNIDENTIFIED DBP GROUP

Participants in this breakout group discussion were: George Gray, William Huber, Jennifer McLain, Chandrika Moudgal, and Linda Teuschler.

This group tackled the questions: How can EPA characterize the "unidentified" DBP? What is the toxicity of unidentified DBP in the drinking water, or of identified DBP for which little to no toxicity data exist? Is it appropriate to use data on a similar chemical as a surrogate for estimating risk for these types of DBP? How can EPA incorporate thresholds for toxicity into the risk estimates for these compounds? How can EPA perform risk estimates now? What (minimal) additional data might be necessary? What newer data or methods should EPA be considering as a way of improving its current methodology? What are the forms of uncertainty? How large might they be? How can expert judgment be incorporated into risk estimates for these compounds?

4.2.1. DBP "Layers". It is important first to characterize what is known and unknown about the DBP in the finished drinking water. The DBP fall into several mutually-exclusive groups that can be thought of as analogous to "layers" as shown in

Figure 4-1. All chemicals in finished water can be divided into those originally present and those produced, or added, by the treatment train. Summary measures of the amount of total organic carbon (TOC) in source water entering the treatment plant are available. Some chemicals are removed from the water by the treatment train. Of those produced by the treatment train, the types of DBP that are found can be grouped into three categories: Total Organic Halides (TOX) (available as summary and component measures, generally measured as μg Cl), non-halogenated organics (component measures), and inorganics (summary and component measures). Although it is not standard practice, methods are available to proportion the TOX into total organic chlorine (TOCl) and total organic bromine (TOBr). These distinctions are important because when source waters high in bromide are treated with ozone, higher levels of the brominated compounds are produced as well as more TOC. The halogenated chemicals formed through disinfection treatment are comprised of: those identifiable, quantifiable chemicals with estimates of biologic potency available (Layer1), and those identifiable chemicals that are not (presently) quantifiable (Layer 2). Of the latter group, some have a known risk endpoint (e.g., cancer, reproductive, developmental) (Layer 2A) and some do not have a risk endpoint that is known (Layer 2B). Layer 3 comprises those halogenated chemicals that are not yet identified. The non-halogenated DBP can be divided into similar “layers”, but the focus is only on the halogenated DBP. Most of the points made about the halogenated DBP should apply, *mutatis mutandis,* to the non-halogenated DBP. During the workshop, it was implicitly assumed that all of Layer 2 consists of Layer 2B, but this is a fine distinction and not important in what follows.

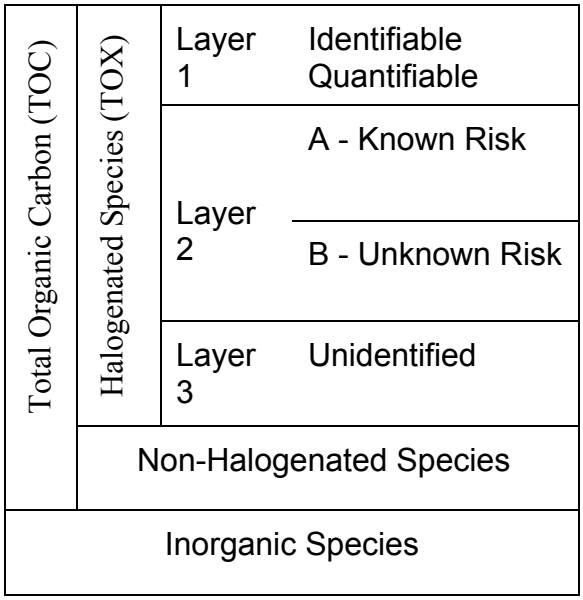


FIGURE 4-1

"Layer" Analogy for Chemicals in Water (Exact Proportions of Layers is Not Known). Refer to Text for Explanation.

The analyses conducted by Richardson (1998) to identify DBP by treatment type have some limitations. There is some uncertainty that all of these compounds are DBP and that they were not produced by the analytical procedure itself. For the ones that have been identified, many have no occurrence data in the environment and no toxicity measures; they may only represent a portion of what is really there. Of the unknown material, some of it is hard to isolate and identify (more polar compounds). The molecular weights of these compounds are unknown; compounds with high molecular weight are generally thought to cause less toxicity.

All layers can be further divided (independently) into those chemicals believed to be associated with a specific risk endpoint such as cancer, developmental or reproductive risk (denoted “h” in the pre-workshop report, U.S. EPA, 1999) and those not associated with that endpoint. There may be some misclassification of these; that’s one (minor) uncertainty.

It is conceptually easier to forget about the finished water and concentrate attention on this collection of DBP. For the halogenated DBP, for practical reasons, consider all concentrations (in the water) as measured in TOX equivalents (regardless of whether those concentrations are known or not). Then, in order to talk about the concentrations of the DBP relative to each other, further normalize all concentrations by the total concentrations. For example, if attention is momentarily focused on the chlorinated DBP, this total concentration is measured by TOX.

The halogenated DBP are thereby partitioned by layer and endpoint association into six mutually exclusive groups. For Layer 1, sufficient information is available to conduct a quantitative risk assessment; concentrations and potencies are available.

Naturally there is uncertainty, but this uncertainty is partially handled by the evaluation in the CRFM case study (U.S. EPA, 1998). Additional uncertainties derive from variation among water systems, variation in water source, temporal variation, and so on. Assessing these uncertainties is relatively straightforward and may be in part accomplished with the ICR data.

Relatively little is known about Layers 2 and 3. To estimate their contribution to risk, it is tempting to suppose that the DBP in Layer 1 are a "representative" sample of all the DBP. They must be representative in terms of:

- relative concentration distribution,
- univariate distribution of potencies, and
- apportioning of risk endpoints.

If Layer 1 chemicals were representative in these senses, then standard statistical estimators could be applied to estimate the risk from the DBP in Layers 2 and 3. The uncertainty in the estimates would depend strongly on: variation in relevant properties of DBP in Layer 1 (in the bullets above) and the proportion of all DBP within Layer 1.

As discussed in Section 3.5, there is variation in TOX and the concentration of certain Layer 1 DBP vary as a function of temperature. This suggests that Layers 2 and 3 constitute between less than 50% to more than 90% of all the DBP (again confining discussion to the halogenated DBP).

Unfortunately, there are many reasons to suppose that the DBP in Layer 1 are <u>not</u> representative of all DBP. Layer 1 DBP are (relatively) well known and well-studied. This means that they have been suspects in observed exposures are readily identified

and quantified, and so on. Most of these properties are closely related to chemical structure, including being relatively light, uncomplex (few rings, bridges, heteroatoms, etc.), and non-polar. By contrast, Layer 2 DBP are not as common or as well-studied, so they may have systematic structural differences (on the whole) compared to Layer 1 chemicals, indicating potentially different modes of action in an organism and different toxic endpoints. Even worse, chemicals in Layer 3 definitely have different chemical structures (sufficiently so to make them difficult to identify, much less quantify, in an aqueous solution).

Without any more information, one cannot say much more about Layer 3 chemicals than that they are chlorinated and may have potencies lying anywhere in the range of potencies observed for any chlorinated compound—or even beyond, as the MX example suggests. (MX was recently discovered, is chlorinated, and has the highest mutagenicity potency yet observed.) Is there another MX lurking in Layers 2 or 3?

Further, many of these systematic differences among the layers may work to make chemicals in Layers 2 or 3 systematically different in properties than those in Layer1. Thus, any hope that differences might "cancel out" is not well-founded.

To reduce this enormous uncertainty, it is imperative to obtain some initial information about what is in Layers 2 and 3. A statistically valid method would randomly sample individual chemicals (stratification and proportional sampling are appropriate) from these layers and attempt to measure important properties of the sampled chemicals. At a minimum, relative concentration (in at least one water sample) and,

very roughly, potency would be needed. Extrapolation from an LD_{50} assay would likely suffice.

The method presented by EPA assumes that the known and unknown compounds are equally toxic. This assumption could be examined by assembling distributions of LD_{50}s for each of the known and suspected compounds and comparing these (Figure 4-2). LD_{50}s can be found from experimental data or could be estimated using Quantitative Structure Activity Relationship (QSAR) models. Mechanisms of toxicity for the unknowns can only be assumed.

Different QSAR models (e.g., TOPKAT, OPP's model, Case, Genetic Activity Profile, or GAP data base) will yield various predictions that may conflict, so that multiple "answers" are provided for analysis. However, this information could be examined as a body of data for estimating the toxicity of the unknowns. Multiple "answers" could be examined by expert judgment, perhaps by holding a workshop. One important concept is to ask whether the QSAR models are asking the same questions or whether they are designed to provide the same information that is directly comparable. Another issue is to examine the misclassification errors for the various models. A technique for looking at this body of QSAR data is to examine the range of predictions (e.g., by ignoring the lower bound by using zero, but for the upper bound, assuming a worst case, such as that all components are carcinogens, and making risk predictions on that basis). For example, one might divide the LD_{50}s of the known components by a large number (Layton et al., 1987) that approximates their RfDs within an order of magnitude (Equation 4-1). If total dose of the unknown compounds is less than the sum of the known RfDs, then perhaps the unknowns could be ignored.

Use LD_{50}s (known or QSAR) ➜

Plot a distribution of ratios: LD_{50}s ➜ Layer 1 (known and quantifiable)

LD_{50}s ➜ Layer 2 (suspected and estimatable)

FIGURE 4-2

Possible Approach for Comparing Toxicity of Known and Unknown Components (Refer to Text for Details)

$$\frac{LD_{50}}{\approx 380{,}000} = RFDx10 \qquad (4\text{-}1)$$

From a few such samples, one would begin to see what the distribution of relative concentration of these chemicals is and what the distribution of potencies might be. These distributions would be compared to those of Layer 1 to estimate, albeit roughly, the degree to which properties of chemicals in Layers 2 and 3 compare to those of Layer 1. In other words, there would be preliminary information—and bounds—on the magnitude of differences among the layers: differences in concentration, potency, even frequency of occurrence (if multiple finished water samples were evaluated).

Such an analysis of the chemicals in Layer 3 cannot yet be conducted because there is no sampling frame; the chemicals in this layer are not known and it is not known whether it even exists. However, estimates of concentrations of chemicals in Layer 2 could be compared to TOX measurements; with enough replication (to overcome the relatively large analytical variability in TOX measurements), the concentration of Layer 3 could be estimated. Further work at identifying individual chemicals in this layer would be necessary if Layer 3 appeared to be "substantial."

4.2.2. The MX Concern. The problem of characterizing Layers 2 and 3 is that there may be one chemical present in relatively high concentrations that has a very large potency. This possibility can be evaluated by estimating distributions of relative concentrations of chemicals in Layers 2 and 3 and assigning potencies to them at random from a distribution of potencies estimated for these layers. Such

distributions—concentration and potency—must be based on some analysis of what is in these layers and not just by using Layer 1 chemicals as a surrogate. Again, the reason is that Layer 1 chemicals may behave very differently in these respects from the other chemicals.

The uncertainty in the risk estimate therefore would depend on the variation in concentrations and the variation in potencies. It seems reasonable to assume that these two values would be independent. At one extreme, all concentrations (in a particular layer) would be equal. To be concrete, suppose that Layer 2 constitutes 50% of the DBP and that 50 chemicals are identified as its constituents. Then, at this extreme (of maximum entropy), each chemical would constitute 1% of the DBP. The distribution of potencies, F, when applied to this distribution of concentrations, would produce a net distribution of risk (potency times concentration) equal to $F/\sqrt{50}$, which has the same shape and location as F but a variance 1/50 that of F. At another extreme, where one chemical accounts for essentially all the concentration in Layer 2, the risk distribution would coincide with F. This simple calculation shows how the distribution of risk depends on the estimated distribution of potencies of the Layer 2 (and Layer 3) chemicals and why it is so important to estimate this distribution in a reasonable way.

4.2.3. Documenting Statistical Models for Risk Assessment. When assessing uncertainty, it is important to write models that explicitly include random components. The tendency to use omnibus, powerful estimation methods such as bootstrapping, resampling, and Monte Carlo analysis is also a tendency to hide or overlook the underlying statistical model. This can lead to the use of ad-hoc or inferior statistical estimators.

To avoid this tendency, and to document statistical procedures accurately, it will be useful to record the models. For example, in Section 3.3, data relating dose to fractional birthweight reduction for a group of chemicals was introduced. Each birthweight reduction datum represented a group of measurements, each having a reported variability (as a standard deviation, s). To combine this information, the idea of a "TCA" equivalent for each chemical was introduced. This would be a chemical-specific conversion factor λ(chemical) used to compare doses. The model is that at equivalent doses, chemicals would produce equivalent fractional birthweight reductions—plus a random error. This can be written as:

$$\text{Birthweight reduction(chemical, dose)} = \text{Intercept} + \text{Slope} \times \lambda(\text{chemical}) \times \text{dose} + e(\text{chemical, dose}) \quad (4\text{-}2)$$

where the e(chemical, dose) are (say) identically and independently distributed with variance equal to s(chemical, dose). The s's are given with the data and the values of intercept, slope and l(chemical) are parameters to be estimated, subject to λ(TCA) = 1. With a change of parameter from λ to λ x slope, this is readily seen to be a weighted least squares (WLS) problem, whose solution is conventional. Thus, writing down the model leads immediately to the appropriate statistical estimator of parameters and their uncertainty. This often avoids having to re-invent appropriate estimators and it makes the nature of the random component of the model apparent. It would be well to write all statistical models used in the risk assessment in this (conventional) form.

In summary, improvements in the EPA's method include putting distributions on the variables in the equations for deriving the toxicity of the unidentified TOX, including distributions on α_h and the TOX amounts. It also might be interesting to statistically

treat the question that if a progressive series of efforts to find DBP identifies fewer and fewer DBP, then what is the likelihood of finding more? This could lead to some level of confidence relative to whether the majority of the DBP have been identified. Finally, it was suggested that the unidentified DBP could be treated only in a qualitative fashion.

4.3. CANCER RISK

Participants in this breakout group have a wide range of scientific and analytic expertise. The members were: Robert Bruce, Josh Cohen, George Gray, Rick Hertzberg, Mike Pereira, Charlie Poole, Rita Schoeny, and William Stiteler. This breakout group addressed five key questions for assessing the potential cancer risks of disinfection byproducts and characterizing the uncertainty in risk estimates:

- What approaches can incorporate the various types of data on health effects and still allow for comparing risks across treatment options?
- What questions regarding cancer could be addressed by expert judgment?
- How can the use of dose-response information for cancer risk be improved?
- How should we address the idea of a threshold for cancer?
- How should data be used for different tumor sites or effects in a mixture risk assessment?

The first two questions are discussed in Sections 4.3.1 and 4.3.2, respectively. The next two questions are discussed together in Section 4.3.3, and Section 4.3.4 presents the discussion of the use of different sites or effects in mixture risk assessment.

4.3.1. What Approaches Can Incorporate the Various Data on Health Effects and Still Allow for Comparing Risks Across Treatment Options? The group addressed several important issues that were raised by this question including characterizing uncertainty in hazard identification, reconciling epidemiologic and toxicologic data, and identifying and quantifying often ignored sources of uncertainty in risk estimates based on epidemiology.

The group believed that there was a need to characterize uncertainty in the hazard identification step when evaluating carcinogens. Any hazard identification for a general human population which relies on data from animal bioassays or occupational exposure has an intrinsic degree of uncertainty. There are clearly differences between chemicals in the degree of certainty that they are capable of causing cancer in humans. To be most useful in a comparative framework, the uncertainty should be characterized quantitatively so that it is reflected in the risk estimates that are compared.

The EPA's cancer classification system under the 1986 guidelines is a sort of qualitative uncertainty evaluation that may have some role in quantitative characterization. It does not address questions of bioassay interpretation, including the findings of widespread chemical treatment related decreases in tumor rates reported in several recent publications (Linkov et al., 1998; Crump et al., 1999). There have been papers making crude quantitative uncertainty adjustments to risk estimates based upon cancer classification to facilitate comparisons. This approach does not help with chemicals that have not been assessed by EPA, including the majority of DBP. The group recommended further efforts to identify or develop methods for characterizing uncertainty in hazard identification.

Additional key hazard identification uncertainties in the DBP comparison involve the comparison of chemical-specific toxicologic results with epidemiologic studies of chlorinated drinking water. Foremost is the lack of concordance of tumor sites between animal bioassays of DBP and the sites indicating possible increases in epidemiologic studies. The group suggested that more efforts with both existing animal and human data and further data development would be most helpful.

With current data, the use of PBPK models for different DBP, combined with some notion of mode of action, might provide insight into patterns of tumor development in animals and humans. Further work controlling for water source in epidemiologic studies might help to identify key DBP associated with increased cancer risk. It was also suggested that re-analysis of some ecologic studies might be useful. Finally, a new meta-analysis with studies completed since 1992, including exploratory meta-analysis to identify important population characteristics, would provide valuable information.

The group also suggested types of new studies that might shed some light on the seeming disparities between epidemiologic and toxicologic results. Investigations in animals and *in vitro* studies might identify the components of chlorinated water that are associated with different types of cancer, studies of gene-environment interaction (e.g., CYP2E1, GST, acetyl) could identify particular subpopulations for further epidemiologic study, and epidemiologic studies focusing on colon polyps might provide important information.

A final source of uncertainty that the group agreed is important for characterization comes from publication bias in epidemiologic studies. This could be a

particular problem if studies of chlorinated drinking water that fail to find an association, or find responses in different sites, are not published and not available for meta-analysis. Characterizing publication bias requires a great deal of effort to find studies that are not generally available. It can be modeled and even corrected for, based on new positive and non-positive studies, to quantitatively characterize the uncertainty.

The group also confronted the fact that quantitative estimates of risk based on epidemiology are about 500 times higher than those based on animal toxicology data. There was some discussion of the possible role of synergism, but the relatively low levels of the DBP made this seem less likely. It is difficult to know if unidentified components of treated water could account for the difference. One suggestion was a quick calculation of the potency that would be required of an unidentified DBP to account for the difference. The group postulated that the quantitative differences might be due simply to the different scales used in epidemiology (where 0.1 increase in relative risk can be quite large for a relatively common tumor) and toxicology-based risk assessment that can calculate (extrapolate to) risk estimates in increments of 10^{-6} or less.

4.3.2. What Questions Regarding Cancer Could be Addressed by Expert Judgment? The group recognized that expert judgment (often implicit rather than explicit) plays an important role in the risk assessment process, from identifying chemicals, endpoints, and studies to addressing choices of models and other critical assumptions. The field of decision analysis recognizes explicit expert judgment as a legitimate means for characterizing uncertain model parameters with little or no directly applicable data or that require the synthesis of several lines of evidence. It was, of

course, recognized that the expert judgment process must be open and transparent with recognition of the potential for bias or conflict of interest.

The cancer breakout group focused on the use of expert judgment to address uncertainties in several key cancer risk assessment assumptions and as a guide to uncertainty or sensitivity analysis of existing models.

The key assumptions that may benefit from expert judgment if a best estimate of risk is to be constructed are:

- whether or not the agent is a human carcinogen,
- if there is non-linearity for carcinogenic action at a specific dose level or dose rate, and
- the mode of action of the compound.

Each of these issues requires synthesis of many different lines of empirical evidence and biologic theory. Expert judgment, when subject to the disciplines discussed in the expert judgment section (Section 3.10) may allow quantification of the certainty of carcinogenicity or the threshold dose level (including uncertainty). Judgment about the mode of action question is a prerequisite to addressing the question of carcinogenicity or shape of the dose response curve.

In addition to estimating uncertain parameter values, the group recognized that expert judgment could help in analyzing and evaluating current risk models. There was a great deal of discussion around the need to disaggregate the epidemiology data and extract results from the meta-analysis. It was also suggested that expert judgment could help define appropriate ranges to use in sensitivity analysis of influential model parameters. There was also a recommendation that expert judgment be used in

understanding different methods of quantification from epidemiology, and for limiting the studies to be analyzed, for plausibility.

Finally, the group discussed the potential for expert judgment to evaluate the chemicals being investigated (e.g., the apparent discordant results from toxicology and epidemiology for bladder cancer). It was recognized that this might be an example of the sort of question that would more usefully be advanced by more analysis or experimentation rather than expert judgment relying on relatively few data. Another suggestion was to use QSAR to prioritize uncharacterized DBP for study and use expert judgment for further processing or reducing the list of chemicals.

4.3.3. How Can the Use of Dose-Response Information for Cancer Risk be Improved? How Should We Address the Idea of Low Dose Non-Linearity for Cancer? These questions were discussed together. The group thought these questions were tightly linked and were dependent on the understanding of the mode of carcinogenic action of each specific compound. Since the comparative framework requires best estimates of risk, it was recognized that this question did not focus on "defaults" or conservative assumptions, but rather on how to judge the weight-of-evidence for a specific mode of action for a specific chemical. The group recognized that there is additional scientific uncertainty in linking particular dose-response models to different modes of action.

The question of response thresholds is critical primarily when significant extrapolation is needed from experimental or observational exposure to those of interest. In the case of DBP, extrapolation is necessary when using animal bioassay data from studies with exposure thousands, or even tens of thousands, of times higher

than exposures in finished drinking water. The epidemiologic data are based on exposure to finished water and have no need for extrapolation. However, the uncertainty in the epidemiologic data are so great that it will be difficult to clearly distinguish a threshold from a nonthreshold dose-response.

"Practical thresholds", which some described as a level of response that is not distinguishable from background responses, were discussed. It was not clear what level of sensitivity or specificity of a test was necessary to establish a response as similar to background. Some proponents believed these "practical thresholds" could then be the launching point for applying EPA's new cancer guidelines. There was concern in the group with the way in which margin-of-exposure calculations (based on the new EPA guidelines) could be used in risk comparisons since no explicit risk estimates are made (see Figure 4-3). The group recognized that the question of combinations of threshold carcinogens needs more work. Accumulation of hundreds of near thresholds may be unacceptable.

The discussion of thresholds and low dose non-linearity raised several important points of scientific uncertainty for the assessment of risk from threshold compounds. First, the question of independence or commonality of modes of action is critical to understanding if risks of threshold chemicals should be treated independently or combined. The question of dose-addition *versus* response addition was discussed in some detail along with attributes of modes of action or responses that would support either notion. There was concern that high-dose toxicologic tests might demonstrate interactions that might not occur, or might be different, at lower exposures.

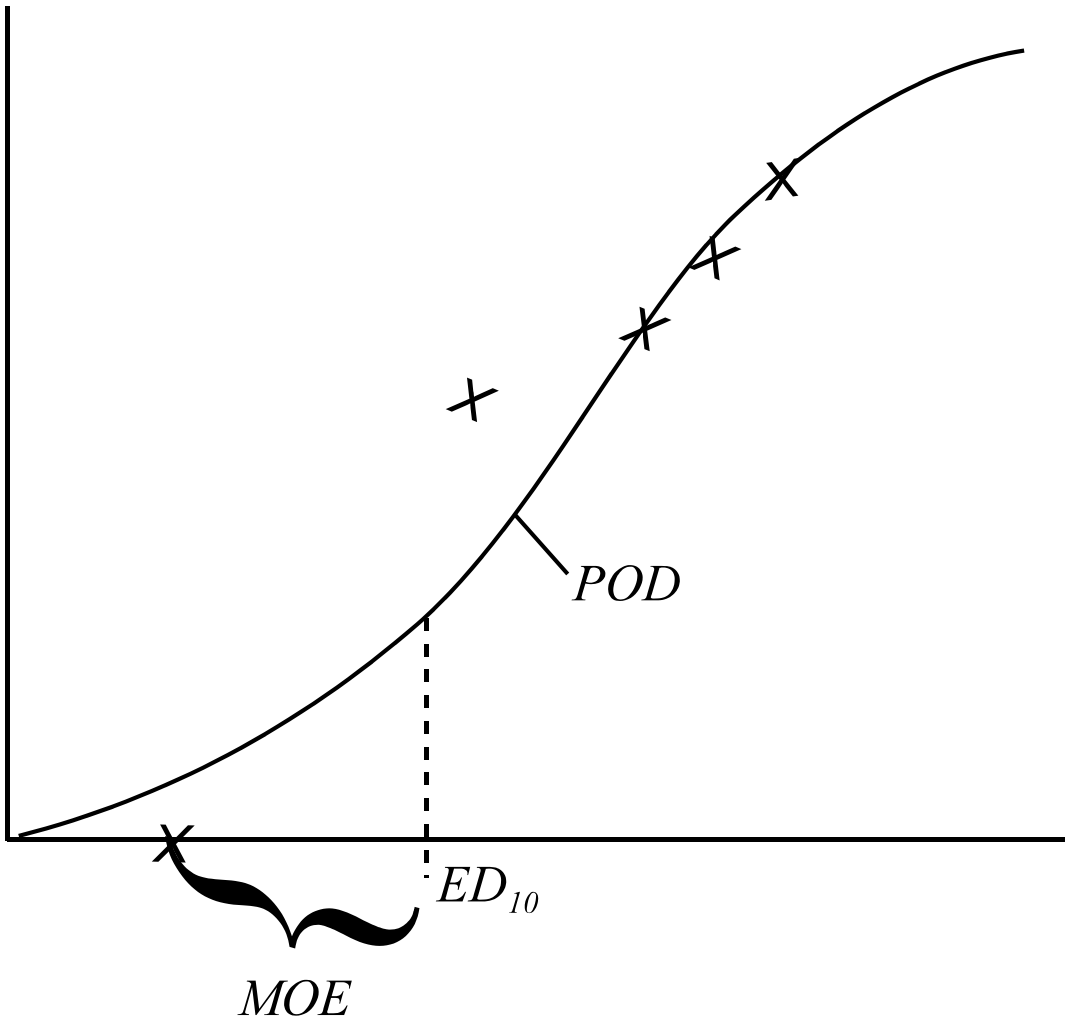


FIGURE 4-3

Margin of Exposure Approach for Carcinogens

Source: Adapted from U.S. EPA, 1996

The question of what degree of similarity of mode of action would negate the assumption of independence was recognized as very difficult. There are the questions of high and low dose interactions mentioned above. It was recognized that a particular toxic endpoint (e.g., liver tumors) might arise from many different mechanisms, which may or may not be independent. Another possibility is commonality of a rate-limiting step or a common pathway, but not necessarily the same main mode of action. This raises the question of how identical modes of action need be and how, or whether, classes of compounds can be identified for which the independence assumption is invalid. It was suggested that the key would be to look for a common mode of action or point of intersection in the biologic pathway. Some examples offered included changes in methylation patterns, depletion of GSH or SAM, or changes in the hormonal systems. The group suggested that if a common point in pathway, which affects the rate-limiting step, cannot be found, then there is no need for response addition, but instead, risks should be added.

Finally, there was some discussion of the different ways in which standard models used in epidemiology address independence of events. Independence of mechanisms is difficult to imagine because mechanisms for the same effect usually have components in common. (Trivially, one must have a uterus to develop endometrial cancer.) Where P(A) and P(B) are the probabilities of being susceptible to the effects of A and B on the same outcome, P(A&B) is the probability of being susceptible to both effects, and A and B do not interact synergistically, the probability of developing the outcome if exposed to A and B is P(A) + P(B) - P(A&B). Additivity of effects would correspond to P(A) + P(B) and, therefore, some degree of sub-additivity is

expected in the absence of synergism. If the susceptibilities to the effects of A and B are uncorrelated, P(A&B)=P(A)P(B), which for carcinogenic effects would usually be a very small probability. However, a correlation of susceptibilities due to a sharing of complementary component causes between etiologic mechanisms involving A and B would lead to P(A&B)>P(A)P(B). With a strong correlation of susceptibilities, the competitive antagonism represented by P(A&B), described as response type 2 in the formulation of Greenland and Poole 1988, could be appreciable.

On the other hand, synergism has been established epidemiologically (e.g., asbestos, smoking, and lung cancer). To complicate matters, epidemiologists regularly assume synergism by assuming uniformity (homogeneity) of relative risks (or odds ratios). Uniformity of relative risk or odds ratios corresponds to additivity of the natural logarithm of RR or OR, not additivity of risk or of risk difference, as in toxicological interaction analysis of quantal response (see, e.g., Helwett and Plackett, 1979). When epidemiologists assess “interaction”, they are almost always assessing departure from a null state of (often substantial) synergism.

If one is looking for explanations for higher potency estimates from the epidemiology of a mixture than from the toxicology of one compound at a time, synergism is a more viable candidate than competitive antagonism separate (though not necessarily independent) effects.

4.3.4. How Should Data be Used for Different Sites or Effects in a Mixture Risk Assessment? This discussion was sharpened by a presentation on the current thinking within EPA about risk assessment of mixtures. The group addressed several issues related to the differences between response addition and dose addition. The

discussion touched on several points discussed under previous questions including the built-in assumption of synergism (as discussed above) in many epidemiologic models.

First, the group pointed out that response addition is not affected by site of action as long as the individual dose-response model is probabilistic risk. Again, it was recognized that if a chemical is considered "nonlinear" for cancer dose-response, then no probabilistic risk is estimated and there is real difficulty with response addition under this scheme. One suggestion that was offered, if the MOE approach is used, is to consider a blend surface and connect the resulting doses reached by the MOE method for each one.

The difficulty of even identifying potential interactions was highlighted again with the observation that high dose interaction may be different from low dose interaction. There was considerable discussion about whether the usual cancer interaction studies (e.g., initiation-promotion, co-carcinogenesis) can even identify, or refute, situations in which the assumption of independence is appropriate.

The group did recommend that the EPA investigators further evaluate proportional response addition as a means to combine dose-response data when risks are characterized using a MOE approach (Figure 4-4). In the area of dose addition, several questions were raised, including the appropriateness of adding points of departure (i.e., ED_{05}s) and how to handle compounds with different weights of evidence for both carcinogenic potential and mode of action. The breakout group was quite adamantly against the combining of tumors from human studies. There were concerns about differential uncertainty in the magnitude of the effect, different confounders with different effects for different sites, and very different biological pathways leading to the

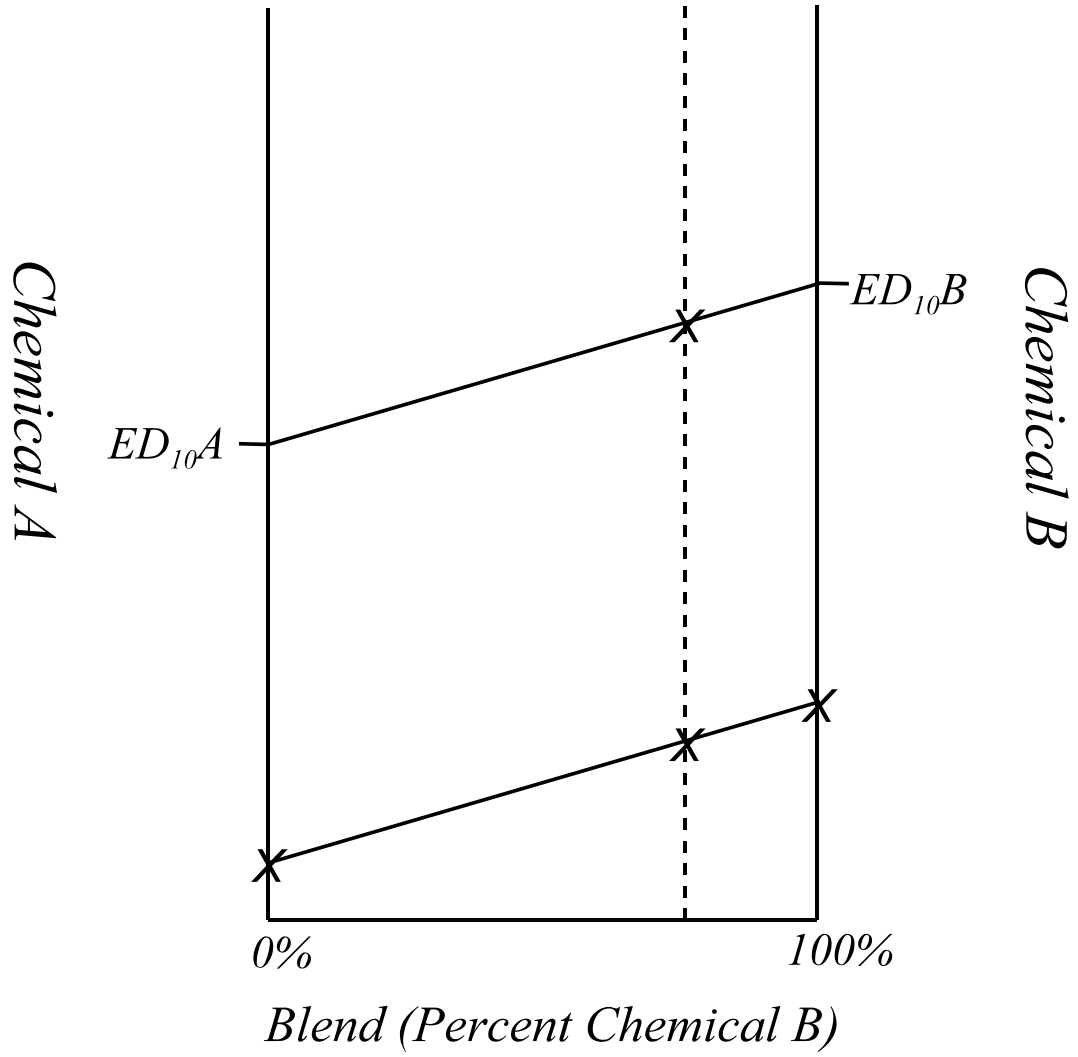


FIGURE 4-4

Application of Proportional Response Addition to Cancer ED_{10} (POD)

tumors. There was also concern about potential double counting in the use of vital statistics in risk estimation.

As an approach to many of the questions raised in the breakout session, the group suggested that further exploration of the analysis be conducted as part of the proposed change to the MCLG for chloroform. This might allow understanding of ways in which uncertainties were, and were not, characterized well and might allow for some generalization to other cases.

4.4. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY GROUP

The participants in this break out group discussion were: Bruce Allen, Joan Colman, Dale Hattis, John Lipscomb, and Jeff Swartout.

4.4.1 Improving the use of Animal Developmental and Reproductive Toxicity Data.

Choices must be made when analyzing animal developmental (and, in general, other reproductive) toxicity tests. The breakout group attempted to identify a process, the first step of which was the appropriate use of an animal data set – i.e., the topic discussed here – but which also included issues related to the extrapolation of animal data to humans (discussed in Section 4.4.2).

As with all analyses of toxicity data, a careful toxicological review and evaluation should initiate the process. Specifically, with respect to the desired dose-response analysis, one would be interested in the presence of dose-related effects (resorptions, fetal deaths, malformations, and perhaps variations, are the most common quantal effects that, along with fetal weight, would be typically considered). One might apply statistical tests to look for evidence of a dose-related trend in incidence or level of effect to identify the effects that suggest that the compound in question causes developmental toxicity. Assuming that the study meets requirements considered toxicologically

necessary for sufficient quality, these endpoints would be the set that would then be used in the subsequent steps (dose-response analysis and extrapolation to humans).

A major issue of the use of laboratory animal developmental toxicity models for prediction of human risk is the inconsistent concordance of specific effects between test animals and humans. Laboratory developmental toxicity studies, however, are valuable for predicting human developmental effects in the general sense. Another possible limitation in the modeling of developmental toxicity studies is that individual fetus data are not generally reported in the literature, requiring separate modeling of each endpoint. For the DBP analysis, however, such data are available. Therefore, one approach to assessing human risk from animal developmental toxicity data is to consider modeling the risk of *any* treatment-related developmental effect, rather than focusing on a specific effect. The general approach would be to aggregate the observed effects in the animal bioassay prior to running the chosen dose-response model. A key issue in this aggregation is the choice of endpoints to aggregate. Should all endpoints be lumped together, or should they be combined on the basis of some classification? Examples of classifications are type of malformation (e.g., visceral, skeletal or external), mechanistic class, or continuous vs. quantal.

The breakout group, consistent with thinking among people who have conducted dose-response modeling for developmental toxicity risk assessments, considered that it appeared to be more appropriate to model individual embryo/fetal responses, as opposed to litter-based summaries of response (e.g., litter with one or more affected fetus are considered to be the responding litters); this was particularly true for quantal responses. Therefore, for quantal responses, a model like the log-logistic model with underlying beta-binomial response variability would be recommended for modeling a single quantal

endpoint. Such models account for the correlated nature of the results from typical developmental toxicity data sets (and from many reproductive toxicity data sets) an allow one to get estimates of the fetal probabilities of response as a function of dose or exposure (and other covariates such as litter size). Of course, other particular model forms (such as those suggested by Rai and Van Ryzin many years ago or more recently by NCTR) could be used in place of (or in addition to) the log-logistic form (these models are discussed in Section 3.2). One could get some sense of model dependency (model uncertainty) by applying more than one model to any particular data set.

For quantal endpoints, one can estimate the dose corresponding to a particular level of response – often referred to as an EDx or a BMDx. (The choice of the value of "x" depends on the objective of the scientist for extrapolating from the animal test results to humans.) A traditional BMD analysis would pick a BMD_{05} (based on the results of Allen et al., 1994), that would subsequently be used with some uncertainty factors to get an RfD. The extrapolation approach proposed by Dale Hattis, referred to here as the lognormal model of tolerances, would estimate the ED_{50}, which in subsequent steps would be used to estimate the median of the human lognormal tolerance distribution (see Section 4.4.2).

For continuous endpoints, such as birth weight, it is not so clear how to model dose-response relationships. One could turn such endpoints into quantal endpoints by selecting a cutpoint to dichotomize normal and abnormal levels (e.g., normal vs. abnormally low birth weights). One could then apply the log-logistic model (or some similar model) to the now-quantal representation of the weight response. Alternatively, one could model changes in the continuous variable itself (i.e., changes in mean birth weight) as a function of dose. The results of such modeling could be used in at least two

ways. First, they could be linked to sequella known or thought to be caused by changes in the continuous endpoint (e.g., infant mortality linked to low birth weight, or infertility linked to low sperm count) by additional modeling – with the notion that the sequella would be the factors used to estimate a dose-dependent probability of a response of concern. Alternatively, the continuous measure itself could be used to determine "risk," where in this instance, the risk at a dose would be determined by the likelihood that a fetus would fall above or below some cutpoint. The idea of the cutpoint is exactly the same here as discussed earlier in this paragraph – it separates normal from abnormal – but note that it is only considered after the modeling is conducted. The endpoint could be defined explicitly – based on toxicological considerations related to biological significance – or it could be defined implicitly, based on the amount of variation observed in the test animals (e.g., control animals) such that it represents a point relatively far out in the tail of the distribution. Either way, the likelihood defining the risk is determined by looking at the implied probability of being above (or below) the cutpoint defined by the dose-specific mean predicted by the model and the variance around that mean (usually also estimated from the data). Gaylor and Slikker (1990) and Crump (1995) have discussed this issue in general; Kavlock et al. (1995) have looked at some of these issues in relation to developmental toxicity.

Another alternative to modeling each selected endpoint separately is to model several endpoints together using a multinomial model. Such models treat the possible outcomes subsequent to implantation (resorption, fetal death, malformation, and variations in birth weight) as a vector of responses that are modeled together to account for possible intrafetal correlations among them. The multinomial modeling approach is a bit more complicated and uses some different statistical approaches (generalized

estimating equations for example), but there may be some instances where such an approach might be appropriate. Ryan, Catalano, Gaylor, and Chen have all published on this topic (see discussion in Section 3.2).

4.4.2. Predicting Human Risk from Animal Developmental and Reproductive Data. The group discussed a variety of approaches for projecting human risks under two broad headings of quantal vs. continuous animal effect data.

For quantal effect data, there are three main choices: the BMD, ED_{50}, and slope factor.

An adaptation of the EPA's standard benchmark dose approach, incorporating relevant uncertainty factors, is one approach that could be used for quantal data. In this type of analysis, a point of departure is first selected from the animal dose response data. Typically, analysts use the ED_{05}, the dose (in mg/kg) expected to produce a 5% excess incidence of the response in question over background, or the LED_{05}—the lower 95% confidence limit on that dose, as estimated from a standard dose response model. This "benchmark dose" is then used to project a human RfD with the application of a list of standard uncertainty factors—usually tenfold for projections from animals to humans, tenfold for possible differences in sensitivity among humans, etc. The RfD thus calculated is assumed to represent a human population threshold—a dose that is below all the thresholds for response of individual people in a potentially exposed population. If some people are potentially exposed at levels above the RfD, then individual risks are projected by drawing a straight line between the assumed zero risk point at the RfD and the expected incidence (e.g., 5%) at the benchmark dose. In more advanced applications, pharmacokinetic or allometric (e.g., dose per unit body weight$^{3/4}$) scaling adjustments could be used to translate the benchmark dose into human equivalents.

Additionally, distributions (for example, see Swartout et al., 1998) rather than point estimates could be used for the uncertainty factors. An advantage of this approach is that it is a relatively modest adaptation of the standard approach for noncancer risk assessment. It incorporates a concept of population thresholds, which has been a standard assumption by many toxicologists. It should be understood, however, that this approach will not provide a convenient way to utilize new relevant information (e.g., human variability data for pharmacokinetic and pharmacodynamic parameters putatively relevant to different toxicants and background rates of reproductive impairment and developmental anomalies in humans.) It is expected that this approach will generally lead to predictions of zero expected incremental risks because disinfectant byproduct exposures are expected to be below the calculated RfD in nearly all cases.

A second way to analyze quantal data is to use the animal data only to identify the kinds of effects produced by specific toxicants and associated potencies, indexed as an ED_{50} (log normal model of tolerances). Human low dose risks are then projected using generic information about human variability in the several steps from exposure through response utilizing recently compiled human variability information (Hattis, 1997, 1998; Ballew and Hattis, 1989; Rees and Hattis, 1994). Important issues for this approach are the assumed form for the distribution of human threshold doses and the degree of spread (e.g., geometric standard deviation [GSD]) of that distribution. Substantial changes in calculated low dose risks can be expected to result from different distributional forms (e.g., assuming a mixture of two or three lognormal distributions corresponding to different genders or genetic variants of an important single-gene determinant of susceptibility) or from different plausible values for the GSD. For these analyses, the latter type of uncertainty is quantified by assuming that the toxicant under study is a

random draw from a series of toxicants/effects whose susceptibility variabilities are documented in the existing data base (either the whole data base or a putatively relevant subset can be selected depending on the available information about the toxicant). An advantage of this approach is that it recognizes the possibility that segments of the human population may differ widely in susceptibility, and that in light of the fact that there is some "background" rate of different developmental anomalies, reproductive impairments, and other physiological failures, some people may well be very close to critical values of relevant physiological parameters required to maintain normal functioning. Existing analyses of the human variability data tends to support approximate log-normality for distributions of pharmacokinetic and pharmacokinetic factors, without obvious limits that might be expected under the generic assumption of population thresholds. This approach also provides a ready means to accommodate new information about relevant animal/human differences in average susceptibility/thresholds and about human variability in pharmacokinetic or pharmacodynamic parameters. A disadvantage is that this approach involves a noticeable departure from previous EPA risk assessment practice and conclusions for non-cancer effects at levels of exposure below the RfD (or their equivalents). This approach will lead to the projection of finite risks for DBP (and estimates of uncertainty) at current exposure levels. Many, if not all, of these projected risks are likely to be below limits of detection in epidemiologic studies.

The current EPA slope factor analysis is another option for handling quantal data. However, this option was not discussed extensively by the breakout group. A disadvantage of this approach is that it assumes a low dose linear dose-response relationship that is generally at variance with the assumed homeostatic, threshold mechanism assumed for most developmental and reproductive effects.

For continuous parameters thought to be important for human effects, the breakout group discussed two alternatives: changing the continuous response to a quantal response or modeling dose-response relationship for the continuous endpoints.

The first approach is to quantize the response in animals (e.g., choose a “cutpoint” such as a 5% reduction in fetal weight from the control average as indicating an “effect”), and treat the effect by the quantal analysis techniques described above (discussed in Section 4.4.1).

Alternatively, the dose-response relationship for the continuous endpoint in animals could be modeled, projected to humans using a pharmacokinetic or allometric dose scaling procedure, and then the implications for human risk using human data interpreted in the context of the continuous parameter (or its human analog) to human clinical outcomes of concern. Such an analysis should, of course, be limited to parameters that do have human analogs that are strongly related to adverse outcomes of concern. For example, the fetal weight reductions seen for various DBP could well be predictive of fetal growth retardation and, therefore, reductions in birth weight for a constant gestational age. Relationships between birth weights and outcomes of concern, such infant mortality, can then be used to project human risks. In the reproductive area, relationships between sperm counts and male fertility can also be used to estimate effects either in terms of the fraction of couples presenting themselves for infertility treatment (in a type of analysis pioneered by Meistrich and Brown (1983) or in terms of the distribution of times to conception. The latter type of information is being prepared for imminent publication by Eric Clegg of EPA ORD in Washington (Clegg, 1999). An advantage of the use of continuous intermediate parameters such as birth weights is that they are more amenable to epidemiologic study and measurement of population effects

than rare quantal effects. The committee wishes to encourage epidemiologic study of relationships between DBP exposures and these types of continuous intermediate parameters that are likely to be predictive of rarer quantal endpoints of ultimate concern.

4.5. MIXTURES RISK CHARACTERIZATION

Participants in this breakout group discussion were: Joan Colman, Richard Hertzberg, Jennifer McLain, Chandrika Moudgal, Glenn Rice, Rita Schoeny, William Stiteler, and Clifford Weisel. This group addressed the questions posed in Section 4.0, with the exception of Questions 2 and 8. The following sections summarize the discussion of this breakout group.

4.5.1 Identification of Approaches that Incorporate Data on DBP Health Effects into the Risk Assessment. The breakout group suggested several approaches: a thorough review of the literature on complete mixtures (including *in vitro* studies); application of three types of data analyses to evaluate additivity (multinomial, response-addition, and proportional response addition); comparison of the results from epidemiological and toxicological studies for consistency in health outcomes for individual DBP or for mixtures of DBP. It was thought that a data base of individual studies exists that has not been considered in its entirety. In trying to compare risks of DBP from different treatment plants, it was suggested that modeling of risk using both a Monte Carlo simulation (to estimate the range of risk estimates across the population served by the plant) and a sensitivity analysis (to evaluate what factors in the different treatment conditions accounts for variability in the risk) be conducted. These approaches are described further in the sections that follow.

4.5.2 Improving the Current Approach to Estimate the Risks Posed by DBP Exposures. A concern of the group was the discrepancy between effects found in

epidemiological studies and toxicological laboratory studies. It was suggested that all existing data be reviewed in order to better plan future whole mixture laboratory testing. It is important to conduct such studies on reasonable representative samples, recognizing that the composition of DBP differs with treatment type and location. Methods need to be developed for comparing whole mixture with component studies, and for combining such studies to get an improved real mixture risk estimate.

Current approaches of risk assessment do not consider additive effects. If there are additive effects, their inclusion in the component approach to risk analysis would result in improvement in the risk estimate. Modeling approaches can provide guidance on the potential toxicity of compounds. Methods such as QSAR and Monte Carlo can be applied to better understand the uncertainties in the risk assessment. However, expertise in these areas is mandatory by the individuals applying them. One concern in the current use of Monte Carlo analysis in risk assessment is that proliferation of computer programs that allow for Monte Carlo analysis to be applied by untrained individuals to any data set. This proliferation of the use of Monte Carlo simulation has resulted in statistical analyses being conducted without proper consideration to the underlying assumptions of that analysis. It was highly recommended that statisticians who are appropriately trained in the evaluation of distributional data be included in both designing and conducting studies that use Monte Carlo methods of analyses.

4.5.3. Handling the Toxicity of DBP, or of Identified DBP, for which Little or No Data Exist. Two methods for evaluating potential risk associated with DBP for which little toxicity data exist is the use of QSAR and expert judgment to predict the probability that a compound can cause a particular adverse health outcome. QSAR, which is based on comparing descriptors within the molecular structure of the unknown chemical to a training set of compounds of known toxicity, does not estimate potency and is currently used for single compounds, not mixtures. Expert judgment relies on the opinions of scientists in the field to predict the potential risk for untested compounds. The group considered that both expert judgment and QSAR model selection, have potential in prioritizing which DBP has the highest potential risk. It was suggested that each procedure be run on the same set of chemicals for comparison. However, it was noted that expert judgment is a time- and personnel-intensive process, so it can have a limited application. Different QSAR models also exist and should be considered for use; the same set of chemicals should be run through each model for comparison.

4.5.4. Handling the Concept of Threshold and the Unidentified DBP. The doses associated with human exposure to DBP are all below the levels administrated to animals, making extrapolation necessary and the existence of a threshold effect level an important consideration. The major concern among the mixture group was whether unidentified chemicals may produce 'surprise' interactions even at low doses. Two major considerations in determining the likelihood of toxicological interactions among DBP mixtures are that the DBP are present at low concentrations in drinking water and that a large number of compounds remain unidentified. Typically, little interaction is expected at the doses associated with exposure to DBP in drinking water. It was the consensus of the group that at the known current concentrations, synergistic toxicological interactions will not occur. However, the large number of uncharacterized compounds preclude completely ruling-out the possibility, although this was a low probability event. An additional consideration that may result in possible interactions is whether there could be accumulation of DBP in the body from the constant exposure or whether there could be an accumulation of impacts of the hundreds of different chemicals, each individually at a low level, but all acting (by the same mechanism) on some precursor stage leading to an adverse health effect.

The use of whole mixture testing can help describe or bound the contribution of the unidentified chemicals without doing individual compound tests. It was recognized, however, that the composition and concentration of the "unidentified" DBP changes with treatment alternative or geographic location, making selection of a representative mixture for testing difficult. The group also was concerned about the need to evaluate multiple health endpoints, and whether and how to focus on one or a few effects. The

question was raised as to the need to use a more conservative model than response addition so that the unidentified DBP are at least partly considered in the analyses.

Cancer, developmental, and reproductive effects have all been suggested to be associated with exposure to DBP. The mechanism of action for each effect may be different. Designing a study to test whether a mixture-effect exists first requires that the health endpoint of concern be defined. It was strongly recommended that a comprehensive review of previous studies on mixtures and components, both from a perspective of animal studies and chemical characterization of the DBP, be conducted before designing future studies. There was no consensus of whether concocted mixtures or whole mixture extracts would provide a better approach for the animal studies. The use of concocted mixtures would allow for alteration of the mixture by spiking it with a known toxic agent to evaluate the plausibility of any observed effects and environmentally realistic doses. The use of whole mixtures would allow for evaluation of representative DBP mixtures without assumptions as to what the biologically active components are. Selecting a real-world representative DBP mixture is problematic because the components and concentrations of the unknown portion (as well as the characterized portion) of the DBP are site-, season-, and treatment-type specific. Differences in toxicological study outcomes and epidemiological outcomes can occur depending on the DBP(s) used or present in each study. The mixtures present in the positive epidemiologic studies (disinfection by chlorine or chloramine, levels of bromide in the water, character of the precursor organic matter) should be used to provide guidance as to what mixtures should be used in future toxicologic studies. The

concocted and whole mixture studies can provide complementary data and the research program should reflect the combination of the results from each type of study.

4.5.5. Interpretation of Human Developmental and Reproductive Risks Based on Animal Data. A series of questions were raised in recognition of the magnitude of the issues. Are there different kinds of sensitivity windows (of exposure) for the reproductive and developmental risks, so that the likelihood of co-occurrence of two such effects is small? How can continuous data be incorporated with quantal response data?

It was suggested that multiple effects might be modeled with a multinomial model rather than with a series of individual binomial models. For example, one approach is to score each fetus, with any developmental effect, as a responder. Risk curves could then be generated for "developmental" as a category of effect for each of the chemicals individually. The risk for the mixture might then be calculated by applying proportional response addition across all of the compounds considered.

The group noted that lifetime risk for developmental and reproductive risks are not adequate since there are different kinds of sensitivity windows (of exposure) for the different effects. The likelihood of two such effects occurring together is small. While not discussed extensively by the group, a potential issue is the appropriateness of summing the risks if different DBP affect development at different stages or critical periods. If considering risk/pregnancy, then it appears to be an appropriate approach, unless the occurrence of an effect early in development precludes the occurrence of an effect later in development. For example, the haloacetic acids and haloacetonitriles that have been tested for developmental toxicity have a spectrum of effects in the postimplantation period including postimplantation loss, depression of fetal body weight and crown-rump length, and visceral and skeletal malformations. Thus, for these DBP, the critical periods

appear to be similar. Should additional data indicate preimplantation effects, however, the approach of summing the risks could be reconsidered.

It was recognized, but not discussed at length, that genotoxic effects may have an impact on development. The possibility that subtle genotoxic changes from one or more DBP may render an organism more susceptible to additional genotoxic effects from other DBP should be investigated.

4.5.6. Summary. The breakout group agreed that additive methods of risk are plausible for low doses even for unidentified compounds; QSAR and Monte Carlo approaches can be applied to evaluating risk, which then can be added to gain better understanding of many mixture issues if adequate expertise is available.

The breakout group recognized that they proposed no solution(s) on how to combine different types of reproductive data; how sensitivity windows could affect combining developmental and reproductive endpoints; or how to quantitatively bound DBP and then eliminate some as not a concern.

4.6. UNCERTAINTY AND VARIABILITY GROUP

Participants in this breakout group discussion were: Bruce Allen, Brenda Boutin, Josh Cohen, Dale Hattis, William Huber, Jeff Swartout, and Linda Teuschler.

This group tried to address five issues: approaches for evaluation of uncertainty and variability; cancer slope factor uncertainty; noncancer dose-response analysis uncertainty; uncertainty in exposure and concentration data; and uncertainties associated with mixtures that contain unknown DBP with unknown toxicity characteristics. Each of these major topics is discussed below.

4.6.1. Approaches for Evaluation of Uncertainty and Variability. It is important in theory (and sometimes difficult in practice) to distinguish between variability and

uncertainty. Variability denotes real differences that exist, as, for example, among various members of a well-defined population with respect to some variable such as body weight. The variable(s) of interest do not all have the same value across members of the population, (i.e., there is heterogeneity so that they display a distribution of values within the population in question, and are, therefore, determined to have a variability of some magnitude). The magnitude of the variability depends on the degree of difference in the parameter values within the population.

Uncertainty denotes a state of imperfect knowledge. In the context of risk assessment, one is typically concerned with uncertainty about the values of variables that are required to characterize risk. Uncertainty can, and does, relate to measures characterizing the distribution of a variable within a population, such as the average value and the variability around the average. Notably, estimates of the magnitude of the variability of variable within a population are almost always subject to uncertainty.

Ignoring, for the moment, measurement errors (that add uncertainty simply because the act of measuring is imperfect), uncertainty about the values of means and variances (the two common characterizations of a variable's distribution within a population) arises because of the limited number of observations available to estimate their magnitudes. In extreme, but all-to-frequent cases, no observations may be available to estimate means and variances for the population of interest; in such cases, inferences based on observations in other populations or other circumstantial evidence may be required to make any guesses about the means and variances of concern. Clearly, there may be a great deal of uncertainty about the estimates in those instances.

Indeed, that inferential (cross-population) uncertainty is the biggest source of uncertainty affecting the risk assessment of DBP mixtures. Stochastic uncertainty (the

uncertainty associated with direct estimation of a mean and variance, or any other distributional parameter, using observations from the population of interest), does contribute to overall uncertainty in DBP mixture risk assessments, but it is suspected that, in relative terms, the magnitude of that uncertainty is small. Moreover, methods for characterization of stochastic uncertainty are well developed. For example, confidence limits for means (or for variances) are well-known and universally recognized methods for expressing stochastic uncertainty. In contrast, methods for characterization of inferential uncertainty have not been developed, and expression of such uncertainty tends to be less quantitatively rigorous.

In the following sections, these considerations will be explored specifically in the context of the DBP mixtures risk assessment. Because a Monte Carlo approach that distinguishes between variability and uncertainty has been (rightly) proposed as a means of summarizing the results of the DBP mixtures risk assessment (U.S. EPA, 1999), specific references to implementation of a Monte Carlo procedure are included.

4.6.2. Characterization of Uncertainty Influencing Estimates of the Cancer Slope Factor. Slope factors were one set of key parameters used to characterize the risks associated with exposures to DBP mixtures (U.S. EPA, 1999). Along with other parameters, the slope factors are treated as uncertain values that are input into U.S. EPA's Monte Carlo procedure in order to determine uncertainty and variability associated with the risk estimates. Because of their use in the Monte Carlo procedure, it is important to get a good characterization of the uncertainty of the slope factors.

However, the characterization of uncertainty for the cancer slope factor for each DBP in the EPA pre-meeting report (U.S. EPA, 1999) reflects only stochastic

uncertainty. Moreover, that characterization is not done appropriately. U.S. EPA (1999) documents an approach based on an assumption that for the slope factor "the distribution of plausible values is lognormal, with a geometric mean equal to the estimated MLE, and a 95th percentile equal to the upper 95% confidence limit on the slope." (U.S. EPA, 1999, p. 40). This is just one of many instances where confidence limits and percentiles of distributions are erroneously represented to be the same thing. Moreover, the additional assumption about the underlying distribution of a slope factor estimate (lognormality) is unnecessary and problematic.

More appropriately, quantification of the stochastic component of the uncertainty for a chemical's slope factor can be computed using resampling (bootstrap) techniques. Such techniques repeatedly compute the cancer slope factor for different, synthetic data sets. The synthetic data sets are constructed by assuming that the response rates within each dose group in a bioassay follow binomial distributions. The underlying probability of response for each dose group, from which the synthetic numbers of responders are generated, can be determined by either the observed fraction of affected animals in that group in the original experiment, or the modeled value of the probability of response. The modeled value is derived from the assumed dose-response curve at that dose-group's dose; the model-based approach uses the MLE parameter values from the fitted dose-response function. Several members of the group recommended the latter approach.

It must be recognized that even in the above discussion, there are elements of inferential uncertainty that impinge on the stochastic uncertainty estimates for the slope factor. The slope factor is itself based on an extrapolation to low doses of a DBP, doses

for which there are no direct observations. The slope factor estimate depends on the suspected probability of response in animals exposed to those low doses, and therefore, one is at least implicitly making inferences about the hypothetical population of animals exposed to those low doses, based on the observations of populations of animals exposed to higher doses. A dose-response relationship is assumed to govern the relationship between high-dose and low-dose responses, but one must remember that the assumed relationship is merely that, an assumption.

In addition to the stochastic uncertainty related to a slope factor estimate, one that is amenable to an improved characterization, there are many other inferential uncertainties. Not least of these is the issue of extrapolating the animal-based estimate to the required estimate relevant to humans. Some assumptions are required to make that extrapolation, assumptions that are themselves uncertain and which lead to uncertainty with respect to the resulting quantitative values of a human-relevant slope factor.

Data comparing potency in animals and humans for a generic set of chemicals could be used to quantify the distribution of plausible human potency estimates associated with the DBP-potency estimates inferred from the animal toxicity data sets. The Allen and Crump analysis of this issue may serve as a useful starting point (Allen et al., 1988a, 1988b; Shipp et al., 1989). Analyses reported by Dale Hattis based on the data compiled by Allen et al. suggest that the distribution of human potency estimates corresponding to a slope-factor estimate inferred from an animal toxicity data set can be characterized as lognormal with a GSD of approximately 10 (see Section 3.1). Therefore, in a Monte Carlo exercise, when determining the value of a human slope

factor to use for a set of simulations, one might take the animal-based slope factor estimate (which itself could be sampled from the distribution representing its stochastic uncertainty) and then sample from a lognormal distribution having a mean equal to that animal-based estimate and a GSD of 10.

With respect to the contribution of stochastic uncertainty to total uncertainty, the following general considerations are relevant. The total slope factor uncertainty for a specific chemical should depend on the magnitude of that chemical's stochastic uncertainty component; the procedure outlined in the preceding paragraph does that by making the starting point (the animal-based slope factor estimate) subject to the degree of uncertainty dictated by the stochastic component. It is therefore the case that the estimated (uncertain) value of the human slope factor is a function of the measured animal slope factor and its attendant uncertainty. However, it may be unlikely that this adjustment of the estimate of total uncertainty to reflect the magnitude of the stochastic component of uncertainty for a specific chemical will have a substantial impact. The variance of the inferential uncertainty ($\log_{10}$) is approximately 1 (recall that the suggested GSD for that uncertainty is 10); the variance of the stochastic uncertainty ($\log_{10}$) was suggested to be in the neighborhood of 0.1 (the GSD for stochastic uncertainty may be around 2, typically, if one wants to characterize stochastic variability in terms of a lognormal distribution). Overall variance, as the sum of these two contributors, would therefore reflect primarily that contributed by inferential uncertainty.

In the discussions above, other important sources of, or contributors to, uncertainty have been ignored. Measurement error was already mentioned as a possible source of error; it is likely that its contribution will be more significant with

respect to exposure and concentration estimation (see Section 4.6.4 below) than in relation to slope factor estimation. However, some of the more important concerns related to slope factors include the existence of multiple (animal) data sets and possible disagreements among them with respect to slope factor estimates. As a specific concern, the treatment of negative studies requires some serious consideration.

Moreover, risk estimates from different sites for cancer may be problematic. Mechanistically, the cell that causes a cancer in the kidney must be a different cell from the one that causes cancer in the liver. It is not clear if an additive approach (e.g., using a proportional response addition approach) would be appropriate or how one would handle the correlations between risk estimates obtained from different cancer sites.

If one adds to these (and other) concerns technical questions regarding the dependency of a resampling technique on maximum likelihood estimation (with possible resolutions related to use of a variety of models, likelihood contours, and variance/covariance matrices for parameter estimates), it is clear that not all of the issues related to uncertainty associated with slope factor estimation have been resolved. It is equally clear that careful deliberation needs to be applied to approach a satisfactory resolution of the representation of uncertainty concerning DBP slope factors.

4.6.3. Characterization of Uncertainty Influencing Estimates of the Noncancer Dose-Response. As in the case of the cancer slope factors, it was suggested that the U.S. EPA (1999) method for dealing with noncancer risks could be improved in some very specific ways. As a simple example, the use of the linearized multistage model imposes assumptions that are consistent neither with biologically plausible models of these health effects nor with other noncancer risk analyses that have appeared in the literature. For developmental toxicity endpoints, in particular, the models chosen are less than optimal.

Also paralleling the discussion above concerning cancer slope factors, it is recognized that the only uncertainty dealt with in the U.S. EPA (1999) assessment of noncancer risks is stochastic uncertainty. The uncertainties related to non-stochastic contributors are very likely to have the greatest impact on uncertainty about human noncancer risks associated with DBP mixtures.

Lately, the use of benchmark dose (BMD) estimates has become standard for noncancer risk analyses. Using an estimate of a dose associated with some fairly low level of response (e.g., an effective dose [ED] associated with less than 10% risk for a quantal endpoint), and a lower confidence limit on that dose to account for stochastic uncertainty, such a risk assessment would apply “uncertainty factors” to determine a dose that was considered to be suitably safe. The uncertainty factors can be viewed as “accounting for” non-stochastic uncertainties such as animal-to-human extrapolation.

Benchmark dose estimation, being reliant on uncertainty factors to derive a “safe dose,” may not be the most appropriate method in the context of the DBP mixtures risk exercise, for the following reasons. The DBP assessment requires risk estimates

associated with all potential exposure levels. Strictly speaking, the benchmark dose approach would not supply those estimates; the BMD methodology specifically avoids using the dose-response model predictions at low levels of exposure because, by and large, the models fit to the data are not selected with biological relevance in mind. Therefore, for doses well beyond the range of the observations, the model predictions may not be good. The use of uncertainty factors in the BMD approach is included as a way around this difficulty; if chosen appropriately, the application of uncertainty factors to BMD estimates yields safe exposure levels (albeit ones with no explicit statement of associated risk).

As an alternative, a modified form of dose-response assessment followed by extrapolation to humans was suggested. Suppose that a dose-response model is still fit to available animal bioassay data, but instead of estimating an ED_{10} or less, one estimates an ED_{50}. The proposal is that the ED_{50} estimated in that manner be assumed equal to a human ED_{50} (when scaled appropriately to account for body weight and/or other relevant species differences). Then, probability of response at other dose levels could be determined by assuming some distribution and a variance for response probability around that ED_{50}.

Dale Hattis has proposed that the distribution of probabilities of response be considered to be lognormal, and that this distribution's variance can be inferred from observed distributions of human physiological responses measured in the context of exposure to various substances. Hattis has estimated the implied GSD for the distribution of human response thresholds. He has also quantified the uncertainty in

this estimate (refer to Sections 3.1, 3.2, and 4.4). Some analogous approaches would have to be developed for use with continuous response data.

Clearly, both the estimates of risk associated with a given human dose and the uncertainty in that estimate would need to be available to inform the two-stage Monte Carlo procedure proposed by U.S. EPA (1999). A careful and deliberate examination of the data used to estimate human variability (and the uncertainties associated with it) must be undertaken, because the use of the "surrogate" variability data (i.e., data that considers variations in human pharmacokinetic and pharmacodynamic parameters that may have more or less relevance to the chemical responses of interest) is the epitome of inferential uncertainty itself. Moreover, the other issues discussed in connection with cancer slope factors (multiple studies, negative results, different endpoints) are pertinent considerations here. Clearly, a much more elaborate development of a noncancer risk assessment method appropriate for DBP mixtures is required and will entail considerable extra effort.

4.6.4. Uncertainty Associated with Exposure and Concentration Data. It would appear to be the case that both exposure and concentration estimates are subject to variability and uncertainty. Even at the most fundamental level, concentrations of some of the DBP are uncertain for any given treatment system simply because the identity of those DBP is unknown. Above and beyond this fundamental difficulty (which is discussed somewhat more in the next section), there are uncertainty and variability issues that need to be recognized in relation to both concentration and subsequent exposures. Measurement errors associated with collection of concentration data (for

which there is substantial laboratory involvement) and tap water intake data (based on survey results) are likely to be a significant contributor to uncertainty.

Again, some technical difficulties in characterizing the variability in known DBP concentrations can be found in U.S. EPA (1999). For example, the assumption of a normal distribution and fixing the value of non-detects at half the detection limit both hamper effective estimation of an appropriate frequency distribution. For concentration data, a lognormal distribution (or a mixture of distributions including a lognormal component) would be a more suitable assumption. Maximum likelihood estimation techniques do not require specification of a value for non-detects; those techniques should be applied without such unnecessary data manipulation.

In addition, because tap water intake is one of the key parameters determining exposure (once a set of DBP concentrations is given), some care must be taken in interpreting and using the tap water intake data to derive distributions characterizing variability and/or uncertainty. Of particular concern here is the lack of differentiation between percentiles of consumption across individuals and percentiles across days of consumption. It is believed that the available consumption data (presented in Ershow et al., 1991) were averaged over 3-day periods. Thus, daily variation probably can not be derived. But derivation of some sort of distribution for temporal variation might be possible, and this would provide information different from that representing interindividual variations. Such information might be important when considering the impact of some noncancer endpoints, where (unlike the typical assumption for a cancer risk assessment) a long-term average daily dose may not be the most appropriate determinant of response.

Even though these concentration and exposure parameters may be considered to be better characterized as variable rather than uncertain, it is worth remembering that populations are defined temporally as well as spatially. The data collected for tap water intake, in particular, may be especially sensitive to temporal changes in the population. In any case, with any of these parameters, one is extrapolating from one population to another (possibly very similar) population, if for no other reason than the fact that DBP concentrations and tap water intake are not things that "exist" and persist over extended periods of time.

4.6.5. Uncertainty Associated with Unknown DBP Fractions. One of the biggest sources of uncertainty for the entire DBP mixtures risk assessment is the treatment of portions of that mixture that are unknown to one degree or another (further discussion is presented in Section 4.2). It was suggested that the DBP might be characterized as belonging to one of three "layers" and associated with any given endpoint as follows:

Layer 1 = identified DBP (known concentrations, toxicity data, and structures);

- let a1 be the proportion associated with an endpoint

Layer 2 = unidentified DBP (names of some of those and their structures, with QSAR information, will be known, but toxicity data will be absent)

- let a2 be the proportion of this layer associated with an endpoint

Layer 3 = unidentified DBP (nothing is known about these except that they exist)

- let a3 be the proportion of this layer associated with an endpoint

The a1 values are used in the U.S. EPA (1999) calculations of risk. Of course, the a1 values are estimated and are subject to (considerable) error. Other uncertainties associated with the DBP in layers 2 and 3 relate to the estimates of their concentrations (C_i) and "potencies" (S_i).

While no specific suggestions were provided by the uncertainty/variability group with respect to dealing with these uncertainties, some suggested approaches related to the following. It might be important to look at trends in toxicity across layers (although this will require additional toxicity testing and may be limited to the first two layers). Molecular weights and polarity data might also be attainable and might be useful surrogates for more detailed information, especially if the known toxicity data could be related (even grossly) to such measures. Moreover, the information presented by Pat Fair relating total TOX to specific by-products may help to quantify magnitudes (and provide bounding estimates at the very least) (see Section 3.5).

Clearly, not many concrete suggestions for dealing with the uncertainties associated with unidentified DBP were provided by this work group. This may be one prime example of the degree to which "nonquantifiable" uncertainties dominate a risk assessment. Even some nonquantitative representation of the most likely implications of these uncertainties may be difficult. Nevertheless, summary tables enumerating all of the sources of uncertainty (or forms of ignorance) associated with the DBP mixtures risk assessment should be provided. Those tables might provide at least rough estimates of the magnitudes of the associated uncertainties; estimates of the level of effort (in time and money) required to reduce those uncertainties would also provide valuable information to decision-makers and other users of the risk assessment. If presented well, such a summary will go a long way toward making a DBP mixtures risk assessment acceptable.

4.7. TOXICOLOGY/EPIDEMIOLOGY AND EXPERT JUDGMENT

The participants in this breakout group were: Gunther Craun, George Gray, John Lipscomb, Patricia Murphy, and Charlie Poole.

The group recognized that both epidemiologic and toxicologic approaches contribute valuable information to the risk assessment process, but that there have been difficulties incorporating the epidemiologic results into the quantitative risk assessment. There is a need to better characterize the uncertainties associated with the underlying epidemiologic literature and when attempting to quantify the human health risks, it should be recognized that insufficient epidemiologic data are available to establish a causal association between DBP and cancer or reproductive risks. There is confusion among epidemiologists and toxicologists about how to interpret the findings or the studies because of inherent differences in the design, execution, and analysis of the studies. Of particular concern are the non-comparability of the water exposures studied, methodological differences among the studies, internally inconsistent findings within studies, and the lack of consensus regarding causality for bladder, colon, and rectal cancers. The literature on reproductive and developmental effects is currently too sparse to use for quantitative risk assessment. One of the problems in attempting to interpret the epidemiologic findings is the incompletely presented dose-response information by the study authors. Use of continuous data (where available) improves both the sensitivity and the power of the analysis, and the panel recommended that these analyses be conducted. As new studies are planned for this area, scientists should consider the experience from the cancer epidemiology literature and strive to avoid similar problems.

The breakout group agreed that the issues that needed to be addressed by both epidemiologists and toxicologists include:

- examining the sensitivities (range of) in humans and animals;
- explicitly considering humanly relevant exposures (levels, routes, cumulative, peak, etc.) and endpoints in the design of new toxicologic studies on DBP;
- quantitatively identifying the uncertainties in exposure-response analysis of the epidemiologic literature (only apply alternative models to the data, use the continuous data that exists);
- providing an explanation of the uncertainties involved;
- refraining from the use of a single value for risk; and
- increasing the understanding of problems associated with using a single aggregate number from a meta-analysis for regulatory decisions, specifically, and for
    - assessing causality,
    - guiding future research, and
    - assessing sensitive subsystems and water treatment differences.

The breakout group recommended that an “expert” panel be convened to identify the important issues regarding better characterization of the uncertainties associated with interpreting the epidemiologic literature and how best to quantify the human health risks of cancer and exposure to drinking water disinfectants and byproducts. Previous reviews have identified many of these uncertainties and potential solutions may not require a large investment of money and time. The discussion of these uncertainties at the present workshop indicates the continued importance of attempting to resolve these issues.

Although the panel would not be engaged in the formal elicitation of expert opinions, the selection of the individual panel members should be considered as carefully as if that were the goal. The general composition of the panel should include epidemiologists, toxicologists, and quantitative analysts who have had experience in complex problem solving. The primary interest of the panel is to objectively evaluate the current studies and analyses of their results, identify the uncertainties, and recommend ways to reduce these uncertainties. They would also oversee the implementation of projects and tasks specifically designed to address the relevant issues and interact frequently with all investigators. The panel should consist of persons who have not been involved in the design and/or conduct of the existing studies, although these individuals would inform the panel in regard to the important subject matter information. It is expected that the work of the panel would be long term (1-2 years). The panel should be actively involved in helping to evaluate how uncertainty can be reduced, designing or guiding the design of specific analyses to be conducted, periodically be informed of progress on recommended analyses, and providing feedback to the analysts. The group envisioned that panel meetings would be held on a quarterly basis to effectively facilitate the implementation of their recommendations (Table 4-2).

4.7.1. Issues for Blue Ribbon Panel Discussion. The following ten issues were suggested by this breakout group for consideration by “Blue Ribbon Panel”.

- *Must a meta-analysis produce a single summary effect estimate for each cancer?*

A common view of meta-analysis is that its purpose is to produce a single summary effect estimate. Further, a meta-analysis that does not produce such a

TABLE 4-2

Objectives for a “Blue Ribbon Panel”

- frame the questions that need to be addressed,
- recommend appropriate analyses,
- set the range of input values for sensitivity analyses,
- conduct (with feedback loops) periodic assessment of status of work, new findings that become available, and inform and assist decision makers in the interpretation of new findings,
- provide feedback between analysts and those framing the issues, and
- consist of a multi disciplinary scientific group with
    - “new blood”
    - subject matter and general experts

summary is often considered a “failed” meta-analysis. An alternative view is that much can be learned from applying meta-analytic techniques to understanding differences among the results from the various studies in relation to the ways the studies were conducted, the populations studied, the exposures and exposure contrasts that were examined, and the way the results were analyzed and presented. The two approaches or motivations in meta-analysis, aggregation and explanation, should be viewed in the context of three major purposes of meta-analysis: to assist in causal inference, to help assess public health impact, and to guide future research. Thus, the alternative view of meta-analysis’ purpose should be more widely publicized and adopted. The single summary effect estimate seems to be of relatively little value for assessing the DBP-cancer risk issue. The panel should consider these questions: Can a meta-analysis that does not produce a single summary effect estimate assist in causal inference? If a meta-analysis provides evidence that all the studies are not merely producing more or less precise estimates of an effect measure that has a single, “one size fits all” value, is a single summary adequate? How can a single summary estimate of effect guide future research?

- *“Inclusive” versus “best evidence” approaches to meta-analysis and quantitative risk assessment using epidemiologic data.*

The epidemiologic literature on chlorinated drinking water and cancer may be divided into three parts: (a) studies that are currently analyzed at the ecologic level; (b) studies at the individual level that lack interview information; and (c) studies at the individual level with interviews. An inclusive approach would involve reanalyzing as many of the current ecologic studies as possible to make them individual-level analyses. The approach would then include these studies and all individual-level studies, with or

without interviews. The recent paper by Bukowski and Murphy (1998) took a "best evidence" approach by confining the analysis to studies that were at the individual level, that had interviews, that included incident cancer cases (as opposed to cancer deaths), and that for which the exposure metrics were variations on the theme of cumulative exposure (e.g., years of residence in communities with chlorinated water). Thus, Bukowski and Murphy (1998) restricted their analysis to a subset of studies at the individual level with interviews. An even more extreme version of the "best evidence" approach would be to base quantitative risk assessments on each study with a quantitative exposure metric, one by one. The choice between the inclusive and best evidence approaches can have important implications. For instance, the best evidence approach leads to reliance on a smaller data base with more stochastic uncertainty. The inclusive approach, on the other hand, might require a reanalysis project to turn as many of the currently ecologic studies into studies at the individual level. However, the data base would be larger with less uncertainty.

- *What can be done about publication bias?*

Appreciable evidence of publication bias was present in the results extracted from individual studies in the 1992 meta-analysis by Morris et al. (Poole, 1997; Murphy et al., 1999; Poole and Greenland, 1999). If this evidence persists when the literature search is replicated and brought up to date should a summary effect estimate be produced anyway or is evidence of publication bias a contraindication to aggregation? Can anything be done to lessen the impact of publication bias? The first of two general options is to "beat the bushes" to find as many unpublished results as possible. This approach is extremely time-consuming, expensive, and labor-intensive, as it requires

personally contacting as many researchers as possible who might have unpublished results on the topic. A second option is an analytic approach of conducting a sensitivity analysis to model the unpublished results. This is a form of missing data imputation. Statistical theoreticians in the field of meta-analysis are developing imputation methods to model missing results due to publication bias. It may be worthwhile to see if any of these methods are suitable for use in the literature on chlorinated drinking water and cancer.

- *How can exchangeable results be extracted from the individual studies?*

Extracting results for meta-analysis from individual studies is a process fraught with decisions, assumptions, and uncertainties. The goal should be to extract "exchangeable" results: results that, by their nature, one would have no reason to expect that they would differ quantitatively from each other. In the data of Morris et al. (1992), this assumption is not met. A key impediment to exchangeability is the use of different exposure metrics. Many, very dissimilar exposure metrics have been used in studies of cancer and chlorinated drinking water. Some are based only on the surface/ground or chlorinated/unchlorinated status of the community of residence of cases and controls at the time of their deaths. Others include quantitative or semi-quantitative information on concentrations of one or more chlorination by-products. Some include residential histories over some or all of the lives of study subjects and thus can support measures of cumulative exposure. These cumulative exposure measures can differ fundamentally, however. Some may be years of residence in "chlorination communities." Others may be in the form of lifetime consumption of one or more chlorination compounds (e.g., in milligrams) or in the form of lifetime cumulative

exposure (e.g., microgram per cubic liter-years). Finally, a small number of studies take interview information on amounts of tap water consumption into account. When studies with polytomous exposure scales report results for categories (e.g., four categories of "chlorinated water years"), options for extracting results include the contrast between the highest and lowest categories, combining all categories but the lowest into a single category, fitting a regression equation to the categorical effect estimates, or fitting a linear (or legit-linear) regression or a more flexible regression to the individual, continuously measured data. The choices, assumptions, and uncertainties involved in putting the extracted results on a common, exchangeable footing are considerable in this literature. The "Blue Ribbon" panel could consider the choices and assumptions and make recommendations.

- *What are the implications of evidence of overall heterogeneity?*

Every worthwhile meta-analysis includes an overall assessment of heterogeneity of the study-specific results. This assessment usually takes the form of a formal test of the hypothesis of homogeneity. When the P-value from such a test is low, what should the analyst do? Some would merely compute an overall summary effect estimate by conducting a variance-inflating random-effects analysis. Others would consider the evidence of heterogeneity as a contraindication to aggregation and would focus the remainder of the analysis on a search for study characteristics that would explain sizable portions of the heterogeneity. An ill-advised approach is to identify a single, influential study that is responsible for more of the apparent heterogeneity than any other study and to exclude that study. To debate and resolve the implications of

evidence of heterogeneity for aggregative meta-analysis would be an important contribution by the “Blue Ribbon” panel.

- *Confounding by water source*.

One of the earliest concerns in the epidemiologic literature on chlorinated drinking water and cancer, raised as early as the study by Alavanja et al. (1978), is that the distinction between chlorinated water and unchlorinated water is tantamount in most studies to the distinction between surface water and ground water. Differences other than chlorination between surface water and ground water thus create the potential for a form of confounding that is built directly into the exposure scale in many studies and that therefore cannot be controlled analytically. Of the existing studies, only those by Brenniman et al. (1980) and Zierler et al. (1986) held water source constant. Brenniman et al. confined their contrast of chlorinated and unchlorinated communities in Illinois to those using ground water. Zierler et al. contrasted primarily surface-water communities in Massachusetts using chlorination with those using chloramination. Few if any municipalities that currently chlorinate would have the option of switching from chlorinated surface water to unchlorinated ground water, or of switching from chlorinated ground water to unchlorinated ground water. Thus, only the study by Zierler et al. comes close to examining the actual choice faced by most community water systems that currently supply chlorinated surface water to their customers: switching from chlorinated surface water to the same surface water disinfected by some other means. The implications of this lack of correspondence of the exposure contrast in almost all studies in the currently available literature to the actual choices faced by municipal water systems is a major source of uncertainty in this literature.

- *Confounding by other factors.*

Confounding by factors other than water source is an additional source of uncertainty in the studies of chlorinated drinking water and cancer. Some studies completely lack information on cigarette smoking, for instance. Smoking has an established association with bladder cancer and a possible or probable association with colorectal cancer. What is the magnitude of these associations? How strongly, and in what direction, might smoking be associated with measures of exposure to chlorination byproducts in the study populations in this literature? Questions such as these need to be answered to conduct sensitivity analyses of uncontrolled confounding, not only by smoking, but by other factors as well. Possible risk factors for colorectal cancer include dietary fiber, physical activity, and others. Incompletely controlled confounding is another problem. In some studies, the information on smoking comes largely from surrogate respondents such as next-of-kin. Inaccuracies in this information may adversely affect the degree to which the confounding can be controlled. In some studies, age has been controlled very approximately, for instance, by dividing it into 10-year or even 20-year intervals. For some cancers, the relation to age is so strong (often expressed as a power function), that risk may vary as much as two-fold across just a 5-year age range. Since the exposure metrics in some of the studies are measures of exposure duration that extend to 30, 40, 50, or 60 years and more, the control for confounding by age should be as complete as possible.

- *Control selection in case-control studies.*

Nearly all of the studies in this literature are case-control studies. The validity of the control groups, therefore, is a major concern. Ideally, the control group accurately

represents the joint distribution of the exposure and of all unmatched confounders in the study population. Thus, a random sample from a roster of the study population would be preferred. Unfortunately, such a roster is virtually never available. In some studies, the controls are persons who died of causes of death other than cancer. Most of these controls would be expected to be persons who died of cardiovascular disease. Is the occurrence of death from cardiovascular disease the equivalent of random selection with respect to water chlorination, smoking, and other potential confounders? In other studies, random-digit telephone dialing was used to select controls. This procedure is known to produce control groups of lower socioeconomic status (SES) than the populations they are intended to represent. Might this bias with respect to SES produce a bias with respect to water chlorination? These and other questions concerning the validity of control selection need to be addressed on a study-by-study basis.

- *Other study characteristics.*

It may be possible that characteristics of studies other than those mentioned above are important determinants of the results these studies produce. Two commonly examined characteristics are the cohort versus the case-control design and year of publication. Year of publication is often an important indicator of publication bias and validity. The earliest studies often tend to be those that report the strongest associations. Often, as a research program matures, better methods are brought to bear. One characteristic of special importance in this literature might be geographic variation in the constituents of the source water. The bromine content, to take but one example, might bear importantly on the mixture of chlorination byproducts to be produced in the finished water.

- *Interaction.*

Many of the studies examine interaction, either formally by including product-interaction terms in logistic regression models, or informally by visual inspection of stratified results. Gender and smoking are popular choices as variables with which to examine interactions with measures of exposure to chlorinated drinking water. Unfortunately, these analyses, whether formal or informal, are virtually always conducted on the multiplicative scale. This fact makes the assessment of interaction in the epidemiologic studies differ fundamentally from the assessment of interaction in the toxicologic literature, where the analysis is almost always conducted on the additive scale. In epidemiologic terminology, there is no interaction on the multiplicative scale when the relative risk or odds ratio for one factor (e.g., chlorinated water) is homogeneous or uniform across levels of the other factor (e.g., smoking), and there is no interaction on the additive scale when the risk difference is homogeneous or uniform. Evidence of etiologic synergism (or antagonism) is provided by evidence of statistical interaction on the additive scale, not on the multiplicative scale. Thus, when epidemiologic investigators ask whether, for instance, the relative risk estimates for chlorinated water differ between smokers and non-smokers, they are looking for departures from a null state (equal relative risks in the two groups) in which a substantial degree of synergism is built in. Viewed in another way, when there is no etiologic synergism or antagonism, one should expect the relative risk for the exposure to be lower among smokers than among non-smokers. The analysis of interaction on the multiplicative scale in epidemiologic studies may have created a considerable degree of confusion in the interpretation of their results. (Assessment of interaction on

the additive scale can be conducted in case-control studies, as long as neither of the factors has been used to match the controls to the cases.)

4.8. CONCLUSIONS, FUTURE RESEARCH AND RECOMMENDATIONS OF THE BREAKOUT GROUPS

4.8.1. Exposure. The exposure breakout group participants offered several recommendations for assessment of DBP mixtures. Multi-route exposures should be considered by the EPA as they are likely important for risk assessments for DBP. The inhalation exposure for volatile DBP and dermal exposure to highly lipophilic DBP can result in exposures equivalent to ingestion for median water uses. Thus, when comparing risks from different water sources and treatments practices (which may result in different types of DBP and concentrations), it is critical to include all exposure routes. Full exposure models linked to a physiologically-based pharmacokinetic (PBPK) model, if available, should be conducted to estimate human doses. Exposure models should be evaluated with experimental and field data.

Potential population distributions of exposure should be considered rather than point values; this is especially important for susceptible or high-risk subpopulations. Some people may have much higher inhalation exposures to volatile DBP and may also have higher dermal exposures (e.g., frequent swimmers, users of hot tubs and spas). Identification of these subgroups and estimation of their ranges of exposures needs to be considered. Consumption data are needed; several data sets are just becoming available, but they may not provide the information needed for pregnant and lactating women. Data are needed on skin permeability, especially for young children. Recreational exposures to DBP through chlorinated swimming pools need to be quantified.

In epidemiologic studies, full exposure models should incorporate the range of water concentrations at both the treatment plant and within the distribution system over the etiologically relevant time period, changes in the mixture of DBP during the exposure period if there have been changes in water sources or treatment practices, water use and consumption patterns that may affect ingestion, inhalation, and dermal exposures, other human behavioral activities or characteristics that may affect exposure, and household/work place characteristics.

Long-term research goals should be to continue to invest time and efforts into identifying chemicals in TOX and further identifying DBP that make up the unknown fraction. It is important that specific DBP be identified and quantified, as the multi-route exposure approach can be problematic for DBP that are not specifically identified and when concentrations are not measured (e.g., compounds identified only as TOX). The extrapolation of the unidentified DBP, based on a surrogate of TOX, is questionable. Expert judgment could possibly be used to help characterize risks posed by TOX and other non-identified DBP in populations. However, to obtain population distribution of exposures, appropriately designed surveys may be better at providing missing data. Volatile DBP may be good surrogates for inhalation exposure to unidentified DBP.

Identification of DBP from ozone, chloramine, and chlorine dioxide treatment processes should also be long-term research goals. More data for chloramines, ozone, and chlorine dioxide by-products are needed as well as predictive models of their concentration at the water treatment plant and/or distribution system. There will be sufficient data on concentrations of THM, HAA, bromate, and aldehydes in water systems throughout the U.S. after the ICR data become available. These data can

serve as inputs to existing mathematical models that predict distribution system exposures, including concentrations at the tap.

Actual exposure data should be used to help define ratios of mixtures for toxicology studies (i.e., brominated/non-brominated species). Ratios of mixtures should also be considered when evaluating exposures in epidemiological studies.

More attention should be paid to the potential value of whole mixture testing. Consideration should be given as to whether whole mixture testing will assist in estimating risks.

4.8.2. Unidentified DBP. This breakout group thought that it is imperative to obtain some information about the identified, but unquantified TOX, and also about the unidentified TOX, in order to reduce the enormous uncertainty in the current risk assessment. The participants suggested a statistically valid method that would randomly sample individual chemicals (stratification and proportional sampling are appropriate) from these groups and attempt to measure important properties of the sampled chemicals. At a minimum, relative concentration (in at least one water sample) and, very roughly, potency would be needed. Extrapolation from an LD_{50} assay would likely suffice as a rough measure of potency.

The method presented by EPA (U.S. EPA, 1998, 1999) assumes that the known and unknown compounds are equally toxic. The group suggested this assumption could be examined by assembling distributions of LD_{50}s for each of the known and unknown compounds and comparing these. LD_{50}s can be found from experimental data or could be estimated using Quantitative Structure Activity Relationship (QSAR) models. Mechanisms of toxicity for the unknowns can only be assumed.

Different QSAR models will yield various predictions that may conflict, so that multiple “answers” are provided for analysis. However, this information could be examined as a body of data for the unknowns. Multiple “answers” could be examined by expert judgment, perhaps by holding a workshop. A technique for looking at this body of QSAR data is to examine the range of predictions. The result would be preliminary information—and bounds—on the magnitude of differences among the identified DBP-- differences in concentration, potency, even frequency of occurrence (if multiple finished water samples were evaluated). Such an analysis cannot yet be conducted on the unidentified DBP because there is no sampling frame, but the concentration of unidentified chemicals could be estimated. Further work at identifying individual DBP would be necessary if the concentration of this group appeared to be “substantial.”

Improvements in the EPA’s method include putting distributions on the variables in the equations for deriving the toxicity of the unidentified TOX, including distributions on α_h and the TOX amounts. It also might be interesting to statistically treat the question that if a progressive series of efforts to find DBP identifies fewer and fewer DBP, then what is likelihood of finding more? This could lead to some level of confidence relative to whether the majority of the DBP have been identified. Finally, it was suggested that the unidentified DBP could be treated only in a qualitative fashion.

4.8.3. Cancer. The group believed that there was a need to characterize uncertainty in the hazard identification step when evaluating carcinogens. Any hazard identification for a general human population that relies on data from animal bioassays or occupational exposure has an intrinsic degree of uncertainty. To be most useful in a

comparative framework, the uncertainty should be characterized quantitatively so that it is reflected in the risk estimates that are compared. The group suggested that more efforts with both existing animal and human data and further data development would be most helpful.

With current data, the use of PBPK models for different DBP, combined with some notion of mode of action, might provide insight into patterns of tumor development in animals and humans. Further work controlling for water source in epidemiologic studies might help to identify key DBP associated with increased cancer risk. It was also suggested that re-analysis of some ecologic studies might be useful. Finally, a new meta-analysis with studies completed since 1992, including exploratory meta-analysis to identify important population characteristics, could provide valuable information.

The group also suggested types of new studies that might shed some light on the seeming disparities between epidemiologic and toxicologic results. Investigations in animals and *in vitro* studies might identify the components of chlorinated water that are associated with different types of cancer, studies of gene-environment interaction (e.g., CYP2E1, GST, acetyl) could identify particular subpopulations for further epidemiologic study.

A final source of uncertainty that the group agreed is important for characterization comes from publication bias in epidemiologic studies. Attempts to characterize, model, and even correct for publication bias, based on new positive and non-positive studies, to quantitatively characterize the uncertainty, could be considered.

Several key assumptions about carcinogenic DBP that may benefit from expert judgment if a best estimate of risk is to be constructed are:

- whether or not the agent is a human carcinogen,
- if there is non-linearity for carcinogenic action at a specific dose level or dose rate, and
- the mode of action of the compound.

In addition to estimating uncertain parameter values, the group recognized that expert judgment could help in analyzing and evaluating current risk models. In addition, expert judgment had the potential to evaluate the chemicals being investigated (e.g., the apparent discordant results from toxicology and epidemiology for bladder cancer). It was recognized that this might be an example of the sort of question that would more usefully be advanced by more analysis or experimentation rather than expert judgment relying on relatively few data. Another suggestion was to use QSAR to prioritize uncharacterized DBP for study and use expert judgment for further processing or reducing the list of chemicals.

There was concern in the group with the way in which margin-of-exposure calculations (based on the new EPA guidelines) could be used in risk comparisons since no explicit risk estimates are made. The group recognized that the question of combinations of carcinogens showing non-linearity at low dose needs more work. It was recognized that if a chemical is considered “nonlinear” for cancer dose-response, then no probabilistic risk is estimated and there is real difficulty with response addition under this scheme. One suggestion that was offered, if the MOE approach is used, is to consider a blend surface and connect the resulting doses reached by the MOE method for each one. The group recommends that EPA further evaluate proportional response

addition as a means to combine dose-response data when risks are characterized using a MOE approach. In the area of dose addition, several questions were raised, including the appropriateness of adding points of departure (i.e., ED_{05}s) and how to handle compounds with different weights of evidence for both carcinogenic potential and mode of action.

As an approach to many of the questions raised in the breakout session, the group suggested that further exploration of the analysis be conducted as part of the proposed change to the MCLG for chloroform. This might allow understanding of ways in which uncertainties were, and were not, characterized well and might allow for some generalization to other cases.

4.8.4. Reproductive and Developmental. The breakout group thought that laboratory developmental toxicity studies are valuable for predicting human developmental effects in the general sense, despite inconsistent concordance of specific effects between test animals and humans. For the DBP analysis individual fetus data are generally reported in the literature, overcoming a possible limitation often seen in the literature. The experts thought that EPA could consider modeling the risk of *any* DBP-related developmental effect, rather than focusing on a specific effect. The general approach would be to aggregate (e.g., type of malformation, mechanistic class, or continuous vs. quantal the observed effects) in the animal bioassay prior to running the chosen dose-response model.

The breakout group considered that it appeared to be more appropriate to model individual embryo/fetal responses, as opposed to litter-based summaries of response; this was particularly true for quantal responses. A model like the log-logistic model with

underlying beta-binomial response variability would be recommended for modeling a single quantal endpoint. Such models account for the correlated nature of the results from typical developmental toxicity data sets (and from many reproductive toxicity data sets) and allow one to get estimates of the fetal probabilities of response as a function of dose or exposure (and other covariates such as litter size). Other particular model forms could also be applied.

Another alternative to modeling each selected endpoint separately is to model several endpoints together using a multinomial model. Such models treat the possible outcomes subsequent to implantation (resorption, fetal death, malformation, and variations in birth weight) as a vector of responses that are modeled together to account for possible intrafetal correlations among them. While a bit more complicated, there may be some instances where a multinomial approach might be appropriate.

For quantal effect data, there are three main choices for predicting human risk from animal developmental and reproductive data: the BMD, ED_{50}, and slope factor. The dose corresponding to a particular level of response, often referred to as an EDx or a BMDx, could be estimated. In more advanced applications, pharmacokinetic or allometric (e.g., dose per unit body weight$^{3/4}$) scaling adjustments could be used to translate the benchmark dose into human equivalents. Additionally, distributions rather than point estimates could be used for the uncertainty factors. It is expected that this approach will generally lead to predictions of zero expected incremental risks because DBP exposures are expected to be below the calculated RfD in nearly all cases.

A second way to analyze quantal data is to use the animal data only to identify the kinds of effects produced by specific toxicants and associated potencies, indexed as

an ED_{50} (log normal model of tolerances). Human low dose risks are then projected using generic information about human variability in the several steps from exposure through response utilizing recently compiled human variability information. An advantage of the use of continuous intermediate parameters such as birth weights is that they are more amenable to epidemiologic study and measurement of population effects than rare quantal effects. A disadvantage is that this approach involves a noticeable departure from previous EPA risk assessment practice and conclusions for noncancer effects at levels of exposure below the RfD (or their equivalents). This approach will lead to the projection of finite risks for DBP (and estimates of uncertainty) at current exposure levels. Many, if not all, of these projected risks are likely to be below limits of detection in epidemiologic studies.

The current EPA slope factor analysis is another option for handling quantal data, but was not discussed extensively by the breakout group. A disadvantage of this approach is that it assumes a low dose linear dose-response relationship that is generally at variance with the assumed homeostatic, threshold mechanism assumed for most developmental and reproductive effects.

For continuous endpoints, such as birth weight, it is not so clear how to model dose-response relationships. One could turn such endpoints into quantal endpoints by selecting a cutpoint to dichotomize normal and abnormal levels (e.g., normal vs. abnormally low birth weights). One could then apply the log-logistic model (or some similar model) to the now-quantal representation of the weight response. Alternatively, one could model changes in the continuous variable itself as a function of dose. The dose-response relationship for the continuous endpoint in animals could be modeled,

projected to humans using a pharmacokinetic or allometric dose scaling procedure, and then the implications for human risk using human data could be interpreted in the context of the continuous parameter (or its human analog) to human clinical outcomes of concern. Such an analysis should, of course, be limited to parameters that do have human analogs that are strongly related to adverse outcomes of concern. For example, the fetal weight reductions seen for various DBP could well be predictive of fetal growth retardation and, therefore, reductions in birth weight for a constant gestational age. Relationships between birth weights and outcomes of concern, such as infant mortality, can then be used to project human risks. The committee encouraged epidemiologic study of relationships between DBP exposures and these types of continuous intermediate parameters that are likely to be predictive of rarer quantal endpoints of ultimate concern.

4.8.5. Mixtures Risk Characterization. The breakout group suggested several approaches to the EPA: a thorough review of the literature on complete mixtures (including *in vitro* studies); application of three types of data analyses to evaluate additivity (multinomial, response-addition, and proportional response addition); and comparison of the results from epidemiological and toxicological studies for consistency in health outcomes for individual DBP or for mixtures of DBP.

It was strongly recommended that a comprehensive review of previous studies on mixtures and components, both from a perspective of animal studies and chemical characterization of the DBP, be conducted before designing future studies. It was thought that a data base of individual studies exists that has not been considered in its entirety.

The use of whole mixture testing can help describe or bound the contribution of the unidentified chemicals without doing individual compound tests. It was recognized, however, that the composition and concentration of the "unidentified" DBP changes with treatment alternative or geographic location, making selection of a representative mixture for testing difficult because the components and concentrations of the unknown portion (as well as the characterized portion) of the DBP are site-, season-, and treatment-type specific. Differences in toxicological study outcomes and epidemiological outcomes can occur depending on the DBP used or present in each study. The mixtures present in the positive epidemiologic studies (disinfection by chlorine or chloramine, levels of bromide in the water, character of the precursor organic matter) should be used to provide guidance as to what mixtures should be used in future toxicologic studies. The concocted and whole mixture studies can provide complementary data, and the research program should reflect the combination of the results from each type of study.

It was suggested that multiple effects might be modeled with a multinomial model rather than with a series of individual binomial models. The risk for the mixture might then be calculated by applying proportional response addition across all of the compounds considered.

The breakout group agreed that additive methods of risk are plausible for low doses even for unidentified compounds; QSAR and Monte Carlo approaches can be applied to evaluating risk which then can be added to gain better understanding of many mixture issues if adequate expertise is available. In trying to compare risks of DBP from different treatment plants, it was suggested that modeling of risk using both a Monte

Carlo simulation and a sensitivity analysis be conducted. It was highly recommended that statisticians who are appropriately trained in the evaluation of distributional data be included in both designing and conducting studies that use Monte Carlo methods of analyses.

The group considered that both expert judgment and QSAR model selection have potential in prioritizing which DBP has the highest potential risk. However, it was noted that expert judgment is a time- and personnel-intensive process, so it can have a limited application. Different QSAR models also exist and should be considered for use; the same set of chemicals should be run through each model for comparison.

4.8.6. Variability and Uncertainty. This group tried to address approaches for evaluation of uncertainty and variability; cancer slope factor uncertainty; noncancer dose-response analysis uncertainty; uncertainty in exposure and concentration data; and uncertainties associated with mixtures that contain unknown DBP with unknown toxicity characteristics.

A Monte Carlo approach that distinguishes between variability and uncertainty has been (rightly) proposed as a means of summarizing the results of the DBP mixtures risk assessment (U.S. EPA, 1999). However, the characterization of uncertainty for the cancer slope factor for each DBP in the EPA pre-meeting report (U.S. EPA, 1999) reflects only stochastic uncertainty. That characterization is not done appropriately. There are many instances where confidence limits and percentiles of distributions are erroneously represented to be the same thing. Moreover, the additional assumption about the underlying distribution of a slope factor estimate (lognormality) is unnecessary and problematic.

Quantification of the stochastic component of the uncertainty for a chemical's slope factor can more appropriately be computed using resampling (bootstrap) techniques. A model-based approach using the MLE parameter values from the fitted dose-response function was recommended by several members of the group.

Other important sources of, or contributors to, uncertainty need to be considered. The contribution of measurement error is likely ro be more significant with respect to exposure and concentration estimation than in relation to slope factor estimation. However, some of the more important concerns related to slope factors include the existence of multiple (animal) data sets and possible disagreements among them with respect to slope factor estimates. As a specific concern, the treatment of negative studies requires some serious consideration. Risk estimates from different sites for cancer may be problematic. If one adds to these (and other) concerns technical questions regarding the dependency of a resampling technique on maximum likelihood estimation (with possible resolutions related to use of a variety of models, likelihood contours, and variance/covariance matrices for parameter estimates), it is clear that not all of the issues related to uncertainty associated with slope factor estimation have been resolved. Careful deliberation needs to be applied to approach a satisfactory resolution of the representation of uncertainty concerning DBP slope factors.

As in the case of the cancer slope factors, it was suggested that the U.S. EPA (1999) method for dealing with noncancer risks could be improved in some very specific ways. As a simple example, the use of the linearized multistage model imposes assumptions that are consistent neither with biologically plausible models of these health effects nor with other noncancer risk analyses that have appeared in the

literature. For developmental toxicity endpoints, in particular, the models chosen are less than optimal. The only uncertainty dealt with in the U.S. EPA (1999) assessment of noncancer risks is stochastic uncertainty. The uncertainties related to non-stochastic contributors are very likely to have the greatest impact on uncertainty about human noncancer risks associated with DBP mixtures. Lately, the use of benchmark dose (BMD) estimates has become standard for noncancer risk analyses. Benchmark dose estimation, being reliant on uncertainty factors to derive a "safe dose," may not be the most appropriate method in the context of the DBP mixtures risk exercise. As an alternative, a modified form of dose-response assessment followed by extrapolation to humans was suggested. Suppose that a dose-response model is still fit to available animal bioassay data, but instead of estimating an ED_{10} or less, one estimates an ED_{50}. The proposal is that the ED_{50} estimated in that manner be assumed equal to a human ED_{50} (when scaled appropriately to account for body weight and/or other relevant species differences). Then, probability of response at other dose levels could be determined by assuming some distribution and a variance for response probability around that ED_{50}.

Both the estimates of risk associated with a given human dose and the uncertainty in that estimate would need to be available to inform the two-stage Monte Carlo procedure proposed by U.S. EPA (1999). A careful and deliberate examination of the data used to estimate human variability (and the uncertainties associated with it) must be undertaken, because the use of the "surrogate" variability data (i.e., data that considers variations in human pharmacokinetic and pharmacodynamic parameters that may have more or less relevance to the chemical responses of interest) is the epitome

of inferential uncertainty itself. Moreover, the other issues discussed in connection with cancer slope factors (multiple studies, negative results, different endpoints) are pertinent considerations here. Clearly, a much more elaborate development of a noncancer risk assessment method appropriate for DBP mixtures is required and will entail considerable extra effort.

Even though DBP concentration and exposure parameters may be considered to be better characterized as variable rather than uncertain, it is worth remembering that populations are defined temporally as well as spatially. Some care must be taken in interpreting and using the tap water intake data to derive distributions characterizing variability and/or uncertainty.

One of the biggest sources of uncertainty for the entire DBP mixtures risk assessment is the treatment of portions of that mixture that are unknown to one degree or another. In addition to the health endpoint of concern, other uncertainties associated with the unidentified relate to the estimates of their concentrations and “potencies”. It might be important to look at trends in toxicity across layers; molecular weights and polarity data might also be attainable and might be useful surrogates for more detailed information, especially if the known toxicity data could be related (even grossly) to such measures. Information relating total TOX to specific by-products may help to quantify magnitudes (and provide bounding estimates at the very least).

The group recommended summary tables enumerating all of the sources of uncertainty (or forms of ignorance) associated with the DBP mixtures risk assessment should be provided. Those tables might provide at least rough estimates of the magnitudes of the associated uncertainties; estimates of the level of effort (in time and

money) required to reduce those uncertainties would also provide valuable information to decision-makers and other users of the risk assessment. If presented well, such a summary will go a long way toward making a DBP mixtures risk assessment acceptable.

4.8.7. Toxicology, Epidemiology and Expert Judgment. The breakout group agreed that there is a need to better characterize the uncertainties associated with the underlying epidemiologic literature. When attempting to quantify the human health risks, it should be recognized that insufficient epidemiologic data are available to establish a causal association between DBP and cancer or reproductive risks.

Numerous issues need to be addressed by both epidemiologists and toxicologists. These include: examining the sensitivities (range of) in humans and animals; explicitly considering humanly relevant exposures (levels, routes, cumulative, peak, etc.) and endpoints in the design of new toxicologic studies on DBP; quantitatively identifying the uncertainties in exposure-response analysis of the epidemiologic literature (only apply alternative models to the data, use the continuous data that exists); providing an explanation of the uncertainties involved; refraining from the use of a single value for risk; and increasing the understanding of problems associated with using a single aggregate number from a meta-analysis for regulatory decisions.

The breakout group recommended that an “expert” or “Blue Ribbon” panel be convened to identify the important issues regarding better characterization of the uncertainties associated with interpreting the epidemiologic literature and how best to quantify the human health risks of cancer and exposure to drinking water disinfectants

and by-products. Several of the questions that the Blue Ribbon panel might address were suggested by the breakout group. These include:

- Must a meta-analysis produce a single summary effect estimate for each cancer?
- Inclusive" versus "best evidence" approaches to meta-analysis and quantitative risk assessment using epidemiologic data.
- What can be done about publication bias?
- How can exchangeable results be extracted from the individual studies?
- What are the implications of evidence of overall heterogeneity?
- Confounding by water source and other factors.
- Control selection in case-control studies.
- Other characteristics such as the cohort versus the case-control design and year of publication.
- Interaction

The breakout group recommended careful selection of the individual panel members and inclusion of epidemiologists, toxicologists, and quantitative analysts who have had experience in complex problem solving. Moreover, the panel should consist of persons who have not been involved in the design and/or conduct of the existing studies, although these individuals would inform the panel in regard to the important subject matter information. The panel would objectively evaluate the current studies and analyses of their results, identify the uncertainties, and recommend ways to reduce these uncertainties. Oversight of projects, participation or guidance of the design of specific analyses, periodic progress evaluations, and feedback to the analysts the relevant issues would also be part of their charge. It is expected that the work of the

panel would be long term (1- 2 years) with quarterly meetings so as to effectively facilitate the implementation of their recommendations.

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Appendix I

Workshop Pre-meeting Report:
The Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems

NCEA-C-0584
April 1999

Workshop Pre-meeting Report:

The Risk Assessment of Mixtures of Disinfection By-products (DBPs) For Drinking Water Treatment Systems

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FOREWORD

The U.S. Environmental Protection Agency's (EPA) National Center for Environmental Assessment - Cincinnati Division (NCEA-Cin), lead by Dr. Terry Harvey, Director, has contracted with Sciences Application international Corporation (SAIC) to hold a workshop on April 26-28, 1999, in Cincinnati, Ohio to examine and further develop the current methodology being used for the risk assessment of mixtures of disinfection by-products (DBPs) for defined drinking water treatment systems and source water conditions. The goal of the workshop is to bring together a multi-disciplinary group of scientists who will work together to crate the range of possible approaches to solving this problem and then reach consensus on the most practical and scientifically sound directions of the EPA should take to improve the risk assessment. This preliminary report was prepared by Dr. Joshua Cohen of Gradient Corporation under subcontract to TN& Associates. it will serve as background information relative to the current state of the science this mixtures risk assessment.

NCEA-Cin's Comparative Risk Project Team (CRPT) has developed a Comparative Risk Framework Methodology (CRFM) for comparing DBP risks with microbial risk from drinking water exposure for different drinking water treatment systems (U.S. EPA, 1998). Members of the CRPT include Brenda Boutin, Mary Beth Brown, John Lipscomb, Patricia Murphy, Glenn Rice and Linda Teuschler. CRPT collaborated with members of the U.S. EPA's National Risk Management Research Laboratory, Water Supply and Water Resources Division and the U.S. Agency for Toxic Substances and Disease Registry. In the course of estimating DBP mixtures risk for applications of the CRFM, NCEA-Cin has been exploring a number of novel approaches for estimating cancer, developmental and reproductive risks to human health from drinking water exposures. These include such risk characterization methods as response addition, proportional-response addition, the development of distributions for input parameters and Monte Carlo simulation techniques. The goal of these different estimation techniques is to estimate human health risks that result from exposures to a range of DBPs that are produced through chemical disinfection of drinking waters.

It is anticipated that a final EPA workshop report will be produced and finalized in the year 2000. The final report will detail the current methods in use, discuss the state of the exposure, toxicity and epidemiologic data, present available methods for mixtures risk characterization that may be applicable, explore alternative methodologies and make recommendations for future applications and future methodology or data development. Discussions will include the assumptions, statistical theory, and biological rationale for the recommended risk characterization methods. The final workshop report will be used as background for research planning, and as information for improving the current DBP mixtures risk assessments.

1. INTRODUCTION

For the last 100 years, drinking water utilities in the United States have played a major role in protecting public health through the reduction of waterborne disease. The reductions in waterborne disease outbreaks were brought about through the use of sand filtration, disinfection, watershed management and the application of drinking water standards.

The United States has nearly 60,000 community water supply systems serving over 230 million people. Figure 1-1 categorizes water systems by type (community or non-community) and source of water (ground water or surface water). Nearly all of the utilities that use surface water have implemented some sort of treatment regime, and many have implemented what is referred to as “conventional treatment,” which is the focus of this report.

Conventional systems use chemical disinfectants, the most common of which is chlorine. Other types of disinfectants include chloramines, chlorine dioxide, and ozone. The majority of the U.S. population is exposed to these chemicals and their “disinfectant byproducts” (DBPs) in their drinking water. The most common DBPs for which concentration data are available include the trihalomethanes (THMs), haloacetic acids (HAAs), haloacetonitriles, haloketones, aldehydes, bromate, chloral hydrate, and chloropicrin, among others (Jacangelo et al., 1989; Krasner et al., 1989; Lykins et al., 1994; Miltner et al., 1990). Figure 1-2 illustrates the chemical structures of some representative DBPs. More recently, Richardson (1998) identified approximately 250 DBPs from various disinfection scenarios. Of the identified DBPs, less than 20 have been subjected to toxicity studies of sufficient quality for use in risk assessment. It is estimated that unknown DBPs may represent up to 60% of DBP total concentrations.

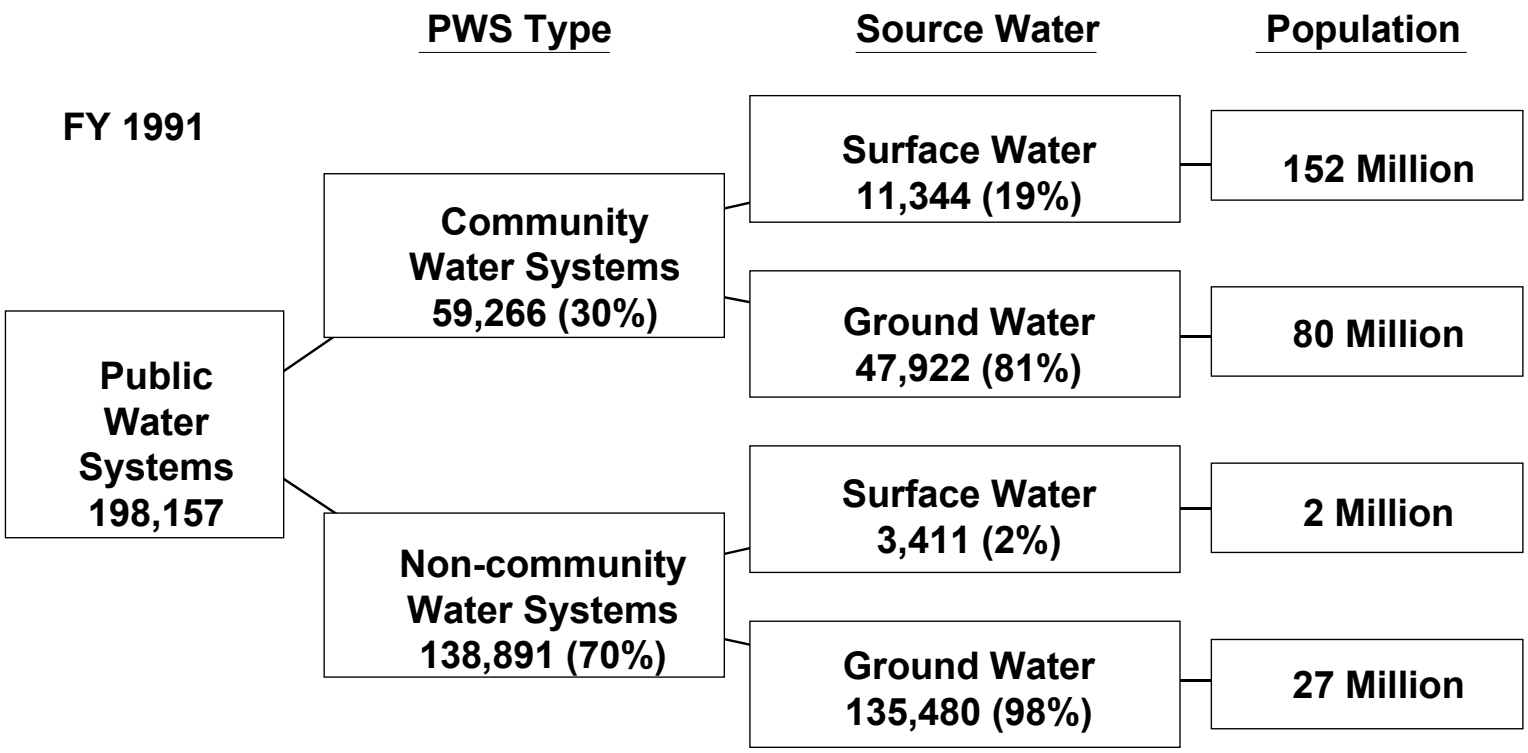
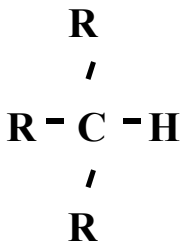
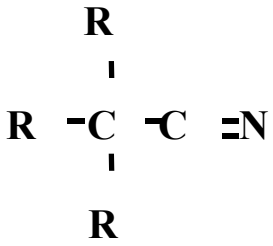


FIGURE 1-1

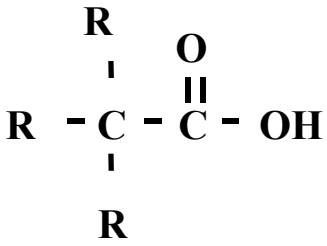
Distribution of Public Water Systems by System Type, Source Water and Population Served



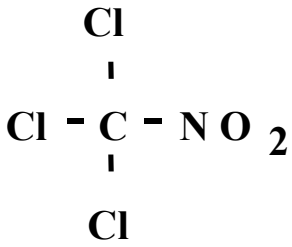
Trihalomethane



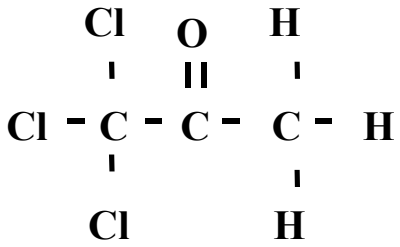
Haloacetonitrile



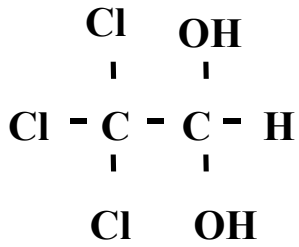
Haloacetic Acid



Chloropicrin



1,1,1-Trichloropropanone



Chloral Hydrate

FIGURE 1-2

Representative Structures of DBPs

Data from both epidemiologic and toxicologic studies indicate that human health effects from DBP exposure are of concern, but neither discipline has been able to confirm this with confidence. DBPs typically occur at low levels in drinking water at which general toxic effects from exposure to the environmental mixture have not been found in animal studies (Bull et al., 1982; Kavlock et al., 1979). In contrast, epidemiologic studies of chlorinated drinking water exposures in humans suggest weak associations with bladder, rectal and colon cancer (Cantor et al., 1985; McGeehin et al., 1993; King and Marrett, 1996; Cantor et al., 1997; Freedman et al. 1997) and limited evidence of reproductive and developmental effects (Bove et al., 1995; Kramer et al., 1992; Swan et al., 1998; Waller et al., 1998). Although there are few studies available on defined mixtures of DBPs, evidence exists of dose-additivity for liver effects in mice exposed to mixtures of trihalomethanes (THMs) (Gennings et al., 1997; U.S. EPA, 1998d) and of synergistic activity by mixtures of dichloroacetic acid (DCA) and trichloroacetic acid (TCA) for promotion of cancer (Pereira et al., 1997). The majority of the available DBP toxicity data consists of single chemical *in vivo* or *in vitro* studies. There is evidence in single chemical animal studies at high DBP dose levels of carcinogenicity, reproductive effects, developmental effects, and other toxic effects, particularly in the kidney and liver (Bull and Kopfler, 1991; NTP, 1985; 1986; 1989; Smith et al., 1989). Finally, there is evidence of mutagenicity from exposure to extracts of finished drinking water in *in vitro* studies (Kool et al., 1981; Loper et al., 1978; Nestmann et al., 1982).

This report discusses a risk assessment for DBPs in drinking water based on work conducted as part of NCEA Cincinnati's Comparative Risk Framework Methodology (CRFM) project (U.S. EPA, 1998). The risk assessment evaluates two

alternative drinking water disinfection strategies, illustrated in Figure 1-3. The top branch in Figure 1-3 illustrates the so-called “filter-chlorine” treatment train. Here, treatment consists of:

- Coagulation / Rapid Mix – Enhances the precipitation of contaminants out of the water
- Flocculation – Further promotes precipitation of contaminants;
- Sedimentation / Clarification – Further filters particulate matter out of the drinking water;
- Filtration – Removes material from drinking water by passing it through a porous medium;
- Disinfection – Adds chemicals to the water to kill or inactivate common microorganisms.

The bottom branch in Figure 1-3 illustrates the “ozone-filter-chlorine” treatment train. This treatment train augments the “filter-chlorine” treatment train (top branch) by inserting a pre-ozonation step prior to coagulation / rapid mix. Ozone is a strong disinfectant, and can also oxidize some DBP precursors, hence depressing their formation.

The remainder of this document consists of 4 sections. Section 2 provides an overview of the methodology used for this risk assessment. This methodology uses Monte Carlo simulation to quantify the impact of uncertainty and variability (population heterogeneity) on estimates of risk. Because Monte Carlo analysis is best suited to address sources of uncertainty that can be characterized in terms of probability distributions (so-called “parametric” uncertainty), the methodology also describes how other sources of uncertainty are addressed outside of the simulation, including so-called “model uncertainty” and “dataset uncertainty,” discussed below.

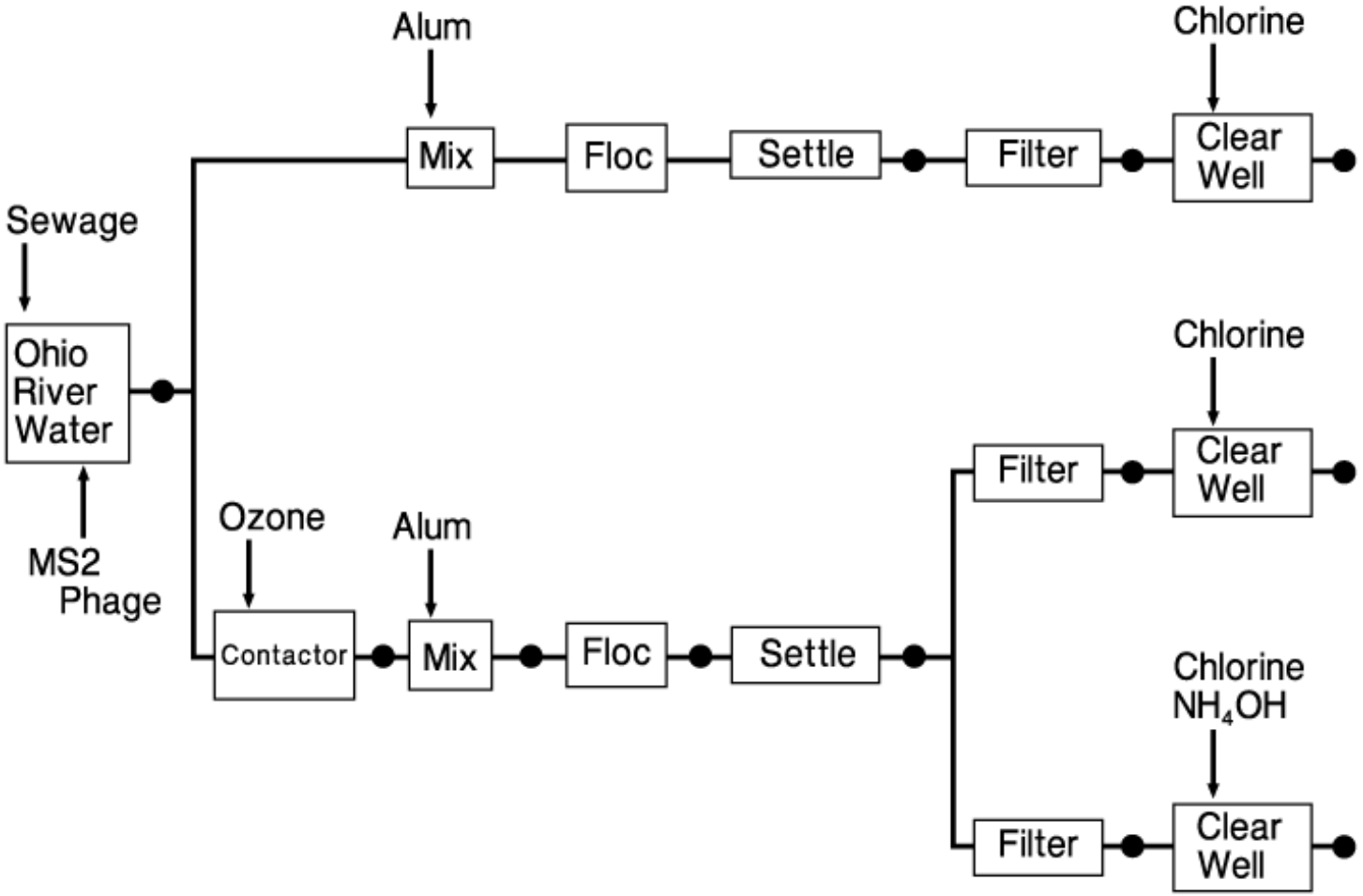


FIGURE 1-3

EPA Pilot Plant Configuration

Section 3 quantifies DBP exposure, presenting estimates of both DBP concentrations in drinking water, and drinking water consumption rate estimates.

Section 4 discusses DBP toxicity (carcinogenic, developmental, and reproductive effects). Information discussed in Section 4 includes the use of animal study data, epidemiological results, and toxicity estimates inferred using Quantitative Structural Activity Relationship (QSAR) modeling.

Finally, Section 5 of this report describes the results of this risk assessment.

Note that Sections 3.1, 3.2, and 4 begin with a summary of the parameter estimates used in this risk assessment, along with their "parametric" uncertainty. These summaries also identify potential sources of "model uncertainty" and "dataset uncertainty." Model uncertainty is introduced when there is more than one plausible mathematical formulation describing some quantity. Dataset uncertainty is introduced when there is more than one data set that can be used to quantify a parameter, and the datasets cannot be directly combined. The results section of this risk assessment investigates the potential implications of the sources of model uncertainty and dataset uncertainty identified in Sections 3 and 4, specifying which of these sources of uncertainty must be resolved in order to quantify risks with an acceptable level of confidence.

2. METHODOLOGY

This section first presents the basic risk equation used in this risk assessment (Section 2.1). Section 2.2 then discusses the distinction between uncertainty and variability and how the Monte Carlo simulation is used to model the impact of these stochastic characteristics on risk. Section 2.3 describes how the results of the Monte Carlo analysis are used to identify which sources of parametric uncertainty (uncertainty that can be characterized as a probability distribution for a parameter) have the greatest influence on the results. Finally, Section 2.4 describes how this risk assessment addresses sources of uncertainty that cannot be readily characterized parametrically, including model uncertainty and data set uncertainty.

2.1. THE RISK EQUATION

This risk assessment estimates the risk associated with exposure to drinking water treated using either of two drinking water disinfection technologies (filter-chlorine referred to as "filter-Cl" and ozone-filter-chlorine, referred to as "O_3-filter-Cl"), as discussed in Section 1. As explained in Section 4, the risk posed by each DBP is assumed to be a linear function of intake. Therefore, the risk posed by each DBP equals the product of three quantities: 1) Tap water intake (Y L/day), 2) the DBP's concentration in tap water (C μg/L), and 3) the incremental risk per mg/kg-day DBP intake (S per mg/kg-day). Section 4 explains the underlying mixtures risk assessment methodology, which employs the response addition approach. Based on response addition, the incremental risk to an individual due to drinking water exposure is the sum of the risks over all the DBPs multiplied by a conversion constant of 1 mg / 1,000 μg. This risk is therefore,

$$risk = Y \times \frac{1}{1000}\left[\sum_{i \in AllDBPs} C_i S_i\right] \quad . \qquad \text{Eq 2-1}$$

As explained in Section 4, values for C_i and S_i are known for only some of the DBPs. For health effect h, the summation over the unknown DBPs is estimated in terms of the values for the known DBPs as

$$\sum_{i \in U} C_i S_i = \frac{\alpha_h C_u^{OX}}{\sum_{i \in K \bigcap H} \rho_i C_i} \sum_{i \in K} C_i S_i . \qquad \text{Eq 2-2}$$

where:

Y = Daily water consumption (L/kg-day) (Section 3.2);

C_u^{OX} = Total concentration of organic halogen (OX) portion of the unidentified DBPs measured in µg Cl/L (Section 3.1);

C_i = The concentration of identified DBP_i (µg/L) (Section 3.1);

ρ_i = The ratio of the DBP i's organic halogen concentration (in µg Cl/L) to DBP i's total concentration;

α_h = The fraction of the unidentified DBPs, weighted by organic halogen (OX) concentration measured as µg Cl/L, associated with inducing health effect h (unitless) (Section 4.3);

S_i = Incremental probability of the outcome per mg/kg-day intake of the ith DBP $(mg/kg\text{-}day)^{-1}$ (Section 4.3);

1/1000 = Conversion factor (mg/µg);

K = The set of known DBPs (i.e., those listed in Table 3.1-1);

H = The set of identified DBPs causing health effect h at environmentally relevant doses.

Substituting the right hand side of Equation 2-2 into Equation 2-1 yields

$$risk_h = Y \times \left[\left(1 + \frac{\alpha_h C_u^{Ox}}{\sum_{i \in K \cap H} \rho_i C_i} \right) \sum_{i \in K} C_i S_i \right] \times \frac{1}{1000}. \qquad \text{Eq 2-3}$$

In order to compute the average risk over all members of the population due to a single year of drinking water exposure, the risk estimated in Equation 2-3 is averaged over all age groups (j), weighted by the fraction of the population in each age group (P_j). Hence,

$$risk_{pop} = \sum_{j \in All\ Age\ Groups} P_j \times\ Y \times \frac{1}{1000} \left[\left(1 + \frac{\alpha_h C_U^{OX}}{\sum_{i \in K \cap H} \rho_i C_i} \right) \times \sum_{i \in K} C_i S_i \right]. \qquad \text{Eq 2-4}$$

2.2. UNCERTAINTY AND VARIABILITY

Many of the parameters in Equation 2-4 can have multiple possible values for any of three reasons. First, a parameter's true value may be uncertain but may not vary across different members of the population. In this case, the parameter has one true value for all members of the population but that value is not known. In the context of this risk assessment, the following parameters are treated as uncertain but not variable:

- DBP concentrations (C_i);
- The total OX concentration for the unknown DBPs, designated C_U^{OX}; and
- The incremental risk per mg/kg-day DBP consumed (S_i).

It may be that some of these quantities (such as the S_i parameters) do vary from member to member of the population because of, for example, differences in sensitivity. However, since these differences cannot be observed in any individual, they are omitted from the analysis.

Second, a parameter's value may vary from member to member of the population but be treated as known with certainty. In this risk assessment, drinking water intake rates are put into this category. Note that while it is of course true that these values are not perfectly known, they are thought to be known well enough that quantitative characterization of their uncertainty would not appreciably alter the results of this analysis.

Finally, a quantity may both be uncertain and vary from member to member of the population. For this risk assessment, there are no quantities that fall into this category.

It is important to segregate the influence of uncertainty and variability because they give rise to two different sets of questions. Uncertainty raises the question of how precise the resulting risk estimates are, whereas variability raises the question of whether there are (identifiable) members of the population at a particularly elevated risk.

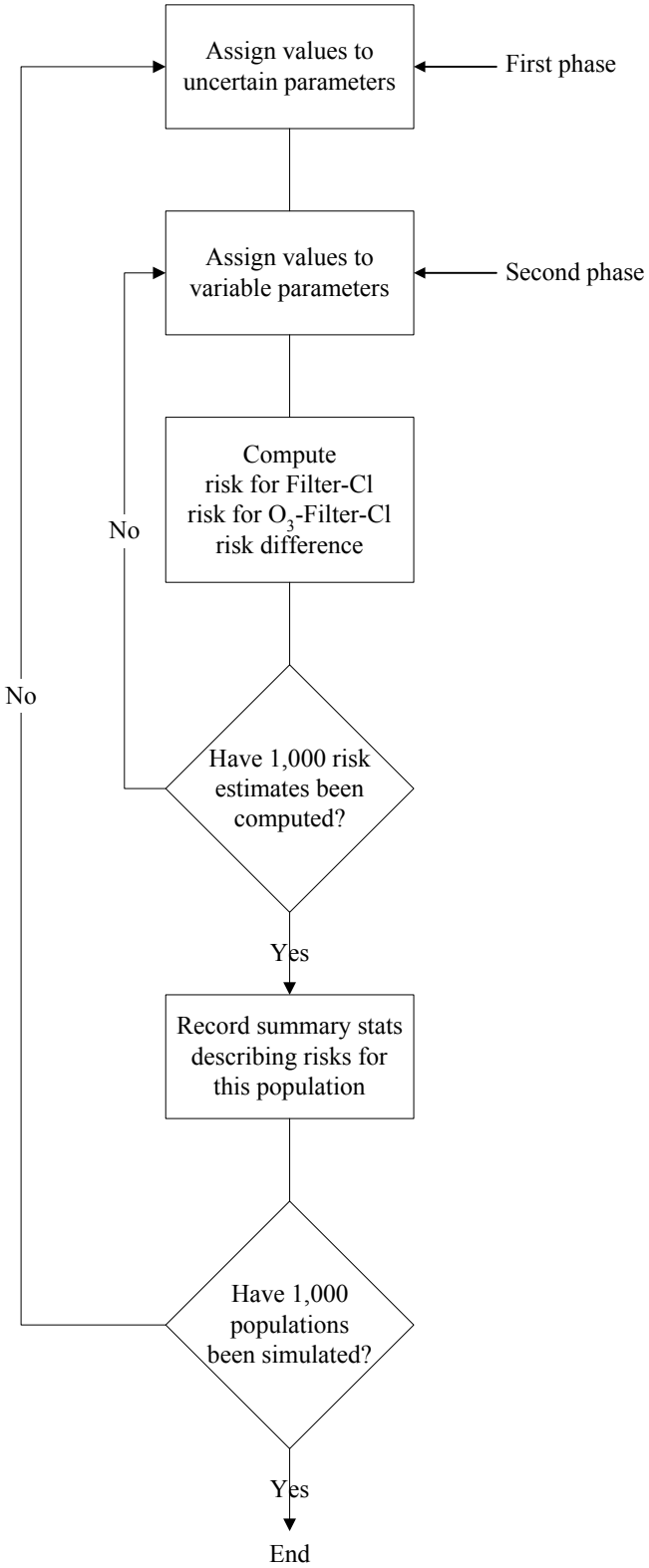
This risk assessment uses a technique known as "two-dimensional" or "two-phase" Monte Carlo analysis to separately characterize the influence of uncertainty and population variability on estimated risk. A "one-dimensional" or "one-phase" Monte Carlo works by repeatedly drawing randomly selected values for each stochastic parameter (a parameter that either varies from person to person or is uncertain). For each set of values drawn, the simulation computes a risk, repeating this process a large number of times (typically 1,000 to 10,000 times). The resulting set of risk estimates

can be plotted as a histogram that approximates the range and relative likelihood of the plausible risks that may exist in the modeled population. This approximation to the probability distribution of risks generated by a one-phase Monte Carlo simulation has embedded within it both variability and uncertainty. Because it reflects both uncertainty and variability, it is broader than the true distribution of risks. Moreover, it cannot be thought of as representing the risk that any one individual would incur.

The two-phase simulation addresses this problem by conducting a large number of separate one-phase simulations. For each one-phase simulation, a fixed set of randomly selected values are assigned to each of the uncertain parameters. However, values for variable parameters are permitted to vary within each one-phase simulation. Hence each one-phase simulation, which produces a large number of risk estimates (in the case of this risk assessment, 1,000 such estimates), represents the set of risks incurred by members of a population, given the assumptions embedded in the fixed values assigned to each uncertain parameter for the duration of that simulation. For this risk assessment, a total of 1,000 one-phase simulations were executed. In practice, the two-dimensional simulation is executed as illustrated in Figure 2-1.

The results of the analysis can be used to quantify the distribution of plausible risks for representative members of the population. For example, the range of plausible risks for the “median individual” (i.e., the individual whose risk is greater than the risk for one-half of the population, and less than the risk for the other half) is estimated by collecting the median risk values generated by each of the 1,000 executed one-phase simulations.

Figure 2-1
Execution of a Two-Phase Simulation



It should also be noted that, as suggested in Figure 2-1, this methodology can be used to estimate the difference in risks between the two drinking water treatment technologies. Each iteration of each one-phase simulation consists of computing: 1) the risk associated with drinking water treated using filter-Cl; 2) the risk associated with drinking water treated using O_3-filter-Cl; and 3) the difference between these two risks.

2.3. QUANTIFYING THE INFLUENCE OF PARAMETRIC UNCERTAINTY

The results from a two-phase Monte Carlo can also be used to identify which uncertain assumptions have the greatest influence on the resulting risk estimate. To do so, the analysis records at the end of each one-phase simulation summary statistics describing the population risk distribution (i.e., key percentiles of the distribution), and the value assigned to each uncertain parameter. Table 2-1 illustrates the results that a two-phase simulation might generate:

TABLE 2-1

Illustrative Results of a Two-Phase Simulation

Simulation	Uncertain Parameters				Risk Estimates	
	P1	P2	P3	P4	Median Person	95th Percentile Person
1	V_{11}	V_{12}	V_{13}	V_{14}	$R_{1.50}$	$R_{1.95}$
2	V_{21}	V_{22}	V_{23}	V_{24}	$R_{2.50}$	$R_{2.95}$
...						
n	V_{n1}	V_{n2}	V_{n3}	V_{n4}	$R_{n.50}$	$R_{n.95}$

Each row in Table 2-1 represents a single one-phase simulation. The quantity V_{ij} is the value assigned to the jth parameter for simulation i. The quantity R_{ij} is the risk for the jth percentile of the population estimated for simulation i. The influence of the parameters on, for example, the median risk, is estimated by regressing the column of values, $R_{1,50}$, ... $R_{n,50}$, against the matrix of parameter values, V_{ij}. This regression model is expressed as,

$$R_{i,50} = a + b_1 V_{i1} + b_2 V_{i2} + b_3 V_{i3} + b_4 V_{i4} + \varepsilon_i \,,$$

Eq 2-5

where ε is a normally distributed random variable. Standard regression techniques can be used to quantify the fraction of (linear) variation in the median risk attributable to each parameter. This procedure is similar to that described by Cohen et al. (1996)[1].

Note that this procedure is a heuristic that quantifies the degree to which each parameter's uncertainty explains the risk's *linear* variation. Since not all the variation is linear, the total explained variation is less than 100%. Moreover, it is not the purpose of this analysis to fully characterize variation in the risk estimate. However, it is likely that a fully explanatory model would be very complex, making it difficult to intuitively grasp the influence of each parameter.

2.4. MODEL UNCERTAINTY AND DATA SET UNCERTAINTY

As stated in Section 1, model uncertainty is introduced when there is more than one plausible mathematical formulation describing some quantity. For example, the

[1] Technically, each parameter's explanatory power is quantified as the variance explained after all other parameters have been added to the model in Equation 2-5. This calculation is insensitive to the order in which the model is specified since the parameter being assessed is always entered after the others. It should be noted, however, that because this approach uses the fraction of variance explained after all other variables are entered into the model, the estimates do not reflect any shared variance. However, this issue will not introduce any complications unless uncertain parameters are correlated, a phenomenon not considered in this risk assessment. For this risk assessment, the incremental variance was computed using SAS (1990) proc GLM. Specifically, the fraction of variance explained is computed as the Type III sums of squares divided by the model sums of squares.

dose-response functions for DBP developmental and reproductive toxicity can be modeled as threshold functions or as non-threshold functions. Dataset uncertainty is introduced when there is more than one data set that can be used to quantify a parameter, and the datasets cannot be directly combined. For example, DBP carcinogenicity can be estimated using either animal bioassay data or epidemiological data.

In some cases, this type of uncertainty cannot be readily characterized parametrically – i.e., as a probability distribution for some parameter. It is therefore not amenable to the methodology described in Section 2.3. Often, these sources of uncertainty cannot be parameterized because there is no available information that can be used to assign probabilities to the relative plausibility of the alternatives. To develop such estimates, it may be necessary to use techniques such as expert judgment elicitation. Evans et al. (1994) describe the use of such techniques to characterize the toxicity of chloroform. Because such techniques are time-consuming and expensive, it is important to focus attention on only those sources of model uncertainty and data set uncertainty that have an important influence on the results of the analysis.

This risk assessment illustrates an iterative approach for the identification of important sources of model and data set uncertainty. The risk assessment starts with what is referred to as a "base analysis." That analysis reflects only that uncertainty that can be quantitatively characterized as a parameter probability distribution using readily available information, i.e., it incorporates only "parametric uncertainty." However, in its development of the assumptions for the base analysis, the risk assessment identifies other sources of uncertainty that cannot be explicitly incorporated into the base analysis. After the results of the base analysis are generated, each source of model

uncertainty and data set uncertainty flagged earlier are revisited, and their potential influence on the results is estimated. Those sources of uncertainty whose potential influence is great are candidates for further investigation. If their influence is great enough, it may be warranted to conclude that until further investigation is conducted, the results of the risk assessment lack adequate precision. Of course, what level of precision is adequate depends on what the results will be used for.

If further information is collected to address the most influential sources of model uncertainty, it may become possible to explicitly incorporate into the risk assessment sources of uncertainty that previously could not be characterized parametrically. The process can then be repeated to determine if any additional sources of uncertainty must be investigated before the results of the risk assessment warrant an acceptable level of confidence.

3. EXPOSURE TO DBPs

Section 3.1 quantifies the concentration of DBPs in tap water, while Section 3.2 quantifies tap water intake.

3.1. DBP CONCENTRATIONS IN DRINKING WATER

With the exception of bromate, this risk assessment uses the results reported by Miltner et al. (1990) to quantify DBP concentrations. Section 3.1.1 discusses the concentration of identified DBPs reported by Miltner et al., and Section 3.1.2 discusses the use of the Miltner et al. results to quantify those DBPs not individually identified in terms of their collective total organic halogen (OX) concentration measured in terms of μg Cl/L. Because the toxicity calculations in Section 4 require a comparison of the known and unknown DBP concentrations, it was also necessary to quantify the OX concentration value for each identified DBP (in terms of μg Cl/L). Section 3.1.3 discusses results from Miltner et al. (1992) used to quantify bromate concentrations. Table 3-1 summarizes the assumed concentration distributions used here for "known" DBPs identified by Miltner et al. (1990, 1992). Note that in all cases, it is assumed that the distributions describing the concentration of each DBP is normal.

There are no appreciable sources of uncertainty that cannot be quantitatively parameterized. In the case of the identified DBPs, there is no reason to believe that the concentration measurements are substantially in error, although they have been compared only to measurements from a pilot treatment plant and simulated distribution system. For the unidentified DBPs, there is no reason to believe that the calculated OX concentration is substantially in error. However, as with the identified DBPs, these measurements are based on data from a pilot treatment plant and simulated distribution system.

TABLE 3-1

DBP Concentrations Used in the Risk Assessment[a,b]

Chemical	Filter-Cl		O_3-Filter-Cl		Ratio of the OX Concentration Value to the Total Concentration
	Mean (µg/L)	Standard Deviation (µg/L)	Mean (µg/L)	Standard Deviation (µg/L)	
$CHCl_3$	55.50	2.01	39.55	2.95	0.891
BDCM	24.40	1.52	21.10	0.18	0.649
CDBM	10.20	0.85	13.00	0.49	0.511
$CHBr_3$	0.35	0.30	1.50	0.18	0.421
CH	4.20	0.30	5.80	0.61	0.643
MCA	1.44	0.10	1.46	0.05	0.375
DCA	30.85	1.49	19.30	0.79	0.550
TCA	20.10	0.97	13.00	0.73	0.651
MBA	0.29	0.02	0.28	0.04	0.255
DBA	1.50	0.12	1.98	0.13	0.326
BCA	8.50	0.06	6.70	0.12	0.409
DCAN	3.50	0.43	2.60	0.24	0.645
TCAN	0.20	0.06	0.05	0.00	0.737
BCAN	1.90	0.24	1.65	0.12	0.459
DBAN	0.15	0.07	0.55	0.14	0.357
Bromate	0.00	0.00	4.00	0.36	0[c]

[a] The concentration of each DBP is assumed to be normal.

[b] The standard deviation was calculated using mean and 95th percentile values developed below, along with the assumption of normality.

[c] Bromate is not an organic halogen and therefore this fraction is zero.

3.1.1. Identified DBPs (Excluding Bromate). EPA has performed a series of studies in its pilot water treatment plant in Cincinnati, Ohio to quantify the impact of chemical disinfectants on DBP concentrations. Miltner et al. (1990) describe the plant and its operation descriptions in detail (see Appendix A). For this study, raw Ohio River water was trucked to the U.S. EPA and treated at 1.7 gpm. For the O_3-filter-Cl treatment train, ozone was applied so that the transferred ozone/TOC (total organic carbon) ratio was approximately 80%. Chlorine was applied in the clear well after filtration to yield a free residual near 0.2 mg/L in samples taken from the clear wells and stored for 3 days to simulate distribution. Chlorine doses were in the range of 2.8 to 3.0 mg/L, resulting in free chlorine residuals in clear well effluents near 1.2 mg/L. Detention time in the clear wells was approximately 9.5 hours.

The mean and 95th percentile values listed in Table 3-2 were developed from data provided by Miltner et al. (1990). Note that these statistics differ slightly from the distributions published by Miltner et al. (1990) because this risk assessment recalculated the means and confidence limits assuming a normal distribution and substituting half the detection limit for non-detects in the Miltner et al. data rather than replacing non-detects with zero, as in the original publication.

3.1.2. Unidentified TOX. The OX concentration for the unidentified DBPs (C_U^{OX}) was calculated as

Eq 3-1

$$C_u^{OX} = C_T^{OX} - \sum_{i \in K} \rho_i C_i \ ,$$

TABLE 3-2

Mean and 95th Percentile Concentrations for Identified DBPs

Chemical	Filter-Cl			O_3-Filter-Cl		
	Mean (µg/L)	5th Percentile (µg/L)	95th Percentile (µg/L)	Mean (µg/L)	5th Percentile (µg/L)	95th Percentile (µg/L)
$CHCl_3$	55.50	52.20	58.80	39.55	34.70	44.40
BDCM	24.40	21.90	26.90	21.10	20.90	21.40
CDBM	10.20	8.80	11.60	13.00	12.20	13.80
$CHBr_3$	0.35	0.00	0.84	1.50	1.10	1.80
CH	4.20	3.60	4.70	5.80	4.90	6.80
MCA	1.44	1.30	1.60	1.46	1.37	1.54
DCA	30.85	28.40	33.30	19.30	18.00	20.60
TCA	20.10	18.60	21.70	10.00	8.90	11.20
MBA	0.29	0.24	0.33	0.28	0.22	0.34
DBA	1.50	1.30	1.70	1.98	1.74	2.20
BCA	8.50	8.30	8.60	6.70	6.50	6.90
DCAN	3.50	2.70	4.20	2.60	2.20	3.00
TCAN	0.20	0.05	0.30	0.05	0.05	0.05
BCAN	1.90	1.50	2.30	1.65	1.44	1.85
DBAN	0.15	0.03	0.27	0.55	0.31	0.78
Bromate[a]	0.00	0.00	0.00	4.00	3.40	4.60

[a] Bromate was not measured in Miltner et al. (1990). Concentrations were estimated using data from new studies (see Section 3.1.3.).

where:

K = Set of identified DBPs;

C_i = Concentration of DBP_i (µg/L)

ρ_i = Fraction of DBP_i concentration due to Cl; and

= The total TOX concentration in µg Cl/L, which is assumed to be normal with:

Mean = 258.8, SD = 39.2 µg Cl/L, for Filter-Cl;

Mean = 207.4, SD = 35.4 µg Cl/L, for O_3-Filter-Cl.

Section 3.1.1. quantifies the values for the C_i. Table 3-3 illustrates the calculation of the values for each parameter, ρ_i. Column 2 lists the total molecular weight for each DBP. Column 3 lists the number of organic halogens in each DBP molecule. Column 4 lists what the molecular weight of those halogens would be if the halogens were all organic chlorides. Finally, column 5 lists the ratio of column 4 to column 2. The product of a DBP's total concentration and this ratio is the OX concentration value. In theory, this value equals the concentration that would be reported if the Miltner et al. (1990) methodology for measuring total OX were applied to the individual DBP.

Finally, Miltner et al. quantified the total OX concentration for the two treatment trains addressed in this risk assessment. For the filter-Cl, the estimated total OX concentration was 258.8 µg/g, with a standard error of 35.4 µg/g. For the O_3-filter-Cl treatment train, the estimated total OX concentration was 207.4 µg/g, with a standard error of 35.4 µg/g.

3.1.3. Bromate. Under water treatment plant conditions, chlorine will not react with bromide to form bromate. Rather, chlorine reacts with bromide to form bromine, which

TABLE 3-3

Calculation of the Ratio of the OX Weight for Each Identified DBP to its Total Weight

Compound	Molecular Weight	Number of Halogens	Cl Equivalent Weight	Ratio of the OX Weight (Cl) to Total Molecular Weight
BDCM	163.8	3	106.35	0.649
CDBM	208.25	3	106.35	0.511
$CHBr_3$	252.7	3	106.35	0.421
DCA	128.9	2	70.9	0.550
TCA	163.35	3	106.35	0.651
BCA	173.35	2	70.9	0.409
MCA	94.45	1	35.45	0.375
DBA	217.8	2	70.9	0.326
MBA	138.9	1	35.45	0.255
DCAN	109.9	2	70.9	0.645
BCAN	154.35	2	70.9	0.459
DBAN	198.8	2	70.9	0.357
TCAN	144.35	3	106.35	0.737
CH	165.35	3	106.35	0.643

reacts with organic compounds to form brominated DBPs. Hence, in the case of the filter-Cl treatment train, the assumed bromate concentration is zero.

Data from Miltner et al. (1992) were used to estimate bromate levels generated by the O_3-filter-Cl treatment train. Transfer efficiencies, gas/liquid ratios, liquid depths, ozone-to-TOC or DOC ratios, pHs, and temperatures were similar to the corresponding conditions reported by Miltner et al. (1990). Miltner et al. (1992) reported an ambient bromide concentration of 37 µg/L. At ozone/TOC ratios below 1 mg/mg, there was no measurable bromate (when the bromate detection level was 7 µg/L). In Shukairy et al. (1994), the ambient bromide concentration was 50.7 µg/L. At an ozone/TOC ratio near 0.8 mg/mg and a dissolved ozone residual near 0.6 mg/L, the bromate concentration was near 4 µg/L. Thus, the estimate for bromate formation in this study would be near 4 µg/L, a level that is below the proposed MCL of 10 µg/L. Replication data described in EPA Method 300.1 for bromate suggests that the expected deviation at 4 µg/L would be ± 0.6 µg/L. Table 3-4 describes the basis for the estimate.

3.2. TAP WATER INTAKE

This risk assessment assumes that risks associated with exposure to tap water depend on the quantity of tap water ingested daily. In the case of DBP-induced risks (cancer, reproductive toxicity, and developmental toxicity), it is assumed that risk is a function of total tap water consumption measured in L/kg-day (see Section 3.2.1.). For this risk assessment, tap water consumption has been quantified by fitting lognormal distributions to age-specific intake data described in U.S. EPA's Exposure Factors Handbook (U.S. EPA, 1997). Table 3-5 summarizes the lognormal distributions used here.

TABLE 3-4

Estimated Bromate Formation in Ohio River Water by Ozonation[a]

	Study		
	Miltner et al., 1990	Miltner et al., 1992	Shukairy et al., 1994
Ozone/TOC, mg/mg	0.8	<1	0.81
pH	7.4-8.1	7.8-8.1	7.4-7.65
Temperature, °C	26-28	23-24	23-24
Residual ozone, mg/L	0.47	<0.47	0.6
Bromide, mg/L	37-50.7[b]	37	50.7
Bromate, mg/L	4 ± 0.6[c,d]	<7	4

[a] All studies utilize same contractor, similar conditions

[b] Assumed

[c] Estimated

[d] Deviation based on replication data presented in EPA Method 300.1

TABLE 3-5

Tap Water Consumption Rate Lognormal Distributions (mL/kg-day)

Age Group	Lognormal Distribution (mL/kg-day)	
	GM	GSD
0 to 4	34.30	2.05
5 to 9	25.95	1.84
10 to 14	17.52	1.87
15 to 19	13.18	1.91
20 to 24	15.25	1.83
25 to 29	15.25	1.83
30 to 34	15.25	1.83
35 to 39	15.25	1.83
40 to 44	15.25	1.83
45 to 49	19.29	1.64
50 to 54	19.29	1.64
55 to 59	19.29	1.64
60 to 64	19.29	1.64
65 to 69	19.63	1.59
70 to 74	19.63	1.59
75 to 79	19.38	1.57
80 to 84	19.38	1.57
85 to 89	19.38	1.57

Section 3.2.1. reviews the tap water consumption data used to derive these estimates. Section 3.2.2. discusses potential differences in consumption among certain subpopulations.

Sources of uncertainty that cannot be quantitatively parameterized include the following (Section 3.2.3.):

- The assumption that ingestion dominates all other tap water intake pathways. Other pathways include inhalation and dermal absorption (e.g., while bathing).
- The assumption that total tap water ingestion is the relevant measure of intake (rather than, for example, unheated tap water intake).

Setting these issues aside, and assuming that ingestion is the only important intake pathway, there do not appear to be any other notable sources of model uncertainty or dataset uncertainty associated with the estimation of tap water intake rates. It must be noted that the data on which these estimates are based was collected more than a decade ago. Since that time, it is believed that some tap water consumption has been replaced by the consumption of bottled water. Nonetheless, it is unlikely that this shift has substantially altered total tap water consumption.

3.2.1. Tap Water Consumption Data. Table 3-6 in U.S. EPA's Exposure Factors Handbook (U.S. EPA, 1997) quantifies total tap water consumption in mL/kg-day for individuals of all ages. Table 3-6 reproduces these rates for the 5th through 95th percentiles of the population.

In order to standardize these data for use in the risk assessment, age-weighted averages of these values have been computed to approximate consumption for age groups defined in 5-year increments. The results appear in Table 3-7. The age-weighted average for each 5-year interval was computed by weighting the values in

TABLE 3-6

Tap Water Consumption in the General Population in mL/kg-day by Age

Age (Years)	Population Percentile						
	5	10	25	50	75	90	95
<0.5	0	0	14.8	37.8	66.1	128.3	155.6
05 to 0.9	0	0	15.3	32.2	48.1	69.4	102.9
1 to 3	11.8	17.8	27.2	41.4	60.4	82.1	101.6
4 to 6	10.3	14.9	21.9	33.3	48.7	69.3	81.1
7 to 10	7.4	10.3	16	24	35.5	47.3	55.2
11 to 14	4.9	7.5	11.9	18.1	26.2	35.7	41.9
15 to 19	3.9	5.7	9.6	14.8	21.5	29	35
20 to 44	4.9	7.1	11.2	16.8	23.7	32.2	38.4
45 to 64	8	10.3	14.7	20.2	27.2	35.5	42.1
65 to 74	8.7	10.9	15.1	20.2	27.2	35.2	40.6
>75	8.8	10.7	15	20.5	27.1	33.9	38.6

Source: Ershow and Cantor (1991) cited in U.S. EPA (1997)

TABLE 3-7

Tap Water Consumption in the General Population in mL/kg-day by 5-Year Age Groups[a]

Age (Years)	Population Percentile							
	5	10	25	50	75	90	95	Arithmetic Mean[b]
0 to 4	91.4	13.66	23.71	38.5	57.4	82.89	103.03	44.4
5 to 9	8.56	12.14	18.36	27.72	40.78	56.1	65.56	31.2
10 to 14	5.4	8.06	12.72	19.28	28.06	38.02	44.56	21.3
15 to 19	3.9	5.7	9.6	14.8	21.5	29	35	16.3
20 to 24	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
25 to 29	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
30 to 34	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
35 to 39	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
40 to 44	4.9	7.1	11.2	16.8	23.7	32.2	38.4	18.3
45 to 49	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
50 to 54	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
55 to 59	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
60 to 64	8	10.3	14.7	20.2	27.2	35.5	42.1	21.8
65 to 69	8.7	10.9	15.1	20.2	27.2	35.2	40.6	21.9
70 to 74	8.7	10.9	15.1	20.2	27.2	35.2	40.6	21.9
75 to 79	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4
80 to 84	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4
85+	8.8	10.7	15	20.5	27.1	33.9	38.6	21.4

[a] Source: Ershow and Cantor (1991) cited in U.S. EPA. 1997

[b] The arithmetic mean value for each age group was computed by fitting a lognormal to the percentile values listed and computing the arithmetic mean corresponding to that distribution's geometric mean and geometric standard deviation.

Table 3-6 by duration contributed to that 5-year interval. Consider, for example, the 5-year interval between ages 5 and 9 (the second row of Table 3-7). The 4th row of Table 3-6 (ages 4 to 6) contributes ages 5 and 6, or 40% of this duration, and the 5th row (ages 7 to 10) contributes ages 7, 8, and 9, or 60% of this duration.

While these values reflect some sampling uncertainty, it is likely that, given the nature of the survey on which it is based, the parametric uncertainty is not substantial.

3.2.2. Adjustments for Special Subgroups. No adjustments are made for subgroups.

3.2.2.1. The AIDS Subpopulation — Perz et al. (1998) report that members of the AIDS subpopulation "*may exhibit significant avoidance of tap water.*" They estimate that unheated tap water consumption among individuals in this subgroup is 70% of that among members of the general population. Perz et al. (1998) do not state whether the total tap water consumption rate for the AIDS subpopulation is also less than it is for the general population. Here, it is assumed that no adjustment is necessary for this population subgroup.

3.2.2.2. Pregnant Women — Because pregnant women are at risk for DBP-induced reproductive health effects, and the fetus is at risk for DBP-induced developmental effects, it is important to determine if pregnancy status affects tap water consumption. Data quantifying tap water consumption rates for pregnant women are limited. However, Ershow et al. (1991) report that the 50th percentile consumption rate among pregnant women is 1.1 L/day, while the 90th percentile daily consumption rate is 2.2 L/day. These values are very close to the 50th and 90th percentile consumption rates, respectively, for members of the general population, ages 20 to 44 years old, as reported by U.S. EPA (1997a, Table 3-7). Those rates are 1.144 L/day and 2.121 L/day, respectively. The risk assessment therefore makes no adjustments to the tap

water consumption rate to reflect potential differences between pregnant women and the general population.

3.2.3. Tap Water Intake — Model Uncertainty. Note that while it is not incorporated into this risk assessment, it is possible that the inhalation pathway is a potential route of exposure for the more volatile DBPs (e.g., Jo et al., 1990a,b provide estimates of exposures to chloroform during showering). Because of a lack of data, this possibility is not treated quantitatively in the risk assessment.

This risk assessment also assumes that the relevant measure of tap water intake is *total* tap water ingestion. Total ingestion is used (rather than *unheated* tap water consumption) because it is assumed that heating does not substantially affect DBP concentrations. This assumption may lead to the slight overestimation of risk since it is known that the more volatile DBPs, specifically, the trihalomethanes, will be removed by heating. On the other hand, many other DBPs, such as the acids, will remain in the water. Because of a lack of data specifically addressing the removal of these DBPs from water by heating, this phenomenon is not treated quantitatively.

4. DBP TOXICITY

The risk assessment considers three types of health endpoints: cancer, reproductive toxicity, and developmental toxicity. The incremental risk for any health endpoint (h) is assumed to be

$$risk_h = Y \times \left[\left(1 + \frac{\alpha_h C_u^{OX}}{\sum_{i \in K \cap H} \rho_i C_i} \right) \sum_{i \in K} C_i S_i \right] \times \frac{1}{1000} \qquad \text{Eq 4-1}$$

where[2]

- Y = Daily water consumption (L/kg-day) (Section 3.2);
- C_u^{OX} = The concentration of the organic halogen (OX) portion of the unidentified DBPs expressed in terms of µg Cl/L (Section 3.1);
- C_i = The concentration of identified DBP_i (µg/L) (Section 3.1);
- ρ_i = The ratio of the organic halogen (OX) portion of DBP i's concentration (in µg Cl/L) to its total concentration;
- α_h = Fraction of measured but unidentified TOX (weighted by concentration in µg Cl/L) associated with inducing health effect h (unitless) (Section 4.3);
- S_i = Incremental probability of the outcome per mg/kg-day intake of the ith DBP $(mg/kg\text{-}day)^{-1}$ (Section 4.3);
- 1/1000 = Conversion factor (mg/µg);
- K = The set of known DBPs (*i.e.*, those listed in Table 3-1);
- H = The set of identified DBPs causing health effect h at environmentally relevant doses.

[2] For the sake of brevity, Equation 4-1 and the remainder of Section 4 omit explicit representation of the summation of risk over different age groups that is explicitly reflected in Equation 2-4.

Section 4.1 discusses the use of "response addition" to develop the dose-response relationship for a DBP mixture. Sources of uncertainty that cannot be quantitatively parameterized include the following:

- The assumption that response addition is the appropriate basis for developing a dose-response relationship for this mixture and for the endpoints considered in this risk assessment;
- The assumption that the cancer dose response function for each individual DBP, with the exception of chloroform, is linear at low doses with no threshold; and
- The assumption that the reproductive toxicity and developmental toxicity dose-response functions should be developed from the single "best" animal bioassay for which the dose-response threshold does not exceed environmental exposure levels.

Section 4.2 explains the basis for scaling the summation in Equation 4-1 by a factor of $(1+\frac{\alpha_h C_u^{Cl}}{\sum_{i\in K\cap H}\rho_i C_i})$ to take into account the potential risk contribution from measured but unidentified DBPs.

This section also explains how the values for the α_h parameters were estimated for each of the three health endpoints considered in this risk assessment. The α parameters are the fractions (by OX concentration in µg Cl/L) of the measured but unidentified DBPs estimated to be associated with each of the three health endpoint considered. These values appear in Table 4-1.

Sources of uncertainty that cannot be quantitatively parameterized include the following:

- The use of Quantitative Structure Activity Relationship (QSAR) modeling to estimate the values for the α proportions.

TABLE 4-1

Proportion of Measured buy Unidentified DBPs Contributing to Toxicity

Endpoint	Proportion of Measured but Unidentified DBPs Associated with Induced Endpoint (α)	
	Filter-Cl	O_3-Filter-Cl
Cancer	58%	55%
Developmental	42%	56%
Reproductive	42%	56%

- The assumption (explained in Section 4.2) that the toxicity of the unidentified DBPs is the same as it is for the identified DBPs when normalized in terms of OX concentration measured as μg Cl/L. Since not all DBPs have organic halogen components, this approach implicitly assumes that unidentified DBPs that have no OX contribute nothing to toxicity.

- The assumption that chloroform is effectively not carcinogenic because of its threshold. Because its concentration is large compared to that of other DBPs, the classification of chloroform affects the value of the summation $\sum_{i \in K \cap H} \rho_i C_i$, and hence the estimated toxicity contribution from the unidentified DBPs.

Section 4.3 describes estimation of the incremental risk per mg/kg-day ingested for identified DBPs (the S_i parameters). The distributions describing the plausible set of values for these parameters, are detailed in Table 4-2. These distributions are assumed to be statistically independent. The values in Table 4-2, the basis for which is described in Section 4.3, have been estimated from high dose animal bioassay data and the extrapolation of these effects down to environmentally relevant doses is a source of model uncertainty. As described in Section 4.3, epidemiological data could also be used to estimate the value of these parameters for the cancer endpoint.

TABLE 4-2

Incremental Risk per mg/kg-day for Identified DBPs*

DBP	Lognormal Distribution for S_i $(mg/kg\text{-}day)^{-1}$					
	Cancer		Developmental		Reproductive	
	GM	GSC	GM	GSD	GM	GSD
$CHCl_3$	0		0		0	
BDCM	5.7×10^{-3}	4.3	0		0	
CDBM	7.2×10^{-4}	18.1	0		0	
$CHBr_3$	3.4×10^{-4}	6.8	0		0	
CH	4.1×10^{-2}	2.0	0		0	
MCA	0		0		0	
DCA	1.4×10^{-3}	13.4	8.6×10^{-3}	1.3	2.5×10^{-2}	1.7
TCA	4.9×10^{-2}	1.4	2.0×10^{-2}	1.3	0	
MBA	0		8.4×10^{-3}	1.8	0	
DBA	0		8.6×10^{-3}	1.3	2.5×10^{-2}	1.7
BCA	0		8.6×10^{-3}	1.3	2.5×10^{-2}	1.7
DCAN	0		5.4×10^{-2}	1.9	0	
TCAN	0		2.1×10^{-1}	1.3	0	
BCAN	0		1.6×10^{-1}	1.3	0	
DBAN	0		2.1×10^{-1}	1.3	0	
Bromate	3.2×10^{-1}	1.3	0		0	

* See Section 4.3 for background on these values.

Sources of uncertainty that cannot be quantitatively parameterized include the following:

- Reliance on animal bioassay data to quantify toxicity.
- The extrapolation from high doses used in animal bioassay experiments down to environmentally relevant doses.
- The assumption that these distributions are statistically independent. Making this assumption tends to decrease the range of plausible risk estimates for the DBP mixture as a whole.

4.1. RISK CHARACTERIZATION METHOD

4.1.1 Response Addition. This risk assessment uses "response addition" as the risk characterization method for the mixture of DBPs in drinking water. Response addition assumes only that the components of a mixture are functionally independent at low doses so that the risks (i.e., the expected response) due to each can be added together (Mumtaz and Hertzberg, 1993). Mathematically, the response addition assumption translates into a dose response function of the form,

$$risk = \sum_{i \in All\ DBPs} r_i \ , \qquad \text{Eq 4-2}$$

where r_i is the risk contribution by DBP_i at a given exposure.

The use of response addition as a risk characterization method is well documented (U.S. EPA, 1986, 1989, 1990). It is particularly useful when the effects of concern are thought to be present at low dose levels for each of the component chemicals, even though they are highly unlikely to be observable at these low levels in the environment; the mixture risk is then the sum of the individually low risks of the independently acting component chemicals. The original U.S. EPA guidelines for mixtures risk assessment (U.S. EPA, 1986) recommend a default no-interaction

approach of response addition for carcinogenic risk. Furthermore, there is strong precedent for use of response addition for carcinogenic risk estimation as employed in the evaluation of mixtures at Superfund sites (U.S. EPA 1989) and in assessments by the Food and Drug Administration (Gaylor et al., 1997). Response-addition is less commonly used for non-cancer endpoints because for many of these endpoints, threshold effects are thought to exist; in this situation, dose-addition is a more common assumption. (See Appendix B.1 for further discussion of alternative models.) Response-addition is different from dose-addition in that it does not assume similar kinetics or a similar mode of action and does not assume parallel dose-response curves (Mumtaz and Hertzberg, 1993). Gaylor et al. (1997) state that,

> "At dose levels far below those having measurable pharmacologic or physiologic activity, synergistic or antagonistic interactions are considered not to be likely. That is, it is assumed that the carcinogens are acting independently. Then, the risk of cancer from the mixtures may be obtained by summing the individual risks."

The DBP mixtures response-addition assessment depends on the fact that we are dealing with low level exposures. Thus, information on how these chemicals interact at high dose levels is not pertinent to the risk assessment. The following text from the newest Agency draft mixtures guidance document (U.S. EPA, 1998e) describes the theoretical statistical basis for the response addition equation.

> "Under response addition, the chemicals are assumed to behave independently of one another, so that the body's response to the first chemical is the same whether or not the second chemical is present. In simplest terms, classical response addition is described by the statistical law of independent events, with "response" measured by the percentage of exposed animals that show toxicity. (Let r_1 and r_2 be risk estimates for chemicals 1 and 2, respectively, and let r_m represent the risk for the mixture)....the statistical law of independence is:

$$r_m = 1 - (1 - r_1)*(1 - r_2)$$

In terms of mixture response, this equation says that the response to either chemical 1 or 2 is one minus the probability of not responding to either chemical. Expanding the right-hand-side, one obtains:

$$r_m = r_1 + r_2 - r_1*r_2$$

which, for small single chemical responses, is well approximated by the simple summation:

$$r_m = r_1 + r_2"$$

Thus, this equation works well for DBP mixtures carcinogenic risk because 1) we expect very small individual risks at the low levels of exposure (i.e., the r_i are small) and 2) we do not expect to see interaction effects at these low doses (i.e., the interaction term, r_1*r_2 can be ignored). For the developmental and reproductive endpoints, points 1) and 2) are also true. The dilemma is whether the individual r_i values are actually equal to zero due to threshold effects. Thus, response addition has been adopted as a default approach, pending further research relative to the true biologic mechanisms for these noncancer effects.

4.1.2. Low Dose Linearity and Calculation of the Incremental Risk per mg/kg-day.

With the exception of chloroform, the DBPs associated with carcinogenicity (see Section 4.3.1) are assumed to have dose-response functions that are linear at low dose.

For the noncancer health endpoints, it is assumed that there may be a threshold at some nonzero dose. As described in Section 4.3.2, the dose-response functions contributing to noncancer risk are effectively linear at low dose because the dose-response curve fitting calculation in these cases failed to identify a threshold exceeding zero.

Because all dose-response functions used in this risk assessment are effectively linear at low dose, the risk for endpoint h due to DBP_i is $\frac{1}{1000} \times Y \times S_i \times C_i$. Summing over the risks contributed by all DBPs yields

$$risk = \frac{1}{1000} \sum_{i \in All\ DBPs} Y \times S_i \times C_i = \frac{1}{1000} \times Y \times \sum_{i \in All\ DBPs} S_i \times C_i \,, \qquad \text{Eq 4-3}$$

where:

Y	=	Daily water consumption (L/kg-day);
C_i	=	The concentration of identified DBP_i (µg/L);
S_i	=	Incremental probability of endpoint h per mg/kg-day intake of the ith DBP $(mg/kg\text{-}day)^{-1}$; and
1/1000	=	Conversion factor (mg/µg).

4.1.3. Chloroform's Carcinogen Dose Response Threshold. The risk assessment assumes that chloroform's carcinogen dose-response function has a threshold, and that as a result, it does not cause cancer at environmentally relevant exposure levels. This assumption reflects the findings of a recent expert panel cancer assessment (U.S. EPA, 1998b) that employed methodology from EPA's 1996 proposed Cancer Risk Assessment Guidelines (U.S. EPA, 1996a). There is increasing evidence that the carcinogenic mechanism of action for chloroform is not relevant at the low concentrations found in drinking water and that, based on a margin of exposure (MOE) assessment, any concentrations less than 300 µg/L of chloroform are not of concern for human health. Thus, since the chloroform concentration for either treatment train considered here is far below this level, EPA also assumed that chloroform does not

contribute to cancer risk. EPA also assumed that chloroform does not interact with other components of the DBP mixture.

4.2. INCORPORATING MEASURED BUT UNIDENTIFIED DBPs

As noted in Section 3.1, Miltner et al. (1990) reported the total organic halogen (total OX) concentrations in water processed by EPA's Cincinnati pilot treatment plant. For those chemicals contributing to total OX concentrations that are not identified, it is, of course, not possible to assign chemical-specific dose-response functions. However, omitting them entirely from this assessment would be equivalent to assuming that they pose no toxicity risk at all. The toxicity of the unidentified DBPs (for cancer, reproductive toxicity, and developmental toxicity) is assumed to be the same as it is for identified DBPs when normalized in terms of OX concentration (µg Cl/L). That is, EPA assumes that the incremental risk per µg OX/L (µg Cl/L) for the unidentified DPBs equals the corresponding value for the identified DBPs.

While it may seem more natural to normalize in terms of total concentrations, rather than in terms of OX concentrations, total concentration information is not available for the unidentified DBPs. Normalization in terms of OX concentrations (µg Cl/L) introduces a source of model uncertainty that cannot be readily quantified.

4.2.1. Dose Response Function Reflecting Unidentified DBPs. In order to quantify the risk posed by the unidentified DBPs, the summation in Equation 4-3 is broken into two parts – the first representing the risk contribution from identified DBPs, and the second representing the risk contribution from the unidentified DBPs. Specifically,

$$risk = \frac{1}{1000} \times Y\left[\sum_{i \in K} S_i C_i + \sum_{i \in U} S_i C_i\right], \qquad \text{Eq 4-4}$$

where:

Y	0	Daily water consumption (L/kg-day);
C_i	0	The concentration of identified DBP_i (μg/L);
S_i	0	Incremental probability of endpoint h per mg/kg-day intake of the ith DBP $(mg/kg\text{-}day)^{-1}$;
1/1000	0	Conversion factor (mg/μg).
K	0	The set of all "known" DBPs identified by Miltner *et al.*; and
U	0	The set of DBPs measured by Miltner *et al.* But not identified.

The values of the parameters in the summation over the set K can be determined explicitly (see Section 3.1 for the value of the C_i parameters and Section 4.3 for the value of the S_i parameters). Of course, the value of the parameters in the second summation are not known. It is instead assumed that for the fraction (by OX concentration in μg Cl/L) of unidentified DBPs associated with inducing health endpoint h (cancer, reproductive toxicity, or developmental toxicity), designated "α_h", the incremental risk per μg Cl/L equals the corresponding value for the identified DBPs associated with inducing endpoint h. If the total OX concentration for the unknown DBPs is designated C_u^{OX}, then the fraction associated with inducing endpoint h has a total concentration of $\alpha_h C_U^{OX}$. The incremental risk per μg OX/L (in μg Cl/L) for the unidentified DBPs is hence $\frac{1}{1000} \times Y \times \frac{1}{\alpha_h C_u^{OX}} \sum_{i \in U} C_i S_i$. For the identified DBPs

associated with inducing endpoint h, the total OX concentration in μg Cl/L is $\sum_{i \in K \bigcap H} \rho_i C_i$, where K is the set of known DBPs, H is the set of DBPs associated with inducing endpoint h, and ρ_i is the ratio of DBP i's OX concentration in μg Cl/L to its total concentration. The incremental risk per μg OX/L (measured as μg Cl/L) for the identified DBPs associated with inducing endpoint h is $\frac{1}{1000} \times Y \times \frac{1}{\sum_{i \in K \bigcap H} \rho_i C_i} \times \sum_{i \in K} C_i S_i$.

Since it is assumed that the incremental risks per μg OX (in μg Cl/L) are the same for identified DBPs and for unidentified TOX,

$$\frac{1}{1000} \times Y \times \frac{1}{\alpha_h C_u^{OX}} \sum_{i \in U} C_i S_i = \frac{1}{1000} \times Y \times \frac{1}{\sum_{i \in K \bigcap H} \rho_i C_i} \times \sum_{i \in K} C_i S_i \qquad \text{Eq 4-5a}$$

so,

$$\sum_{i \in U} C_i S_i = \frac{\alpha_h C_u^{OX}}{\sum_{i \in K \bigcap H} \rho_i C_i} \sum_{i \in K} C_i S_i . \qquad \text{Eq 4-5b}$$

Substituting the right side of Equation 4-5b into Equation 4-6 yields

$$risk_h = \frac{1}{1000} \times Y \left[\sum_{i=K} C_i S_i + \frac{\alpha_h C_u^{OX}}{\sum_{i \in K \bigcap H} \rho_i C_i} \sum_{i \in K} C_i S_i \right]. \qquad \text{Eq 4-6}$$

Simplifying yields Equation 4-1, which is reproduced here for convenience:

$$risk_h = \frac{1}{1000} \times Y \left[\left(1 + \frac{\alpha_h C_u^{OX}}{\sum_{i \in K \cap H} \rho_i C_i} \right) \sum_{i \in K} C_i S_i \right] \quad \text{Eq 4-7}$$

4.2.2. The Fraction of Unidentified DBPs Associated with Each Endpoint. The parameter α_h is the proportion of unidentified DBPs *by OX concentration* (in µg Cl/L) associated with inducing endpoint h. Since each unidentified DBP's concentration in treated drinking water is unknown, it has been assumed that the proportion of unidentified DBPs *by concentration* associated with inducing endpoint h equals the proportion of unidentified DBPs associated with inducing that health endpoint. For example, if 15 of 30 unidentified DBPs were determined to be associated with inducing cancer, it would be assumed that α_{cancer} is 50%.

The following discussion describes first how the set of unidentified DBPs produced by each drinking water treatment train was created. It then describes how Quantitative Structural Activity Relationship (QSAR) analysis was used to determine which of these unidentified DBPs are associated with inducing each health endpoint, and hence what fraction of unidentified DBPs are associated with inducing each health endpoint.

4.2.2.1. Identifying all DBPs Generated by Each Drinking Water Treatment Train — Richardson (1998) identified 70 compounds in water treated with chlorination, and 62 in water treated with ozone and then chlorination. The former set was assumed

to represent all DBPs in drinking water treated by filter-Cl, while the latter was assumed to represent all DBPs in drinking water treated by O_3-filter-Cl. The sets of *unidentified* DBPs in water treated using O_3-filter-Cl and filter-Cl were determined by subtracting from Richardson's results the DBPs identified by Miltner et al. (1990).

4.2.2.2. Determining the Fraction of the Unidentified DBPs Associated with Inducing Toxicity — QSAR was used to assess the toxicity of each of the unidentified DBPs listed by Richardson. For each health endpoint, the resulting fraction of chemicals testing positive was used as an estimate for α_h. QSAR predictions of carcinogenicity and developmental toxicity were produced by the TOPKAT® software package (Toxicity Prediction by Komputer-assisted Technology), first introduced in 1987 by Health Designs, Inc. Because the TOPKAT® software does not currently have a model to predict potential reproductive toxicity, the results of the developmental toxicity evaluations were used as surrogates for the reproductive toxicity endpoints. This software program uses statistical models that have been developed from data bases of animal and *in vitro* assay results. These models predict assay results for an untested substance based on the substance's molecular structure. Appendices B.2 and B.3 describe the QSAR methodology and its application to the DBPs in further detail. Tables 4-4 and 4-5 summarize the QSAR results.

4.2.2.3. Results — The fractions of unidentified DBPs (by µg Cl/L) found to be associated with inducing cancer (α_{Cancer}) were 58% (33/57) and 55% (23/41) for the filter-Cl and O_3-filter-Cl treatments, respectively. The fractions of DBPs found to be associated with inducing developmental toxicity (α_{Devel}) were 42% (18/43) and 56% (26/47) for filter-Cl and O_3-filter-Cl treatments, respectively. These values were also

TABLE 4-4

TOPKAT® OSAR Predictions by Endpoint for Known DBPs Not in the Miltner 1990 Sample

Total unidentified DBPs generated by the Filter-Cl treatment train and number associated with inducing toxicity

Chemical Class	Total Developmental	Total Cancer	Cancer Female Mouse	Cancer Male Mouse	Cancer Female Rat	Cancer Male Rat
Aldyhydes	0	1	1	0	0	0
Acids	3	5	4	2	3	0
Ketones	7	8	0	7	0	3
Lactones	0	3	1	1	1	0
Alcohols	0	1	0	1	0	0
Esters	1	1	0	0	0	1
Nitriles	4	2	1	0	1	0
Amides	0	0	0	0	0	0
Halo/Nitro Alkanes and Alkenes	3	12	7	5	6	6
Count / Total*	18/43	33/57	-	-	-	-
% Associated with Endpoint	42	58	-	-	-	-

* Total varies by endpoint because DBPs for which a model was unable to make a prediction were eliminated.

TABLE 4-5

TOPKAT® OSAR Predictions by Endpoint for Known DBPs Not in the Miltner 1990 Sample

Total unidentified DBPs generated by the O_3-Filter-Cl treatment train and number associated with inducing toxicity

Chemical Class	Total Developmental	Total Cancer	Cancer Female Mouse	Cancer Male Mouse	Cancer Female Rat	Cancer Male Rat
Aldyhydes	1	4	3	0	0	2
Acids	5	3	1	0	1	0
Ketones	5	7	1	5	0	2
Lactones	0	1	1	0	0	0
Alcohols	0	1	0	1	0	0
Esters	1	2	1	1	0	1
Nitriles	4	1	0	0	1	0
Amides	1	1	0	1	0	1
Halo/Nitro Alkanes and Alkenes	6	6	1	1	1	3
Count / Total*	23/41	26/47	-	-	-	-
% Associated with Endpoint	56	55	-	-	-	-

* Total varies by endpoint because DBPs for which a model was unable to make a prediction were eliminated.

used as surrogates for the fraction of unidentified DBPs that may be associated with inducing reproductive toxicity (α_{Repro}).

Note that the QSAR model was unable to classify some of the chemicals with respect to some health endpoints. These chemicals were omitted from the analysis. Since the number of chemicals that could not be classified differed by endpoint, thedenominators for the fraction of DBPs associated with inducing cancer (57 and 41 for the filter-Cl and O_3-filter-Cl treatments, respectively) differed from the denominators of the corresponding fractions for developmental toxicity (43 and 47, respectively).

It is recognized that there is considerable uncertainty in these estimates due to many factors: the assumption that the proportion of unidentified chemicals associated with inducing a health effect is equal to the proportion of chemicals by OX concentration in µg Cl/L associated with inducing that health endpoint; unknowns relative to the actual number, proportions, and molecular weights of chemicals that make up the unidentified TOX; potential risks from the unidentified material that does not fall into the classification of organic halides; and possible classification errors by the TOPKAT® program. This is only one method that could be used for estimating toxicity for unidentified TOX. Increased information relative to the uncertainties listed here or use of additional QSAR models could improve the accuracy of the estimates. Because of these uncertainties, it is recognized that the estimated risks from exposure to the unidentified TOX could be very broad in range and could conceivably include zero.

4.2.3. Model Uncertainty Introduced by Estimates of TOX Potency. It is recognized that there are a number of uncertain factors affecting the estimate of the risk contributed by unidentified DBPs

- The actual number of and molecular weights of the chemicals that make up the unidentified DBPs unknown.
- The proportion of unidentified DBPs associated with each endpoint has been estimated from a generic list of DBPs, rather than from lists specific to each drinking water treatment train under consideration.
- Statistical models built into the TOPKAT® software may have introduced classification errors.
- The risk posed by the unidentified DBPs assumed to be the same as it is for the identified DBPs on a µg OX/L basis. This assumption implies that DBPs with no OX component pose no risk.

Additional information addressing the sources of uncertainty listed here or use of additional QSAR models could improve the accuracy and precision of the estimates. Because of these uncertain factors, it is recognized that the plausible range of risks from exposure to the unidentified DBPs is very broad and could conceivably include zero.

4.3. INCREMENTAL RISK PER µg/L FOR THE IDENTIFIED DBPs

Carcinogenicity (Section 4.1), developmental toxicity (Section 4.2), and reproductive toxicity (Section 4.2) were estimated using animal bioassay data. Appendix B.4 summarizes these data. Section 4.3.3 discusses the use of epidemiological data to estimate risks associated with DBP exposure. Section 4.3.4 discusses the implications of assuming that the DBP slope factor distributions are statistically independent.

4.3.1. Cancer. The distribution of plausible values for each DBP's cancer slope factor was estimated using the linearized multi-stage model results applied to animal bioassay data. It was assumed that the distribution of plausible values is lognormal, with a geometric mean equal to the estimated MLE, and a 95th percentile equal to the upper 95% confidence limit on the slope. While maximum likelihood theory suggests that

parameter values have a normal distribution, the skewed nature of the confidence intervals for these slope parameters (very large standard errors relative to the mean estimate) suggests that the normality assumption does not hold in this case. Table 4-6 summarizes the slope factor estimates for those DBPs that are suspected carcinogens.

With the exception of DCA, TCA, and chloroform, the oral upper bound slope estimates for the cancer endpoint were taken directly from EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 2000) for bromate, chloroform ($CHCl_3$), bromodichloromethane (BDCM), chlorodibromomethane (CDBM), and bromoform ($CHBr_3$). The upper bound slope estimate for chloral hydrate (CH) is a verified IRIS workgroup value that has not been loaded onto IRIS to date. All of these values were computed for excess risk, using the linearized multistage model that assumes a low dose linear response. The mean slope estimates for these chemicals were computed by re-running the linearized multistage model on the IRIS/workgroup data sets and taking the Maximum Likelihood Estimate (MLE) value. Because the body weight conversions for the DBPs on IRIS were based on the assumption of 2/3 power, this assumption was maintained for consistency. The 1996 draft Cancer Guidelines (US EPA, 1996) have proposed the use of 3/4 power for the conversion.

As discussed in Section 4.1.3, this risk assessment assumes that for mechanistic reasons, chloroform's cancer dose-response relationship has a threshold well above environmentally relevant levels. Since chloroform's estimated concentration is below its estimated threshold, this DBP is assumed not to contribute to carcinogenicity. (If the assumption of linearity were imposed, the methodology used here would estimate chloroform's slope factor distribution to be lognormal with a geometric mean of 3.1×10^{-3}, and a geometric standard deviation of 1.5.)

TABLE 4-6

Incremental Cancer Risk per mg/kg-day for Identified DBPs

Chemical	Weight of Evidence Classification[a]	MLE	Slope Factor $(mg/kg\text{-}d)^{-1}$			Observed Effect
			95th Percentile UCL	GM	GSD	
BDCM	B2	5.7×10^{-3}	6.2×10^{-2}	5.7×10^{-3}	4.3	Renal adenomas and adenocarcinomas
CDBM	C	7.2×10^{-4}	8.4×10^{-2}	7.2×10^{-4}	18.0	Hepatocellular adenomas and adenocarcinomas
$CHBr_3$	B2	3.4×10^{-4}	7.9×10^{-3}	3.4×10^{-4}	6.8	Neoplastic lesions in large intestine
CH	C	4.1×10^{-2}	1.3×10^{-1}	4.1×10^{-2}	2.0	Hepatocellular adenomas and adenocarcinomas
DCA	B2	1.4×10^{-3}	1.0×10^{-1}	1.4×10^{-2}	13.4	Hepatocellular adenomas and adenocarcinomas
TCA	C	4.9×10^{-2}	8.4×10^{-2}	4.9×10^{-2}	1.4	Live neoplasms
Bromate	B2	3.2×10^{-1}	4.9×10^{-1}	3.2×10^{-1}	1.3	Renal adenomas and adenocarcinomas
$CHCl_3$ [b]	B2	3.1×10^{-2}	6.1×10^{-3}	3.2×10^{-3}	1.5	Renal tumors

[a] Chemicals classified as B2 have sufficient evidence of carcinogenicity in animals with inadequate or a lack of evidence in humans. For chemicals classified as C, there is limited evidence of carcinogenicity in animals and inadequate or a lack of evidence in humans.

[b] As discussed below, chloroform has been excluded from the risk assessment because it is thought to be a threshold carcinogen, and its concentration for either treatment train considered is less than chloroform's estimated threshold.

For dichloroacetic acid (DCA) and trichloroacetic acid (TCA), quantitative cancer estimates are not available on IRIS, but qualitative assessments there list B2 and C cancer classifications, respectively. The upper bound and mean (MLE) slope factors for DCA and TCA were back-calculated from risk levels given in Bull and Kopfler (1991). DCA was also reviewed by the same expert panel as chloroform; the panel indicated that there is insufficient evidence that tumors occur at low doses of DCA in animal studies (U.S. EPA, 1998b); thus it is questionable whether the mechanism of action for cancer is active at the low levels to which humans are exposed. However, the Agency position on DCA falls short of employing the same MOE methodology as was applied in the case of chloroform. For this reason, and because Agency text (U.S. EPA, 1998b) leaves open the question of low dose mechanism, DCA was kept in the case study analysis of cancer risk.

4.3.2. Developmental and Reproductive Toxicity. As with cancer, the distribution of plausible values for the "slope factors" for developmental and reproductive toxicity were estimated using the linearized multi-stage model results applied to animal bioassay data. Likewise, it was assumed that the distribution of plausible values is lognormal, with a geometric mean equal to the estimated MLE, and a 95^{th} percentile equal to the upper 95% confidence limit on the slope. Tables 4-7 and 4-8 summarize these estimates.

Several of these chemicals have Reference Doses (RfDs) listed on IRIS (U.S. EPA, 2000), so the estimation of risks at exposures below the RfDs is of concern. However, the RfD values are not useful in this risk assessment for several reasons. First, RfDs are endpoint-specific sub-threshold levels that do not yield the dose-response information needed for the case study. Second, this risk assessment

TABLE 4-7

Incremental Developmental Toxicity Risk per mg/kg-day for Identified DBPs

Chemical	MLE	Slope Factor $(mg/kg\text{-}d)^{-1}$			Observed Effect
		95th Percentile UCL	GM	GSD	
DCA	8.6×10^{-3}	1.3×10^{-2}	8.6×10^{-3}	1.3	Visceral malformations - Total
TCA	2.0×10^{-2}	3.0×10^{-2}	2.0×10^{-2}	1.3	Fetal body weight - male
MBA	8.4×10^{-3}	2.3×10^{-2}	8.4×10^{-3}	1.8	Fetal crown rump length
DBA	8.6×10^{-3}	1.3×10^{-2}	8.6×10^{-3}	1.3	Estimated using DCA as a surrogate
BCA	8.6×10^{-3}	1.3×10^{-2}	8.6×10^{-3}	1.3	Estimated using DCA as a surrogate
DCAN	5.4×10^{-2}	1.6×10^{-1}	5.4×10^{-2}	1.9	Visceral malformations - cardiovascular
TCAN	2.1×10^{-1}	3.4×10^{-1}	2.1×10^{-1}	1.3	Visceral malformations - Total
BCAN	1.6×10^{-1}	2.4×10^{-1}	1.6×10^{-1}	1.3	Visceral malformations - Total
DBAN	2.1×10^{-1}	3.4×10^{-1}	2.1×10^{-1}	1.3	Estimated using TCAN as a surrogate
BDCM*	4.0×10^{-2}	3.1×10^{-2}	4.0×10^{-2}	-	Complete litter resorption
MCA*	9.0×10^{-5}	6.0×10^{-3}	9.0×10^{-5}	2.6	Crown rump length

* As discussed below, BDCM and MCA are assumed not to contribute to risk because the linearized multistage model always predicted a threshold exceeding total DBP levels. The BDCM upper 95% UCL value is larger than the MLE because the dose-response model estimated the 95^{th} percentile UCL assuming a threshold of zero. Thus, the GSD is not computed.

TABLE 4-8

Incremental Reproductive Toxicity Risk per mg/kg-day for Identified DBPs

Chemical	MLE	Slope Factor $(mg/kg\text{-}d)^{-1}$			Observed Effect
		95th Percentile UCL	GM	GSD	
DBA	2.5×10^{-2}	6.0×10^{-2}	2.5×10^{-2}	1.7	Number of cauda sperm
DCA	2.5×10^{-2}	6.0×10^{-2}	2.5×10^{-2}	1.7	Estimated using DBA as a surrogate
BCA	2.5×10^{-2}	6.0×10^{-2}	2.5×10^{-2}	1.7	Estimated using DBA as a surrogate

assumes additivity is operational, that is, that the chemicals are acting in a joint fashion, a fact that the RfDs themselves do not take into account. Third, the DBPs in Tables 4-7 and 4-8 may actually be the chemicals of concern, or they may be only surrogates for other chemicals responsible for effects observed in epidemiologic studies. Finally, for these endpoints, it is possible that a mixtures toxicity threshold exists that would potentially be lower than any of the individual component thresholds, such that estimation of mixtures risk at these individual subthreshold dose levels is reasonable. Using a dose-response approach, rather than depending on RfDs, works well for this risk assessment because of the need to compare DBP-induced risks for the endpoints of concern at extremely low environmental exposures.

Table 4-9 summarizes the availability of developmental and reproductive dose-response data for six of the haloacetic acids (MCA, DCA, TCA, MBA, DBA and BCA), four of the haloacetonitriles (DCAN, TCAN, BCAN and DBAN) and one of the trihalomethanes (BDCM).

TABLE 4-9

Availability of Developmental and Reproductive Dose-Response Data

	Developmental Toxicity[a]	Reproductive Toxicity[a]
Haloacetic Acids		
MCA	y, (+)	
DCA	y, +	y, +
TCA	y, +	
MBA	y, +	y, -
DBA		y, +
BCA		
Haloacetonitriles		
DCAN	y, +	
TCAN	y, +	
BCAN	y, +	
DBAN	y, (-)[b]	y, (-)[b]
Trihalomethanes		
BDCM	y, +	

[a] Data are from gavage studies in rats unless otherwise noted.

[b] Data are from a screening-level drinking water study in rats.

Key: y yes, adequate data available
+ results were positive for adverse effect
- results were negative for adverse effect
(+) results were marginally positive
(-) results were negative, but a toxicity-based MTD could not be achieved due to taste aversion and consequent refusal to drink higher concentrations of the chemical, and this was a short-term screening study

Seven of these DBPs (MCA, DCA, TCA, MCA, DCAN, TCAN, BCAN) have been subjects of developmental toxicity studies by a single group of investigators, and three (DCA, MBA, DBA) have been the subjects of male reproductive studies by another group of investigators. These studies were all conducted in rats using gavage administration. The results for developmental toxicity were positive. For reproductive toxicity, the dihalogenated haloacetic acids produced positive results, but the monohalogenated acetic acid (MBA) produced negative results. DBAN was tested in a short-term developmental and reproductive toxicity screening study in rats by the NTP (1992), with negative results. BDCM was tested in a developmental toxicity screening bioassay with positive results. Developmental toxicity data are inadequate for DBA, BCA, and for DBAN. A surrogate approach seemed appropriate to address these data gaps because the available data indicated that developmental toxicity may be common to the haloacetic acid and haloacetonitrile DBPs. As a provisional measure, DCA was selected as a surrogate for the haloacetic acids and TCAN was selected as a surrogate for the haloacetonitriles.

Dose-response modeling was performed on all possible developmental and reproductive endpoints using human equivalent doses in a linearized multi-stage model with a threshold parameter estimated by the modeling procedure. Note that some of the data are quantal, but other data (body weight, crown-rump length) are continuous and were converted to a quantal measure prior to modeling. Modeling results for all data sets are found in Table 4-10. For many of the data sets, the threshold estimates were above concentration levels for the treatment trains and were therefore not included in any of the risk estimates. This criteria excluded MCA and BDCM entirely from the risk calculations. For the other DBPs, the modeling procedure failed to

TABLE 4-10

Non-Cancer Dose-Response Modeling Results Using $BW^{2/3}$ Scaling Factor

Data Set [note all are for rats except when noted (DCA, Cicmanec et al.)]	Equiv Human ED_{01} (mg/kg-d)	Equiv Human ED_{10} (mg/kg-d)	Threshold (mg/kg-d)
MCA Smith et al., Fetal body weight	18.9	26.7	11.2
MCA Smith et al., Crown-rump length	15.7	20.2	11.2
MCA Smith et al., Visceral Malformations	16.5	21.8	11.2
DCA Smith et al., Fetal body weight - male	4.7	27.3	2.2
DCA Smith et al., Fetal body weight - female	18.6	40.4	16.3
DCA Smith et al., Crown-rump length - male	5.1	36.2	1.0
DCA Smith et al., Crown-rump length - female	5.1	36.2	1.0
DCA Smith et al., Visceral malformations Total	1.2	12.2	0
DCA Smith et al., Visceral malformations Cardiovascular	1.7	17.6	0
TCA Smith et al., Complete litter resorption	110.5	143.2	106.3
TCA Smith et al., % Postimplantation loss/litter	51.1	88.9	46.8
TCA Smith et al., Fetal body weight - male	0.5	5.2	0
TCA Smith et al., Fetal body weight - female	0.6	6.0	0
TCA Smith et al., Fetal crown-rump length - male	16.2	26.8	15.0
TCA Smith et al., Fetal crown-rump length - female	22.9	37.9	21.4
TCA Smith et al., Visceral malformations Total	25.7	32.2	25.0
TCA Smith et al., Visceral malformations Cardiovascular, total	11.9	23.4	10.7
TCA Smith et al., Visceral malformations Levacardia	1.3	13.8	0

Data Set [note all are for rats except when noted (DCA, Cicmanec et al.)]	Equiv Human ED_{01} (mg/kg-d)	Equiv Human ED_{10} (mg/kg-d)	Threshold (mg/kg-d)
TCA Smith et al., Skeletal malformations	129.7	145.3	128.0
MBA Randall et al., Fetal body weight	4.4	13.7	3.4
MBA Randall et al., Fetal crown-rump length	1.2	12.5	0
MBA Randall et al., Visceral malformations (% affected/litter)	10.2	15.5	6.1
DCA Cicmanec et al., Testicular lesions: degeneration, dog	Failed to converge		
DCA Linder et al., Number caput sperm	33.3	74.6	28.8
DCA Linder et al., Number cauda sperm	Failed to converge		
DCA Linder et al., % Motile sperm	12.6	16.5	9.7
DCA Linder et al., Progressive motility	10.8	15.4	9.7
DCA Linder et al., Testicular histopathology: Faulty spermiation	Failed to converge		
DBA Linder et al., Number caput sperm	5.6	7.7	5.4
DBA Linder et al., Number cauda sperm	0.4	4.2	0
DBA Linder et al., % Motile sperm	9.4	13.9	5.4
DBA Linder et al., Progressive motility	9.4	13.9	5.4
DBA Linder et al., Retention Stage IX spermatids per tubule	0.1	1.1	0
DCAN Smith et al., Complete litter resorption	2.4	3.2	2.3
DCAN Smith et al., % Postimplantation loss/litter	2.3	3.6	1.9
DCAN Smith et al., Fetal body weight - male	2.1	4.3	0.8
DCAN Smith et al., Fetal body weight - female	2.6	3.6	2.4
DCAN Smith et al., Fetal Crown-rump length - male	2.8	4.1	2.4
DCAN Smith et al., Fetal Crown-rump length - female	2.3	3.4	2.2
DCAN Smith et al., Visceral malformations Total	1.5	2.3	1.5

Data Set [note all are for rats except when noted (DCA, Cicmanec et al.)]	Equiv Human ED_{01} (mg/kg-d)	Equiv Human ED_{10} (mg/kg-d)	Threshold (mg/kg-d)
DCAN Smith et al., Visceral malformations Cardiovascular	0.2	1.8	0
DCAN Smith et al., Visceral malformations Urogenital	0.9	2.3	0.8
DCAN Smith et al., Skeletal malformations	1.1	3.2	0.8
TCAN Smith et al., Complete litter resorption	0.24	0.97	0.16
TCAN Smith et al., % Postimplantation loss/litter	0.5	1.2	0.4
TCAN Smith et al., Fetal body weight - male	0.2	1.7	0
TCAN Smith et al., Fetal body weight - female	0.1	1.1	0
TCAN Smith et al., Visceral malformations Total	0.05	0.5	0
TCAN Smith et al., Visceral malformations Cardiovascular	0.09	0.9	0
TCAN Smith et al., Visceral malformations Urogenital	0.06	0.7	0
BCAN Christ et al., Complete litter resorption	1.1	3.7	0.8
BCAN Christ et al., % Postimplantation loss/litter	0.6	6.5	0
BCAN Christ et al., Fetal body weight - male	0.8	2.0	0.6
BCAN Christ et al., Fetal body weight - female	1.0	2.8	0.8
BCAN Christ et al., Fetal crown-rump length - male	0.5	4.8	0
BCAN Christ et al., Fetal crown-rump length - female	0.2	1.9	0
BCAN Christ et al., Visceral malformations Total	0.06	0.6	0
BCAN Christ et al., Visceral malformations Cardiovascular	0.07	0.7	0
BCAN Christ et al., Visceral malformations Urogenital	0.5	1.9	0.4
BCAN Christ et al., Skeletal malformations	1.0	3.4	0.8

Data Set [note all are for rats except when noted (DCA, Cicmanec et al.)]	Equiv Human ED_{01} (mg/kg-d)	Equiv Human ED_{10} (mg/kg-d)	Threshold (mg/kg-d)
BDCM Narotsky et al., Complete litter resorption	3.8	6.1	3.5

[+] High Dose Dropped

* Dose conversions performed prior to modeling.

Dose Conversion Factor to convert animal dose in mg/kg-day to equivalent human dose in mg/kg-day = $(BW_a/BW_h)^{1/3}$

For rat developmental data (HAAs, HANs): = 0.16
(BDCM): = 0.14

For male rat reproductive data: = 0.18

For male dog reproductive data: = 0.52

BW_a = animal body weight in kg = 0.30 kg for rat developmental data on HAAs and HANs, 0.21 kg for rat developmental data on BDCM, 0.41-0.42 kg for male rat reproductive data, 10 kg for male dog reproductive data

BW_h = human body weight = 70 kg

estimate a threshold value for one or more of the data sets such that the threshold was effectively set to zero. For these cases, scientific judgment was used to look across these data sets for the strongest data set and model results, using factors such as evidence of dose-response in the raw data, larger sample sizes, and adequate goodness-of-fit of the model, to choose a dose-response model. For the calculations of extra risk that were made from these data sets, the estimates made directly from the model were identical to those calculated from the slope factors alone because the low dose region of the dose-response curve is relevant in this context. Therefore, MLE and upper bound slope factors were taken from the modeling results for use in risk estimation.

For MCA and BDCM, all the data sets produced thresholds exceeding likely total environmental DBP levels (thresholds of 11.2 mg/kg-day and 3.5 mg/kg-day, respectively). These chemicals therefore contributed nothing to the non-carcinogen risk estimates. For the other DBPs, the modeling procedure failed to estimate a positive threshold value for one or more of the data sets. For these data sets, the threshold was assumed to be zero. In these cases, scientific judgment was used to identify the strongest single data set to quantify risk, using factors such as evidence of dose-response in the raw data, sample size, and model goodness-of-fit. For the calculations of extra risk that were made from these data sets, the estimates made directly from the model were identical to those calculated from the slope factors alone because the low dose region of the dose-response curve is relevant in this context. Therefore, MLE and upper bound slope factors from the modeling results were used for risk estimation.

Note that in place of the approach used here of estimating risk from the single best data set for which there was no positive threshold, the risk assessment could have

alternatively summed the risks (i.e., the slopes) calculated for all such data sets for each DBP. It may be appropriate to sum the risks from multiple data sets if these data sets truly represent distinct types of developmental or reproductive toxicity. For example, in the case of developmental toxicity, if the unit risk for a DBP is 5×10^{-4} for visceral malformations and 3×10^{-4} for fetal crown-rump length, it may be appropriate to conclude that, in the absence of other data, the collective unit risk for either visceral malformations *or* an abnormal fetal crown-rump length is 8×10^{-4}. On the other hand, if in the case of reproductive toxicity, there is a unit risk estimate based on testicular histopathology and another risk estimate for abnormal caput sperm count, it may be inappropriate to sum risks if it is believed the abnormal caput sperm count is a manifestation of cellular abnormalities that were assessed in the histopathology data set.

It should also be noted that while some of the data listed in Table 4-10 are quantal, other data (body weight, crown-rump length) are continuous. The continuous data were converted to quantal data (*estimated # of litters affected* in the table) prior to modeling. Conversion of the continuous-response developmental data to quantal form was performed by assuming a normal distribution with a constant variance across dose groups for the response, and a 5% background response rate. Because individual animal data were not available, the number of responders in each dose group was estimated by first establishing a critical value representing the point above which (or below which, depending on the direction of adverse response) 5% of the control group lies. Then for each dose group the proportion exceeding this critical value was estimated. This proportion was applied to the number of animals in the dose group to determine the number of responders. The doses were converted to equivalent human

doses using the scaling factor of body weight to the 2/3 power, an approach that is consistent with the conversions used for the Agency verified cancer slope factors used in this risk assessment.

4.3.3. Use of Epidemiological Data to Estimate Risk. This section summarizes epidemiological data that could be used in place of or in conjunction with the animal bioassay data to quantify DBP carcinogenicity. This literature is further described in Appendix C. While this literature is not used in the risk assessment's base analysis, it will be used in Section 5 to investigate the potential importance of model and data uncertainty introduced by reliance on animal bioassay data to estimate toxicity. For reasons discussed in Appendix C, the epidemiological literature will not be used to produce alternative estimates of developmental and reproductive toxicity. However, the epidemiological literature investigating the putative association between drinking water disinfection and cancer will be used to calculate an alternative incremental cancer risk per µg/L total OX (in µg Cl/L).

Use of this information to estimate risks associated with the treatment trains investigated here is complicated by the following factors:

- The studies do not provide quantitative measures of exposure to specific DBPs;
- The studies are not directly applicable to the treatment trains investigated here;
- The results are expressed in terms of relative risk, rather than the incremental probability of some outcome per unit intake; and
- The results are affected by general design problems affecting observational epidemiological studies (e.g., confounding, loss to follow-up, etc.).

Appendix C.2 is a review performed by NCEA Cincinnati of the epidemiological literature investigating the putative association between drinking water disinfection and cancer. Although investigators have reported an association between exposure to chlorinated drinking water and several types of cancer, the review concludes that a lack of findings or inconsistencies in these results preclude the derivation of a reasonable odds ratio (OR) estimate in all cases except bladder cancer. In that case, NCEA finds that the OR may be as high as 1.5, although it is very likely to be lower, and perhaps even 1.0, indicating no excess risk.

4.3.4. The Assumption of Statistical Independence. As noted in the introduction to Section 4, the baseline risk assessment assumes that the slope factor distributions for each of the DBPs are statistically independent. That is, new information, for example, that the true slope factor for DBP_1 is much higher than its original central estimate does not make it more likely that the slope factor for DBP_2 is also much higher than its original central estimate. It is conceivable that, for each health endpoint, the slope factors are positively correlated if the same type of error affects all of the animal bioassays in the same way. For example, the animals used in the bioassays may be more sensitive to DBP carcinogenicity than humans. In this case, all the DBP carcinogenicity estimates may be too high. Section 5 investigates the potential impact of incorrectly assuming statistical independence among the slope factor estimates.

5. RESULTS

5.1. ESTIMATED RISK

Figures 5-1 through 5-9 illustrate the cancer risks (5-1 through 5-3), developmental toxicity risks (5-4 through 5-6), and reproductive toxicity risks (5-7 through 5-9) associated with the two drinking water treatment trains considered here; they also illustrate the difference in risk between the two treatment trains:

- The first of the three figures for each health endpoint illustrates risks associated with the filter-Cl treatment train.
- The second illustrates risks associated with the O_3-filter-Cl treatment train.
- The third illustrates the risk reduction achieved by supplementing filter-Cl with ozone pretreatment. Negative values represent cases in which ozone pretreatment *increases* risk (i.e., the "improvement" is negative).

The horizontal axis in each figure represents variability (population heterogeneity introduced by differences in tap water consumption), and the vertical axis in each figure represents uncertainty. For example, the cancer risk incurred by the median individual exposed to water treated by the filter-Cl treatment train (Figure 5-1) is represented by the box and whiskers plot lying above the 50th percentile point on the horizontal axis. The box and whiskers plot above that point on the horizontal axis illustrates the following for the median individual:

The median risk, indicated by the horizontal line inside the rectangle;

- The interquartile confidence interval for risk (i.e., the 25th and 75th percentile for risk), indicated by the top and the bottom of the rectangle;
- The "upper confidence limit" and "lower confidence limit,"[3] indicated by the whiskers extending from the rectangle;

[3] The box and whisker plot was created using Systat version 8.0 (SPSS, 1998, Graphics Volume, p. 94). The documentation states that the lower whisker extends to a value that equals the 1st quartile minus 1.5 times the difference between the median and the lower quartile. The upper whisker extends to a value that equals the 3rd quartile plus 1.5 times the difference between the upper quartile and the median.

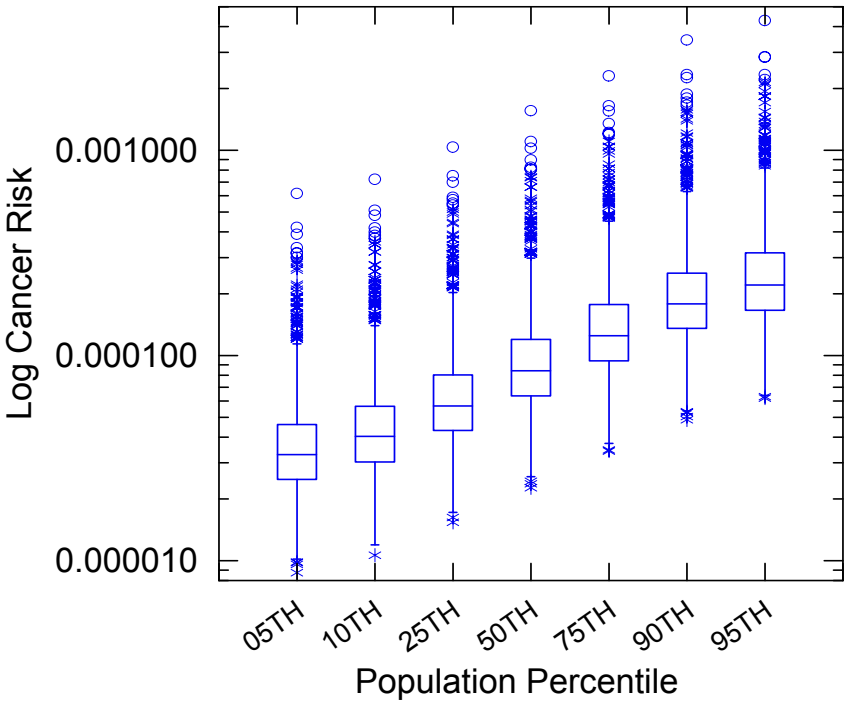


FIGURE 5-1

Lifetime Cancer Risk: Filter-Cl Treatment

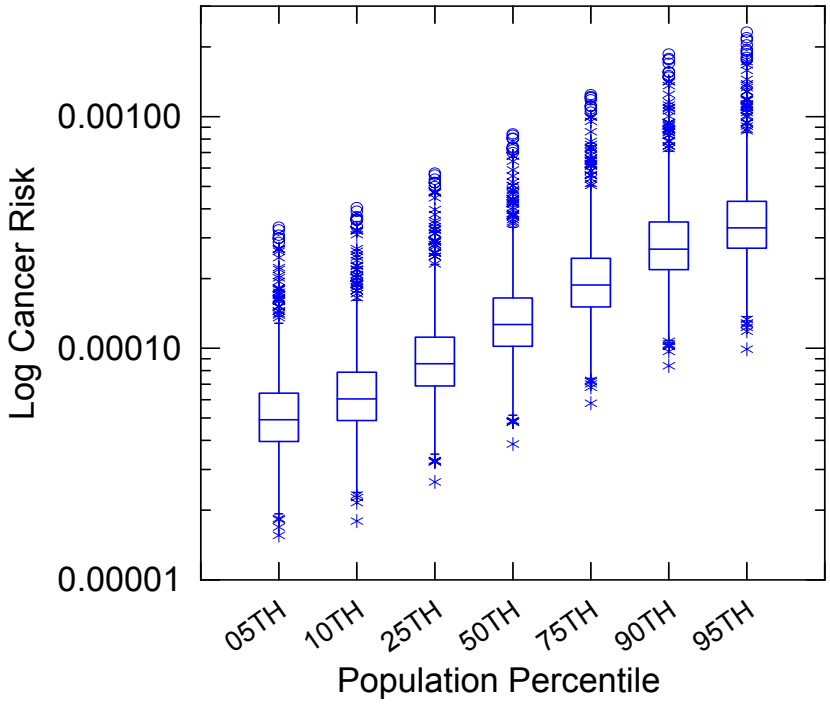


FIGURE 5-2

Lifetime Cancer Risk: O_3-Filter-Cl Treatment

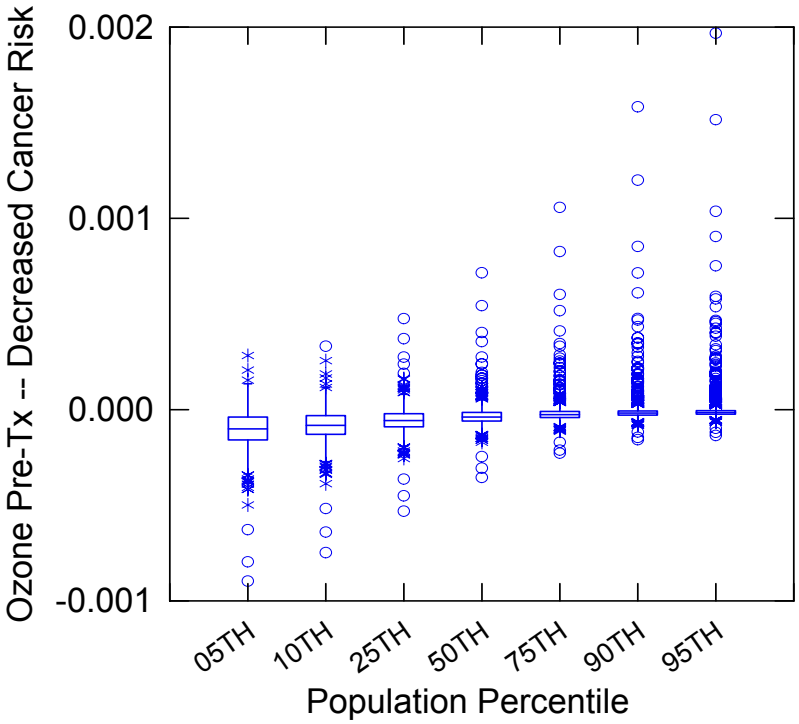


FIGURE 5-3

Reduction in Lifetime Cancer Risk Achieved by Adding Ozone Pretreatment

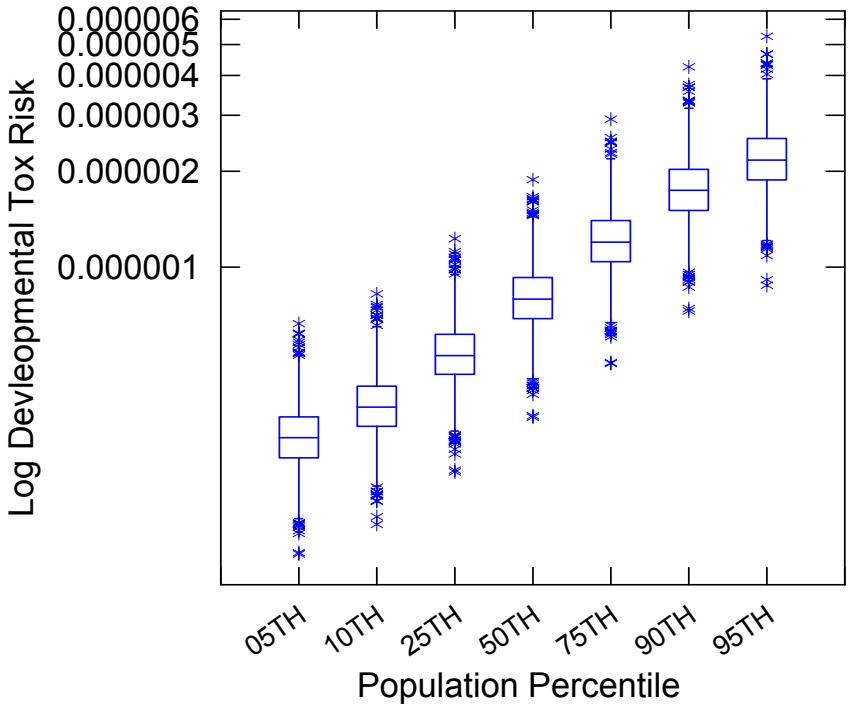


FIGURE 5-4

Lifetime Developmental Toxicity Risk: Filter-CI Treatment

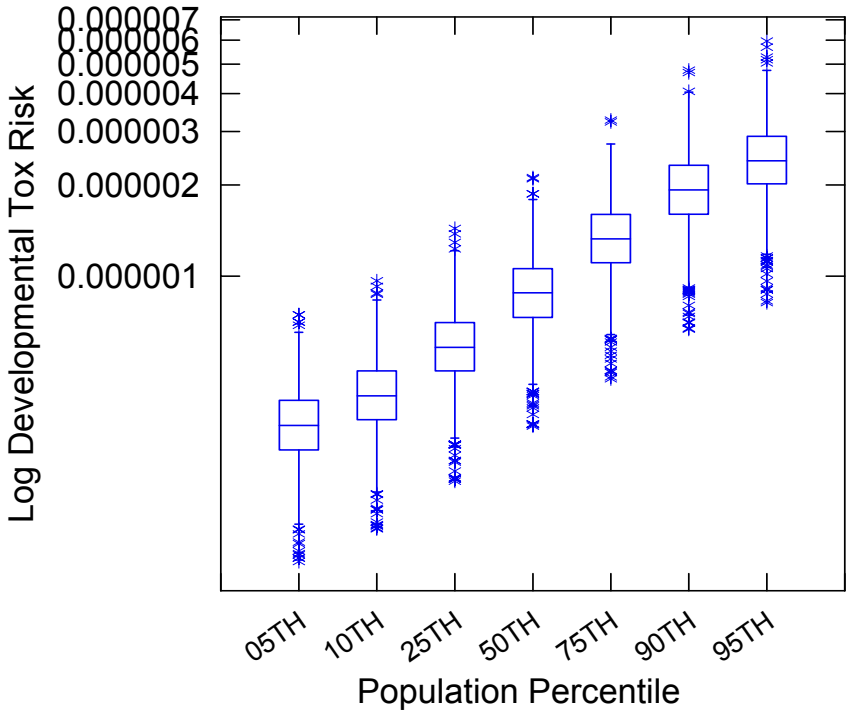


FIGURE 5-5

Lifetime Developmental Toxicity Risk: O_3-Filter-Cl Treatment

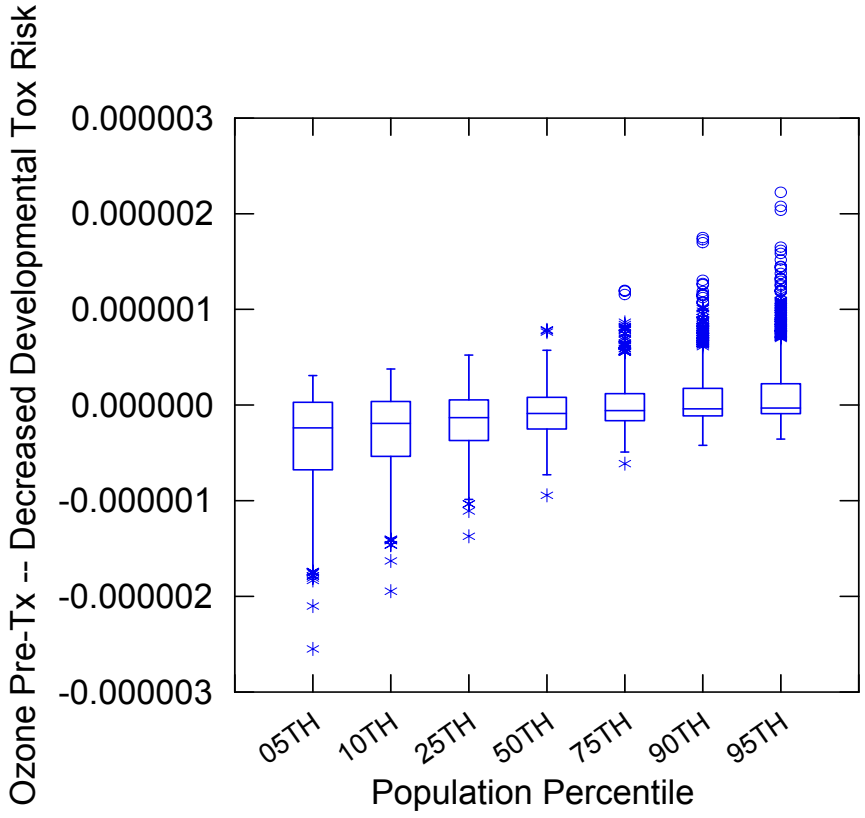


FIGURE 5-6

Reduction in Lifetime Developmental Toxicity Risk Achieved by Adding Ozone Pretreatment

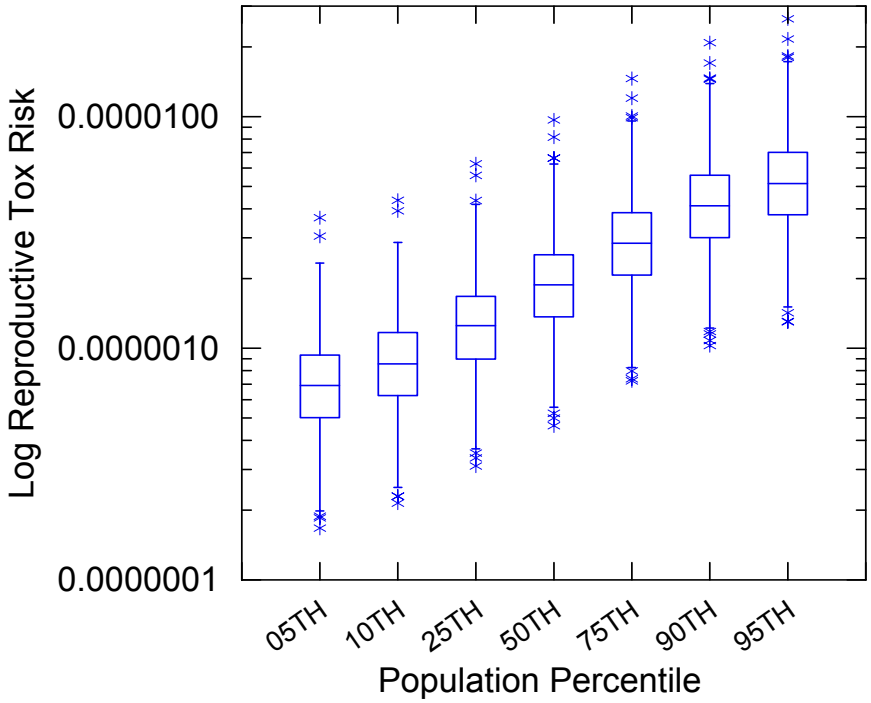


FIGURE 5-7

Lifetime Reproductive Toxicity Risk: Filter-Cl Treatment

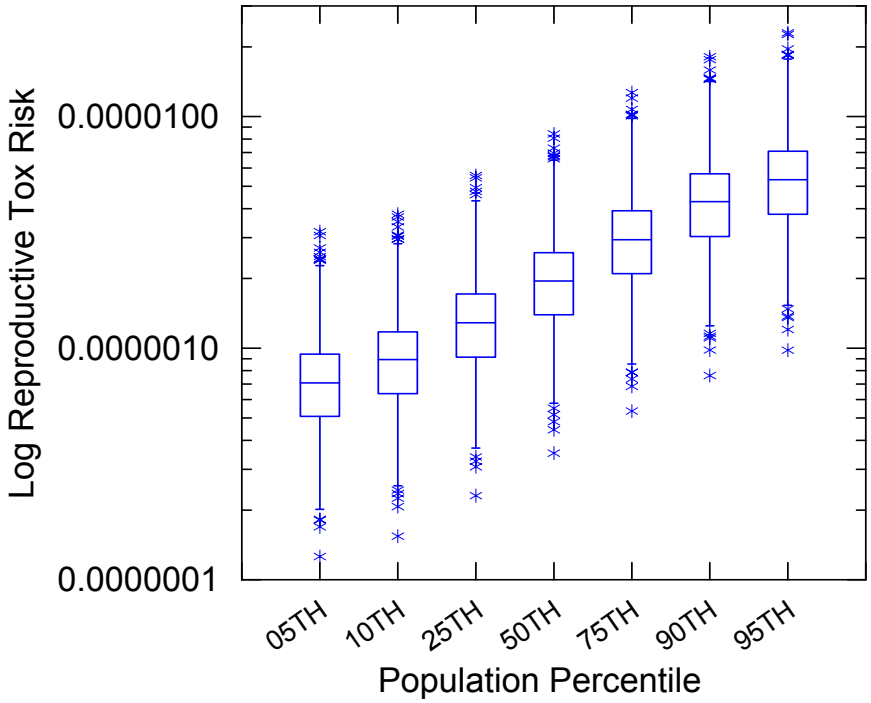


FIGURE 5-8

Lifetime Reproductive Toxicity Risk: O_3-Filter-Cl Treatment

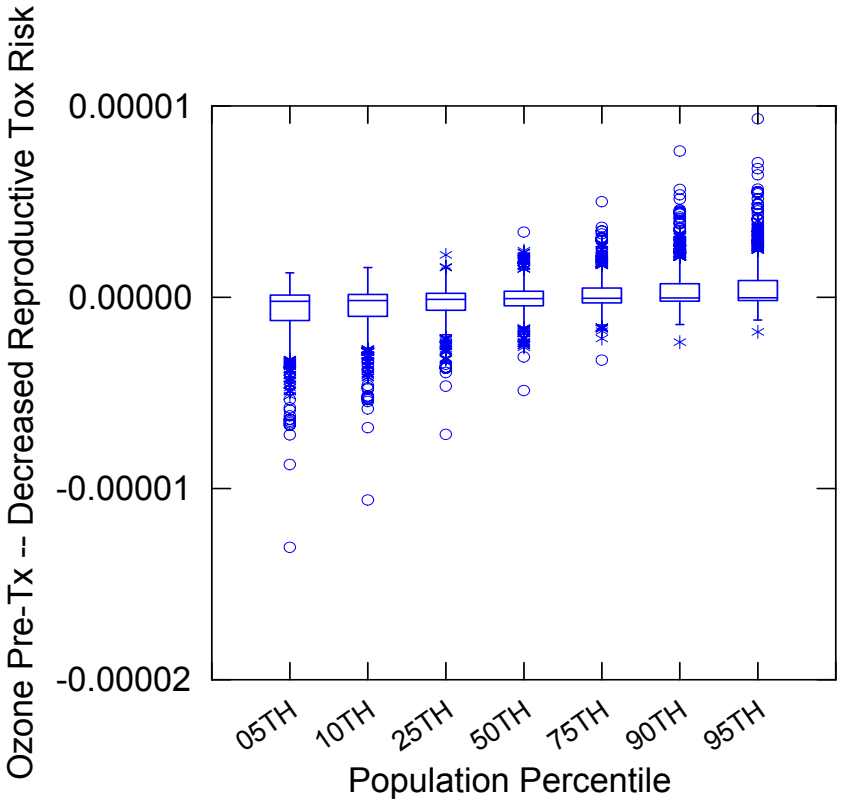


FIGURE 5-9

Reduction in Lifetime Reproductive Toxicity Risk Achieved by Adding Ozone Pretreatment

- Additional simulation results extending beyond the confidence limits, indicated by individually plotted points.

Note that in the first two figures in each set of three (Figures 5-1, 5-2, 5-4, 5-5, 5-7, and 5-8), the values on the vertical axis have been log-transformed (log base 10) because these values span several orders of magnitude in some cases. Because the risk "improvement" plotted in the third figure in each pair (Figures 5-3, 5-6, and 5-9) is negative in some cases, it was not possible to log-transform these results.

Finally, Table 5-1 quantifies uncertainty for the population average risk.

The population average statistics serve as a useful benchmark for the purpose of assessing the relative importance of parametric uncertainty (reflected in Table 5-1) and other sources of uncertainty (reviewed in Section 5.3).

5.2. PARAMETRIC UNCERTAINTY

Tables 5-2, 5-3, and 5-4 list for cancer, developmental toxicity, and reproductive toxicity, the fraction of the variance explained by each of the uncertain quantities considered in the risk assessment. Note that for each health endpoint, the tables include only those DBPs thought to contribute to toxicity.

5.3. NON-PARAMETRIC UNCERTAINTY

This section reviews the sources of uncertainty identified in Sections 3 and 4 that could not be quantitatively parameterized and hence are not addressed in Section 5.2.

5.3.1. Exposure Assumptions.

5.3.1a. Tap Water Intake: The Assumption that the Ingestion Pathway Dominates Intake. While there are no comprehensive and readily available data on the quantity of water that taken into the body via pathways other than ingestion, it is difficult to imagine that these alternative pathways more than double total intake. However, exposure via

TABLE 5-1

Plausible Range of Population Average Risk Values

Summary Statistic	Cancer		
	Filter-Cl	O_3-Filter Cl	Ozone Pre-Treatment Risk Reduction
Mean	1.4E-4	1.8E-4	-4.0E-5
5th percentile	5.2E-5	8.4E-5	-1.2E-4
10th percentile	5.9E-5	9.8E-5	-1.0E-4
25th percentile	7.6E-5	1.2E-4	-7.2E-5
50th percentile	1.0E-4	1.5E-4	-4.6E-5
75th percentile	1.4E-4	2.0E-4	-1.7E-5
90th percentile	2.3E-4	2.6E-4	1.2E-5
95th percentile	3.7E-4	3.6E-4	4.5E-5
95th pctl ¸ 5th pctl	7.1	4.3	
Summary Statistic	Developmental Toxicity		
	Filter-Cl	O_3-Filter Cl	Ozone Pre-Treatment Risk Reduction
Mean	9.9E-7	1.1E-6	-9.9E-8
5th percentile	6.5E-7	6.2E-7	-6.0E-7
10th percentile	7.1E-7	7.2E-7	-4.7E-7
25th percentile	8.3E-7	8.8E-7	-3.0E-7
50th percentile	9.6E-7	1.1E-6	-1.1E-7
75th percentile	1.1E-6	1.3E-6	9.6E-8
90th percentile	1.3E-6	1.5E-6	2.8E-7
95th percentile	1.4E-6	1.6E-6	3.9E-7
95th pctl ¸ 5th pctl	2.2	2.6	
Summary Statistic	Reproductive Toxicity		
	Filter-Cl	O_3-Filter Cl	Ozone Pre-Treatment Risk Reduction
Mean	2.5E-6	2.6E-6	-7.7E-8
5th percentile	1.1E-6	1.1E-6	-1.4E-6
10th percentile	1.3E-6	1.2E-6	-1.1E-6
25th percentile	1.7E-6	1.7E-6	-5.4E-7
50th percentile	2.3E-6	2.4E-6	-8.9E-8
75th percentile	3.1E-6	3.1E-6	3.9E-7
90th percentile	4.0E-6	4.3E-6	9.8E-7
95th percentile	4.8E-6	5.1E-6	1.3E-6
95th pctl ¸ 5th pctl	4.4	4.6	

TABLE 5-2

Proportion of Parametric Uncertainty in Cancer Risk Explained[a,b]

Concentration Filter-Cl	Disinfection Technology		
	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
BDCM			
CDBM			
$CHBr_3$			
CH			
DCA			
TCA			
Bromate			
Unidentified TOX	3%		13%
Concentration O_3-Filter-Cl	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
BDCM			
CDBM			
$CHBr_3$			
CH			
DCA			
TCA			
Bromate			1%
Unidentifed TOX		9%	26%
Slope Factor	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
BDCM	10%	13%	
CDBM	10%	24%	2%
$CHBr_3$			
CH		1%	
DCA	72%	46%	44%
TCA	2%		2%
Bromate		3%	10%

[a] The proportion of variance explained is equal to incremental sums of squares after all other parameters have been added to the regression model (see Equation 2-5) divided by the total model sums of squares.

[b] For clarity, only values exceeding 1% are displayed.

TABLE 5-3

Proportion of Parametric Uncertainty in Developmental Toxicity Risk Explained[a,b]

Concentration Filter-Cl	Disinfection Technology		
	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
DCA			
TCA			
MBA			
DBA			
BCA			
DCAN			
TCAN			
BCAN	1%		
DBAN			
Unidentified TOX	48%		32%
Concentration O_3-Filter-Cl	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
DCA			
TCA			
MBA			
DBA			
BCA			
DCAN			
TCAN			
BCAN			
DBAN			1%
Unidentified TOX		60%	62%
Filter-Cl	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3FilterCl
DCA	5%	2%	
TCA	8%	3%	
MBA			
DBA			

TABLE 5-3 cont.			
Filter-Cl	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3FilterCl
BCA			
DCAN	29%	22%	
TCAN			
BCAN	6%	6%	
DBAN		1%	1%

[a] The proportion of variance explained is equal to incremental sums of squares after all other parameters have been added to the regression model (see Equation 2-5) divided by the total model sums of squares.

[b] For clarity, only values exceeding 1% are displayed

TABLE 5-4

Proportion of Parametric Uncertainty in Reproductive Toxicity Risk Explained[a,b]

Concentration Filter-Cl	Disinfection Technology		
	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
DCA			
DBA			
BCA			
DBA			
BCA			
Unidentified TOX	93%		34%
Concentration O_3-Filter-Cl	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
DBA			
BCA			
Unidentified TOX		97%	68%
Slope Factor	Filter-Cl	O_3-Filter-Cl	Filter-Cl-O_3-Filter-Cl
DCA	7%	3%	
DBA			
BCA			

[a] The proportion of variance explained is equal to incremental sums of squares after all other parameters have been added to the regression model (see Equation 2-5) divided by the total model sums of squares.

[b] For clarity, only values exceeding 1% are displayed

alternative pathways may pose a different unit-risk. The extent to which this may be the case depends on factors such as the efficiency of DBP absorption via ingestion.

5.3.1b. Total Tap Water Ingestion is the Relevant Measure of Intake. As noted in Section 3.2.3, heating tap water may remove some of the volatile DBPs. Therefore, using total tap water as a measure of tap water intake may somewhat overstate exposure for some DBP compounds. The Canada Department of Health and Welfare (1981) reports both total tap water consumption and unheated tap water consumption for individuals of various ages.[4] These figures appear in Table 5-5.

Even if heating eliminated all DBPs, the data from the Canada Department of Health indicate that the impact on exposure would not be substantial, ranging from a decrease of 22% among children between the ages of 6 and 17, to a decrease of 62% among some adult age groups. These results translate into a difference of a factor of 1.3 (1 ÷ 78%) to 2.5 (1 ÷ 38%). Since not all DBPs are removed by heating, the actual impact of heating is probably less.

5.3.2. Toxicity Assumptions.

5.3.2.1. The Use of QSAR to Quantify the Fraction of Unidentified DBPs Associated with Each Health Endpoint — The true fraction of unidentified DBPs associated with inducing any of the three health endpoints analyzed here may range from 0% to 100%. Table 5-6 summarizes the impact of these extreme alternative assumptions on the mean population average risk.

[4] Beverages included as unheated were drinking water, ice/mix, other types of mixes, and reconstituted milk. Categories excluded were tea, coffee, soup, homemade beer and wine, popcycles, and baby formula.

TABLE 5-5

Fraction of Tap Water Consumed that is Unheated

	Age (Years)					
	<3	3 to 5	6 to 17	18 to 34	35 to 54	>55
Unheated (L/day)	0.46	0.74	0.9	0.68	0.59	0.59
Total (L/day)	0.61	0.86	1.14	1.38	1.55	1.57
Fraction unheated	75%	86%	78%	49%	38%	38%

TABLE 5-6

Impact of Alternative Assumptions for a α_h on Estimated Risk
(Excepted Value of the Population Mean Risk)

Health Endpoint	Base Analysis	Alternative Analyses	
		α = 0%	α = 100%
Filter-Chlorine			
Cancer	1.4E-4	5.2E-5	2.1E-4
Developmental Tox	9.9E-7	3.7E-7	1.8E-6
Reproductive Tox	2.5E-6	6.3E-7	5.1E-6
O_3-Filter-Chlorine			
Cancer	1.8E-4	6.6E-5	2.7E-4
Developmental Tox	1.1E-6	2.7E-7	1.7E-6
Reproductive Tox	2.6E-6	4.3E-7	4.3E-6

5.3.2.2. The Assumption that Unidentified DBPs Pose the Same Risk as Identified DBPs on a µg OX/L Basis — In place of the assumption that the unidentified DBPs pose the same risk as the identified DBPs on a mg OX/L basis (in µg Cl/L), the analysis could alternatively assume that the unidentified DBPs pose a lesser or greater risk. Table 5-7 summarizes the results of assuming that the risk from the unidentified DBPs is only 50% as great as it is for the identified DBPs on a mg Cl/L basis, or that the unidentified DBPs pose twice the risk on a mg Cl/L basis.

5.3.2.3. The Assumption that Chloroform is a Threshold Carcinogen — To assess the impact of the assumption that chloroform is a threshold carcinogen, an additional simulation was conducted using the assumption that the cancer dose-response function for this DBP has no threshold. The results appear in Table 5-8.

Whether or not chloroform is a carcinogen affects the cancer risk estimate for two reasons. First, because the concentration of chloroform substantially exceeds that of many of the other DBPs (see Section 3.1), its potential contribution to carcinogenicity is substantial. Second, because chloroform's concentration is large compared to that of other DBPs, its classification as a carcinogen affects the estimated risk associated with exposure to *unidentified* DBPs (see Equation 4-5b). However, chloroform's slope factor is less than the concentration-weighted average slope factor of the other identified DBPs (1.5×10^{-2} per mg/L for the filter-Cl treatment train and 2.8×10^{-2} per mg/L for the O_3-filter-Cl treatment train[5]). Hence, classifying it as a carcinogen increases the concentration of DBPs thought to be carcinogenic, but decreases the concentration-weighted toxicity of those carcinogens. On net, these two phenomena have a minimal,

[5] These values were computed using arithmetic mean estimated concentrations (Table 3-2) and geometric mean estimated slope factors (Table 4-2).

TABLE 5-7

Impact of Alternative Assumptions for the Relative Toxicity of Unidentified DBPs vs. Known DBPs on Estimated Risk
(Excepted Value of the Population Mean Risk)

Health Endpoint	Base Analysis	Alternative Analyses	
		Relative Tox = 50%	Relative Tox = 200%
Filter-Chlorine			
Cancer	1.9E-4	5.2E-5	2.4E-4
Developmental Tox	9.9E-7	3.7E-7	1.6E-6
Reproductive Tox	2.5E-6	6.3E-7	4.4E-6
O_3-Filter-Chlorine			
Cancer	1.8E-4	6.6E-5	2.9E-4
Developmental Tox	1.1E-6	2.7E-7	1.9E-6
Reproductive Tox	2.6E-6	4.3E-7	4.8E-6

TABLE 5-8

Plausible Range of Population Average Risk Values

Summary Statistic	Cancer					
	Filter-Cl		O_3-Filter-Cl		Ozone Pre-Treatment Risk Reduction	
	Base Analysis	Alternate Analysis[a]	Base Analysis	Alternate Analysis[a]	Base Analysis	Alternate Analysis[a]
Mean	1.4E-4	1.1E-4	1.8E-4	1.3E-4	-4.05E-5	-2.9E-5
5th percentile	5.2E-5	4.3E-5	8.4E-5	7.2E-5	-1.2E-4	-8.2E-5
10th percentile	5.9E-5	4.9E-5	9.8E-5	7.9E-5	-1.0E-4	-7.0E-5
25th percentile	7.6E-5	6.1E-5	1.2E-4	9.5E-5	-7.2E-5	-5.0E-5
50th percentile	1.0E-4	7.9E-5	1.5E-4	1.2E-4	-4.6E-5	-3.1E-5
75th percentile	1.4E-4	1.1E-4	2.0E-4	1.5E-4	-1.7E-5	-1.4E-5
90th percentile	2.3E-4	1.8E-4	2.6E-4	2.0E-4	1.2E-5	6.7E-6
95th percentile	3.7E-4	2.6E-4	3.6E-4	2.7E-4	4.5-E-5	3.0E-5

although somewhat negative, impact on the overall cancer risk estimate for each of the two treatment trains considered. It may be noted that the science of chloroform as a carcinogenic compound and its risk application are controversial and at this time (April, 1999) are undergoing additional external peer review by EPA's Science Advisory Board.

5.3.2.4. The Assumption that the DBP Slope Factor Distributions are Statistically Independent — The results in Table 5-9 compare the plausible range of population average risk values for the base analysis (slope factor estimates statistically independent) and an alternative analysis (slope factor estimates perfectly correlated for each health endpoint). For both the filter-Cl treatment train and the O_3-filter-Cl treatment train, the range of plausible values is wider when the slope factor estimates are assumed to be perfectly correlated. However, the two sets of analyses do not differ substantially, indicating that this source of uncertainty does not have an important impact on the results.

TABLE 5-9

Plausible Range of Population Average Risk Values

Summary Statistic	Cancer					
	Filter-Cl		O_3-Filter-Cl		Ozone Pre-Treatment Risk Reduction	
	Base Analysis	Alternate Analysis	Base Analysis	Alternate Analysis	Base Analysis	Alternate Analysis
Mean	1.4E-4	1.1E-4	1.8E-4	1.8E-4	-4.05E-5	-3.9E-5
5th percentile	5.2E-5	3.4E-5	8.4E-5	6.1E--5	-1.2E-4	-1.0E-4
10th percentile	5.9E-5	4.0E-5	9.8E-5	7.0E-5	-1.0E-4	-8.4E-5
25th percentile	7.6E-5	5.2E-5	1.2E-4	9.1E-5	-7.2E-5	-6.0E-5
50th percentile	1.0E-4	7.7E-5	1.5E-4	1.3E-4	-4.6E-5	-4.1E-5
75th percentile	1.4E-4	1.3E-4	2.0E-4	1.8E-4	-1.7E-5	-2.2E-5
90th percentile	2.3E-4	2.4E-4	2.6E-4	2.9E-4	1.2E-5	-3.4E-6
95th percentile	3.7E-4	4.3E-4	3.6E-4	4.2E-4	4.5-E-5	2.5E-5
95th pctl ÷ 5th pctl	7.2	12.8	4.3	6.9		
Developmental Toxicity						
Mean	9.9E-7	9.9E-7	1.1E-6	1.1E-6	-9.9E-8	-7.9E-8
5th percentile	6.5E-7	5.2E-7	6.2E-7	5.3E-7	-6.0E-7	-5.7E-7
10th percentile	7.1E-7	5.8E-7	7.2E-7	6.0E-7	-4.7E-7	-4.4E-7
25th percentile	8.3E-7	7.2E-7	8.8E-7	7.7E-7	-3.0E-7	-2.4E-7
50th percentile	9.6E-7	9.2E-7	1.1E-6	1.0E-6	-1.1E-7	-6.6E-8
75th percentile	1.1E-6	1.2E-6	1.3E-6	1.3E-6	9.6E-8	9.8E-8
90th percentile	1.3E-6	1.5E-6	1.5E-6	1.6E-6	2.8E-7	2.6E-7
95th percentile	1.4E-6	1.7E-6	1.6E-6	1.8E-6	3.9E-7	3.5E-7

TABLE 5-9 cont.						
Summary Statistic	Cancer					
	Filter-Cl		O_3-Filter-Cl		Ozone Pre-Treatment Risk Reduction	
	Base Analysis	Alternate Analysis	Base Analysis	Alternate Analysis	Base Analysis	Alternate Analysis
95th percentile	2.2	3.3	2.5	3.5		
Reproductive Toxicity						
Mean	2.5E-6	2.6E-6	2.6E-6	2.6E-6	-7.7E-8	7.8E-9
5th percentile	1.1E-6	8.5E-7	1.1E-6	8.6E-7	-1.4E-6	-1.3E-6
10th percentile	1.3E-6	1.1E-6	1.2E-6	1.0E-6	-1.1E-6	-9.1E-7
25th percentile	1.7E-6	1.5E-6	1.7E-6	1.5E-6	-5.4E-7	-4.1E-7
50th percentile	2.3E-6	2.2E-6	2.4E-6	2.3E-6	-8.9E-8	9.1E-9
75th percentile	3.1E-6	3.2E-6	3.1E-6	3.2E-6	3.9E-7	4.5E-7
90th percentile	4.0E-6	4.6E-6	4.3E-6	4.5E-6	9.8E-7	9.4E-7
95th pctl ÷ 5th pctl	4.4	6.7	4.8	6.5		

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APPENDIX A

EPA Pilot-Scale Investigation of the Formation and Control of Disinfection Byproducts

PILOT-SCALE INVESTIGATION OF THE FORMATION AND CONTROL OF DISINFECTION BYPRODUCTS

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Ozone's role in water treatment in the USA is increasing for a number of reasons. It is a powerful disinfectant, resulting in lower C-t (concentration x time) requirements than chlorine, chlorine dioxide or chloramines. It will not form trihalomethanes (THMs), except in the case of high bromide in the source water. It will react with THM precursors, under appropriate conditions, to lower THM formation potential (THMFP). It can also enhance the flocculation of particulates, improve taste and odor, remove color, and control iron and manganese.

Maximum contaminant levels (MCLs) of THMs will likely be lowered in 1991 under the Disinfection-Disinfection Byproducts (D-DBP) Rule. The 1986 Amendments to the Safe Drinking Water Act require that the EPA regulate new contaminants beginning in 1991. Candidate contaminants are given in the Drinking Water Priority List (DWPL) and include THMs, numerous other halogenated DBPs and ozone byproducts. The DWPL and a summary of the D-DBP Rule are given in the Journal AWWA (1).

This study, which was conducted by EPA's Drinking Water Research Division (DWRD), examined byproduct formation and control in three parallel pilot plants employing conventional treatment of Ohio River water. In one plant, chlorine was applied following filtration, allowing conventional treatment to remove precursor materials. In a second plant, chlorine was also applied following filtration, but ozone was applied to the raw water to enhance precursor control. In a third plant, monochloramine was applied to filtered water with ozone applied to raw water. The DBPs that were studied are given in Table 1.

Analytic methods for the ozone byproducts and for several of the non-THM halogenated DBPs in Table 1 are under development. The methods and sample preservatives used in this study are given in the Journal AWWA (2-4).

HALOGENATED DBP SAMPLING

Samples were collected for both instantaneous and terminal total trihalomethanes (inst TTHM and term TTHM). In the terminal sample the THM reaction is driven to completion thereby exhausting the precursor material that is present and forming the highest concentration of THMs. In this study, term TTHM concentrations occurred when samples were taken from the pilot plants and chlorinated on the bench with 12 mg/L added chlorine and stored headspace-free, in the dark, for seven days, at 25°C. The pH was that of the pilot plant finished water, i.e., near 8.1. Free chlorine residuals were present after seven days to ensure that the reactions were not chlorine limited. For any sample, the unreacted precursor is represented by the THMFP which is the difference between the term TTHM and the back-ground or inst TTHM. The term TTHM and the THMFP allow an assessment of the control of precursor during treatment. This approach to THM sampling is described in detail by Stevens and Symons (5).

For compliance with MCLs, distribution system inst TTHM is important. In this study, the inst TTHM in a simulated distribution system (SDS TTHM) was determined by storing finished water samples in the dark, at 25°C, headspace-free, for three days, without added chlorine. Chlorine or chloramine was applied according to the Ten States Standards (TSS) (6); residuals after three days were near 0.2 mg/L free chlorine or 0.7 mg/L monochloramine.

Because of limited analytic resources, term TTHM samples were not collected at each sample point, but only for raw, settled and finished waters, as previous studies indicated that most removal of precursor occurred with sedimentation and that little additional removal occurred with filtration (7).

Instantaneous and SDS samples were collected for all halogenated DBPs, Terminal samples were not collected for haloacetonitriles, 1,1,1-tri-chloroporopanone or chloral hydrate because those byproducts are not stable for seven days near pH 8 (2), or for cyanogen chloride because it is not stable in the presence of free chlorine.

PILOT-SCALE FACILITIES

DWRD's pilot plants and its counter-current ozonation chamber are described in detail elsewhere (8). These parallel plants were operated continuously for one week. Following start-up and the establishment of steady-state operation, samples were collected daily. Sample points were selected to isolate unit processes and are indicated by circles in Figure 1.

For this study, mean values are reported. Temperatures in pilot plant waters ranged from 26 to 28°C. pH ranged from 7.4 to 8.1. Raw water turbidity ranged from 9 to 20 Ntu; settled water turbidity averaged 1.6 Ntu; filtered water turbidities were less than 0.18 Ntu. Each filter was backwashed with water from its dedicated clear well. Backwashing occurred near 30 inches head loss (every three days approximately) and followed TSS practices. To apply chlorine, calcium hypochlorite was added. To apply monochloramine, calcium hypochlorite and ammonium hydroxide were added in that order ahead of in-line mixers in series. The ammonia was added in stoichiometric excess. Samples taken immediately downstream of the two in-line mixers showed only traces of free chlorine.

Mean ozonation conditions are given in Table 2. An applied ozone-to-TOC ratio of 0.8 was chosen as representative of conditions typically employed in Europe as a pre-oxidant. At the time of this study, the DPD method was used to determine dissolved ozone residuals. Mean residuals effluent from the contactor and mix tank were 0.47 and 0.14 mg/L, respectively. No ozone was detected in the floc tank effluent.

MICROBIOLOGICAL SAMPLING

Bacteria and phage were spiked into raw water to increase microbiological densities to approximately 4 logs so as to monitor their control through the various unit processes. Total coliform (TC) and heterotrophic plate count (HPC) bacteria were added as primary sewage (1 to 1,000 dilution). As viral indicators, MS-2 phage were added via in-line mixer. Assimilable organic carbon (AOC) was monitored, following the procedure of van der Kooij, et al (9), to assess the effect of ozone on conversion of natural organic matter (NOM) to materials assimilable by heterotrophs that could potentially cause regrowth:problems in distribution systems. Similarly, coliform growth response (CGR) was monitored, following the procedure, of Rice (10), to assess the effect of ozone on materials assimilable by coliforms.

RESULTS AND DISCUSSION

Halogenated DBPs

Using TOX as a surrogate for halogenated DBPs, comparative formation and control may be seen in Figure 2, where data representing the three parallel plants are given. Approximately 19 percent of the precursor material was removed (comparing mean terminal concentrations of 521 and 421 µg Cl/L) by conventional treatment. With ozone applied ahead of conventional treatment, 27 percent of the precursor was removed;

however, removal in this case must be considered as both the separation of precursor as a result of coagulation and clarification and the oxidation of precursor as a result of ozonation. Because these data represent mean values over a week's operation, the difference in means of settled waters were t-tested. At the 95 percent confidence level, the means were not different suggesting that ozone's effect on precursor control, at the ozone conditions selected, was not significant. Further t-testing indicated that, for most compounds, apparent changes in precursor from settled water, through filtration, to clear well storage were insignificant at the 95 percent confidence level. In Figure 2, for example, there was no difference, statistically, in mean term TOX concentrations of 421 and 440 ug Cl/L for waters that were pre-ozonated. Data on control of precursor for TOX and other parameters are presented in Table 3, and similarly suggest that ozone's effect on precursor was not significant for TOC or for specific halogenated DBPs. Indeed, for the more heavily brominated DBPs and for chloropicrin, ozone's effect is detrimental, as will be discussed. (In Table 3, data from the two chlorinated plants were statistically tested.)

Tables 4 and 5 present mean DBP concentrations from the three pilot plants and statistical tests of data from the two plants applying chlorine. These tables reveal much about the formation and control of halogenated DBPs:

(1) The use of ozone and chloramine resulted in the lowest formation of halogenated DBPs because free chlorine was not present to drive these reactions. The only exception to this was cyanogen chloride which was not detected until monochloramine was applied.

(2) When free chlorine was applied, concentrations were higher in SDS water (3-day stored) than in finished water (clear well) indicating that as long as a residual is present and precursor has not been exhausted, concentrations will continue to increase. This increase in instantaneous concentration may be seen in Figure 2 for TOX and in Figure 3 for chloroform. These figures both indicate sufficient precursor remaining in finished water to react with residual chlorine. 1,1,1-Trichoropropanone was the exception in this case. Its instability near pH 8 at 25°C over three days accounts for the decrease, as seen in Figure 4.

(3) When monochloramine was applied, concentrations in finished and SDS waters were statistically the same for most halogenated DBPs. Exceptions were cyanogen chloride, as noted, 1,1,1-trichlaropropanone (Figure 4), and chloral hydrate. Clearly, monochloramin drives these reactions, but factors effecting the formation of these non-THM DBPS are not well understood and require research.

(4) On a weight basis, the haloacetic acids account for more halogenated DBP production than other compounds, with the exception of THMs. Table 6 converts each halogenated DBP to its TOX equivalent, i.e., as ug Cl/L, and illustrates that the haloacids and the THMs comprise more than three-fourths of accounted-for TOX. It is interesting to note that over half the TOX remains unaccounted for; therefore, analytic means to elucidate other halogenated DBPs remain a research priority.

(5) Although differences in precursor control were small with and without ozonation and not significant at the 95 percent confidence level (Table 3), changes in precursor were apparent when examining differences in instantaneous DBPs found in chlorinated finished and SDS waters (Tables 4 and 5). In the SOS water that was ozonated, the mean chloroform concentration was 39.6 ug/L, while in the parallel water that was not ozonated, the mean concentration was 55.5 ug/L. Figure 3 illustrates this advantage of ozonation for chloroform. Results of statistical tests in Tables 4 and 5 show that (a) this advantage holds for other more heavily chlorinated DBPs, i.e., di- and trichloroacetic acid, (b) the effects of ozonation can not be statistically differentiated for many of the DBPs, and (c) for the more heavily brominated DBPs and for chloropicrin, ozonation results in more, rather than less, DBP formation. This advantage of ozone on the formation of the more heavily chlorinated DBPs is seen in Figure 3 for chloroform and in Figure 5 for dichloroacetic acid. The disadvantage of ozone in the case of the more heavily brominated DBPs is seen in Figure 6 for dibromochloromethane and in Figure 7 for dibromoacetic acid. In the case of dibromoacetic acid, the precursor increased 26 percent (comparing mean terminal concentrations of 1.39 and 1.5 ug/L), as seen in Figure 7 and Table 3, and continued to increase in downstream Processes. This increase in precursor is not well understood. The THM reaction will proceed more rapidly when driven by bromine (which is converted from bromide by chlorine) than when driven by chlorine. Note in Figures 6 and 7 that the concentrations of these more heavily brominated DBPs in 3-day stored waters reached those of the raw water THMFP when chlorine alone was used. However, in Figures 3 and 5, the concentrations of the more heavily chlorinated DBPs in 3-day stored waters did not reach those of their raw water THMFP when chlorine alone was used because the chlorine-driven reactions are slower. Conversely, in Figures 6 and 7 the concentrations of the more heavily brominated DBPs in 3-day stored waters where both ozone and chlorine were used exceeded those of the raw water THMFP. Perhaps intermediate oxybromine species were created in the ozone contactor that continued to slowly increase the precursor concentration in downstream processes in the absence of an ozone residual. Another contributing factor may be the change in the bromine-to-chlorine ratio. As will be discussed, ozone lowered the chlorine demand thereby increasing this ratio on the

ozone/chlorine plant. This would favor the formation of the more heavily brominated DBPs. The conversion by ozone of bromide to bromine that would rapidly drive the THM or haloacid reaction does not appear to be significant because no increase in either inst dibromochloromethane (Figure 6) or inst dibromoacetic acid (Figure 7) was observed in ozonated and settled waters. The detrimental effect of ozone on precursor in the presence of bromide appears to be significant and needs to be studied.

(6) The precursor to the chloropicrin reaction also increased significantly upon ozonation. It continued to increase in downstream processes after the dissolved ozone residual had dissipated. See Figure 8. The concentration in the 3-day stored water exceeded the raw water THMFP in the plant where preozonation occurred. This behavior is likely related to the nitrogenous nature of the chloropicrin's precursor material and ozone's reaction with this material. This was discussed by Hoigne and Bader (11).

(7) Ozonation lowered the chlorine demand of the water. On the plant were chlorine only was applied, a mean dose of 3.04 mg/L was sufficient to carry a 3-day mean residual of 0.2 mg/L; on the ozone/chlorine plant, a mean dose of only 2.82 mg/L was required to carry the same residual. The effect of chlorine dose on the formation of many of these halogenated DBPs is not well known. Therefore, the lower concentrations of inst DBPs observed on the ozone/chlorine plant, compared to the chlorine-only plant, may be due to the lower chlorine dose and/or ozone's effect on precursor as discussed previously.

Microbiological Parameters

On the plants where ozone was employed, significant reduction in bacterial and phage densities took place in the contactor. Figure 9 describes microbiological control on the plant employing ozone and monochloramine. Bacterial counts were higher in finished waters when chloramine was applied (Figure 9) than when chlorine was applied. Ozone brought about approximately two-and-one-half log reductions in both TC and HPC. No MS-2 phage were detected in the effluent from tile contactor, indicating greater than a three-and-one-half log reduction of that viral indicator. This single counter-current contactor would be similar to the first chamber in a full-scale, multi-chambered contactor. It is interesting to note that current language in the Surface Water Treatment Rule (SWTR) allows no credit for viral or Giardia disinfection in a first chamber, assuming that ozone is being used in that chamber to satisfy demand (12). These data suggest that language is too restrictive. It is also interesting to note that counts of surviving heterotrophs significantly increased downstream of the ozone contactor. It is assumed that they utilized the lower molecular weight, easily assimilable NOM produced from the reaction between

ozone and higher molecular weight NOM. Both filtration and post disinfection provided control of heterotrophs. Coliforms surviving the ozone contactor apparently utilize different materials; consequently, their counts decreased through conventional treatment.

On the plant employing chlorination only, conventional treatment lowered TC, HPC and MS-2 phage densities approximately two logs. Post-chlorination lowered the densities of all three parameters to their detection levels.

Ozone Byproducts

The production of formaldehyde is seen in Figure 10. Upon ozonation, mean formaldehyde concentrations reached 26.3 ug/L. Concentrations subsequently declined through conventional treatment but were boosted again upon either clear well chlorination or chloramination. Figure 11 illustrates similar behavior of acetone and glyoxal to that of formaldehyde on the ozone/chlorine plant. Glaze, et al. (13,14) discussed possible mechanisms for the formation of aldehydes upon ozonation. Chlorine's ability to produce formaldehyde was also seen on the plant employing chlorination only.

The loss of formaldehyde, acetone and glyoxal during conventional treatment is assumed to be due to biodegradation by bacteria represented by the HPC. This is described on the ozone/chlorine plant in Figure 12 wherein the decline in formaldehyde concentration through flocculation and sedimentation is matched by an increase in HPC densities. Since formaldehyde is common to both Figures 11 and 12, acetone and glyoxal are, like formaldehyde, assumed to be utilized by the bacteria.

Figure 12 also plots AOC and illustrates that it correlates well with formaldehyde concentrations, therefore, with acetone and glyoxal concentrations also. The bacteria apparently utilizing the aldehydes and ketone as nutrients are doing the same with AOC. Indeed, AOC was developed as a tool to measure bacterial regrowth potential in distribution systems (9). It is clear that increases in AOIC upon ozonation should be controlled in the treatment plant before release to the distribution system, and that optimizing bioactivity in the processes downstream of the ozone contactor is a prudent approach. In this study, concentrations of AOC, aldehydes and ketones were apparently biodegraded in the filter. The filter was backwashed with chlorinated water from its clear well. While sufficient samples of AOC and HPC were not collected to confirm this, it appears that the periodic exposure to chlorine was either not sufficient to destroy bioactivity on the filter, or the filter reestablished its bioactivity quickly following backwashing as it was again exposed to HPC bacteria received

from the settled water. The detrimental effect of backwashing biological filters with disinfected water needs to be studied.

Coliform growth response attempts to measure the regrowth potential of coliforms in the same manner that AOC attempts to measure the regrowth potential of heterotrophs. Figure 12 shows that CGR and AOC correlated well through the ozone/chlorine plant indicating that the CGR enhanced by ozonation was also biodegraded. With post chlorination, however, their behavior was different. AOC increased. with chlorination suggesting regrowth potential for species like Pseudomonas fluorescens, P-17, on which the parameter is based (9). The increase in AOC with clear well chlorination, to near 200 ug/L C-eq/L, is unusually high compared with similar data (10). The CGR decreased with chlorination suggesting no coliform regrowth potential.

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TABLE 1
Disinfection Byproducts

trihalomethanes (THM)	haloacetic acids (HAA)
chloroform ($CHCl_3$)	trichloroacetic acid (TCAA)
bromodichloromethane ($CHBrCl_2$)	dichloroacetic acid (DCAA)
dibromochloromethane ($CHBr_2$,cf)	chloroacetic acid (CAA)
bromoform ($CHBr_3$)	bromochloroacetic acid (BCAA)
haloacetonitriles (HAN)	bromoacetic acid (BAA)
trichloroacetonitrile (TCAN)	dibromoacetic acid (DBAA)
dichloroacetonitrile (DCAN)	aldehydes and ketones
bromochloroacetonitrile (BCAN)	formaldehyde
dibromoacetonitrile (DBAN)	glyoxal
chloral hydrate (CH)	acetone
1,1,1-trichloropropanone (111-TCP)	chloropicrin (CP)
cyanogen chloride (CNC1)	total organic halogen (TOX)

TABLE 2
Ozone Conditions

counter-current column, 6-inch diameter
60 micron, 1-inch spherical stone diffuser

water depth, ft = 8.67
water flow rate, gpm = 1.67
0_3 gas phase, wt % :1.45
gas flow rate, Lpm :0.63
gas/liquid = 0.1

contact time to min - 2.3
contact time: theoretical, min. - 7..5
contact time, $t_{100,}$ min - 22.4

applied 0_3, mg/L - 1.93
off gas, mg/L - 0.09
transferred 0_3, mg/L - 1.84
dissolved residual 0_3, mg/L - 0.47
0_3 demand, mg/L - 1.37

transfer efficiency, % = 95.6

0_3/TOC = 1.93/2.41 - 0.8

Table 3

PRECURSOR CONTROL

COMPOUND	PERCENT REMOVAL			T-TEST		
	O_3/NH_2C1	O_3/NH_2C1_2	POST $C1_2$	BETTER WITH O_3	SAME	BETTER WITHOUT O_3
TOC	20	20	11		X	
TOX	27	27	19		X	
TTHM	33	33	30		X	
$CHCl_3$	39	39	33		X	
$CHBrCl_2$	20	20	25		X	
$CHBr_2Cl$	--31	-31	-11			X
CP	-53	-53	31			X
TOTAL HAA						
TCAA	30	30	21		X	
DCAA	24	24	11		X	
CAA	35	35	29		X	
BCAA	18	18	18		X	
DBAA	21	21	11		X	
	-26	-26	-13			X

- At 95 percent confidence level

Table 4

DBP FORMATION IN FINISHED WATERS

COMPOUND	FORMATION ug/L			T-TEST		
	O_3/NH_2C1	O_3/NH_2C1_2	POST $C1_2$	BETTER WITH O_3	SAME	BETTER WITHOUT O_3
TTHM	5.0	32.8	55.2	X		
$CHCl_3$	4.2	13.0	30.4	X		
$CHBrCl_2$	0.6	10.3	17.6	X		
$CHBr_2Cl$	0.1	9.2	7.0			X
$CHBr_3$	ND	0.3	ND		X	
TOTAL HAN	3.3	3.2	3.8		X	
DCAN	2.8	1.9	2.4		X	
TCAN	ND	0.1	ND		X	
BCAN	0.3	0.6	1.0		X	
DBAN	0.3	0.7	0.4		X	
111 – TCP	0.1	2.4	2.1		X	
CP	ND	0.6	0.1			X
CH	ND	2.0	3.2		X	
CNCI	1.6	ND	ND			
TOTAL HAA	3.6	19.6	36.0	X		
TCAA	1.5	5.3	11.8	X		
DCAA	1.7	8.0	17.0	X		
CAA	0.2	0.7	0.7		X	
BCAA	0.2	3.9	5.3	X		
BAA	0.1	0.2	0.2		X	
DBAA	ND	1.6	1.0			X

ND-NOT DETECTED

AT 95% CONFIDENCE LEVEL

Table 5

DBP FORMATION IN SIMULATED DISTRIBUTION WATERS

COMPOUND	FORMATION ug/L			T-TEST		
	O_3/NH_2C1	O_3/NH_2C1_2	POST $C1_2$	BETTER WITH O_3	SAME	BETTER WITHOUT O_3
TTHM	5.6	75.1	90.4	X		
$CHCl_3$	4.5	39.6	55.5	X		
$CHBrCl_2$	0.8	21.1	24.4		X	
$CHBr_2Cl$	0.2	13.0	10.2			X
$CHBr_3$	ND	1.5	0.3			X
TOTAL HAN	2.9	4.8	5.7		X	
DCAN	2.4	2.6	3.5		X	
TCAN	ND	ND	0.2		X	
BCAN	0.4	1.7	1.9		X	X
DBAN	0.2	0.6	0.1			
111 – TCP	0.4	1.1	0.8		X	
CP	0.1	1.6	0.5			X
CH	0.8	5.8	4.2			X
CNCI	2.5	ND	ND			
TOTAL HAA	0.1	39.7	62.6	X		
TCAA	1.5	10.0	20.1	X		
DCAA	3.9	19.2	30.9	X		
CAA	0.5	1.5	1.4		X	
BCAA	0.3	6.8	8.5	X		
BAA	0.1	0.3	0.3		X	
DBAA	ND	2.0	1.5			X

ND-NOT DETECTED

AT 95% CONFIDENCE LEVEL

Table 6

PERCENT OF TOX IN SIMULATED DISTRIBUTION WATER

COMPOUND	O_3/NH_2C1	O_3/NH_2C1_2	POST $C1_2$
TTHM	8.8	26.6	26.5
$CHCl_3$	7.7	17.0	19.1
$CHBrCl_2$	0.8	5.2	4.8
$CHBr_2Cl$	0.3	4.1	2.6
$CHBr_3$	0.0	0.3	0.1
TOTAL HAA	6.5	10.1	13.4
DCAA	4.1	5.1	6.6
TCAA	1.9	3.1	5.1
BCAA	0.2	1.3	1.3
CAA	0.3	0.3	0.2
DBAA	0.0	0.3	0.2
BAA	0.1	0.1	0.1
TOTAL HAN	3.3	1.3	1.2
DCAN	2.9	0.8	0.9
BCAN	0.3	0.4	0.3
DBAN	0.1	0.1	0.1
TCAN	0.0	0.0	0.1
CH	0.9	1.8	1.1
CP	0.1	0.5	0.1
111 - TCP	0.5	0.4	0.2
CNCI	2.8	0.0	0.0
ACCOUNTED	22.9	40.7	42.5
UNACCOUNTED	77.3	59.3	57.5

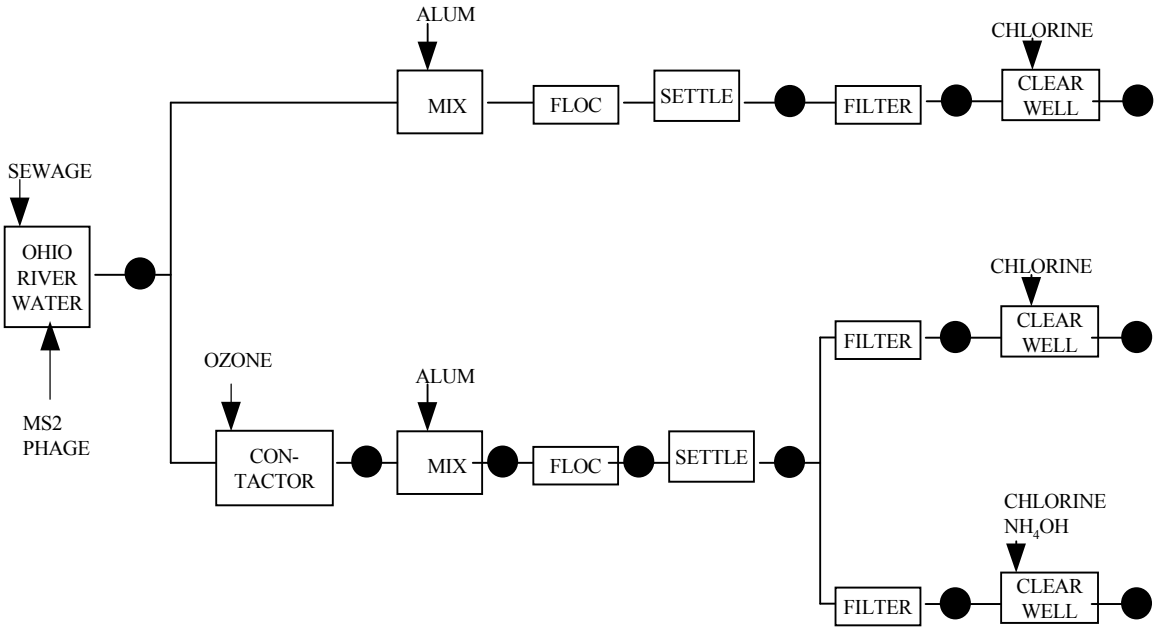

Figure 1.
DWRD PILOT PLANT

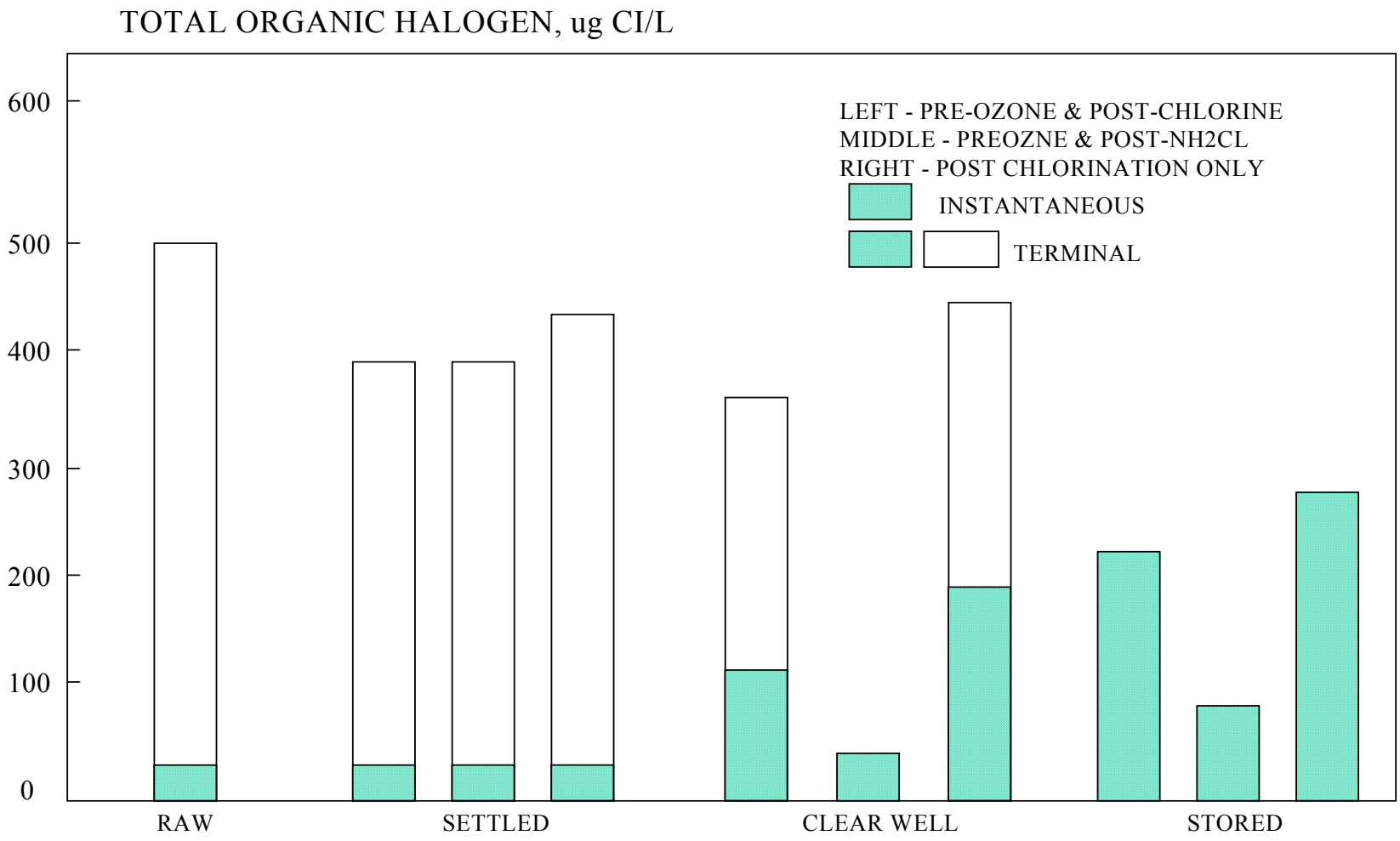

Figure 2. Formation and Control of TOX

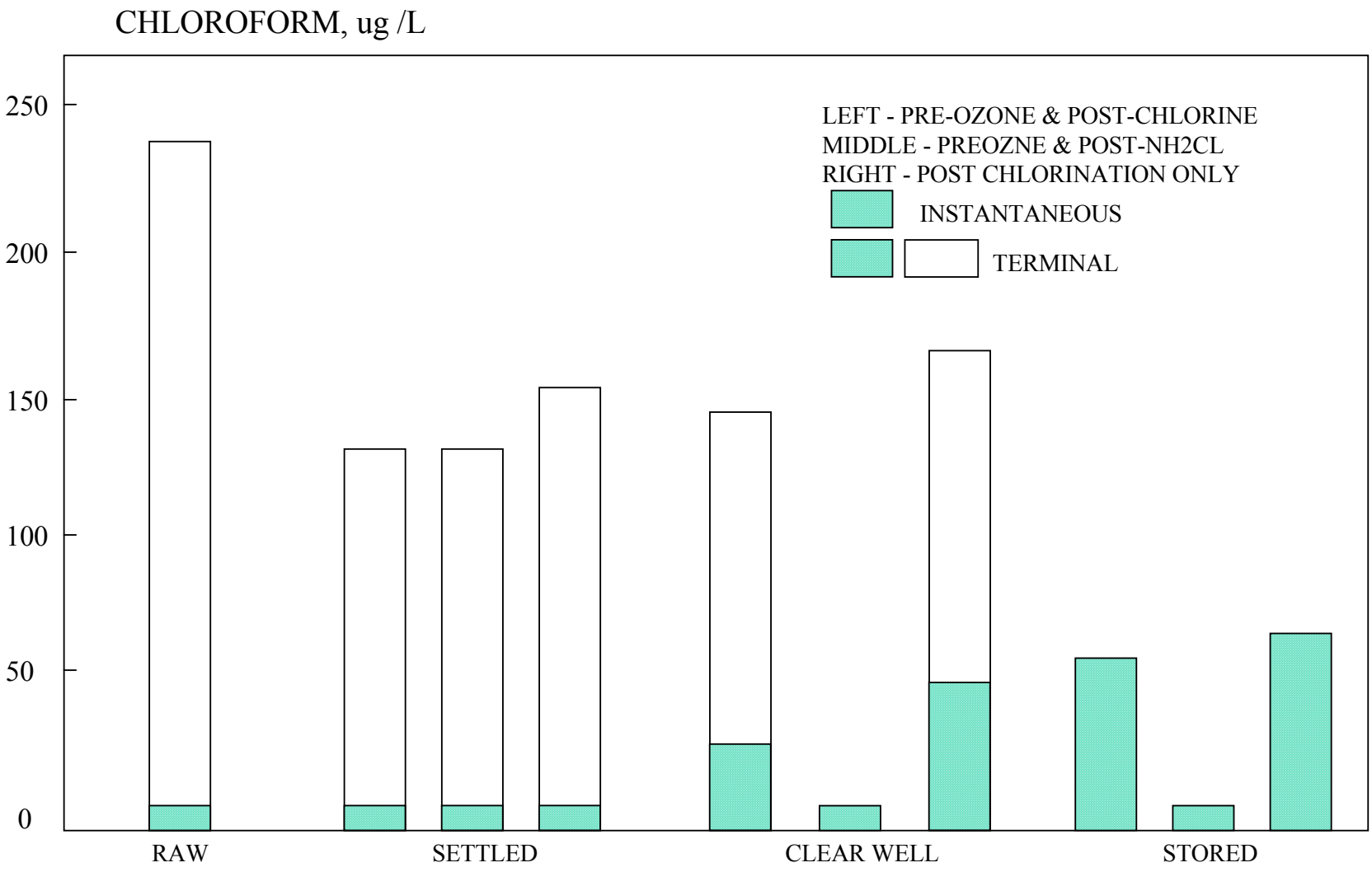

Figure 3. Formation and Control of Chloroform.

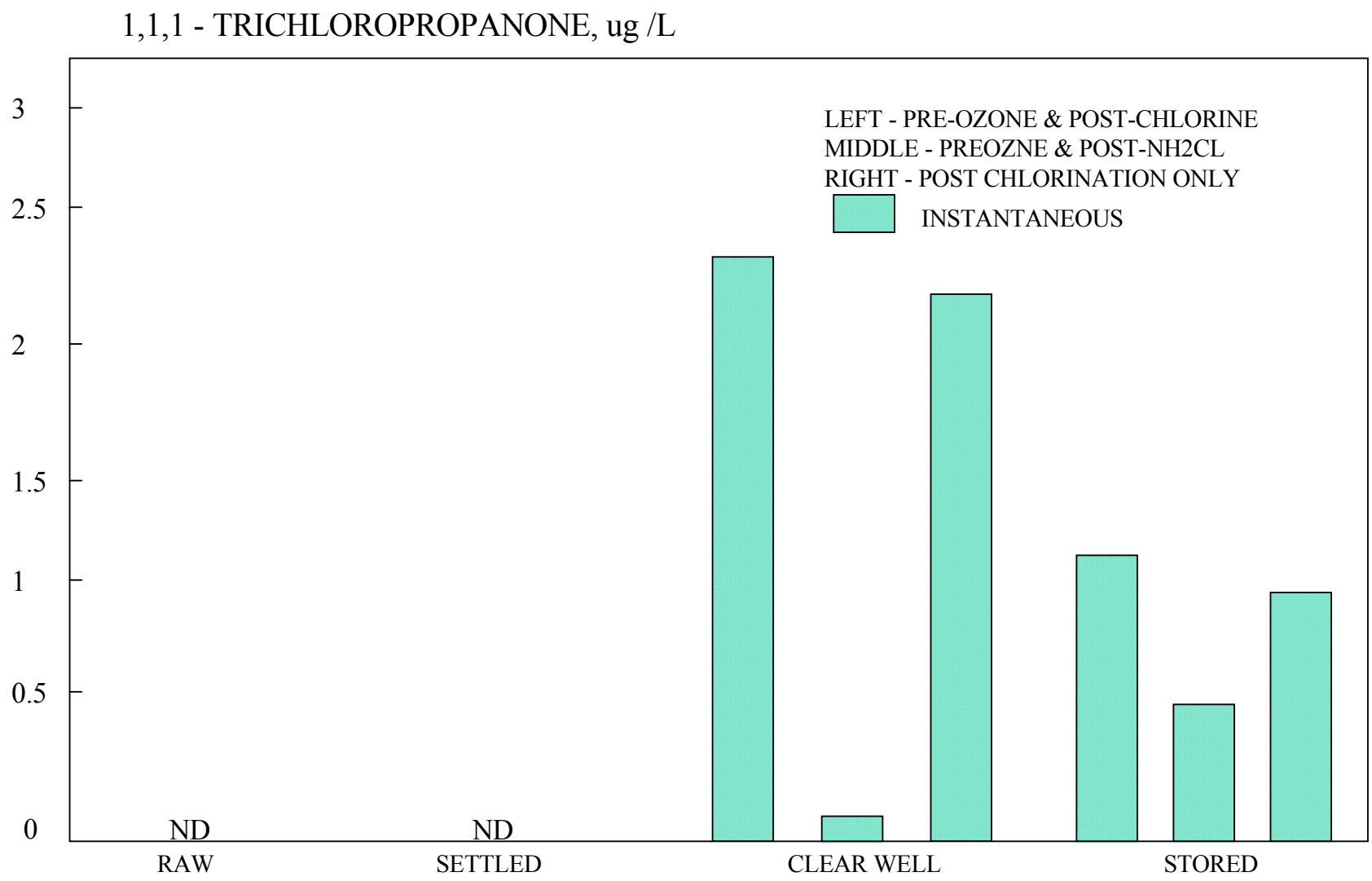

Figure 4. Formation and Control of 1,1,1Trichloropropanone.

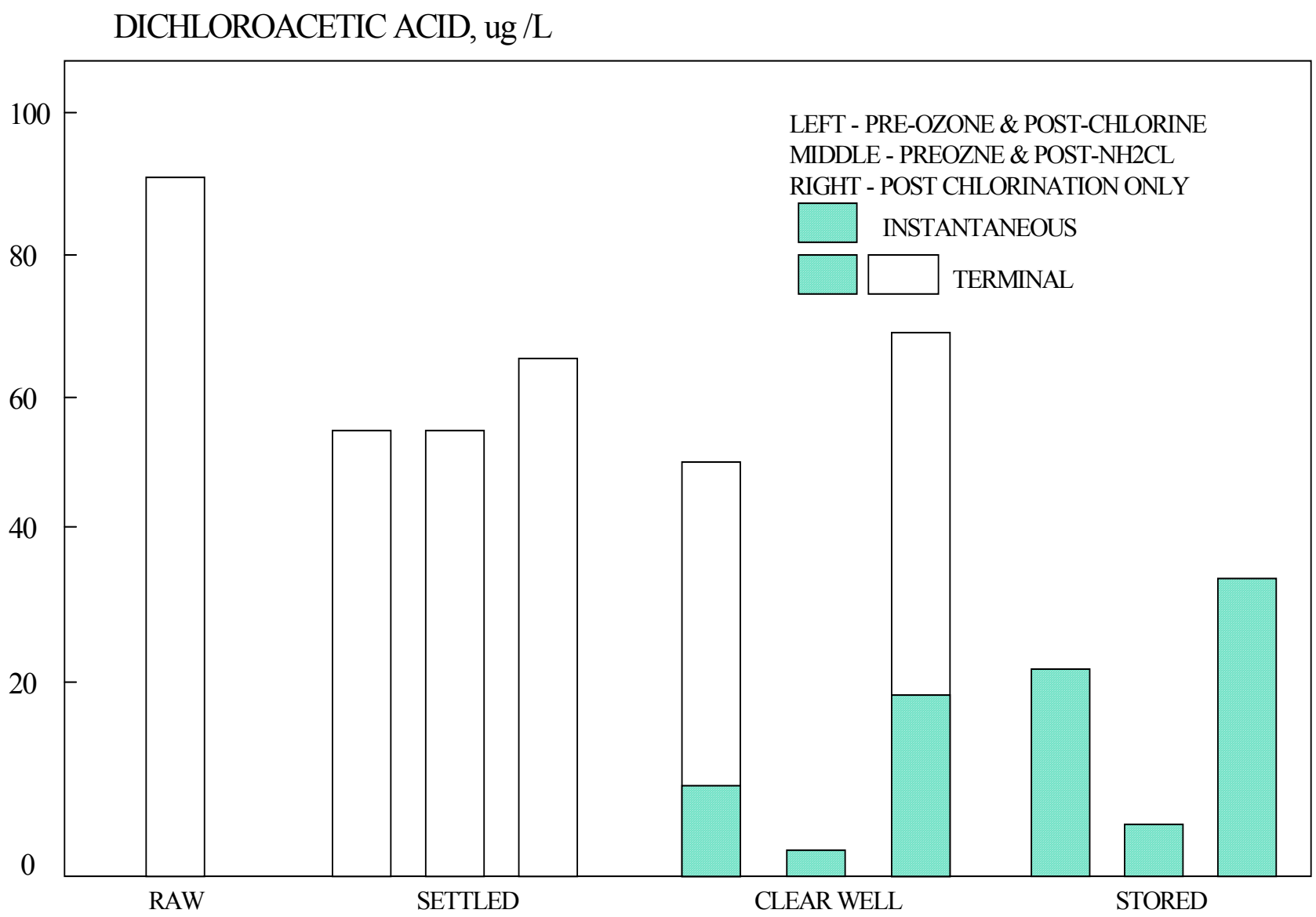

Figure 5. Formation and Control of Dichloroacetic Acid.

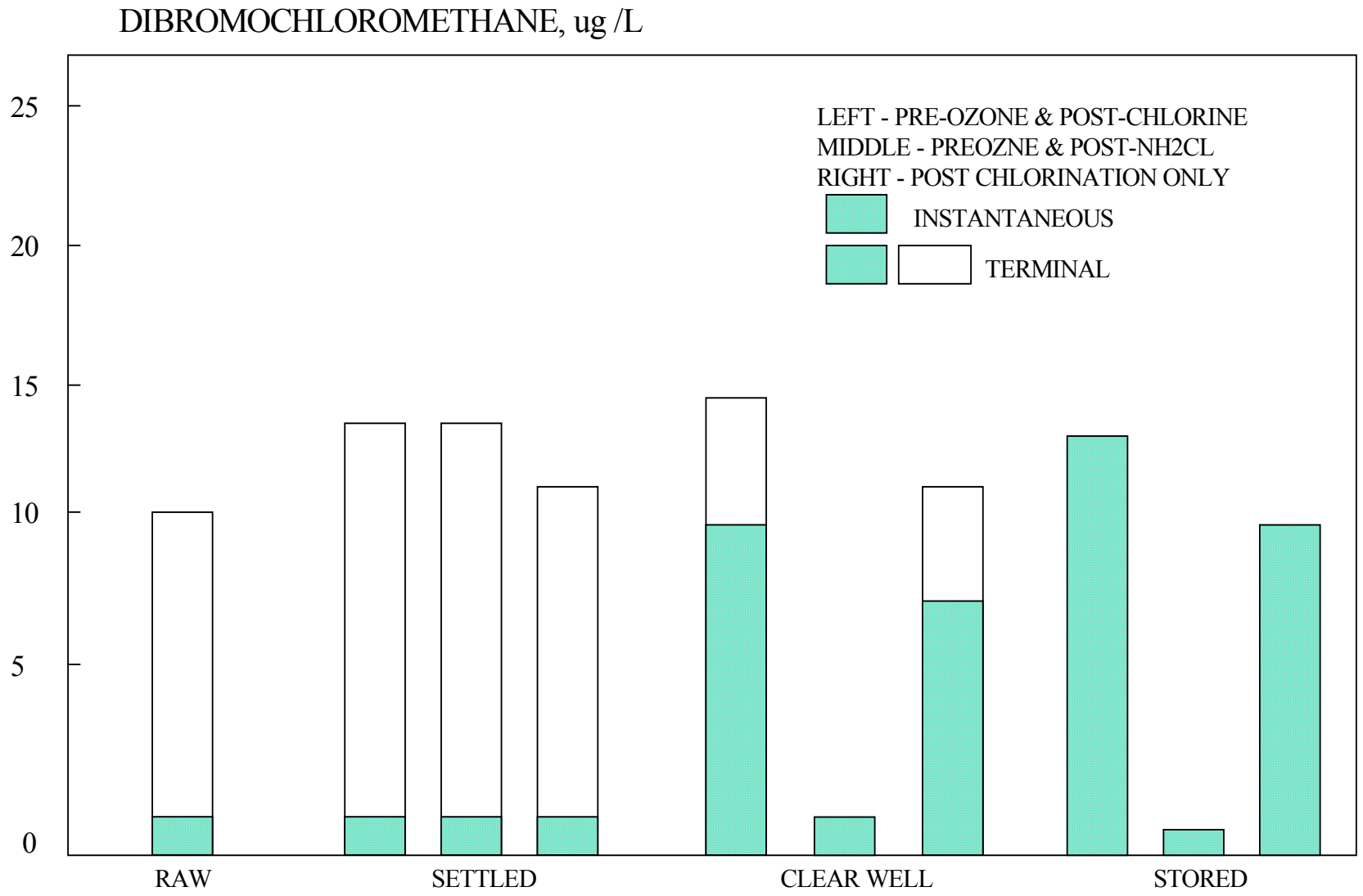

Figure 6. Formation and Control of Dibromochloromethane.

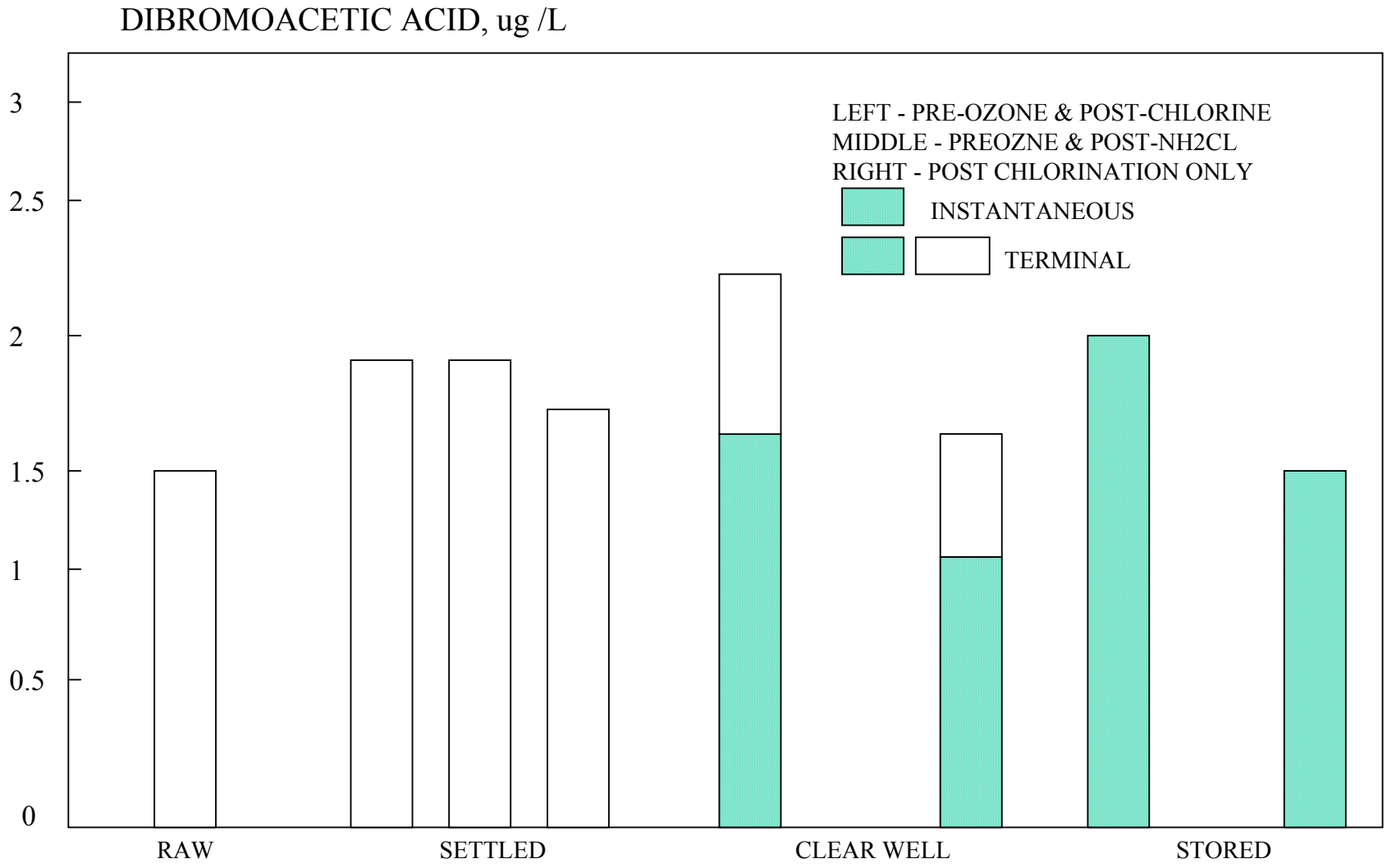

Figure 7. Formation and Control of Dibromoacetic Acid.

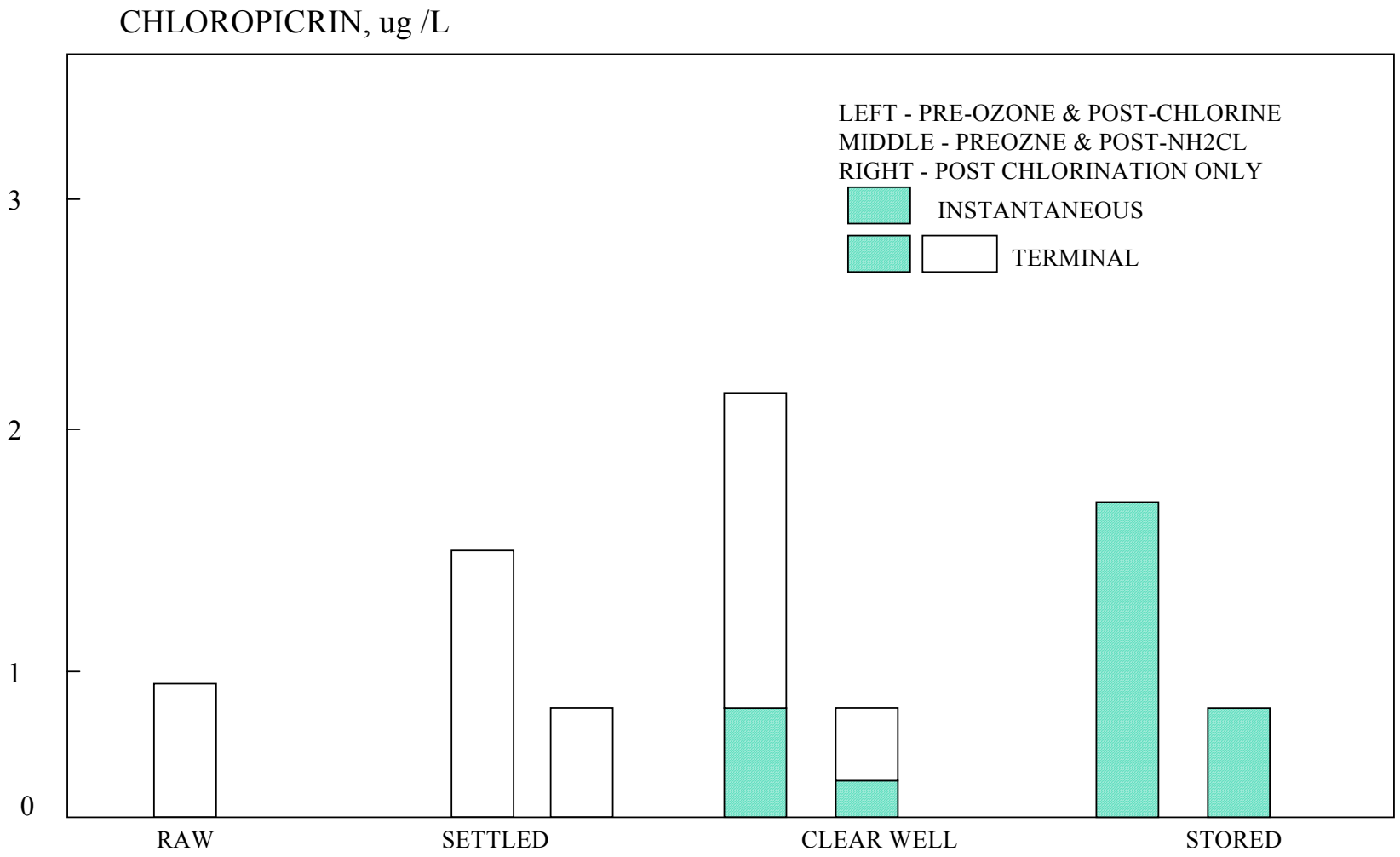

Figure 8. Formation and Control of Chloropicrin.

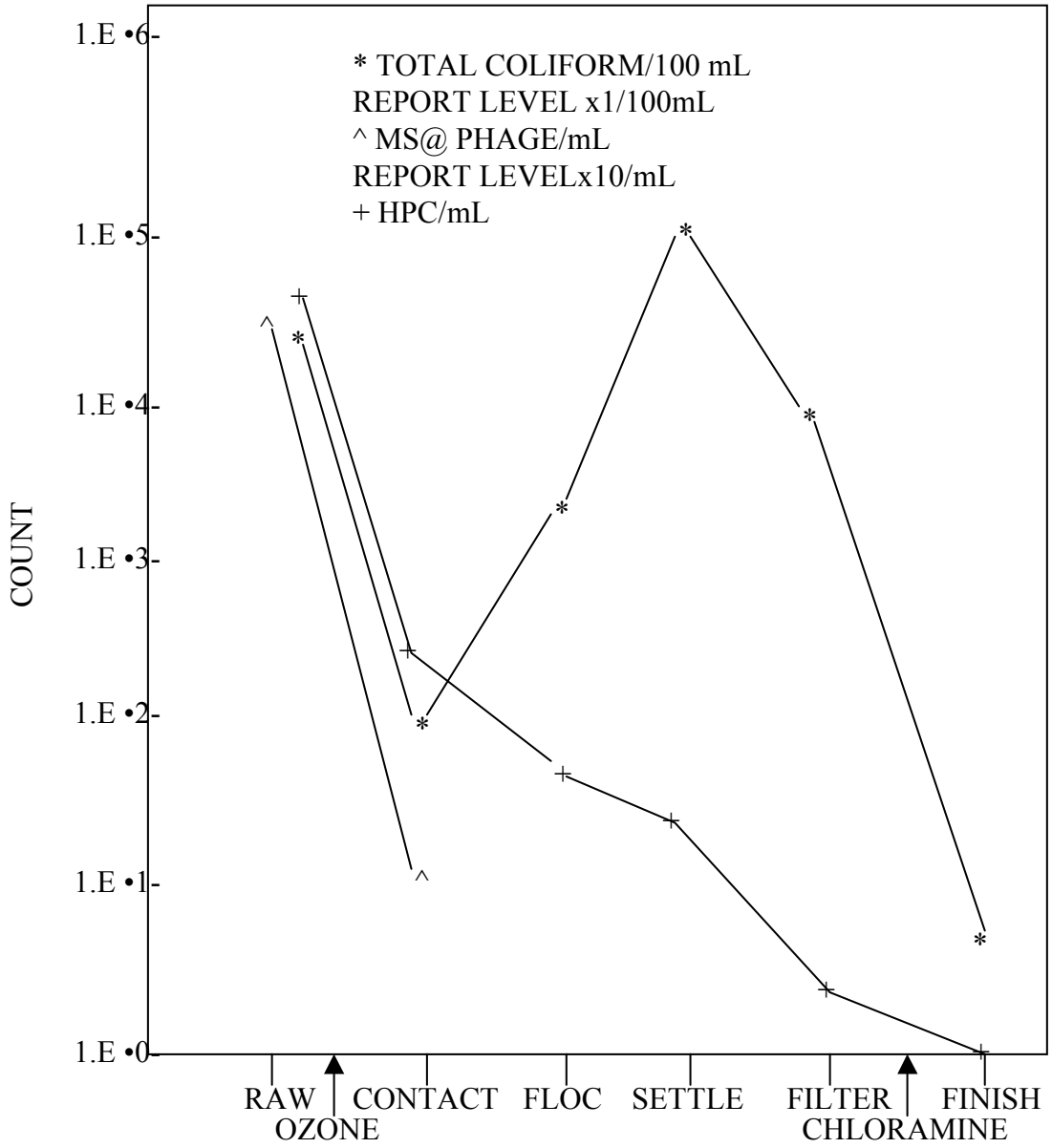

Figure 9. Microbiological Control Using Pre-Ozone and Post-Chloramine..

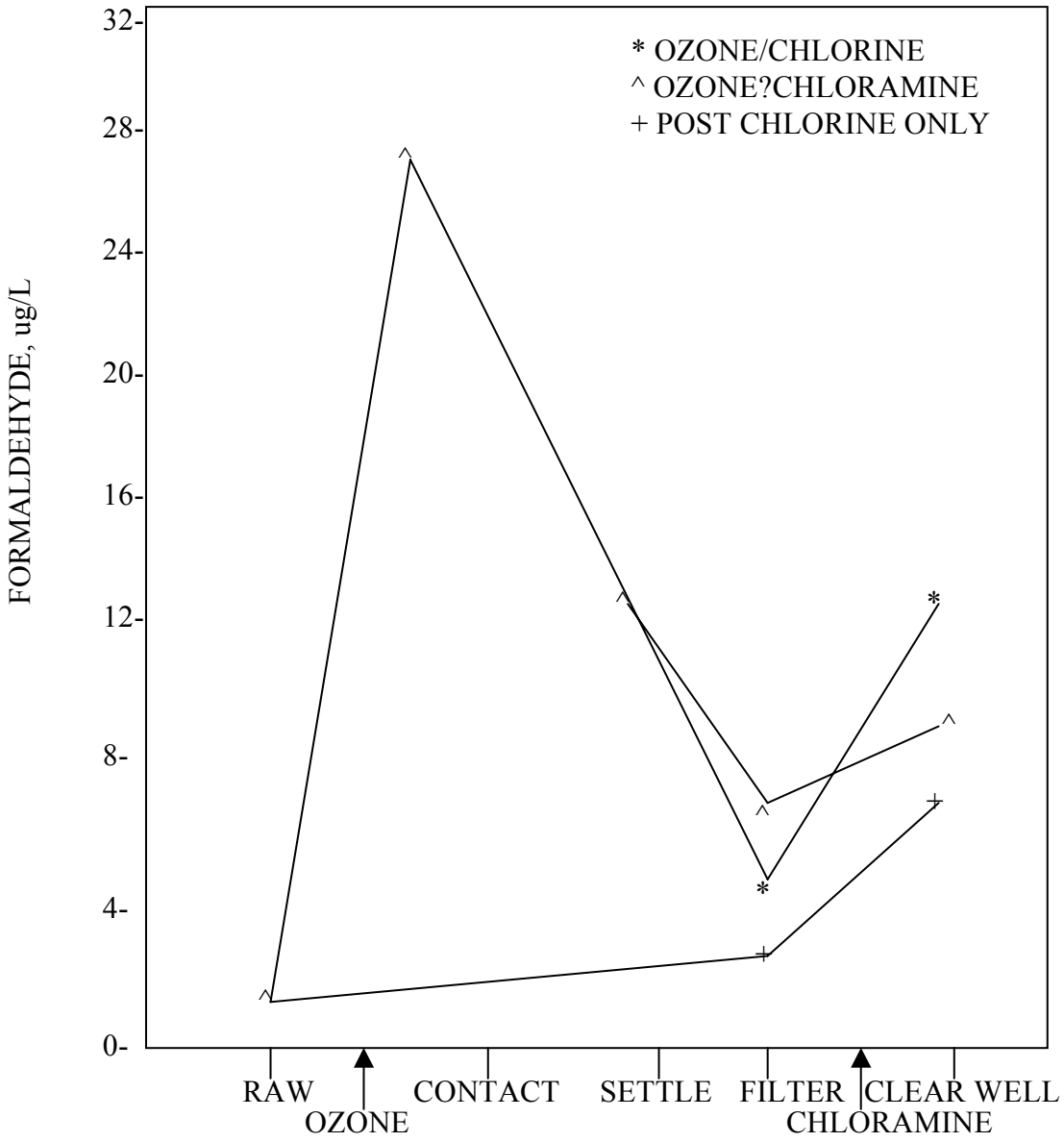

Figure 10. Formation and Control of Formaldeyde.

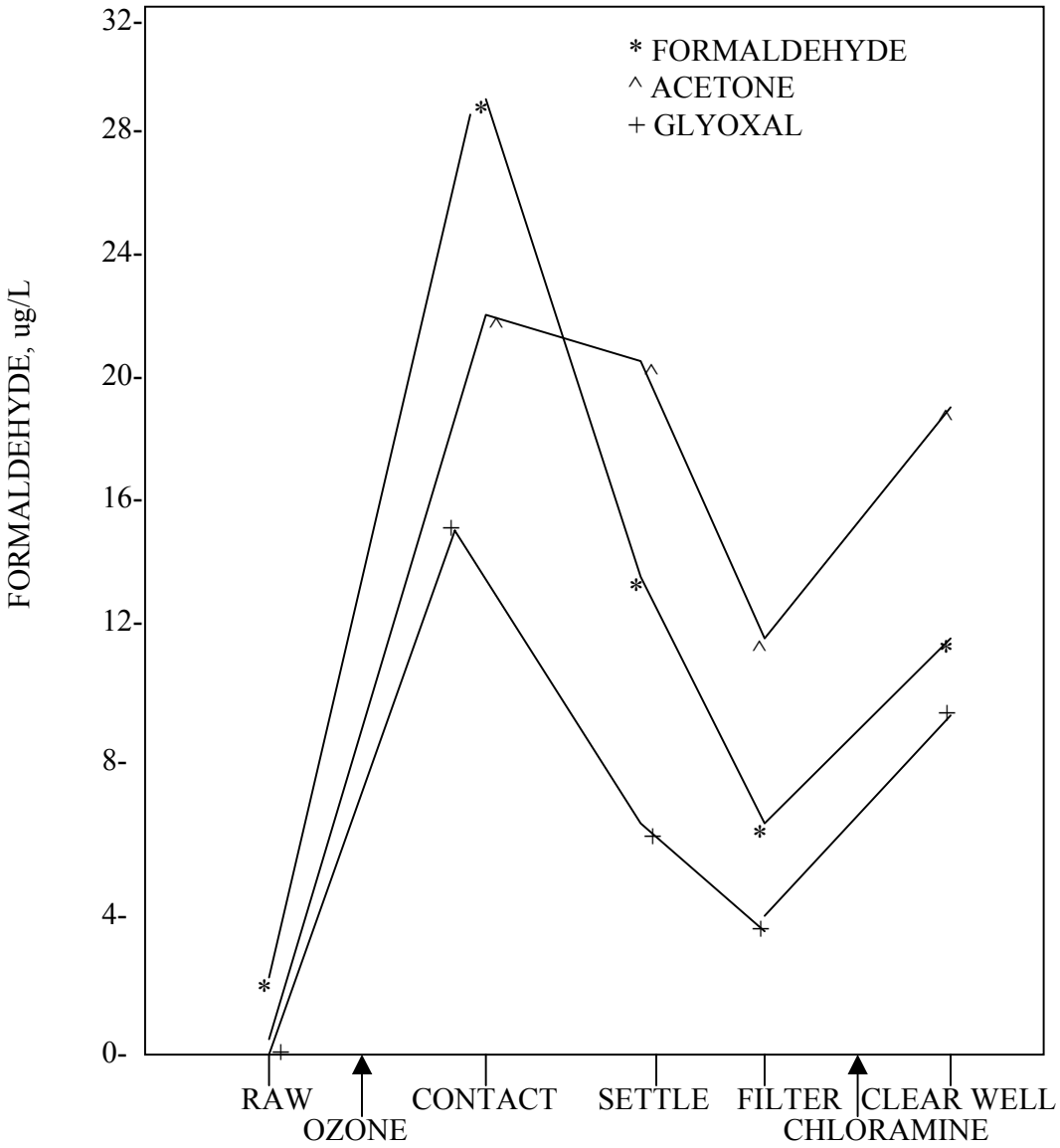

Figure 11. Formation and Control of Aldehydes and Ketones Using Pre-Ozone and Post-Chlorine.

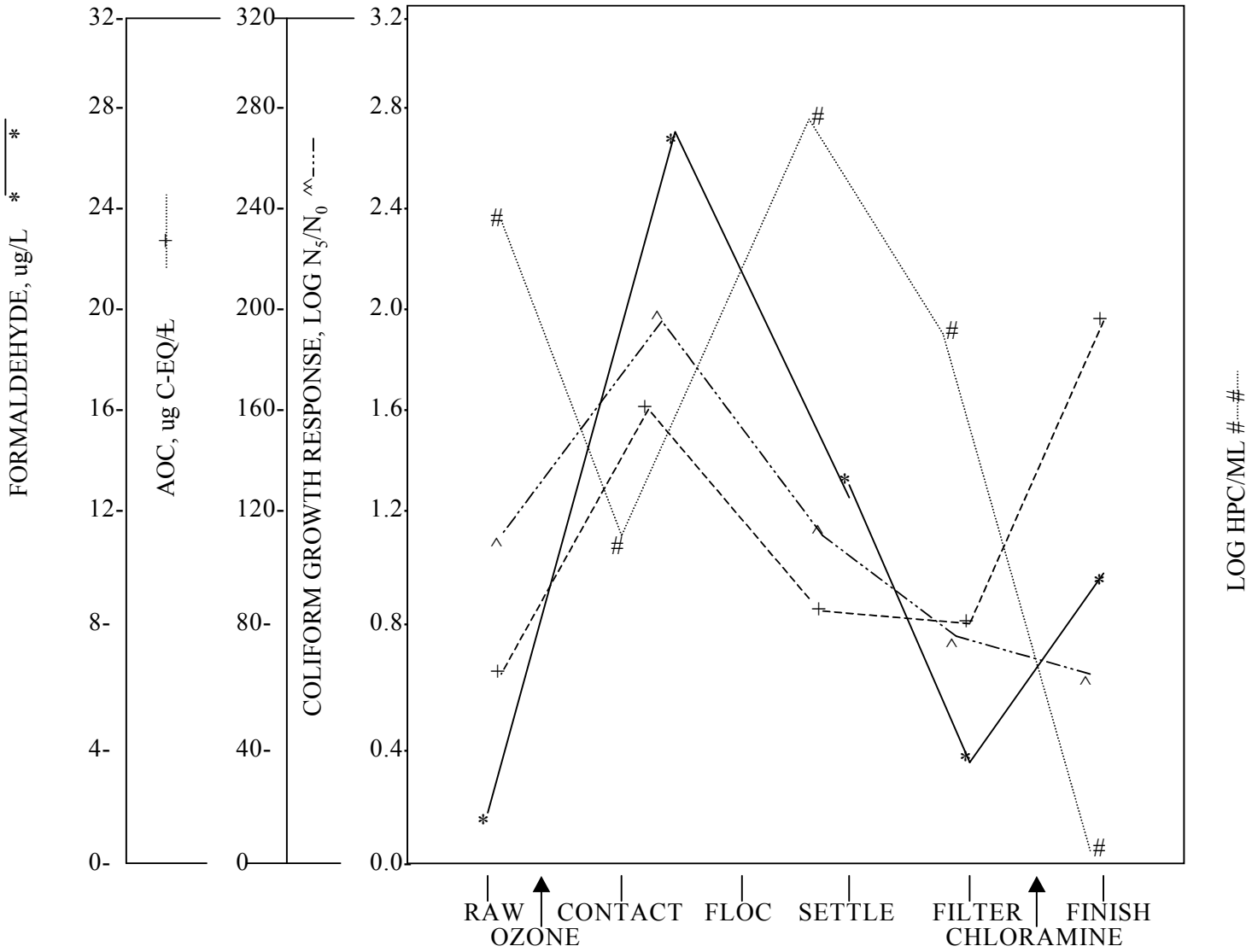

Figure 12. Formation and Control of Microbiological Nutrients Using Pre-Ozone and Post-Chlorine.

APPENDIX B

Animal Bioassay and *In Vitro* Testing

APPENDIX B.1 DBP MIXTURE RISK ESTIMATION – ALTERNATIVE MODELS

The U.S. EPA published the Guidelines for the Health Risk Assessment of Chemical Mixtures (U.S. EPA, 1986) in which three approaches to quantitation of health risk for a chemical mixture are recommended, depending upon the type of available data (Teuschler and Hertzberg, 1995). In the first approach, toxicity data on the mixture of concern are available; the quantitative risk assessment is done directly from these preferred data. In the second approach, when data are not available for the mixture of concern, the Guidelines recommend using data on a "sufficiently similar" mixture. Similarity is judged from data on component composition of the mixture, component proportions within the mixture, source of emission, and health effects due to exposure to these similar mixtures. If the mixture of concern and the similar mixture are judged to be similar, then the quantitative risk assessment for the mixture of concern may be derived from health effects data on the similar mixture. Finally, the third approach is to evaluate the mixture through an analysis of its components, e.g., using dose-addition for systemic effects and response-addition for estimates of cancer risk. These procedures include a general assumption that interaction effects at low dose levels either do not occur at all or are small enough to be insignificant to the risk estimate.

The Guidelines recommend the incorporation of interactions data when available, if not as part of the quantitative process, then as a qualitative evaluation of the risk. There are many terms used to describe interaction effects among chemicals, but the two most common are synergism (the effect of the combination is greater than that suggested by the component toxic effects under additivity) and antagonism (the effect of the combination is less than that suggested by the component toxic effects under

additivity) (Hertzberg et al., in press). Interaction effects are more likely to occur at higher dose levels where toxicologic processes are affected, e.g., competition for receptor sites by a mixture of chemicals with a similar mechanism of action can result in an antagonistic effect.

As stated above, dose-addition and response-addition are similar in that they are both component based approaches that do not include interactions information because they are generally applied to mixtures that occur together at low dose levels. Under dose-addition, the first step is to scale the doses of the components for potency and add the doses together; the mixtures risk is then estimated for the combined mixtures dose. Under response-addition, the risks are first determined for the individual components; the mixtures risk is then estimated by adding the individual risks together. These processes are fundamentally different and require different assumptions of the data in order for them to be used appropriately.

Dose-addition is different from response-addition because two assumptions are made: that all of the components have similar uptake, pharmacokinetics and toxicologic processes, and that the (log probit) dose-response curves of the components are parallel (Teuschler and Hertzberg, 1995). This means that, for equal effects, the dose of one component is a constant multiple of the dose of a second component. Usually the assumption is made that the same constant multiple applies to any effect. Hertzberg et al. (1999) note that dose-addition often does a reasonable job of predicting the toxicities of mixtures composed of a variety of both similar and dissimilar compounds (Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980; Ikeda, 1988; Feron et al., 1995), although exceptions have been noted. Dose-addition is particularly useful in situations

where the dose for each individual component is at a level at which effects are not expected to occur or be observable; when the doses are combined, effects are then expected or observed in response to the higher dose level of the mixture. Often, dose-addition is applied by scaling the potencies of all the components in the mixture to an index chemical, adding the scaled doses together to give the equivalent dose in terms of the index chemical, and using the index chemical's dose-response curve to estimate risk for the total mixture dose.

Response-addition is different from dose-addition in that it does not assume similar kinetics or a similar mode of action and does not assume parallel dose-response curves. It assumes that the components of the mixture are considered to be functionally independent of one another at low exposure levels (Mumtaz and Hertzberg, 1993), so that the risks may be added together. Because response-addition does not require a similar mode of action across the chemicals in the mixture, it allows for combining risks across different types of endpoints, unlike dose-addition. Response-addition is particularly useful when the effect of concern is thought to be present at low dose levels for each of the component chemicals, even though it is highly unlikely to be observable at these low levels in either epidemiologic or toxicologic studies; the mixture risk is then the sum of the individually low risks of the independently acting component chemicals. For example, response-addition has often been used for the risk assessment of mixtures of carcinogens (Gaylor et al., 1997; U.S. EPA, 1989).

The approach that is to be applied within the comparative risk decision analysis is to work with component information, using appropriate additivity assumptions to combine data on exposure levels for specific drinking water treatment scenarios with

dose-response estimates from animal data to generate human health risk estimates for the mixtures of concern. The advantage of using the single chemical dose-response toxicity data and combining them with treatment-specific exposure information is that this method allows for relative comparisons of health risks across the treatments. In addition, it allows for future health risk comparisons of any proposed decreases in the allowable levels of DBPs in the finished drinking water. Any available interactions data indicating that the mixture components may interact in a synergistic or antagonistic way will be used only as qualitative information in the analysis.

Although estimates of human cancer, reproductive or development risks may be taken from the epidemiologic literature, these data do not distinguish the risks across various treatment scenarios. Most of the epidemiologic data simply distinguishes between chlorinated or non-chlorinated water, or between chlorinated surface water and groundwater without a detailed exposure characterization (Morris, 1992). Therefore, dose-response estimates of health risks across treatments cannot be easily obtained. Additional data from epidemiologic studies may be used from the perspective of generating data used in establishing the human dose-response relationship, as a guidepost indicating which biochemical mechanism to evaluate for potential interaction with other chemicals, to corroborate estimates of human health risk calculated from the animal data, or to provide upper bound risk estimates as part of the sensitivity analysis. Human exposures are difficult to interpret, owing to exposure to a multitude of chemicals daily. Some epidemiologic studies have been criticized for this, but those studies still present data which may be useful, if only qualitative. Studies correlating observed toxicity with exposure to agent(s), whether from laboratory animals or

humans, are of more value when specific components are identified. Some investigations have been performed on human populations where the only identifier is "disinfection with chlorine" versus "disinfection with chlorine dioxide". While those data are better than none at all, a more clearly defined exposure regimen would be beneficial. This is rarely the case in more well controlled studies with laboratory animals, where exact doses of DBP chemicals are known.

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APPENDIX B.2 THE QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP MODELING METHODOLOGY

B.2.1 BACKGROUND

The earliest version of TOPKAT® (Toxicity Prediction by Komputer-assisted Technology) was introduced in 1987 by Health Designs, Inc. A complete redevelopment of the earliest version led to the introduction of TOPKAT 3.0 in 1995. Subsequently, TOPKAT 3.0 was enhanced to 5.0 in 1997 to include support for moiety analysis. These software packages are designed for the accurate and rapid assessment of the toxicity of chemicals solely from their molecular structure. Both software packages utilize robust, cross-validated Quantitative Structure-Toxicity Relationship (QSTR) models for assessing specific health- related endpoints, e.g. rodent oral carcinogenicity (NTP), Ames mutagenicity, developmental toxicity potential, rat oral chronic Lowest-Observed-Adverse-Effect Levels (LOAEL), rat oral LD_{50}, skin sensitization, fathead minnow LC_{50}, and Daphnia magna EC_{50}. In addition, a Log P QSAR model is also available, where P is the ratio of the solubility in octanol compared to the solubility in water and is known as the octanol-water partition coefficient.

B.2.2 STRUCTURE-BASED MODELS

Structure-based toxicity assessment approaches can be classified into two types; namely, Expert Systems (Human and Artificial) and QSTR approaches. Expert Systems approaches are based on a collection of rules derived from existing subject knowledge and stored in computer memory. QSTR-based model is a quantitative relationship between numerical measure of toxicity and a set of structural descriptors. The backbone of this approach is the effective quantification of salient structure attributes.

Such attributes include electronic (valence, sigma, pi and lone-pair), bulk (molecular weight, size corrected E-values) and shape (molecular shape and symmetry) (Gombar, 1998). Such models are developed for predicting various endpoints (e.g. carcinogenicity and developmental toxicity) and are based on very carefully selected studies from the literature using extremely stringent criteria.

B.2.3 STRUCTURE-BASED MODEL DEVELOPMENT

In principle, a structure-based toxicity model is a quantitative relationship between a numerical measure of toxicity and a set of structure descriptors, i.e.,

$$T = f(S),$$

where T is a measure of toxicity (e.g. LD_{50} , LOAEL, indicator of carcinogenicity), S is a set of numerical quantities representing different structural attributes, and f is a mathematical function (HDI, 1995). These structure-toxicity relationships are generally called quantitative structure-toxicity relationships (QSTR) models or equations, because by knowing the function, f, and providing the values of S for any chemical one could estimate its toxicity, T.

A special case in which (f) represents a linear multiple discriminant function is the QSTR equation below which is a algebraic summation of all identified descriptors to compute a probable value of toxicity for a submitted chemical structure. The form of a QSTR is:

$$\begin{aligned} \text{Computed Toxicity Value (Discriminant Score)} = {} & \text{Coeff}_1 \times \text{Var}_1 \\ & + \text{Coeff}_2 \times \text{Var}_2 \\ & + \text{Coeff}_3 \times \text{Var}_3 \\ & + \quad \ldots \\ & + \text{Coeff}_n \times \text{Var}_n \\ & + \quad \text{constant} \end{aligned}$$

The variables in the above QSTR equation are the calculated values of the structure descriptors; the coefficients are the statistical weights associated with these descriptors. During the development of the equation these weights are optimized. The product of the descriptor variable and the coefficient is the descriptor's contribution to the estimated toxicity. If the contribution is positive it increases the probability of toxicity whereas a decrease in probability is denoted by a negative value. The descriptors used in TOPKAT 3.0/5.0 models quantify the electronic, shape and symmetry attributes of a molecular structure. The electronic attributes are expressed in terms of the electrotopological E-state values (Gombar, 1998) of specially designed 1-atom and 2-atom fragments of non-hydrogen atoms in different hybrid and hybridization states called HDi substructures.

Toxicity values are computed by summing the contributions of the individual descriptors. For assessing toxicity values such as the LOAEL and LC_{50}, this sum is transformed into a weight/weight unit (mg/kg) and weight/volume unit (mg/L). For carcinogens, mutagens, and developmental toxicants, this sum is transformed into a probability value between 0.0 and 1.0. For such 2-group classifications, a value between 0.0 and 0.3 is considered negative or of low probability; a value between 0.3 and 0.7 is considered indeterminate (i.e., too near equal probability) for an assessment to be meaningful and a value above 0.7 is considered to be positive.

B.2.4 MODEL VALIDATION

These models are based on both discriminant and regression analyses using dichotomous and continuous scales, respectively. It is relatively easy to develop a tentative QSTR with good correlation (r^2); however, a good R^2 does not necessarily

indicate that the model is appropriate for predictive purposes. Therefore, it is essential to further validate these models based on a variety of diagnostics (Gombar et al., 1997). These diagnostics include: (a) all descriptors in the function are significant, (b) no compounds with unique variables are in the training set, (c) no influential or outlier compounds remain in the training set, (d) residuals are normally distributed and (e) cross validation performance (r^2_{cv}) is not significantly different from the performance (r^2) on the training set. Unless these characteristics are established in a QSTR, it cannot be considered robust and, therefore, its statistical quality is questionable.

B.2.5 MODEL ACCURACY

In the case of the Developmental Toxicity Model (Gombar et al., 1995) stringent criteria was applied to 5559 open literature citations containing experimental data on developmental toxicity with the selection of 1238 rat studies for the development of the model. However, 830 of these bioassays were not usable due to inherent problems in protocols and 34 bioassays were deleted due to uncertain structure, organometallics and mixtures. Ultimately, the compounds suitable for QSTR models were reduced from 374 to 273 based on the fact that some studies were performed at only one dose only and both DT and MT were observed at that dose, and for some studies, neither DT nor MTD was reported even at the highest dose. Based on specific criteria a DTP score between 1 and 4 was assigned to each of the 273 chemicals. Ultimately, 273 chemicals were used in the development of three developmental toxicity submodels (aliphatic, carboaromatic and heteroaromatic). The cross-validation (leave-one-out) accuracy of the three submodels range from 86.1% to 88.6% in terms of sensitivity (known developmental toxicants identified as positive) and 86% to 97.4% in terms of specificity

(known non-developmental toxicants identified as negative). The indeterminants ranged from 2.2 to 2.5%. Each submodel is comprised of about the same number of compounds to give a total of 273 compounds.

The NTP Rodent Carcinogenicity Model comprises four statistically significant and cross-validated QSTR models, and the data from which these models were derived. Each QSTR model relates to a specific sex/species combination: female rat, male rat, and female mouse, male mouse. The basis for each model are the 366 rodent carcinogenicity studies conducted by the National Cancer Institute (NCI) and the National Toxicology Program (NTP) utilizing inbred rats and hybrid mice. In selecting the most appropriate studies, stringent criteria was uniformly applied to all NCI/NTP studies and any studies not conforming to the predefined standards of purity, exposure duration, route of exposure, dose levels, etc., were not included in the training sets for developing QSTR models for carcinogenicity. For instance, results from 158 carcinogenicity assays in the female rat could not be included in the training set for various reasons (Gombar et al., 1997). With respect to the accuracies of these four carcinogenicity submodels, the sensitivity (% of known carcinogens predicted as carcinogens) ranged from 82% in the case of the male rat to 91% in the case of the female rat. Prediction of non carcinogens as non carcinogens (specificity) ranged from 82% in the case of the male rat to 94% for the male mouse. Percent indeterminants were 11, 1, 1 and 5 for the male rat, female rat, male mouse and female mouse, respectively. There were approximately equal number of compounds in each submodel to give a total of 815 compounds.

B.2.6 QUALITY ASSURANCE/CONTROL

An established data base was used to develop the QSTR models for predicting the various health-related endpoints of novel structures have been accumulated, evaluated and standardized the software developer. These data include, but are not limited to, chemical structure depictions, Chemical Abstract Service (CAS) Registry numbers, experimental toxicity values, and reference citations. All of the models in the software package have been developed by qualified statisticians, toxicologists, computational chemists, and computer programmers, specializing in QSTR.

B.2.7 QSTR ANALYSES

B.2.7.1 Developing the Hypothesis (Prediction) via Univariate and Multivariate Analyses

In general, QSTR models are limited in their applicability, since they are derived from experimentally measured toxicity values involving a limited number of descriptors. Consequently, it is important to determine whether the structural attributes (descriptors) of the query compound are represented in the compounds used for model development. In order to assess whether the estimated toxicity is meaningful or not, and to assure reproducibility of all the results, this software program has incorporated algorithms that have been thoroughly tested. These algorithms (Gombar, 1998; HDI, 1995) are termed univariate (Coverage Examination) and multivariate [Optimum Prediction Space Examination (OPS)] analyses.

The univariate analysis determines whether all of the structural fragments of the query structure are well-represented in the model data base or training set and the multivariate analysis determines whether the query structure fits within or near the

periphery of the OPS of the equation. The OPS of a QSTR is a multi-dimensional space, the number of dimensions being one more than the number of model descriptors of the QSTR. An important characteristic of the OPS is that within and near its periphery (permissible limits) the QSTR may be applied with confidence. If either of these criteria (univariate and multivariate analyses) are not satisfied, a warning is displayed; however, if they are satisfied "All Validation Criteria Satisfied" is displayed.

B.2.7.2 Testing the Hypothesis via Similarity Search

Using "Similarity Search" (HDI, 1995) this hypothesis can be tested against compounds in the data base based on their QSTR similarity to the query structure. TOPKAT displays the actual experimental and predicted results, whether the compound was used in the training set, and the similarity distance (normalized to the query compound) from the query on a scale of 0.0 to 1.0. The smaller the distance, the greater the similarity. Acceptable results are obtained if one finds that the experimental and predicted values of the "similarity search" compounds are in agreement and the normalized similarity distance is 0.35 or less for discriminant analysis and less than 0.2 for regression analysis. If the experimental and predicted values do not agree then the "similarity search" is considered unacceptable.

APPENDIX B.3 QSAR RESULTS FOR DBPs

A total of 253 compounds, identified as disinfection by-products (DBPs) by the Office of Water, were analyzed for carcinogenicity and developmental toxicity using TOPKAT®/QSTR software. All submitted query structures for either endpoint were automatically subjected to univariate (Coverage) and multivariate (Optimum Prediction Space) analyses, and ultimately generated a "hypothesis" in terms of probability. Subsequently, the confidence in the hypotheses were tested by application of the "similarity search" algorithm. The application of such diagnostic tools within the software ensures the accuracy for each model prediction in terms of false-positives and false-negatives.

The initial agreement between NCEA-Cin and the Office of Water (OW) was to subject the 252 DBPs submitted by OW to QSTR analyses using TOPKAT software. In view of the time constraints it was agreed upon that such prioritization of DBPs would not include any rationalization as to why certain classes of chemicals based on functional groups are active and others inactive. In general, there are two reasons for prioritization; namely, regulatory decision making and research needs. This effort focuses principally on the research needs for Stage 2 DBPS Rule for which there is little health data available. Such data will assist OW in selecting high priority DBPs or classes of DBPs for additional health effects studies and eliminating others.

The results of the 253 DBPs analyzed were tabulated (Table B.3-1) and prediction patterns were observed within and between classes based on their functional groups (e.g. alcohols, acids, etc.) and specific health related endpoints. A visual representation of the QSAR analyses for the principal functional groups are presented

TABLE B.3-1

QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
ALDEHYDE'S					
ALIPHATICS					
Formaldehyde	-	+	-	IND	IND(NO)
Cyanoformaldehyde	+	-	-	-	+
Acetaldehyde	+	-	-	-	IND(NO)
Chloroacetaldehyde	OPS	-	-	OPS	-
Trichloroacetaldehyde monohydrate (chloral hydrate)	IND	-	OPS	OPS	OPS
Dichloroacetaldehyde	+	-	-	IND	-
Bromodichloroacetaldehyde	+	-	-	-	IND
Chlorodibromoacetaldehyde	+	-	-	-	IND
Tribromoacetaldehyde	+	-	-	+	+
Propanal (Propionaldehyde)	+	-	-	-	-
Methyl propanal	+	-	-	+	+
Butanal (Butyrladeheyde)	+	-	-	-	-
Butanedial (succinic diadehyde)	-	-	-	+	-
3-Methylbutanal	+	-	-	IND	IND
Methyl glyoxal (pyruvic aldehyde)	+	-	-	-	+
4-Chloro-3-keto-1-butanal	-	-	-	+	-
Pentanal (valeraldehyde)	+	-	-	-	-
Hexanal (hexaldehyde; caproaldehyde)	+	-	-	-	-
2-Hexenal	OPS	-	-	-	-
Heptanal (heptaldehyde)	+	-	-	-	-
Octanal (octyl aldehyde; caprylic aldehyde)	+	-	-	-	-
Nonanal (nonyl aldehyde; pelargonaldehyde)	+	-	-	IND	-
Decanal (decyl aldehyde)	+	-	-	OPS	-
Undecanal (undecylic aldehyde)	+	-	-	OPS	-
Dodecanal (dodecyl aldehyde; lauraladehyde)	+	OPS	-	OPS	-
Tridecanal	+	OPS	-	OPS	-
2-Methydecanal (2-methyldecyl aldehyde)	+	-	-	+	-
Tetradecanal (tetradecyl aldehyde; myristyl aldehyde)	+	OPS	-	OPS	-
AROMATICS					
Benzaldehyde	+(DB)	-	-	-	-
Benzene acetaldehyde	-	-	-	-	-
ALIPHATICS ACID'S					
MONO-CARBOXYLIC ACIDS					

TABLE B.3-1
QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
HALOGENATED ACETIC ACIDS					
Acetic Acid	-	-	+	-	+
Monofluoroacetic acid	-	IND	-	-	+
Chloroacetic acid	-(DB)	-(DB)	-(DB)	-(DB)	+
Bromoacetic Acid	+	-	+	-	+
Difluoroacetic acid	-	-	-	-	-
Dichloroacetic acid	IND	+	OPS	-	-
Dibromoacetic acid	-	+	OPS	-	-
Trifluoroacetic acid	-	+	+	+	+
Trichloroacetic acid	-	+	-	+	+(DB)
Tribromoacetic acid	-	+	+	+	+
Bromochloroacetic Acid	+	+	OPS	-	-
Bromodichloroacetic acid	-	IND	+	-	+
Dibromochloroacetic acid	-	-	+	-	+
CHLORINATED CARBOXYLIC ACIDS					
2-Chloropropanoic acid (2-chloropropionic acid)	+	+	-	-	IND
3-Chloropropanoic acid (3-chloropropionic acid)	-	-	IND	-	+
2,2-Dichloropropanoic acid (2,2-dichloropropionic acid)	-	IND	-	-	+
3,3-Dichloropropenoic acid (3,3-dichloroacrylic acid)	+	IND	+	-	IND
2,2-Dichlorobutanoic acid (2,2-dichlorobutyric acid)	-	IND	-	-	+
2,3-Dichloro-4-oxobutenoicacid (mucochloric acid)	+	-	+	OPS	OPS
5,5,5-Trichloro-4-oxopentanoic acid	-	-	-	IND(NO)	+
NON-HALOGENATED CARBOXYLIC ACIDS					
Glyoxylic acid	+	-	+	-	+
2-Oxopropanoic acid (pyruvic acid)	-	-	+	-	+
1,2-Dioxopropanoic acid	+	-	+	-	+
2-Methyl propanoic acid	-	-	+	IND	+
Butanoic acid	-	-	IND	-	+
Dioxobutanoic acid	-	-	+	-	+
2-Methyl butanoic acid	-	-	IND	IND	+
Pentanoic acid (valeric acid)	-	-	IND	-	+
2-Oxopentanoic acid (2-ketovaleric acid; 2-oxovaleric acid)	-	-	IND	-	-
4-Oxopentanoic acid	-	-	+	-	+
2-Methyl pentanoic acid	-	-	-	IND	-
Hexanoic acid (caproic acid)	-	-	-	-	IND
Heptanoic acid	-	-	-	-	-

TABLE B.3-1
QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
Octanoic acid (caprylic acid)	-	-	-	-	-
Nonanoic acid	-	-	-	IND	-
Decanoic acid (capric acid)	-	-	-	+	-
Undecanoic acid	-	-	-	+	-
Dodecanoic acid (lauric acid)	-	-	-	+	-
Tridecanoic acid	-	OPS	-	OPS	-
Tetradecanoic acid (myristic acid)	-	OPS	-	OPS	-
Pentadecanoic acid	-	OPS	-	OPS	-
Hexadecanoic acid (palmitic acid)	-	OPS	-	OPS	-
9-Hexadecanoic acid (cis-palmitoleic acid)	OPS	OPS	-	OPS	OPS
Heptadecanoic acid	-	OPS	-	OPS	OPS
Octadecanoic acid (stearic acid)	-	OPS	-	OPS	OPS
Heneicosanoic acid	-	OPS	-	OPS	OPS
Tetracosanoic acid (lignoceric acid)	-	OPS	OPS	OPS	OPS
DI-CARBOXYLIC ACIDS					
CHLORINATED DI-CARBOXYLIC ACIDS					
Chlorobutanedioic acid (chlorosuccinic acid)	-	+	OPS	-	-
2-Chlorobutenedioic acid	+	-	+	-	+
2-Chloro-3-methyl-cis-butenedioic acid (2-chloro-3-methyl maleic acid)	-	-	OPS	-	IND
NON-HALOGENATED DI-CARBOXYLIC ACIDS					
Propanedioic acid (malonic acid)	-	-	IND	-	+
Oxopropanedioic acid (ketomalonic acid)	-	-	+	-	+
cis-Butenedioic Acid (maleic acid)	-	-	+	-	+
trans-Butenedioic acid (fumaric acid)	-	-	+	-	+
2-Oxobutanedioic acid (ketosuccinic acid)	-	-	+	-	+
2,2-Dimethylbutanedioic acid (2,2-dimethylsuccinic acid)	-	-(NO)	IND	-	+
Tert-Butyl-cis-butenedioicacid(tert-butyl maleic acid)	+	IND(NO)	+	-	+
2-Ethyl-2-methyl-cis-butenedioic acid (2-ethyl-3-methyl maleic acid)	-	-(NO)	+	-	+
Pentanedioic acid (glutaric acid)	-	-(NO)	+	-	+
2-Methylpentanedioic acid	-	-(NO)	IND	-	+
2,2-Dimethylpentanedioic acid (2,2-dimethylglutaric acid)	-	-(NO)	+	-	+
Hexanedioic acid (adipic acid)	-	-(NO)	+	-	+
Heptanedioic acid	-	-(NO)	+	-	IND
Octanedioic acid (suberic acid)	-	-(NO)	+	-	-
Nonanedioic acid (azelaic acid)	-	-(NO)	+	IND	-
Tridecanedioic acid (1,11-Undecanedicarboxylic acid; brassylic acid)	-	-(NO)	-	OPS	-

TABLE B.3-1
QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
AROMATICS					
Benzoic Acid	-	-	+	-	-
3-Hydroxybenzoic acid	-	-	-	-	-
3,4-Dihydroxybenzoic acid (protochatechuic acid)	-	-	+	-	-
3-Methylbenzoic acid	-	-	+	-	-
4-Methylbenzoic acid	-	-	+	-	-
1,2-Benzene dicarboxylic acid	-	-	IND	-	-
1,3-Benzene dicarboxylic acid	-	-	+	-	-
1,4-Benzene dicarboxylic acid	-	-	+	-	-
1,2,3-Benzene tricarboxylic acid	-	OPS	OPS	-	-
1,2,4-Benzene tricarboxylic acid	-	OPS	OPS	-	-
1,3,5-Benzene tricarboxylic acid	IND	OPS	OPS	-	-
Phenylacetic acid	-	-	+	-	+
KETONE'S					
ALIPHATICS					
HALOGENATED KETONES					
Dichloroacetone	-	-	OPS	-	-
1,1-Dibromoacetone (1,1-Dibromopropanone)	-	+	OPS	-	-
1-Chlorodimethylglyoxal	-	-	-	-	+
Chloropropanone (chloroacetone)	-	-	-	-	+(NO)
1,1-Dichloropropanone	-	-	OPS	-	-
1,3-Dichloropropanone	-	+	-	-	+
1,1,1-Trichloropropanone	-	+	-	-	+
1,1,3-Trichloropropanone (1,1,3-trichloroacetone)	-	+	OPS	-	-
1,1,1,3-Tetrachloropropanone	-	+	OPS	+	+
1,1,3,3-Tetrachloropropanone	OPS	OPS	OPS	+	OPS
1,1,1,3,3-Pentachloropropanone	OPS	+	OPS	IND	-
Hexachloropropanone	-	+	-	+	+
1,1-Bromochloropropanone	+	+	OPS	-	-
1-Bromo-1,1-dichloropropanone	-	-	-	-	+
1,1-Dichloro-2-butanone	-	-	OPS	-	-
3,3-Dichloro-2-butanone	-	-	-	-	+
1,1,1-Trichloro-2-butanone	-	+	-	IND	+
2,2-Dichloro-3-pentanone	-	-	-	-	+
NON-HALOGENATED KETONES					
Acetone	-	-	-	+	+

TABLE B.3-1

QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
Glyoxal	+	-	-	+	+
Dimethylglyoxal (2,2-butanedione; diacetyl)	-	-	-	IND	+
Butanone	-	-	-	-	+(NO)
3-Methyl-2-pentanone (sec-butyl methyl ketone)	-	-	-	+	+
Methyl isobutyl ketone	-	-	-	+	+
3-Hexanone	-	-	-	-	-
3-Methyl-2,4-hexanedione	-	-	-	OPS	OPS
2,6-Dimethyl-2,5-heptadiene-4-one	OPS	OPS	OPS	OPS	-
6-Methyl-5-hepten-3-one	OPS	OPS	OPS	-	-
6, 10-Dimethyl-5,9-undecadiene-2-one (Nerylacetone/Geranylacetone)	OPS	OPS	OPS	OPS	OPS
CYCLIC KETONES					
2,2,4-Trichloro-1,3-cyclopentenedione	+	-	-	-	-
2-Chlorocyclohexanone	-	OPS	-	-	-
3-Methyl-1,2,4-cyclopentanetrione	-	-	-	-	OPS
2,5-Dimethylcyclopentanone	-	-	-	-	OPS
2,3,4-Trimethylcyclopent-2-en-1-one	-	-	-	-	OPS
2,6,6-Trimethyl-2-cyclohexene-1,4-dione	-	-	-	IND	OPS
1,3,3-Trimethyl-1-7-oxabicyclo-[4.1.0]-heptane-2,5-dione	-	-	-	IND	-
AROMATICS					
1-[4-(1-Hydroxy-1-methylethyl) phenyl]-ethanone	-	-	-	-	-
1-[4-(1-Methylethyl) phenyl]-ethanone	-	+	-	+	-
1,1-(1,4-Phenylene) bis-ethanone	-	+	-	+	-
2,6-Tert-butyl-1,4-Benzoquinone	+	-	-	IND	-
LACTONE'S					
Dihydro-4,5-dichloro-2-(3H)-furanone	-	-	-	-	OPS
5-Hydroxy-5-trichloromethyl-2-furanone	+	+	-	IND	IND
3-Chloro-4 (dichloromethyl)-2-(5H)-furanone (red-MX)	-	-	OPS	-	OPS
3-Chloro-4-dichloromethyl-5-hydroxy-2-(5H)-furanone (MX)	-	IND	OPS	-	-
3-Chloro-4-(bromochloromethyl)-5-hydroxy-2(5H)-furanone (BMX-1)	+	OPS	OPS	-	-
3-Chloro-4-(dibromomethyl)-5-hydroxy-2(5H)-furanone(BMX- 2)	-	+	OPS	-	-
3-Bromo-4-(dibromomethyl)-5-hydroxy-2(5H)-furanone (BMX-3)	-	+	OPS	-	-
2-Chloro-3-(dichloromethyl)-butenoic acid (ox-MX)	-	+	OPS	-	-
(E)-2-Chloro-3-(dichloromethyl)-4-oxobutenoic acid (EMX)	+	-	OPS	-	-
(E)-2-Chloro-3-(dichloromethyl) butenedioic acid (ox-EMX)	-	+	OPS	-	-
5-Methyl-2-furancarboxylic acid	-	+	+	-	-
4-Dodecyl-5-ethyl-2(5H)furanone	-	OPS	-	OPS	OPS

TABLE B.3-1

QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
ALCOHOL'S					
ALIPHATICS					
Di (ethylene glycol) butyl ether (check under ether activity)	-	-	-	-	-
2-[2-(2-Butoxyethoxy) ethoxyl]-ethanol	-	-	-	IND(NO)	-
1-[2-(2-Methoxy-1-methylethoxy)-1-methylethoxyl]-2-propanol	+	-	OPS	+	-
3-Chloro-2-butanol	OPS	-	OPS	-	-
4,5-Dichloro-2-pentanol	OPS	IND	-	IND	-
AROMATICS					
2-Chlorophenol	-	-	-	-	-
2,4-Dichlorophenol	-(DB)	-(DB)	-(DB)	-(DB)	-
2,4,6-Trichlorophenol	-	+	-	-	-
4,6-Dichloro-1,3-benzenediol (4,6-dichlororesorcinol)	-	-	-	-	-
4-(1-Methylethyl)-benzene methanol	+	-	+	-	+
2,6-Di-tert-butyl-4-nitrophenol	-	-	-	+	-
ETHER'S					
ALIPHATICS					
Bromochloromethyl Acetate	+	+	+	-	-
1-Chloroethanol acetate	-	-	IND	+	+
2-Chloroethanol acetate	OPS	-	-	-	-
1,2-Dichloroethanol acetate	+	+	-	-	-
2-Methyl-3,3-dichloro-2-propenyl dichloromethylether	IND	-	+	-	-
3-Bromopropylchloromethylether	+	+	+	+	+
3-Chloro2-butanol acetate	OPS	-	-	-	-
Hexanedioic acid, dioctyl ester	-	OPS	-	OPS	-
AROMATICS					
1,4-Dioxane	+(DB)	+(DB)	-	+(DB)	+(DB)
1,4-Benzodioxin	OPS	-	-	-	-
NITRILE'S					
ALIPHATICS					
Methyl Cyanide (Acetonitrile)	-	-(DB)	-(DB)	-	+(DB)
Cyanogen chloride	-	-	-	-	+
Cyanogen bromide	-	-	+	-	+
Chloromethyl cyanide (chloroacetonitrile)	-	-	-	-	+
Bromoacetonitrile	+	-	+	-	+
Dichloromethyl cyanide (dichloroacetonitrile)	+	-	-	IND	+

TABLE B.3-1

QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
Dibromoacetonitrile	-	-	-	IND	+
Trichloromethyl cyanide (trichloroacetonitrile)	IND	-	-	+	+(DB)
Tribromoacetonitrile	IND	-	-	+	+
Bromochloroacetonitrile	+	+	-	-	-
Bromodichloroacetonitrile	IND	-	-	-	+
Dibromochloroacetonitrile	IND	-	-	-	+
Trichloropropenenitrile	-	-	+	-	+
2,3-Dichloropropanenitrile	+	OPS	OPS	-	OPS
3,4-Dichlorobutanenitrile (3,4-dichlorobutyronitrile)	+	-	-	IND	-
cis-2,3,4-Trichloro-2-butenenitrile	-	-	OPS	OPS	OPS
trans-2,3,4-Trichloro-2-butenenitrile	-	-	OPS	OPS	OPS
3-Methylbutane nitrile	-	-	-	+	+
Heptanenitrile	-	-	-	-	-
AROMATICS					
Benzo Nitrile	-	-	-(NO)	-	-
Benzyl Cyanide	-	-	-(NO)	-	-
AMINE'S					
ALIPHATICS					
1-Chloro-3,3,3-trichloro-1-propen-1-amine	+	+	-	-	+
5-Methyl-3-isoxazolamine	-	+	-	-	-
AMIDE'S					
ALIPHATICS					
2,2-Dichloroacetamide	-	-	OPS	-	IND
2,2,2-Trichloroacetamide	-	+	-	+	+
HALO/NITRO ALKANE'S & ALKENE'S					
HALOGENATED METHANES					
Chloromethane (Methyl Chloride)	-	-	-	IND	-
Dichloromethane (methylene chloride)	-	+(DB)	IND	+	+(DB)
Dibromomethane	+	+	+	+	+
Trichloromethane (Chloroform)	OPS	-	-	+	-
Tribromomethane (bromoform)	-(DB)	-(DB)	+(DB)	+(DB)	-
Tetrachloromethane (carbon tetrachloride)	-	-	-	+	IND
Carbon Tetrabromide	-	-	-	+	IND
Bromochloromethane	+	-	+	IND	IND
1,2-Bis(1-methylethenyl) benzene	+	-	-	+	-
Bromochloroiodomethane	+	-	+	-	-

TABLE B.3-1
QSTR ANALYSES of DBPs

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
Bromodichloromethane	+(DB)	+(DB)	+(DB)	+(DB)	-
Dibromochloromethane	+(DB)	-(DB)	+(DB)	+(DB)	-
Dibromodichloromethane	-	-	-	IND	-
Chlorotribromomethane	-	-	-	+	-
Trichloronitromethane (Chloropicrin)	-(DB)	-(DB)	OPS	+	+
Bromopicrin	-	-	OPS	+	+
Bromodichloronitromethane	-	-	OPS	IND	+
Nitrodibromomethane	-	+	OPS	-	-
HALOGENATED ALKANES & ALKENES					
1-Ethoxy-1-hydroxymethane	-	-	IND	-	+
1-Chloro-2-ethoxy-2-methoxy ethane	-	-	+	+	-
1-Nitro-1,1-dichloroethane	-	-	OPS	IND	+
Hexachloroethane	+(DB)	+(DB)	-(DB)	+(DB)	+(DB)
1,1,1-Tribromo-2-bromo-2-chloroethane	+	IND	OPS	OPS	OPS
3,3,3-Trichloro-2-methyl-1-propene	-	+	-	+	-
2,3-Dichlorobutane	-	-	-	-	-
1,2-Dichloro-2-methyl butane	-	-	-	-	+
2-Bromobutane	-	+	+	-	IND
1,1,5,5-Tetrachloropentane	OPS	OPS	-	+	OPS
1-Hydroxy-3-methyl-2-hexene	+	OPS	OPS	-	-
1-Chlorooctane	-	IND	-	+	-
2-Chlorododecane	OPS	OPS	-	OPS	-
ODD BALL ALKANES & ALKENES					
Undecane	-	-	-	OPS	-
Methane sulfonyl chloride (mesyl chloride)	-	-	-	-	+
CYCLIC ALKANES & ALKENES					
Tetrachlorocyclopropene	-	-	+	-	-
Hexachlorocyclopentadiene	-	-(DB)	+	OPS	-
Cyclododecane	-	+	-	+	IND
HALO & NITRO AROMATICS					
Benzene	+(DB)	+(DB)	-(DB)	+(DB)	OPS
Chlorobenzene	-(DB)	-(DB)	-(DB)	-(DB)	-(DB)
Benzyl Chloride	-(DB)	-	IND	-	-
(2-Chloroethenyl)-benzene	-	-	-	-	-
1,2-Dichlorobenzene	-(DB)	-(DB)	-(DB)	-(DB)	-(DB)

Compound Name	Female Mouse	Male Mouse	Female Rat	Male Rat	Developmental Toxicity
1,3-Dichlorobenzene	+	-	-	-	-
1,4-Dichlorobenzene	+(DB)	+(DB)	-(DB)	+(DB)	IND
2-Bromobenzothiazole	-	-	-	-	-
Toluene	-	IND	+(NO)	-	-
	+	OPS	OPS	OPS	-

DB: Compound is in the database
NO: Actual and predicted values of the similarity search do not agree, prediction unacceptable
OPS: Outside the optimum prediction space
OPS: Probability is less than 0.300
IND: Probability is between 0.300 and 0.700 (the probability is inderminant due to equal chance probability)

"+": Probability is greater than 0.700

as bar graphs. An examination of the results obtained should aid in the prioritization of these health-related endpoints for performing additional bioassay studies.

B.3.1 ALDEHYDES

Carcinogenicity

The carcinogenicity of aliphatic aldehydes is predicted to be gender specific in that the majority aliphatic aldehydes (22/28) were predicted as carcinogens in the female mouse and noncarcinogens in the male mouse. All aliphatic aldehydes were predicted as noncarcinogens in female rats with a mixture of carcinogens/ noncarcinogens (5/28) in male rats. The two aromatic aldehydes, benzaldehyde and benzacetaldehyde are predicted as noncarcinogens in all submodels with the exception of the female mouse which predicts benzaldehyde to be carcinogenic.

Developmental Toxicity

With the exceptions of cyanoformaldehyde, tribromoacetaldehyde, methyl propanal and methyl glyoxal, all other aliphatic and aromatic aldehydes (20/30) are predicted negative for developmental toxicity.

Mono Carboxylic Acids

Halogenated Acetic Acids

Carcinogenicity

All monohalogenated acetic acids are predicted as noncarcinogens for both female and male rats and mice with the exception of bromoacetic acid which is predicted as a carcinogen in female rats and mice. Dihalogenated acetic acids are predicted as noncarcinogens for all submodels with the exception of dichloro- and dibromoacetic acids which are predicted as carcinogenic in male mice. With the

exception of trichloroacetic acid in the female rat, all other trihalogenated acetic acids are predicted as carcinogens in male and female rats and male mice. However, in the case of the female mouse submodel all trihalogenated acetic acids were predicted as non-carcinogens.

Dichloro-, dibromo- and bromochloroacetic acids are predicted as noncarcinogens and carcinogens in male rats and mice submodels, respectively. In female mice submodel, bromochloroacetic acid is predicted as a carcinogen.

Trifluoro-, tribromo- , dibromochloro- and dichlorobromoacetic acids are predicted as carcinogens and noncarcinogens in female rats and mice submodels, respectively.

Developmental Toxicity

In contrast to carcinogenicity, all three classes of the halogenated acetic acids (mono-, di- and tri, including mixed di- and trihalogenated acetic acids, show a distinct pattern. All the mono- and trihalogenated acetic acids of fluorine, chlorine, bromine and iodine, are predicted as developmental toxicants; whereas, all the dihalogenated acetic acids for the same halogens are predicted negative for developmental toxicity.

Chlorinated carboxylic acids (C3,C4,C5):

Carcinogenicity

Due to the limited quantity of C3 to C5 chlorinated carboxylic acids, analyses failed to produce an overall pattern with respect to carcinogenicity, although 3/7 acids were predicted positive in more than one rodent model.

Developmental Toxicity

All chlorinated carboxylic acids are predicted as developmental toxicants, with the exception of those that were judged to be indeterminant (2-chloropropanoic acid,

and 3,3-dichloropropenoic acid) or outside the Optimum Prediction Space (OPS) [(2,3-dichloro-4-oxobutenoic acid)].

Nonhalogenated Carboxylic acids:

Carcinogenicity

The majority (21/27) of non-halogenated carboxylic acids were predicted as non-carcinogens for all four submodels (male/female rats and mice). The exceptions were glyoxylic acid and 1,2-dioxopropanoic acid, which were predicted as carcinogens in female mice and rats, 2-oxopropanoic acid, 2-methyl propanoic acid, dioxobutanoic acid, 4-oxopentanoic acid which were predicted as carcinogens in female rats submodel, and decanoic acid, undecanoic acid and dodecanoic acid which were predicted as carcinogens in male rats submodel. Many of these compounds were judged to be outside the OPS in the male mouse and rat submodels.

Developmental Toxicity

Nonhalogenated carboxylic acids ranging in carbon chain lengths from C2 to C5 are predicted as developmental toxicants, with the exception of 2-oxopentanoic acid, which is predicted negative. Acids with carbon chain lengths greater than C6 are all predicted negative, with several of these compounds judged to be outside the OPS.

Di Carboxylic Acids:

Chlorinated Di-Carboxylic Acids:

Carcinogenicity -

As in the case of chlorinated mono-carboxylic acids, there were not enough chlorinated di-carboxylic acids analyzed to see an overall distinct pattern in prediction.

Developmental Toxicity -

Of the three compounds analyzed, 2-chlorobutenedioc acid is predicted as a developmental toxicant, chlorobutanedioic acid was predicted as a nondevelopmental toxicant and 2-chloro-3-methyl-cis-butenedioic acid was predicted as indeterminant.

Nonhalogenated Di-Carboxylic Acids:

Carcinogenicity -

The majority (14/16) of nonhalogenated di-carboxylic acids were gender and species specific for carcinogenicity, with carcinogenicity limited to the female rat submodel. These acids were predicted noncarcinogens in male rats and mice and female mice submodels. Tert-butyl-cis-butenedioic acid and tridecanedioic acid are exceptions, being predicted as carcinogenic in female mice and noncarcinogenic in female rats submodels, respectively.

Developmental Toxicity -

Most nonhalogenated di-carboxylic acids (12/16) are predicted as developmental-toxicants, except octanedioic acid, nonanedioic acid and tridecanedioic acid, which are predicted negative, and heptanedioic acid which is indeterminate.

Aromatic Carboxylic Acids:

Carcinogenicity -

Aromatic carboxylic acids (7/12) are predicted as carcinogens in the female rat submodel and noncarcinogens in the male mouse and rat and female mouse submodels. Three acids (1,2,3-, 1,2,4- and 1,3,5-benzene tricarboxylic acids) are judged to be outside the OPS in male mice and female rats submodels.

Developmental Toxicity -

All aromatic carboxylic acids are predicted negative for developmental toxicity, with the exception of phenylacetic acid which is predicted positive.

B.3.2 KETONES

Halogenated Ketones:

Carcinogenicity -

Most halogenated ketones are predicted as carcinogens in the male mouse submodel and predicted as non-carcinogens in the female mouse and rat and male rat submodels with the exception of 1-chlorodimethylglyoxal, chloropropanone, 1,1-dichloropropanone, 1-bromo-1,1-dichloropropanone, 1,1-dichloro-2-butanone and 3,3-dichloro-2-butanone which are predicted as noncarcinogens in the male mouse submodel. 1,1,1,3-, 1,1,3,3-tetrachloropropanone and hexachloropropanone are predicted positive for carcinogenicity in the male rat and 1,1-bromochloropropanone is predicted positive in female mouse and male mouse. Approximately 50% of these ketones (19/40) were determined to be outside the OPS.

Developmental Toxicity -

Except for 1,1-dibromoacetone, 1,1-dichloropropanone, 1,1,3-trichloropropanone, 1,1,1,3,3-pentachloropropanone, 1,1-bromochloropropanone, and 1,1-dichloro-2-butanone, all halogenated ketones are predicted positive for developmental toxicity.

Nonhalogenated Ketones:

Carcinogenicity -

Of the 11 nonhalogenated ketones, most appear to be gender and species specific for carcinogenicity, in that they are predicted carcinogenic in the male rat

submodel with a few exceptions. These exceptions being, butanone, 3-hexanone and, 6-methyl-5-hepten-3-one which are predicted noncarcinogens. Glyoxal is predicted positive in the female mouse as well as the male rat submodel. Three compounds are determined to be outside the OPS for all four submodels.

Developmental Toxicity -

Most nonhalogenated ketones show a positive trend for developmental toxicity. Geranylacetone and 3-methyl-2,4-hexanedione are judged to be outside the OPS and 3-hexanone, 2,6-dimethyl-2,5-heptadiene-4-one and 6-methyl-5-hepten-3-one are predicted negative.

Cyclic Ketones:

Carcinogenicity -

All cyclic ketones appear to follow a noncarcinogenic trend in all four submodels, with only 2,2,4-trichloro-1,3-cyclopentenedione being predicted positive in the female mouse. 2-Chlorocyclohexanone is determined to be outside the OPS in the male mouse and 2,6,6-trimethyl-2-cyclohexene-1,4-dione and 1,3,3-trimethyl-1,7-oxabicyclo-[4.1.0]-heptane-2,5-dione are indeterminant.

Developmental Toxicity -

Of the seven cyclic ketones, four are judged to be outside the OPS, whereas 2,2,4-trichloro-1,3-cyclopentenedione, 2-chlorocyclohexanone and 1,3,3-trimethyl-1,7-oxabicyclo-[4.1.0]-heptane-2,5-dione are predicted negative for developmental toxicity.

Aromatic Ketones:

Carcinogenicity -

There is no clear pattern evident for carcinogenicity in aromatic ketones. 1-[4-(1-methylethyl)phenyl]-ethanone and 1,1-(1,4-phenylene)bis-ethanone are predicted positive in the male mouse and rat submodels, whereas 2,6-tert-butyl-1,4-benzoquinone is predicted positive in the female mouse submodel and is indeterminant in the male rat submodel. The remaining aromatic ketones are predicted as noncarcinogens.

Developmental Toxicity -

All aromatic ketones are predicted negative for developmental toxicity.

B.3.3 LACTONES

Carcinogenicity -

The lactones appear to have their carcinogenicity restrained to the male mouse submodel. Apart from dihydro-4,5-dichloro-2-(3H)-furanone, red-MX, EMX and 4-dodecyl-5-ethyl-2(5H)furanone which are predicted noncarcinogens in the male mouse and MX which is predicted indeterminant in the male mouse all other lactones are predicted as carcinogens in the male mouse submodel. 5-Hydroxy-5-trichloromethyl-2-furanone, BMX-1 and EMX are predicted as carcinogens in the female mouse submodel. Many of the lactones are judged to be outside the OPS, especially in the female rat.

Developmental Toxicity -

Most lactones are predicted negative for developmental toxicity. The few exceptions being 5-hydroxy-5-trichloromethyl-2-furanone, which is predicted indeterminant, and dihydro-4,5-dichloro-2-(3H)-furanone, red-MX and 4-dodecyl-5-ethyl-2(5H)furanone, which are judged to be outside the OPS.

B.3.4 ALCOHOLS

Aliphatic Alcohols:

Carcinogenicity -

The number of aliphatic alcohols analyzed is insufficient to indicate a trend in carcinogenicity. Of the five alcohols analyzed, only 1-[2-(2-methoxy-1-methylethoxy)-1-methylethoxy]-2-propanol was predicted carcinogenic in the female mouse and male rat submodels, was predicted noncarcinogenic in the male mouse submodel and was outside the OPS in the female rat submodel. The remaining alcohols were either predicted noncarcinogens or were outside the OPS for all four submodels.

Developmental Toxicity -

All the aliphatic alcohols are predicted negative.

Aromatic Alcohols:

Carcinogenicity -

As in the case of aliphatic alcohols not enough aromatic alcohols were analyzed to realize a trend in carcinogenicity. Most alcohols are predicted as noncarcinogens in all four submodels with a few exceptions. These exceptions are 2,4,6-trichlorophenol, which is predicted as a carcinogen in the male mouse; 4-(1-methylethyl)-benzene methanol, which is predicted positive in the female mouse and female rat submodels; and 2,6-di-tert-butyl-4-nitrophenol, which is predicted carcinogenic in the male rat submodel.

Developmental Toxicity -

With the exception of 4-(1-methylethyl)-benzene methanol all aromatic alcohols are predicted negative.

B.3.5 ETHERS

Aliphatic Ethers:

Carcinogenicity -

The carcinogenic activity is random and spread out for aliphatic ethers, due to the limited number of compounds analyzed. Bromochloromethyl acetate is predicted as a carcinogen in the female mouse/rat and male mouse. 1-Chloroethanol acetate is predicted as a carcinogen in the male rat submodel. 1,2-Dichloroethanol acetate is predicted as a carcinogen in the female and male mice. 2-Methyl-3,3-dichloro-2-propenyl dichloromethylether is predicted positive in the female rat. 1,4-Dioxane is predicted as carcinogenic in female and male mice and male rats, whereas 3-bromopropylchloromethylether is predicted as carcinogenic in all four submodels. Few compounds are judged to be outside the OPS in various submodels.

Developmental Toxicity -

All aliphatic ethers are predicted negative for developmental toxicity with the exception of 1-chloroethanol acetate, 3-bromopropylchloromethylether and 1,4-dioxane which are predicted positive.

Aromatic Ethers:

Carcinogenicity -

The only chemical analyzed for carcinogenicity, 1,4-benzodioxin is predicted a noncarcinogen in the male mouse, female and male rat submodels. It was determined to be outside the OPS in the female mouse.

Developmental Toxicity -

1,4-Benzodioxin is predicted negative for developmental toxicity.

B.3.6 NITRILES

Aliphatic Nitriles:

Carcinogenicity -

The carcinogenic potential of most aliphatics nitriles is predicted as negative by QSAR technique. Carcinogenic activity of aliphatic nitriles seems to be limited to chlorine and bromine substitutions of single and double carbon chains. Cyanogen bromide is predicted as a carcinogen in the female rat. Bromoacetonitrile is predicted positive in female mouse and female rat. Dichloromethyl cyanide is positive in female mouse. Trichloro- and tribromoacetonitriles are predicted to be carcinogenic in male rats. Bromochloroacetonirile is predicted as a carcinogen in female and male mice, trichloropropenenitrile is predicted positive in the female rat. 2,3-Dichloropropanenitrile and 3,4-dichlorobutanenitrile are predicted as carcinogens in female mice and 3-methylbutane nitrile is predicted positive in the male rat. Few aliphatics nitriles are determined to be outside the OPS.

Developmental Toxicity -

As in the case of halogenated and short chain carboxylic acids, aliphatic nitriles show a tendency toward developmental toxicity. With the exception of bromochloroacetonitrile and 3,4-dichlorobutanenitrile, all other chlorinated and brominated nitriles are predicted as developmental toxicants. Three chlorine substituted nitriles, 2,3-dichloropropanenitrile, cis- and trans-2,3,4-trichloro-2-butenenitrile are determined to be outside the OPS. Of the nonhalogenated nitriles, 3-methylbutane nitrile is predicted positive and hepatanenitrile is predicted negative for developmental toxicity.

Aromatic Nitriles:

Carcinogenicity -

The two aromatic nitriles analyzed, are predicted to be noncarcinogenic in all four submodels.

Developmental Toxicity -

Both aromatic nitriles are predicted negative for developmental toxicity.

B.3.7 AMINES

Aliphatic Amines:

Carcinogenicity -

The number of amines analyzed were too few to recognize a trend in carcinogenicity. For the two amines analyzed, 1-chloro-3,3,3-trichloro-1-propen-1-amine is predicted carcinogenic in the female and male mouse submodels, whereas 5-methyl-3-isoxazolamine is predicted carcinogenic in the male mouse. Both compounds are predicted as noncarcinogens in the remaining submodels.

Developmental Toxicity -

As in the case of carcinogenicity, no trend can be observed due the fact that only two compounds were analyzed. 1-Chloro-3,3,3-trichloro-1-propen-1-amine is predicted positive, whereas 5-methyl-3-isoxazolamine is predicted negative for developmental toxicity.

Aromatic Amines:

No aromatic amines were analyzed, either for carcinogenicity or developmental toxicity.

B.3.8 AMIDES

Aliphatic Amides:

Carcinogenicity -

Of the two amides analyzed, 2,2-dichloroacetamide is predicted noncarcinogenic in three of the four submodels and is determined to be outside the OPS in the female rat submodel. 2,2,2-Trichloroacetamide is predicted noncarcinogenic in the female mouse and rat submodels and is predicted carcinogenic in the male mouse and rat submodels.

Developmental Toxicity -

2,2-Dichloroacetamide is predicted indeterminant and 2,2,2-trichloroacetamide is predicted as a developmental toxicity.

Aromatic Amides:

No aromatic amines were analyzed, either for carcinogenicity or developmental toxicity.

B.3.9 HALO & NITRO COMPOUNDS

Aliphatic Alkanes and Alkenes:

Carcinogenicity -

The aliphatic alkanes and alkenes have been subdivided into four groups:

1. The group encompassing halogenated (mainly chlorine and bromine) and nitro methanes, show a carcinogenic trend in the male rat submodel, and a noncarcinogenic trend in the other three submodels for the most part. Methyl chloride and bromodichloronitromethane are predicted as indeterminant and bromochloroiodomethane and nitrodibromomethane are predicted as noncarcinogens in the male rats. Methylene chloride is also predicted as a carcinogen in the male mouse. Dibromomethane and bromodichloromethane are predicted positive in all four submodels. Apart from being carcinogenic in the male rat submodel, bromoform is predicted carcinogenic in female rats, dichloroiodomethane is predicted positive in female mice, bromochloroiodomethane and dbromochloromethane are

predicted carcinogenic in female mice and rats and nitrodibromomethane is predicted carcinogenic in the male mouse model. Four of the nitro/halo methanes are determined to be outside the OPS in the female rat submodel.

2. The halogenated and nitro alkanes and alkenes (C2 and greater) are noncarcinogenic with a few exceptions. These exceptions are, 1-chloro-2-ethoxy-2-methoxy ethane, which is predicted as a carcinogen in female and male rats, hexachloroethane is predicted positive in female and male mice and male rats, 1,1,1-tribromo-2-bromo-2-chloroethane is predicted carcinogenic in the female mouse, 3,3,3-trichloro-2-methyl-1-propene is predicted positive in male mice and rats, 2-bromobutane is predicted as a carcinogen in male mice and female rats, 1,1,5,5-tetrachloropentane is predicted carcinogenic in the male rat submodel, 1-hydroxy-3-methyl-2-hexene is predicted positive in female mice and 1-chlorooctane is predicted positive in male rats.

3. Two compounds identified as outliers, undecane and methane sulfonyl chloride are predicted noncarcinogens in all four submodels with the exception of undecane, which is determined to be outside the OPS in male rats.

4. The cyclic halogenated and non-halogenated alkanes and alkenes show no pattern in carcinogenicity. Tetrachlorocyclopropene and hexachlorocyclopentadiene are predicted as a carcinogens in female rats and cyclododecane is predicted positive in the male mouse and rat submodels.

Developmental Toxicity -

Unlike the carcinogenicity model, there is no specific order to toxicity among the various subgroups. Methylene chloride, dibromomethane, trichloronitromethane, bromopicrin, bromodichloronitromethane, 1-ethoxy-1-hydroxymethane, 1-nitro-1,1-dichloroethane, hexachloroethane, 1,2-dichloro-2-methyl butane and methane sulfonyl chloride are predicted as developmental toxicants, whereas the rest are either predicted negative, indeterminant or are determined to be outside the OPS.

Aromatic Compounds:

Carcinogenicity -

Most of the aromatic compounds are predicted to be noncarcinogens with a few exceptions. The few exceptions being, benzene and 1,4-dichlorobenzene which are predicted to be carcinogenic in female and male mice and male rats. 1,3-Dichlorobenzene and 1,2-bis(1-methylethenyl)benzene are predicted positive in the female mouse submodel and, toluene is predicted to be carcinogenic in female rats. Some of these compounds are predicted to be indeterminant or determined to be outside the OPS.

Developmental Toxicity -

All aromatic compounds are predicted negative for developmental toxicity with the exception of benzene which is determined to be outside the OPS and, 1,4-dichlorobenzene which is predicted as indeterminant.

B.3.10 CONCLUSIONS

In addition to our initial agreement with OW of prioritizing the list of DBPs in terms of potential carcinogenicity and developmental toxicity based on probability, NCEA-Cincinnati has categorized these DBPs by chemical class based on functional groups. Based on these classifications, patterns of prediction have been identified that should aid OW in eliminating certain chemical classes based on functional groups. However, in contrasting these predicted data with the available literature, one must follow the criteria used to develop the respective models for all literature published before and after model development. It should be well understood that all QSAR models are closed systems and ultimately should not be used to replace bioassays. However,

QSAR predictions are independent of equilibrium changes that are pH dependent, such as the activity of MX compounds at different pH's in the Ames mutagenicity assay. Using QSAR the authors have been able to distinguish the mutagenic potential of the closed (lactone) and open forms of MX compounds which is not possible under Ames assay conditions.

Developmental toxicity was identified as a health-related endpoint common to the majority of aliphatic mono- and dicarboxylic acids; most aliphatic halogenated and non-halogenated ketones and most aliphatic haloacetonitriles. In the case of the NTP carcinogenicity submodels, most aliphatic aldehydes were identified as likely carcinogens only in the female mouse submodel. The majority of the aliphatic and aromatic dicarboxylic acids were identified as likely carcinogens in the female rat submodel. All other functional groups were for the most part predicted as noncarcinogens in all NTP cancer submodels (male/female rats and mice). An analyses of these QSTR/DBPS results should aid in the prioritization of chemicals to evaluate for these health-related endpoints in the absence of *in vivo* bioassays.

Additional research will include an investigation of which features (descriptors) in a molecule for various chemical classes are responsible for the positive and/or negative predictions and why? In addition, all "similarity search" data for each model and chemical class will be reviewed with the idea of identifying those compounds in the data base that are most similar electronically (in terms of descriptor contribution) to the query compounds and why. Hopefully, this type of information will extend our knowledge and understanding of the structural basis for activity within these classes, whereas a simple

list of TOPKAT predictions provides no such insight. Lastly, the authors welcome the opportunity to compare their results to those obtained by other QSAR models.

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APPENDIX B.4 SUMMARY OF DBP-SPECIFIC TOXICITY DATA

B.4.1 SELECTION OF COMPOUNDS FOR EVALUATION

The selection of treatment trains for consideration was one factor in the determination of which DBPs were investigated. We have focused on DBPs identified in a split-sample treatment study of Ohio River water (Miltner et al., 1990).

B.4.2 INDIVIDUAL CHEMICAL SUMMARIES

The goal of this section is to present chemical summaries for several demonstrative chemicals. Due to logistical constraints of this document, and because such summaries for other chemicals may be presently available, the chemicals summarized here are only examples of the toxicologic data that are available on the DBPs. Full chemical summaries should be compiled for the DBPs pertinent to decisions using the CRFM. We have focused our evaluation on compounds previously identified under a pilot-scale investigation conducted and previously reported (Miltner et al., 1990; see Table B.4-1). Although bromate levels were not measured in Miltner et al. (1990), this risk assessment used levels measured by Miltner et al. (1992).

The following summaries provide pertinent details of the chemicals for focus in this comparison. While more exhaustive reviews are available for some compounds, and more data are available for some than others, these sections highlight the important points for consideration. Because of the primary importance of the oral route of exposure for DBPs in drinking water, we have not addressed regulatory concern for exposures other than oral, unless specifically applicable or dictated by lack of orally-relevant data. In reporting reproductive and developmental effects, we have included some data available with whole-embryo culture studies, an in vitro design whose results

are not deemed applicable in determining regulatory levels (e.g. RfD) of exposure. They are, nonetheless, useful in estimating the potential for such an effect to occur *in vivo.*

TABLE B.4-1

EPA - Verified Data Available for Compounds Evaluated in this Case Study

Compound [CASRN]	RfD	Carcinogenic Risk	
		Oral Slope	Unit Risk
Chloroform [67-66-3]	1 E–2 mg/kg/day (09/01/92)	6.1 E–3 (03/01/91)	1.7 E-7
Bromodichloromethane [75-27-4]	2 E–2 mg/kg/day (03/01/91)	6.2 E-2 (03/01/91)	1.8 E-6
Dibromochloromethane [124-48-1]	2 E–2 mg/kg/day (03/01/91)	8.4 E-2 (01/01/92)	2.4 E-6
Bromoform [75-25-2]	2 E–2 mg/kg/day (03/01/91)	7.9 E-3 (01/01/91)	2.3 E- 7
Trichloroacetic Acid [76-03-9]	1 E-1 mg/kg/day (05/06/93)	N/A	N/A
Dichloroacetic Acid [79-43-6]	4 E-3 mg/kg/day (06/15/93)	N/A	N/A
Chloroacetic Acid [79-08-3]	2 E–3 mg/kg/day (02/01/96)	N/A	N/A
Chloral Hydrate [75-87-6]	2 E-3 mg/kg/day (02/01/96)	N/A (?)	N/A (?)
Potassium Bromate [7758-01-2]	N/A	4.9 E-1 (12/11/92)	1.4 E-5

Trihalomethanes: The early identification of carbon tetrachloride as a potent liver carcinogen may have heightened the concerns over finding chloroform in drinking water supplies in 1974. This finding stimulated research on THMs which has focused on dose-response relationships, exposure estimates for humans, biomarkers of exposure, and studies of the mechanism(s) underlying cancer. These efforts have spread to other halomethane compounds, resulting in reduced uncertainty about toxicity

data generated in rodent species. However, the differences in response noted with different dose regimens/schedules and vehicles complicate the extrapolation of some responses following the administration of bolus doses of THMs. The EPA's Science Advisory Board reviewed the Office of Water's draft Drinking Water Criteria Document (October 25-26, 1990) and advised that the concern over corn oil as vehicle for gavage studies dictated that the hepatocarcinogenic effects (as noted with chloroform) should be utilized only in making a weight-of-evidence classification, and should "be disregarded in making a quantitative estimation of the carcinogenic risk of a trihalomethane." The IRIS file for all three brominated THMs (revised 03/01/91) states that, "No adequate data on the teratogenic or reproductive effects of trihalomethanes are available", but the IRIS file for chloroform (revised 09/01/92) does not contain such a statement.

Chloroform ($CHCl_3$): Chloroform is the THM which has received the most attention. Care should be taken that chloroform data are not extrapolated without specific and detailed justification. A weight-of-evidence classification of B2 (probable human carcinogen) has been assigned to chloroform. There are no epidemiologic studies for chloroform itself, although chloroform was the major identified DBP in epidemiologic studies which have associated increased incidences of rectal, bladder and colon cancer with drinking water chlorination. Chloroform induces CNS depression and cardiac sensitization, though at doses not likely encountered in drinking water (Bull and Kopfler, 1991). Chloroform is considered highly fetotoxic, but not teratogenic (Schwetz et al., 1974 and Thompson et al., 1974 in U.S. EPA, 1998a); and inhalation exposure produced a dose-dependent increase in post-implantation death and reduced

crown-rump length and weight gain in rat pups (ATSDR, 1996). Savitz et al. (1995) used data from case-controlled studies on miscarriages, preterm delivery and low birth weight as related to THM concentration in drinking water to demonstrate that although no dose-response was observed, a significant elevation of miscarriage was present in the highest sextile of THM concentration. Increased association (odds ratios >1.50) of adverse birth outcomes which included low birth weight, "CNS defects", cleft palate and cardiac defects (Bove et al., 1995).

CHCl3: The oral RfD (revised 09/01/92) is based on the finding of fatty cysts in liver of dogs chronically exposed to chloroform in toothpaste (Heywood et al., 1979), and demonstrated a LOAEL of 15 mg/kg/day, which was converted to 12.9 mg/kg/day when dosing schedule was converted to 7 days/week (U.S. EPA, 1998a). Application of uncertainty and modifying factors totaling 1,000 reduce the oral RfD to 10 µg/kg/day (700 µg/day for a 70 kg human). For carcinogenic risk (updated 03/01/91), an oral slope factor of 6.1x10E-3 per mg/kg/day and a drinking water unit risk of 1.7x10E-7 per µg/L have been assigned to chloroform. A carcinogenic risk of 1.0x10E-6 results from exposure to a concentration of 6 µg chloroform/L drinking water.

Bromodichloromethane (BDCM): A weight-of-evidence classification of B2 (probable human carcinogen) has been assigned to BDCM. BDCM produces tumors at multiple sites in multiple species, and the kidney tumors produced are independent of alpha-2-micro-globulin. There are no epidemiologic studies for BDCM alone, although ecologic and epidemiologic studies which have associated increased incidences of rectal, bladder and colon cancer with drinking water chlorination. Because of the complex mixture of DBPs in drinking water and the co-exposure to other factors which

modify cancer formation, these data are insufficient for assessing the carcinogenic risk of BDCM to humans. BDCM is reported to be mutagenic in several *in vitro* evaluations and is structurally similar to other known animal carcinogens. Klinefelter et al. (1995) reported that the exposure of rats to BDCM in drinking water (at 39 mg/kg/day) sperm velocity was significantly decreased.

BDCM: The oral RfD (revised 03/01/91) is based on the finding of renal cytomegaly in micechronically exposed to BDCM via gavage in corn oil (NTP, 1986), which demonstrated a LOAEL of 17.9 mg/kg/day (U.S. EPA, 1998a). Application of uncertainty and modifying factors totaling 1,000 reduced the oral RfD to 20 µg/kg/day (1400 µg/day for a 70 kg human). For carcinogenic risk (revised 03/01/93), an oral slope factor of 6.2x10E-2 per mg/kg/day and a drinking water unit risk of 1.8x10E-6 per µg/L have been assigned to BDCM, based on the "linearized multistage model, extra risk". A carcinogenic risk of 1.0x10E-6 results from exposure to a concentration of 0.6 µg BDCM/L drinking water.

Dibromochloromethane (DBCM): A weight-of-evidence classification of C (possible human carcinogen) has been assigned to DBCM. There are no epidemiologic studies for DBCM alone, although ecologic and epidemiologic studies have suggested increased incidences of rectal, bladder and colon cancer associated with drinking water chlorination. DBCM is mutagenic and carcinogenic in male and female mice, however, liver tumors are found only at levels of DBCM which produced liver damage and only with corn oil as vehicle. The IRIS file for all three brominated THMs (revised 03/01/91) states that, "No adequate data on the teratogenic or reproductive effects of trihalomethanes are available", but the IRIS file for chloroform (revised 09/01/92) does

not contain such a statement. However, a study by Ruddick et al. (1983) evaluated the developmental toxicity of some THMs. Unfortunately, the low number of fetuses examined from DBCM-exposed dams did not allow the developmental toxicity of DBCM to be confirmed or refuted.

DBCM: The oral RfD (revised 03/01/91) is based on the finding of hepatic lesions in rats exposed subchronically via corn oil gavage (NTP, 1985), which demonstrated a NOEL of 30 mg/kg/day, which was converted to 21.4 mg/kg/day (U.S. EPA, 1998a). A LOAEL of 60 mg/kg/day was observed, which converted to 42.9 mg/kg/day. Application of uncertainty and modifying factors totaling 1,000 (to the NOEL) reduce the oral RfD to 20 µg/kg/day (1400 µg/day for a 70 kg human). For carcinogenic risk (revised 01/01/92), an oral slope factor of 8.4x10E-2 per mg/kg/day and a drinking water unit risk of 2.4x10E-6 per µg/L have been assigned to DBCM. A carcinogenic risk of 1.0x10E-6 results from exposure to a concentration of 0.4 µg DBCM/L drinking water. There are no published data on teratogenicity or reproductive effects of trihalomethanes (IRIS, 1998; updated 03/01/91), however, BDCM produced dose-dependent skeletal malformations in rats (Ruddick et al., 1983).

Bromoform (CHBr3): A weight-of-evidence classification of B2 (probable human carcinogen) has been assigned to chloroform. There are no epidemiologic studies for bromoform itself, although ecologic and epidemiologic studies have suggested increased incidences of rectal, bladder and colon cancer associated with drinking water chlorination. Geographic studies have suggested correlations between the levels of trihalomethanes in drinking water and incidences of bladder, colon, rectal and pancreatic cancer in humans. Interpretation of these studies is complicated due to

the study design which did not allow for the consideration of other factors which modify carcinogenic response. Bromoform is genotoxic and induced colorectal tumors in mice following intraperitoneal administration and tumors in rats following oral administration. There are no adequate published data on teratogenicity or reproductive effects of trihalomentanes (U.S. EPA, 1998a; chronic oral RfD for bromoform was updated on 03/03/91), although bromoform (and BDCM) produced a dose-dependent increase in skeletal malformations in rats (Ruddick et al., 1983).

CHBr3: The oral RfD (revised 03/01/91) is based on the finding of hepatic lesions in rats exposed subchronically by gavage (NTP, 1989), which demonstrated a NOEL of 25 mg/kg/day, which was converted to 17.9 mg/kg/day (U.S. EPA, 1998a). Application of uncertainty and modifying factors totaling 1,000 reduce the oral RfD to 20 µg/kg/day (1400 µg/day for a 70 kg human). For carcinogenic risk (revised 01/01/91), an oral slope factor of 7.9x10E-3 per mg/kg/day and a drinking water unit risk of 2.3x10E-7 per µg/L have been assigned to bromoform. A carcinogenic risk of 1.0x10E-6 results from exposure to a concentration of 4 µg bromoform/L drinking water.

Haloacetic Acids: The primary exposure to TCA and DCA is through drinking water. While these are the only two HAAs for which an IRIS file exists, and they are the most commonly encountered HAA DBPs, their carcinogenic dose-response curves are dissimilar. TCA produces a linear dose-response for liver tumors, while that for DCA demonstrates a distinct dose level, below which tumors are not observed. TCA, DCA and the other HAA DBPs were assessed for *in vitro* developmental effects. Rogers et al. (1995) removed mouse conceptuses (at the 3 to 6 somite stage) and subjected them to whole embryo culture in the presence of mono-, di- and tri-brominated and

chlorinated acetic acids for 24 hours. Neural tube defects were observed for all compounds and benchmark concentrations for a 5% increase in defects for the compounds were: dichloroacetic acid, 2452 μM; acetic acid, 1888 μM; tribromoacetic acid, 1403 μM; trichloroacetic acid, 1336 μM; dibromoacetic acid, 162 μM; chloroacetic acid, 91.5 μM; bromoacetic acid, 2.68 μM. While these *in vitro* effects should not be used in risk estimation, they may indicate the qualitative likelihood of an adverse effect. This cannot be further determined from *in vitro* data sets due to lack of physiological parameters such as pharmacokinetics or the inclusion of limits of maternal toxicity. A summary of HAA reproductive and developmental effects is presented in Table B.4-2.

TABLE B.4-2

HAA Reproductive and Developmental Effects

CMPD	Dose Range (mg/kg/day)	Critical Effect	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	Reference
TCA (rat)	330 - 1800	Cardiovascular, eye	330	-	Smith et al., 1989
DCA (rat)	140 - 400	Cardiovascular	140	14	Smith et al., 1992
DCA (rat)	31.3 - 125	Preputial gland, epididymes	31.3	-	Toth et al., 1992
DCA (mouse)	30 -947	No clear effects	-	947	Narotsky et al., 1996
MCA (rat)	17 - 140	Cardiovascular	140	70	Smith et al., 1990
MBA (rat)	25 - 100	Cardiovascular / craniofacial	100	50	Randall et al., 1991
DBA (rat)	2 - 250	Sperm effects	50	10	Linder et al., 1995
DBA (mouse)	24 - 806	Fetal weight, tail defects	610	392	Narotsky et al., 1996

Trichloroacetic Acid (TCA): A weight-of-evidence classification of C (possible human carcinogen) has been assigned to TCA. This has its basis in a lack of human data and the production of tumors in male and female mice, but there is no evidence of carcinogenicity in rats. Genotoxic evaluations have produced mixed results, and TCA does not appear to induce point mutations. No epidemiologic studies have shown an association between exposure to TCA and the production of site-specific tumors. Smith et al. (1989) report a LOAEL of 330 mg/kg/day for developmental effects (resorption, heart and eye defects, decreased fetal weight gain and reduced maternal weight gain) in rats.

TCA: The oral RfD for TCA was not established during the revision accomplished on 01/01/94 (U.S. EPA, 1998a). No quantitative estimates of carcinogenic risk from oral exposure to TCA were established during the revision of the Carcinogenesis Assessment section of IRIS (08/04/93) (U.S. EPA, 1998a). The Agency is exploring the development of a biologically-based model to accommodate the existing database and other data under development.

Dichloroacetic Acid (DCA): A weight-of-evidence classification of B2 (probable human carcinogen) has been assigned to DCA. This is based on a lack of human carcinogenicity data and an increased incidence of hepatocellular adenoma and carcinomas in female mice. Nodules expected to progress into hepatocellular adenomas and carcinomas were also increased in both rats and mice. No epidemiologic studies have shown an association between exposure to TCA and the production of site-specific tumors. Smith et al. (1992) reported a NOAEL of 14 mg/kg/day for developmental (cardiac) defects.

DCA: An oral RfD is not available on IRIS at this time. There are no quantitative estimates of carcinogenic risk from oral exposure to DCA available at this time (U.S. EPA, 1998a). The Agency is exploring the development of a biologically-based model to accommodate the existing database and other data under development. A subchronic (14-day) dose of 25 mg/kg dose of BAA produced adverse effects on epididymal sperm morphology or histology.

Chloroacetic Acid (MCA): MCA in drinking water at concentrations of up to 1100 mg/L (time-averaged concentration) did not produce liver tumors, pathology, peroxisome or hepatocyte proliferation, or alterations of serum enzymes. Chronic (104 week) exposure of rats to MCA produced increased spleen weights in all doses 3.5 to 59.9 mg/kg/day) (DeAngelo et al., 1997).

Bromochloroacetic Acid (BCA): The only available published findings with BCA involve a drinking water exposure (21 days) to male mice. Parrish et al. (1996) demonstrated that BCA and DBA produce oxidative stress in liver tissue, as evidenced by hydroxylated DNA adducts, while TCA and DCA do not. The authors suggest that oxidative damage may modulate chronic toxicity associated with brominated HAAs.

Bromoacetic Acid (MBA): Regulatory levels and toxicity assessments for bromoacetic acid are not available on IRIS. Randall et al. (1991) gavaged pregnant rats with MBA in distilled water and noted a LOAEL of 100 and a NOAEL of 50 mg/kg/day for developmental effects including cardiovascular and craniofacial defects.

Dibromoacetic Acid (DBA): A single dose of 1250 mg/kg DBA produced significant alterations in sperm motility, abnormal sperm head morphology and flagellar degeneration, decreased sperm counts (85% of control) in caput epididymus and

decreased serum testosterone (17% of control). Subsequent studies of DBA with male rats indicated a subchronic NOAEL of 10 mg/kg/day with respect to sperm motility of fertility (Linder et al., 1995). Narotsky et al. (1996) reported a delay in partutition in mice administered DBA by gavage in water; the effect was produced by all doses of DBA (24 to 806 mg/kg/day) and in a dose-dependent manner.

Haloacetonitriles (HANs): As a group, the data base for haloacetonitriles is not as rich as that for trihalomethanes of haloaceto acids. Due to this constraint, the data presented in this section are combined for ease of presentation.

HAN Toxicity: The target organ(s) for HANs have not been established. Subchronic (90-day) studies with rats dosed via gavage using corn oil vehicle (Hayes et al., 1986) have been performed with DCAN and DBAN. Critical effects of increased liver weight (DCAN) and decreased body weight gain (DBAN) were identified. A NOAEL for DCAN was established at 8 mg/kg/day and a NOAEL for DBAN was established at 6 mg/kg/day. No such values are available for the other HANs. Application of uncertainty factors of 3,000 to these NOAEL values produce “provisional RfDs” of 3x10E-3 mg/kg/day for DCAN and 2x10E-3 mg/kg/day for DBAN. These values generally agree with provisional reference doses from reproductive and developmental toxicity studies Table B.4-3.

All compounds except DBAN (drinking water) were administered in TCAP via gavage to Long-Evans rats over GD 6-18. Values derived from TCAP-based doses may produce somewhat conservative estimates of risk because TCAP stimulates a higher delivery of HANs to the fetus than does corn oil (Gordon et al., 1991).

TABLE B.4-3

HAN Reproductive and Developmental Effects

CMPD	Dose Range (mg/kg/day)	Critical Effect	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	UF	Provis. RfD	Reference
DCAN	5 - 45	Embryo-lethality	25	15	300	5 x 10E-2	Smith et al., 1989
TCAN	1 - 55	Litter Resorption	7.5	1	300	3 x 10E-3	Smith et al., 1988
BCAN	5 - 65	Cardio-vascular Malforma-tions	5	-	3000	2 x 10E-3	Christ et al., 1995
DBAN	1 – 9.9	None Identified	-	9.9	300	3 x 10E-2	NTP, 1997

HAN Mechanistic and Metabolic Considerations: For developmental effects, halogenation seems to be critical, as acetonitrile itself does not produce developmental effects, even at doses which produce maternal toxicity. There is some evidence that interaction with the glutathione-based detoxication system in rodents may modify or modulate some of the toxic effects noted with the HANs. HANs deplete hepatic and GI tract (but not kidney) GSH levels and inhibit GST activity following their administration (Ahmed et al., 1991); depletion of hepatic GSH prior to HAN (chloroacetonitrile) administration is associated with increased HAN delivery to the fetus (Abdel-Aziz et al., 1993). Although the target organ(s) for HAN toxicity have not been named as such, these effects and the finding of increased liver weight in rats administered DCAN may indicate the liver as a potential target for HAN toxicity. Although there are no published reports indicating the contribution of metabolism to toxicity per se, HANs are metabolized to cyanide and eliminated in the urine as thiocyanates (Lin et al., 1986).

Halide displacement or oxidation of a hydrogen atom via mixed function oxidase to produce a hydroxyacetonitrile has been proposed to account for cyanide liberation.

Miscellaneous Compounds

1,1,1-Trichloropropanone (1,1,1-TCP): 1,1,1-Trichloropropanone (trichloronitromethane; 1,1,1-TCP) is one of the less well-studied DBPs. 1,1,1-TCP is mutagenic in vitro, and the mutagenicity of related compounds decreases with increasing degree of chlorination, and is lower for chlorinated than for brominated analogs.

Chloropicrin (CP): Chloropicrin is the most acutely toxic of the DBPs examined in this document. Few studies on its long-term toxicity (e.g. carcinogenicity, NCI, 1978) have been successfully completed, owing to lethality. In vitro tests have demonstrated CP's mutagenic potential (gene reversion, primary DNA damage and the induction of sister chromatid exchanges in human lymphocytes. Paucity of reported details precludes the quantitative use of developmental toxicity findings (decreased fetal weight) in rats and rabbits. The acute (4-hour) toxicity of CP is evidenced by temporally biphasic lethality, with animals expiring either within 24 hours, or at approximately 10 days. The LC50 for CP (12 ppm) approximates that of phosgene. A 13-week exposure of rats to CP by inhalation identified the lung as the primary organ for toxicity (dose-dependent increases in weight and bronchiolar lesions), and identified 0.67 ppm CP as a NOAEL . The relevance of lung as target organ for inhalation exposures is supported by a report of lacrymation, respiratory distress, coughing and bronchitis in humans inhabiting a house which had been previously fumigated with CP (measured concentration of CP was 48 ppb). Exposure of rats to CP via gavage in a 90-day study

produced lethality, which was attributed to pulmonary complications from CP aspiration, and necrosis of the stomach as the primary histopathological finding with a NOAEL of 8 mg/kg/day. Although lung was evaluated, no adverse effects were noted at doses of up to 32 mg/kg/day. Together, these data may indicate that CP's toxic is directed at the portal of entry.

Chloral Hydrate (CH): This agent has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential. Sallenfait et al. (1995) exposed chloral hydrate (0, 0.5, 1.0, 1.5, 2.0 and 2.5 mM) to rat embryos in *in vitro* whole embryo culture and noted dose-dependent effects such as decreased crown-rump length, head length and number of somites at doses above 0.5 mM.

CH: The oral RfD (revised 02/01/96) is based on the finding of hepatotoxicity in mice exposed subchronically via drinking water (Sanders et al., 1982), which demonstrated a LOAEL of 15.7 mg/kg/day (U.S. EPA, 1998a). Application of uncertainty and modifying factors totaling 10,000 (to the LOAEL) reduce the oral RfD to 2 µg/kg/day (140 µg/day for a 70 kg human). Carcinogenic risk for CH has not been established (U.S. EPA, 1998a).

Potassium Bromate (Bromate): To date there have been no surveys reporting concentrations of bromate in drinking water. However, several laboratory and bench-scale pilot treatment studies have identified factors which contribute to the formation of bromate. Drinking water studies with rats have shown the production of kidney tumors (males and females) and peritoneal mesotheliomas (males only) (Kurokawa et al., 1983). While these results indicate that bromate is a complete carcinogen, additional experiments in this study demonstrated its tumor promoting activity in the kidney, and

demonstrated that the lowest dose producing kidney tumors was 6.5 mg/kg/day (doses employed were 0.7, 1.3, 2.5, 5.6, 12.3 and 33.4 mg/kg/day). Interestingly, there was no increase in liver tumors following initiating treatment (with EHEN). Kurata et al. (1992) treated rats with acute doses of bromate followed by promoting doses of barbital sodium to examine tumor initiating activity, but could demonstrate none. The lack of tumor initiating activity may support that longer doses are necessary to initiate tumors or that bromate produces renal tumors through promotional activity. An evaluation of the impact of bromate (either KBrO3 or NaBrO3) indicates that these chemicals, but not KBr induce alpha-2-micro-globulin accumulation in the kidneys of male, but not female, rats (Umemura et al., 1993). These data, coupled with the lack of renal carcinogenicity in mice and hamsters (Kurokawa et al., 1986b; Takamura et al., 1986b), raise the question of the relevancy of bromate-induced renal tumors to the evaluation of cancer risk in humans. The involvement of alpha-2-micro-globulin as an exclusive mechanism of tumorigenicity in rat kidneys is confounded by the finding of renal tumors in female rats (Kurokawa et al., 1983). Alternately, the production of oxidative stress in renal tissue may stimulate cell replication, resulting in tumor promotion (Umemura et al., 1995). Although the finding of renal tumors in female rats may reduce the perceived importance of alpha-2-micro-globulin as an event modifying renal carcinogenicity, its association with male rat kidney tumors may indicate that the mechanism may increase the incidence of tumors in male rats beyond the incidence in female rats. This may raise questions about the validity of carcinogenic risk estimates for bromate, as they are mainly based on the incidence and dose-response relationship demonstrated for male rat kidney tumors. Consistent with the finding of renal toxicity in rodents, humans

acutely exposed to bromate (potassium and/or sodium bromate) in permanent hair wave neutralizing solutions have demonstrated severe renal damage as well as permanent hearing loss. There are no available published reports on the potential of bromate to produce developmental toxicity. Recently, published data (DeAngelo et al., 1998) have confirmed the multi-site carcinogenicity of bromate (in rats). A slight dose-response was noted for kidney tumors in mice. The U.S. EPA (1998a) has considered this evidence supportive of earlier MCL (0.01 mg/L) and MCLG (zero) values.

APPENDIX C-1

Human Data on Health Risks from Exposure to Disinfected Drinking Water: Epidemiologic Studies of Cancer and Reproductive/Developmental Effects

Both epidemiological and toxicological methods have been used to assess human health risks from exposure to disinfected drinking water. Results from experiments in animals must be extrapolated from exposures that are several orders of magnitude higher than actual human exposures, and synergistic and antagonistic effects of mixtures of chemicals are not taken into account when evaluating the carcinogenic risks of individual DBPs. Epidemiology offers the opportunity to study directly mixtures of chemicals at relevant exposures in humans. The studies must be properly designed, conducted with minimal systematic bias, and should be sufficiently large to provide information to confidently judge the impact of observed associations.

Since the early 1970's, a large number of epidemiologic studies of varying design and quality have been published in the scientific literature. The studies have focused almost exclusively on chlorinated drinking water and its association with cancer rather than on individual chemical exposures. Reproductive and developmental epidemiologic studies on this topic first appeared in the literature in the late 1980's. However, only recently have investigators collected information to quantitatively estimate exposures to individuals from different chemical families and species of DBPs and begun to study disinfectants other than chlorine.

The purpose of this section is to provide a brief overview of the existing epidemiologic literature suggesting a potential hazard from exposure to disinfected drinking water and its associated DBPs.

C.1 CANCER STUDIES

Several types of epidemiological studies have been conducted to assess the association between cancer and chlorinated drinking water. Ecological (Harris, 1974; Page et al., 1976; Cantor et al., 1978; Hogan et al., 1979; Carlo and Mettlin, 1980;

Tuthill and Moore, 1980; Wigle et al., 1986; Flaten, 1992), cohort (Wilkins and Comstock, 1981; Doyle et al., 1997), and case-control designs (e.g., Brenniman et al., 1980; Cragle et al., 1985; Gottlieb et al., 1981, 1982; Cantor et al., 1987, 1998; Ijsselmuiden et al., 1992; McGeehin et al., 1993; King and Marrett, 1996; Hildesheim et al., 1998; Young et al., 1987) have evaluated both incident and decedent cases. These studies differ in their basic approach and the evidence they can provide about the possible causality of an epidemiological association between chlorinated drinking water and cancer. These studies are not reviewed in detail in this document. However, a summary of the more methodologically sound studies, e.g, those based on incident cases, and having interviews and individual exposure estimates, is provided in Appendix C.2.

Because meta-analytic methods can be used to quantitatively summarize a body of literature and provide a single point estimate of effect for a body of literature, it seems logical to pursue such an estimate for application in this cost effectiveness case study. In an attempt to quantitatively review the literature, Morris et al. (1992) presented an aggregate meta-analysis of the published epidemiologic literature relating to water chlorination and cancer. They identified 10 articles published between 1966 and 1991 that evaluated exposure to chlorinated water and cancer at the level of the individual (ecological studies were excluded). The authors of these 10 articles evaluated a dozen different cancer sites and reported overall odds ratios (OR) ranging from less than one to almost three. The cancer sites most frequently examined were bladder and colon (7 articles each), followed by stomach, rectum, and pancreas (6 articles each). Morris et al. generated summary (weighted average) OR and 95% confidence interval estimates for each of the 12 cancer sites and reported significantly elevated ORs of 1.21 (95% CI

= 1.09-1.34) and 1.38 (95% CI = 1.01-1.87) for bladder and rectal cancer, respectively. The OR for all cancer sites combined was reported to be 1.15 (95% CI = 1.09-1.20).

At the request of U.S. EPA, this work was independently evaluated and reanalyzed by Dr. Charles Poole of Boston University (Poole, 1997). Poole found that there was considerable heterogeneity among these data and that there was evidence of publication bias within this body of literature. He also found that the aggregate estimates reported by Morris et al. (1992) were unstable and were sensitive to reasonable changes in the analytical methods and to the addition or deletion of a single study. For these and other reasons, Poole recommended that these data not be combined into a single summary estimate and that they had limited utility for risk assessment purposes. Furthermore, he concluded that the issue of whether or not water chlorination caused cancer was still an open question (Poole, 1997). Because of these findings, a summary OR from which probabilities of cancer occurrence in relation to DBP exposure could be derived is not currently available, and has not been used in the current case study. Several additional studies of cancer and exposure to D/DBPs have been published since the conclusion of the analysis by Poole. The U.S. EPA is currently developing a further quantitative analysis of the available epidemiologic literature which is designed to include an updated literature search extended to the present time and an evaluation of the body of relevant studies on the basis of more meaningful exposure groupings. Of particular interest will be creating study groupings formed from the perspective of the type of source water, specific treatment technologies, and type and amount of the specific chemical byproducts present in the delivered water. If the epidemiologic studies can be meaningfully categorized and summarized in this way (including the determination that aggregation of study results is

appropriate), the human data can be used in future applications of this cost effectiveness methodology.

Current toxicological assessment, based on only a small percentage of DBPs with adequate toxicological data, suggest a relatively small risk from the chlorination of drinking water. Additional epidemiological evidence is needed to clarify both the causal nature of the observed associations between chlorinated water and any site-specific cancers, and the magnitude of change in risk if it is real. In addition, toxicological studies implicate different target organs (primarily liver and kidney) than epidemiological studies (primarily bladder and colon/rectum), yet the basis of these differing responses has not received serious study.

C.2 REPRODUCTIVE/DEVELOPMENTAL STUDIES

Although fewer in number than the body of cancer literature, epidemiological studies of reproductive and developmental outcomes have been performed. The outcomes considered have included stillbirth, spontaneous abortion (Aschengrau et al., 1989; Savitz et al., 1995; Swan et al., 1998; Waller et al., 1998), low birth weight (<2500 g) (Lynberg, 1987; Kramer et al., 1992; Savitz et al., 1995), intrauterine growth retardation (Kramer et al., 1992), somatic effects (Kanitz et al., 1996), and birth defects including cardiac and neural tube defects (Bove et al., 1995; Aschengrau et al., 1993). Almost all examined multiple outcomes and multiple exposure variables. In 1993, an expert scientific panel convened by EPA and ILSI (ILSI, 1993; Reif et al., 1996) reviewed the epidemiologic literature on reproductive/developmental endpoints and DBP and disinfectant exposures. The panel concluded that the research in this area was in a very early and evolving stage and that the studies should be viewed as preliminary. A second expert panel convened by EPA in 1997 reviewed more recently

published work, e.g., Kanitz et al. (1996) and Savitz et al. (1995), and reached a similar conclusion. The panel stated that "The results of epidemiological studies reported to date do not provide compelling evidence about the association of adverse outcomes of pregnancy and DBPs. Associations found in most studies may be due to one or more sources of bias or residual confounding from unidentified risk factors." (U.S. EPA, 1998c, p. 2-15).

This same panel also reviewed an unpublished version of a study by Waller et al. that has been published subsequently as two companion articles (Swan et al., 1998; Waller et al., 1998). This well-designed and -conducted prospective cohort study from California reported an increased risk of spontaneous abortion associated with high consumption of drinking water with high levels of total THMs and with BDCM exposures >18 µg/L, controlling for other THMs. No information was available for other DBPs of interest, including the HAAs. The expert panel found these results to be provocative, but noted that this is the first and only study to date to have reported these specific findings. The experts encouraged further research and specifically recommended that efforts be made both to replicate the work of Waller et al. (1998) and Swan et al. (1998) in other geographic areas, and to evaluate additional drinking water exposures in the same cohort (U.S. EPA, 1998c, p. 3-2).

Because the human data base is both uncertain and sparse, the epidemiologic studies of reproductive and/or developmental outcomes have not been used in the current case study. Instead, the results from laboratory animal studies of individual DBPs have been combined to produce a "non-specific" estimate of the reproductive/developmental risk produced by each water treatment option (see Section 4) Similar to the cancer studies described in Appendix C.1, additional analyses of the

human studies on reproductive and/or developmental outcomes will also be developed and will be applied in future applications of this cost-effectiveness methodology.

C.3 SUMMARY/CONCLUSIONS

Assessing the potential health risks to humans from exposure to DBPs is plagued by inadequate data and inconsistencies in the available epidemiologic literature. Many of the studies reporting associations between chlorinated water and/or DBPs and various cancers or adverse reproductive/developmental outcomes may have biases that limit the interpretability of their findings. Moreover, the studies vary according to the amount of information available on exposure to chlorinated byproducts, specific DBPs, and other water contaminants.

The above-noted inconsistencies and methodologic problems in the epidemiologic studies make it difficult to select valid and reliable data points from these human studies for input into the case study. Various alternative approaches for quantifying the epidemiologic literature are being pursued currently and, at a minimum, these data may be used as part of a future sensitivity analysis for the case study.

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APPENDIX C-2

A Suggested Approach for Using the Current Epidemiologic Literature to Estimate the Possible Cancer Risk from Water Chlorination, for the Purposes of Regulatory Impact Analysis

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BACKGROUND AND OVERVIEW

Infectious diseases have far reaching socio-economic implications in both industrialized and developing countries, especially for the very young, the aged, nutritionally deficient, and those whose immune system may be compromised by disease or therapeutic agents. The World Health Organization estimates that in developing countries about half the population suffer from health problems associated with insufficient or contaminated water, 80% of all disease and over one-third of deaths are water-related, and as much as one-tenth of a person's productive time is sacrificed to water-related diseases (Galal-Gorchev, 1993, 1996). Unsafe, inadequate water supplies play a major role in the transmission of diarrheal diseases in countries with poor sanitation, and 1.6 billion cases of diarrhea and over 3 million associated deaths occur annually among children under 5 years of age (Galal-Gorchev, 1996). Although infectious diseases are largely under control in the United States, waterborne outbreaks that result in disease and mortality continue to occur (Hughes, 1993). Also, because waterborne disease often goes unrecognized and unreported in the US, the risk may be even more important than indicated by current statistics (Craun, 1990).

Although the benefits of water disinfection are well recognized, the discovery in 1974 that chlorine reacts with organic matter to form chloroform (Rook, 1974; Bellar et al., 1974) raised questions about its possible health risks. In the past 25 years, an increasing number of disinfection by-products (DBPs) have been identified, and concerns have intensified about health risks, such as cancer and adverse outcomes of pregnancy. These concerns have prompted both laboratory and epidemiology research into the possible health risks caused by exposure to DBPs.

Meta-analysis

In 1992, Morris et al. published an aggregate meta-analysis of the published epidemiology literature relating to water chlorination and cancer. They identified 10 articles published between 1966 and 1991 that evaluated exposure to chlorinated water and cancer at the level of the individual (ecological studies were excluded). The authors of these 10 articles evaluated a dozen different cancer sites and reported overall odds ratios (OR) ranging from less than one to almost three. The cancer sites most frequently examined were bladder and colon (7 articles each), followed by stomach, rectum, and pancreas (6 articles each). Morris et al. generated summary (weighted-average) OR and 95% confidence interval estimates for each of the 12 sites and found that there were significantly elevated OR of 1.21 and 1.38 for bladder and rectal cancer, respectively. These summary OR were used to generate estimates of the number of cases of cancer within the general population that could be prevented by eliminating exposure to chlorinated drinking water. These population attributable risk (PAR) estimates suggested that over 10,000 cancers were attributable to chlorinated drinking water exposure nationwide.

In order to determine if the above PAR estimates might be useful for risk assessment purposes, the National Center for Environmental Assessment of the US EPA contracted with Dr. Charles Poole to review the work of Morris et al. and make recommendations regarding whether these data should be aggregated and their utility for risk assessment purposes. Dr. Poole found that there was considerable heterogeneity among these data and that there was evidence of publication bias within this body of literature. He also found that the aggregate estimates reported by Morris et

al. (1992) were unstable and were sensitive to both reasonable changes in the analytical methods and to the addition or deletion of a single study. For these and other reasons, he recommended that these data not be combined into a single summary estimate and that they had limited utility for risk assessment purposes. Furthermore, he concluded that the issue of whether or not water chlorination caused these cancers was still an open question (Poole, 1997). Dr. Poole's report was peer reviewed by 5 epidemiologic experts, who generally agreed with these conclusions and recommendations (ERG, 1998).

Overall Quality of the Current Literature

Although Morris et al. (1992) excluded early ecological studies from their meta-analysis, most of the articles they included were mortality case-control studies with exposure based only on residence at death and with little control for major confounding factors (Alavanja, 1978; Brenniman, 1980; Zierler, 1986, 1988; Lawrence, 1984; Gottlieb, 1982; Young, 1981). Such studies have limited utility for determining the existence or magnitude of any association between water chlorination and cancer. However, the findings from these and later studies have raised concerns over possible associations between chlorination and some cancers, specifically bladder, colon, and rectal cancers.

Since Morris et al. (1992) reported their findings, several additional studies have been published (McGeehin, 1993; King, 1996; Doyle, 1997; Freedman, 1997; Cantor, 1998; Hildesheim, 1998; Koivusalo, 1996; Vena, 1993; Ijsselmuiden, 1992). These studies primarily focused on the three previously mentioned cancer sites, although two (Doyle, 1997; Koivusalo, 1996) were cohort studies that examined many different

cancer sites and one (Ijsselmuiden, 1992) evaluated only pancreatic cancer. In the current report, six of these published articles (McGeehin, 1993; King, 1996; Doyle, 1997; Freedman, 1997; Cantor, 1998; Hildesheim, 1998) and three earlier ones (Cragle, 1985; Cantor, 1987; Young, 1987), were considered further because they met four general quality criteria: 1) they investigated incident cancer cases; 2) they collected information directly from participants via personal interviews; 3) they generated exposure histories using both personal interviews and water utility data; and 4) they adjusted for major confounding factors, including cigarette smoking. These can be considered strengths of this set of epidemiologic data. These nine references represent studies of sufficient quality to be potentially useful for investigating the association between water disinfection and bladder, rectal, or colon cancer. The general characteristics of these studies are summarized in Table 1.

Problems Inherent in the Higher Quality Studies

Although the articles cited above could be viewed as a "best" subset of studies, there are still problems associated with them that limit their utility for risk assessment purposes. One problem is that these studies generally compared chlorinated surface water with untreated ground water. This raises the issue of the appropriateness of the comparison group, which is a fundamental issue in epidemiology. Ground and surface water sources have many differences other than their level of DBPs, such as mineral content and the presence of chemical contamination. Furthermore, populations receiving ground water may be inherently different (e.g. rural lifestyles, etc.) from those receiving surface water. Therefore, it may be impossible to completely separate the independent effect of DBP exposure from any effect tied to water source. Although

most investigators have also tried to estimate individual DBP exposures (Cantor, 1998; Hildesheim, 1998; King, 1996; McGeehin, 1993; Young, 1987; Doyle, 1997), these estimates were often based on only one or a few measurements taken at each municipal water source. Such measurements do not account for seasonal or other fluctuations in DBP levels. Also, these estimates of exposure may still be correlated to water source and chemical contamination, because run-off tends to increase both the chemical contamination and level of organic DBP- precursors in surface waters, compared to ground waters. This would tend to artificially elevate any estimates of risk from water chlorination.

Another generic problem with epidemiologic studies, including these "best" studies, is that the exposure histories generated for these studies are only rough approximations of what the true values might be and could be subject to considerable random misclassification. It has often been suggested that this type of nondifferential misclassification would attenuate any effects, rather than inflate them. However, this epidemiologic maxim does not always hold true and is especially problematic when multiple exposure categories are defined, as frequently occurs in these cancer studies (Wacholder, 1995; Flegal, 1991; Mustaffa, 1990; Birkett, 1992). Furthermore, the potentially confounding factors identified within these studies also would be subject to random misclassification, despite the best efforts of the investigators, permitting only incomplete control of confounding. This would result in residual confounding that might create a weak association that is not DBP-related. This is recognized as a potential problem in all environmental epidemiology studies, especially when the confounders are

strong risk factors for cancer, such as occupational exposures, smoking, and unhealthy diet (Greenland, 1980; Savitz, 1989; Marshall, 1996; Brenner, 1993).

The main factor that weakens the utility of the above studies for risk assessment purposes is the inconsistency of their findings. These studies do not generally report consistent results regarding either cancer sites or subgroups (Table 2). For example, a recent population-based case-control study in Iowa found elevated risk for rectal cancer, but not colon cancer (Hildesheim, 1998). However, a recent cohort study of women in Iowa, which would have included some of the same cancer cases, found elevated risk ratios for colon cancer but not rectal cancer (Doyle, 1997). Cantor et al. (1998) and Freedman et al. (1997) reported elevated bladder cancer risks only for male smokers, while Cantor et al. (1987) reported increased risks primarily among nonsmokers and women. Doyle et al (1997) reported no increased bladder cancer risk for Iowa women. King et al. (1996) reported bladder cancer risks that were slightly higher among smokers, but McGeehin et al. (1993) reported similar bladder cancer risks for smokers, nonsmokers, men, and women. Cragle et al. (1985) found colon cancer risks that were decreased below age 60 and increased above age 60, but Young et al. (1987) found no consistently increased colon cancer risks at all. These disparate findings weaken the assumption of causality that has been made in using these epidemiologic data to calculate possible estimates of risk.

ESTIMATION OF THE IMPACT ON THE GENERAL POPULATION

It is clear that these epidemiology studies alone are not sufficient to demonstrate a causal relationship and that they are somewhat inconsistent. Therefore, it is difficult to argue that these studies can be used to generate reliable estimates of risk. However,

if we make the assumptions that DBPs have the potential to increase risk in exposed humans and that the increased OR estimated in the studies were due solely to DBPs and not to any residual bias, the available epidemiologic data can be used to gauge the theoretical impact that DBP exposure could have on the population, for use in an economic regulatory impact analysis.

Given the above assumptions, the OR reported within the individual studies may be useful for estimating a range of possible excess risks. These OR represent measures of association that can be used for hazard characterization. The range of OR could be used to set the limits of a sensitivity analysis that would permit the calculation of hypothetical population risks under different excess risk assumptions. Such an approach would allow the possible magnitude of risk to be explored, without focusing on individual outcomes within data sets and while acknowledging the uncertainty inherent in the data.

Because the intent of this report is to try to gauge the possible magnitude of risk that might be experienced by the general population, it is most appropriate to use overall summary estimates for each of the populations studied (Table 2). This exercise is aimed only at gauging the number of individuals that might be affected, not predicting who in the population will be affected. However, it should be recognized that these summary estimates do not take into account any subgroup effects (effect modification) that might be present and assume that the distribution of these subgroups within the general population would be similar to the distribution within the population studied. Also, such an evaluation assumes that the magnitude and pattern of exposure experienced within each studied population would be stable and similar to that within the

general population. The attributable risks calculated from this exercise are subject to considerable uncertainty and should only be considered rough estimates of population risk, based on limited data. The plausible risks are likely to be less than estimated and could easily include zero (0).

The overall OR reported in each of these nine articles are listed in Tables 3 and 4. Whenever possible, estimates based on years of exposure to chlorinated water are listed, because these values were available for most studies and provided a common summary metric for comparison. This information was not available for Young et al. (1987) and Doyle et al. (1997), so estimates of the magnitude of exposure to DBPs were included instead. Whenever possible, adjusted summary results, i.e., the adjusted overall OR for the individual study, are listed in the tables. For Cantor et al. (1987) no overall combined results were presented, so results for those with above-median tap water consumption were used. Cragle et al. (1985) modeled results by age, so the results for a typical 60-year-old are presented.

Few studies were available for rectal cancer (2 studies) and colon cancer (4 studies). Furthermore, the results for these studies are conflicting, with half of the studies for each cancer type failing to detect the suggestion of an overall effect. For these reasons, we have chosen to examine only the 6 studies dealing with bladder cancer (Table 2) for estimating this range of risk. Such an approach will underestimate the number of cancer cases due to drinking water, if water disinfection causes more than one cancer type. However, a decision had to be made to limit the analysis at some point, or one would have to consider other cancer sites for which significant

associations had been reported, such as brain, breast, skin, lung, esophagus, and pancreas (Morris, 1992; IJsselmuiden, 1992; Doyle, 1997).

A graphical presentation of the six bladder cancer studies (see Figure) shows that almost all of the confidence intervals, including those for the highest levels of exposure, encompass the null (OR=1.0) and several of the individual OR are at or below 1.0. This is partly due to the summary nature of these results and partly due to the overall uncertainty in these data. These data suggest that the overall measure of association is weak, because all of the summary OR are less than 2 (even at the highest exposure levels) and all of the upper 95% confidence limits are less than 3.

This graphical view (see Figure) suggests that an overall (population-average) estimate of the association between water chlorination and bladder cancer is unlikely to exceed 1.5 (50% excess risk). Therefore, this value was used as the upper limit OR for a sensitivity analysis evaluating the possible impact of DBPs over a reasonable range of excess risk assumptions. Because the human data are consistent with a range of OR from 1.0 to 1.5 (inclusive), excess risk estimates of 0, 10%, 20%, 30%, 40%, and 50% were used. The standard equation for PAR,

$$PAR = \frac{Pe(OR - 1)}{1 + Pe(OR - 1)}$$

was used, where Pe is the prevalence of exposure for the general population. For the purpose of this exercise, the assumption by Morris et al. (1992) that 54% of the population consumes chlorinated surface water was used to define Pe. The annual U.S. expected number of 47,000 bladder cancers cited by Morris et al. (1992) was also

used to calculate estimates of the cancers prevented. Using these 1992 figures, and given our assumptions, the number of cancers attributable to DBP exposure is estimated not to exceed 2200-9900 per year (Table 5). This range will vary from year to year, depending on the baseline incidence of bladder cancer and chlorinated water consumption.

ALTERNATIVE APPROACHES FOR GENERATING PAR ESTIMATES

There are at least two other approaches that could be applied to use the epidemiologic literature to gauge the range of cancer risks potentially attributable to water disinfection. One could calculate a weighted-average OR and PAR from the data, as Morris et al. (1992) did in their meta-analysis. The range of risks associated with such a summary estimate would be reflected in the confidence interval. One could also calculate PAR estimates directly for each of the individual studies included in the analysis. The weighted -average approach (using the older data set of Morris et al.) suggests that 2000-7000 bladder cancers might be due to water chlorination annually (Morris, 1995), while the study-specific approach suggests that this figure might be 1100-9300 (US EPA, 1998). These two ranges are quite similar to the 2200-9900 bladder cancers suggested in the current report. This is to be expected, because no new data have been generated and all three approaches are based on the same, or similar, studies that span only moderate to weak elevations in excess risk.

However, we feel that the visual ranging presented in the current approach is more appropriate for generating PAR values because it reduced the potential for overinterpreting or implying a high degree of precision in the data and highlights or makes transparent the inconsistencies and uncertainties inherent in the data. This

avoids leading the uninformed reader to the conclusion that the PAR estimates have greater accuracy or certainty than is expressed by the data. Simplifying assumptions about effects and exposure must be made when attempting to use PAR values to estimate the potential benefits of DBP reductions. The uncertainties related to these simplifying assumptions, especially those concerning the dose-response relationship between DBP exposure reduction and risk, outweigh those inherent in the calculation of the PAR values regardless of the approach used.

The approach described herein generates PAR values through a sensitivity analysis, essentially disassociating them from the data. This places the exercise within the realm of a theoretical ranging, which is probably more appropriate given the inconsistencies of the available data and the lack of a well defined causal link between DBP exposure and specific types of cancer. The hypothetical nature of the approach limits the potential for over interpretation of the results and places them within their proper perspective. Also, the current approach uses individual ORs, which are solely measures of association, to establish this theoretical range, not individual PAR estimates, which assume a causal relationship between exposure and disease that has not yet been clearly established. Furthermore, the current approach explicitly acknowledges the distinct possibility that the cancer risks from water chlorination might actually be 0.

CONCLUSIONS AND RECOMMENDATIONS

If one assumes: 1) that DBP exposure has the potential to increase risk in exposed people, 2) that this risk is due solely to exposure and is not the result of uncontrolled bias, and 3) that the population distribution within each study is similar to

that of the general population, then the available data can be used to bound the theoretical impact that water chlorination might have on the general population. The range of excess cancer risk calculated under these assumptions spans less than an order of magnitude (Table 5). By risk assessment standards, this amount of variation is small compared to the uncertainty of the epidemiologic data and suggests that any risks calculated from the epidemiologic data are relatively insensitive to reasonable, alternative excess risk assumptions. However, this apparent consistency is due to the weak nature of the overall association between water chlorination and bladder cancer (OR≤1.5) and should not be construed as implying unwarranted consistency in the data.

The above exercise highlights the need for continued research to try and explore and explain the uncertainties and inconsistencies of the epidemiologic data. This would include laboratory investigations into both the mechanisms by which DBPs might cause cancer and the biologic plausibility of different target sites. It would also include expanded and refined epidemiologic investigations of populations within which more appropriate exposure contrasts could be evaluated (e.g., alternative treatment scenarios for the same water source) as well as studies using more specific markers of exposure and/or disease. In fact, given the potential public health impact of this issue, it may even be possible to implement a long-term community intervention trial comparing the impact of different treatment technologies among populations with the same drinking water source. Although such an approach would be costly and require 10-20 years before providing useful data on cancer, such data would be an improvement over existing information. Furthermore, it would provide additional information on the impact

of DBPs on adverse reproductive outcomes and other possible short-term health effects.

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TABLE 1

SUMMARY OF INTERVIEW-BASED CASE-CONTROL AND COHORT STUDIES*

Overview	Population	Exposure Assessment	Analysis
Reference: Cantor et al., 1998 *Type of study*: case-control (incidence) *Cancer site(s)*: bladder; 5 other sites also studied	*Population base*: residents of Iowa. *Cases*: 1,123 bladder cancers, ages 40-85 yrs., histological confirmation of all cases, identified primarily through State Health Registry of Iowa *Controls*: 1,983 age-gender-race frequency matched sample of the general population; no previous cancer diagnosis	*Exposure measure*: mailed questionnaire obtained estimates of fluid and tap water consumption, residential and water source history; duration of use of chlorinated surface water, unchlorinated ground water, fluid and tap water consumption. *Ascertainment of D/DBPs*: water source and treatment from water company records and recent measures of water contaminants such as THMs.	*Method*: logistic regression adjusted for potential confounders, such as age, farm occupation, diet, physical activity, cigarette smoking. *Findings*: little overall association between bladder cancer risk and exposure to chlorination by-products. Bladder cancer risk increased with exposure duration , but opposite trends were found in males and females; further analyses that included total lifetime and average lifetime TTHM levels show all risk increases are apparently restricted to male smokers.
Reference: Cantor et al., 1987 *Type of study*: case-control (incidence) *Cancer site(s)*: Bladder (National Bladder Cancer Study)	*Population base*: white U.S. residents in 10 locations. *Cases*: 2,805, age 21-84, diagnosed 1977-1978, identified from tumor registries. *Controls*: 5,258 from general population; frequency matched to cases by sex, age, and geographic area; identified through phone sampling (to age 64) or sample of Medicareroster (age 65 and over).	*Exposure measure*: duration of use of chlorinated surface water vs. nonchlorinated ground water; tap water consumption. *Ascertainment of D/DBPs*: information on water source (surface vs. ground) and chlorination from survey of utilities; residential history, and level of consumption of tap water and beverages, by personal interview.	*Method*: logistic regression; adjusted for age, gender, study area, smoking, usual or high-risk occupation, and urbanicity of place of longest residence. *Findings*: for whites with >59 years exposure to chlorinated water overall OR = 1.1 (0.8-1.5), non-smokers OR = 2.3 (1.3-4.2), current smokers OR = 0.6 (0.3-1.2); for whites with 40-59 years exposure to chlorinated water overall OR = 1.0 (0.8-1.3), non-smokers OR = 1.4 (0.9-2.3), current smokers OR = 0.7 (0.5-1.2); for those with 40-59 years of chlorinated surface water use, OR for highest quintile of tap water consumption relative to lowest quintile = 1.7 (p for trend = 0.006); for those with $\geq$60 years of use, OR = 2.0 (p for trend = 0.014).

Overview	Population	Exposure Assessment	Analysis
Reference: McGeehin et al., 1993 *Type of study*: case-control *Cancer site(s)*: bladder (incidence)	*Population base*: white Colorado residents from the State Cancer Registry. *Cases*: 327. *Controls*: 261 frequency matched by gender and 5-year age group randomly selected from cancer registry during same period, excluding lung and colorectal cancers.	*Exposure measure*: residential history and level of tap water consumption; duration of use of chlorinated/chloraminated surface water, chlorinated/unchlorinated ground water, bottled water; tap water consumption. *Ascertainment of D/DBPs*: information on water source and chlorination or chloramination from site visit to water utilities; water quality data collected for total THMs, chlorine residual, and nitrates.	*Method*: logistic regression adjusted for smoking, coffee, history of kidney stones and familial bladder cancer, and occupation. *Findings*: OR for bladder cancer = 1.8 (1.1-2.9) for >30 years' exposure to chlorinated water. Cases consumed more tap water per day than controls ($p<0.01$); OR for bladder cancer = 2.0 (1.1-2.8) for cases consuming >5 glasses of tap water. Risk of bladder cancer decreased with increased duration of exposure to chloraminated surface water ($p<0.01$); OR = 0.6 (0.4-1.0) for those consuming chloraminated water >40 years. Level of total THMs, residual chlorine, or nitrates not associated with bladder cancer risk controlling for years of exposure.
Reference: Freedman et al., 1997 *Type of study*: nested case-control *Cancer site(s)*: bladder (incidence)	*Population base*: white residents of Washington County, MD, included in 1975 county census. *Cases*: 294 new cases reported to Washington County cancer registry, 1975-1992. *Controls*: 2,326 frequency matched by age and gender, randomly selected from 1975 census.	*Exposure measure*: chlorinated vs. nonchlorinated drinking water (Municipal, vs. nonmunicipal source); fluid consumption not obtained. *Ascertainment of D/DBPs*: information on water treatment from prior study; drinking water source obtained in 1975 county census.	*Method*: logistic regression adjusted for age, sex, smoking level and history, urbanicity, marital status, education. *Findings*: OR = 1.2 (0.9-1.6) using 1975 measure of exposure to chlorinated vs. nonchlorinated water; slight gradient of incresing risk with increasing duration of exposure noted only among smokers; further stratification by gender showed elevated ORs to be restricted to subcategory of male smokers.

Overview	Population	Exposure Assessment	Analysis
Reference: King and Marrett, 1996 *Type of study*: case-control *Cancer site(s)*: bladder (incidence); colon and rectal cancers also studied, but results not yet reported	*Population base*: residents of Ontario, Canada, ages 25-74 years. *Cases*: 696. *Controls*: 1545 age-gender frequency matched sample of the general population from households randomly selected from residential phone listings; controls also used to study colon and rectal cancer and age-gender distribution based on that expected for all 3 sites combined.	*Exposure measure*: mailed questionnaire/telephone interview obtained estimates of fluid and tap water consumption, residential and water source history: duration of use of chlorinated surface water, unchlorinated ground water, fluid and tap water consumption. *Ascertainment of D/DBPs*: water source and treatment from water company records and questionnaire; combined with model to estimate past total THMs summer levels (annual peak value) by year.	*Method*: logistic regression adjusted for age, gender, education, cigarette smoking, caloric intake. *Findings*: bladder cancer risk increased with increasing number of years exposure to chlorinated surface water, but was statistically significant only for lengthy exposures. OR for bladder cancer = 1.41 (1.09-1.81) for >34 years exposure to chlorinated surface water compared to <10 years exposure. OR for bladder cancer =1.44 (1.10-1.88) for exposure to >1956 ug/l-years THMs compared to <584 ug/l-years; risk increases by 11% with each 1,000 ug/L THMS-years. Results provide no support for an interaction between volume of water consumed and years of exposure to THMs level >49 ug/L. Among those with relatively homogenous exposures for >29 years, trend for increased bladder cancer risk with increased THMs levels (p=0.006) and OR for bladder cancer = 1.39 (1.09-1.79) for chlorinated surface water compared to ground water.
Reference: Young et al., 1987 *Type of study*: case-control *Cancer site(s)*: colon (incidence)	*Population base*: WI residents, age 35-90. *Cases*: 347 new cases reported to WI Cancer Registry over 2-year period. *Controls*: 639 new cases of non-gastrointestinal/urinary tract cancer reported to registry; also 611 population controls, a random sample of WI drivers.	*Exposure measure*: high or medium vs. low lifetime exposure (and period-specific exposure) to total THMs. *Ascertainment of D/DBPs*: water source and treatment from water company records and questionnaire; combined with model to estimate past total THM levels by year; residential history, drinking water sources, and use of tap water from self-administered questionnaire.	*Method*: logistic regression; adjusted for age, sex, and urbanicity of residence. *Findings*: for lifetime exposure: for high exposure group, OR = 0.93 (0.55-1.57) using cancer controls and 0.73 (0.44-1.21) using population controls; for medium-exposure group, OR = 1.05 (0.66-1.68) using cancer controls and 1.10 (0.68-1.78) using population controls.

Overview	Population	Exposure Assessment	Analysis
Reference: Cragle et al., 1985 *Type of study*: case-control *Cancer site(s)*: colon (incidence)	*Population base*: white NC residents with residency $10 years. *Cases*: 200 new cases over 18-month period from 7 NC hospitals, resident in NC $10 years. *Controls*: 407 non-cancer hospital patients with admission date nearest diagnosis date of case, matched to case in age, race, gender, vital status, and hospital.	*Exposure measure*: duration of exposure to chlorinated drinking water (none vs. 1-15 years vs. 16-25 years), 1953-1978. *Ascertainment of D/DBPs*: queried local water treatment plants about water source and treatment; residential history by questionnaire (phone or self-administered).	*Method*: logistic regression adjusted for sex, age, genetic risk, dietary fiber, region of NC, urban residence, smoking, alcohol use, education, and number of pregnancies. *Findings*: for age 60: OR = 1.38 (1.10-1.72) for longer exposure and 1.18 (0.94-1.47) for shorter exposure; for age 70: OR = 2.15 (1.70-2.69) and 1.47 (1.16-1.84); for age 80: OR = 3.36 (2.41-4.61) and 1.83 (1.32-2.53).
Reference: Hildesheim, 1998 *Type of study*: case-control *Cancer site(s)*: colon and rectal cancers (incidence)	*Population base*: residents of Iowa *Cases*:560 colon cancers, 537 rectal cancers ages 40-85 yrs., histological confirmation of all cases, identified primarily through State Health Registry of Iowa *Controls*: 1983 age-gender-race frequency matched sample of the general population ; no previous cancer diagnosis Cases and controls studies had at leasts70% of lifetime drinking water exposures documented	*Exposure measure*: mailed questionnaire obtained estimates of fluid and tap water consumption, residential and water source history; duration of use of chlorinated surface water, unchlorinated ground water, fluid and tap water consumption. *Ascertainment of D/DBPs*: water source and treatment from water company records and recent measures of water contaminants such as THMs.	*Method*: logistic regression adjusted for potential confounders, such as age, farm occupation, diet, physical activity, cigarette smoking, urbanicity. *Findings*: No association between colon cancer and estimates of past chlorination by-product exposure. Rectal cancer risk increased siginificantly with duration of exposure to chlorinated surface water and increasing lifetime THMs exposure; larger odds ratios found among those with low fiber intake and low levels of physical activity.

Overview	Population	Exposure Assessment	Analysis
Reference: Doyle, 1997 *Type of study*: cohort *Cancer site(s)*: Eleven anatomic sites including bladder, colon, rectum, liver, kidney, pancreas, breast (incidence)	*Population base*: 36,127 female residents of Iowa in Women's Study, ages 55-69; followed for cancer incidence and mortality thru 12/93 *Exposed*: Women served by 100% surface water or mixed surface and groundwater *Unexposed*: Women served by 100% groundwater (referent category)	*Exposure measure*: mailed questionnaire for drinking water source; other info obtained at baseline 1986 via questionairre *Ascertainment of D/DBPs*: mailed questionnaire for drinking water source; water company records and statewide survey used for recent measures of water contaminants for 4 specific THMs	*Method*: Cox proportional hazards regression, adjusting for age, smoking, education, physical activity, vegetable and fruit intake, total calorie intake, and anthropomorphic measures. *Findings*: Compared to consumers of 100% ground water, RR for colon cancer were 1.67 (95% CI=1.07, 1.52) for consumers of 100% surface water, 1.52 (95% CI=1.08, 2.14) for consumers of mixed ground and surface sources; elevated risk for combined total cancer also noted; significant dose-response noted for colon with increasing chloroform exposure; no elevated risks observed for rectal cancer; bladder cancer RR inconsistent.

■ Studies with historical water exposure information; 95 percent confidence interval for OR in parentheses unless otherwise noted.

Table 2. General results for the "best"[6] subset of studies investigating the association between chlorinated drinking water and cancer.

	Cancer Types			
Study	**Bladder**	**Colon**	**Rectum**	**High-risk subgroups**
Cantor, 1998[7]	+[8]	NA	NA	Increased risk only among male smokers
Hildesheim, 1998[2]	NA	-	+	Increased risk only among those with low fiber intake or low physical activity
Doyle, 1997[2]	-	+	-	Study restricted to women only
Freedman, 1997	+	NA	NA	Increased risk only among male smokers
King, 1996	+	NA	NA	Similar risk for smokers and nonsmokers
McGeehin, 1993	+	NA	NA	Similar risk for smokers, nonsmokers, men, and women
Cantor, 1987	+	NA	NA	Increased risk primarily among nonsmokers and women
Young, 1987	NA	-	NA	Subgroup analyses not reported
Cragle, 1985	NA	+	NA	Decreased risk below age 60 and increased risk above age 60

[6]"Best" is defined as those studies that: 1)use incidence cancer cases, 2)use interview data on potentially important confounding factors and 3)link individuals to adequate estimates of exposure to chlorinated drinking water.

[7]These studies evaluated the same (or overlapping) populations in Iowa.

[8]A generally positive finding is indicated by + and a generally negative one is indicated by -. An NA indicates a case-control study that did not investigate this association.

Table 3. Summary Odds Ratios and 95% confidence intervals reported for the bladder cancer studies in Table 1[9].

Exposure		LCI	OR	UCI	Study
Chlorinated surface water	1-19	0.8	1.0	1.2	Cantor, 1998
(yrs exposed)	20-39	0.8	1.1	1.4	
	40-59	0.8	1.2	1.7	
	> 59	0.9	1.5	2.6	
Chlorinated surface water	1-19	0.9	1.2	1.7	Cantor, 1987
(yrs exposed)	20-39	1.8	1.1	1.6	
	40-59	0.9	1.3	1.9	
	>59	0.9	1.4	2.3	
Chlorinated water 1-10		0.4	0.7	1.3	McGeehin, 1993
(yrs exposed)	20-39	0.8	1.4	2.5	
	21-30	0.8	1.5	2.9	
	>30	1.1	1.8	2.9	
Municipal water	1-10	0.6	1.0	1.5	Freedman, 1997
(yrs exposed)	11-20	0.6	1.0	1.6	
	21-30	0.6	1.1	1.8	
	31-40	0.6	1.1	2.2	
	>40	0.7	1.4	2.9	

[9]Results from Cantor, 1987 are for those with tap water consumption above the median. All other results are for the combined study population. LCI = the lower 95% confidence limit, UCI = the upper 95% confidence limit.

Exposure		LCI	OR	UCI	Study
Chlorinated surface water	10-19	0.7	1.0	1.5	King, 1996
(yrs exposed)	20-34	0.9	1.2	1.5	
	>34	1.1	1.4	1.8	
Chloroform level	1 - 2	0.4	0.9	2.0	Doyle, 1997
(ug/l)	3 - 13	0.6	1.2	2.7	
	14 - 287	0.3	0.6	1.6	

Table 4. Summary Odds Ratios and 95% confidence intervals reported for the colon and rectal cancer studies in Table 1[10].

Exposure		LCI	OR	UCI	Study (cancer)
Chlorinated surface water	1-19	0.8	1.0	1.3	Hildesheim, 1998 (colon)
(yrs exposed)	20-39	0.7	1.0	1.5	
	40-59	0.8	1.2	1.8	
	> 59	0.4	0.8	1.7	
Chlorinated surface water	1-19	0.8	1.1	1.4	Hildesheim, 1998 (rectal)
(yrs exposed)	20-39	1.1	1.6	2.2	
	40-59	1.0	1.6	2.6	
	>59	1.4	2.6	5.0	
Chlorinated water	<15	0.9	1.2	1.5	Cragle, 1985 (colon)
(yrs exposed)	≥15	1.1	1.4	1.7	
Lifetime TTHM exposure (mg)	100-300	0.7	1.1	1.7	Young, 1987 (colon
(results using cancer controls)	>300	0.6	0.9	1.6	
Chloroform level (ug/l)	1-2	0.5	0.8	1.5	Doyle, 1997 (rectal)
	3-13	0.4	0.8	1.5	
	14-287	0.6	1.1	1.9	

[10]Results from Cragle, 1987 are modeled for a 60 year old. All other results are for the combined study population. LCI = lower 95% confidence limit, UCI = upper 95% confidence limit

Exposure		LCI	OR	UCI	Study (cancer)
Chloroform level (ug/l)	1-2	0.7	1.1	1.7	Doyle, 1997 (colon)
	3-13	0.9	1.4	2.2	
	14-287	1.1	1.7	2.5	

Table 5. PAR estimates for different assumptions of excess bladder cancer risk.

Suggested OR for sensitivity analysis	Population Attributable Risk (PAR)[11]	Estimated annual number of cancers eliminated nationally	Estimated national excess cancer rate[12]
1.00	0	0	0
1.10	5%	2400	1 EE-5
1.20	10%	4700	2 EE-5
1.30	14%	6600	3 EE-5
1.40	18%	8500	3.5 EE-5
1.50	21%	9900	4 EE-5
Animal data[13]	0.002%	1	4 EE-9

[11]PAR= Pe(OR-1)/(1+Pe(OR-1)), where Pe is assumed to be 0.54
[12]Assuming a national population of 250,000,000
[13]Animal data suggests an OR of < 1.00002

Appendix II

Draft Peer Review Workshop Report
Peer Review of the “Research Report: The Risk Assessment of Mixtures of Disinfection Byproducts (DBPs) for Drinking Water Treatment Systems”
June 20-12, 2000

Draft Peer Review Workshop Report Peer Review of the "Research Report: The Risk Assessment of Mixtures of Disinfection Byproducts (DBPs) for Drinking Water Treatment Systems" June 20-21, 2000

National Center for Environmental Assessment
U.S. Environmental Protection Agency
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TABLE OF CONTENTS

PAGE

1. INTRODUCTION 1

1.1 Background 1
1.2 Purpose 2

2. CHARGE TO THE PEER REVIEWERS 3

2.1 Specific Charge Questions 3
2.2 Workshop Agenda 5

3. COMMENTS IN RESPONSE TO EPA CHARGE 7

3.1 Q 8 - Overall Evaluation (All Sections DBP Report) 8
3.2 Q 1 - Introduction and Current State of Science (Section 1&2 DBP Report) . . 9

3.2.1 Introduction (Section 1 DBP Report) 9
3.2.2 Current State of the Science (Section 2 DBP Report) 10

3.3 Overall Section 3 (Section 3.1-3.7 DBP Report) 14

3.3.1 Q 4-*Epidemiological & Toxicologic Data* (Section 3.1 DBP Report) 15
3.3.2 Q 2- *Exposure Characterization* (Section 3.2 DBP Report) 17
3.3.3 Q 3-*Unidentified DBPs* (Section 3.3 DBP Report) 20
3.3.4 Q 2-*Developmental & Reproductive* Effects (Section 3.4 DBP Report) . 22
3.3.5 Q 2-*Risk Assessment of Carcinogenic Effects* (Section 3.5 DBP Report) 23
3.3.6 Q 2-*Uncertainty & Variability* (Section 3.6 DBP Report) 24
3.3.7 Q 2-*Mixtures Risk Characterization* Methods (Section 3.7 DBP Report) 26

3.4 Q 5 - *Cumulative Risk Assessment* (Section 4 DBP Report) 27
3.5 Q 6 - *Future Research Needs* (Section 5 DBP Report) 29

3.5.1 *Methods Research* (Section 5.1 DBP Report) 29
3.5.2 *Cumulative Relative Potency Factor* (Section 5.2 DBP Report) 30
3.5.3 *Epidemiology Research* (Section 5.3 DBP Report) 30
3.5.4 *Development of Toxicologic Data* (Section 5.4 DBP Report) 31
3.5.5 *New Section Addition* (Section 5.5 DBP Report) 31

3.6 Q 7 - *New Data* (Overall DBP Report) 32

1. INTRODUCTION

The purpose of this document is to present a preliminary summary of a peer review workshop that was held on June 20 - 21, 2000 in Cincinnati, OH, to peer review the **Research Report: The Risk Assessment of Mixtures of Disinfection Byproducts (DBPs) for Drinking Water Treatment Systems.** The primary objective of this workshop was to obtain the input of 7 peer reviewers on the scientific and technical aspects of the DBP document.

1.1. BACKGROUND

The U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD), National Center for Environmental Assessment - Cincinnati Office (NCEA-Cin) has developed a report that contains information concerning the conduct of risk assessments for mixtures of disinfection by-products (DBPs) across various drinking water treatment systems. Under 42 USC § 300 of the Safe Drinking Water Act Amendments of 1996, it is stated that the Agency will "develop new approaches to the study of complex mixtures, such as mixtures found in drinking water..." This report reflects the current results relative to research in this area over the past five years. It presents: an illustrative DBP mixtures risk characterization; the summary of an expert scientific workshop on this subject; EPA conclusions and recommendations subsequent to the workshop; a conceptual cumulative risk approach; and ideas on future research needs.

The approach to this effort has resulted in the production of three research reports that are contained in the current document that is being submitted for external peer review. Appendix I contains an initial report that was generated as a pre-meeting report to an April 1999 workshop on this subject. It is entitled, *Workshop Pre-meeting Report: The Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems* (U.S. EPA, 1999a) and was developed to detail the response addition approach to estimating DBP mixture risk that has been developed by NCEA-Cin. Having performed this initial assessment, NCEA-Cin scientists recognized a number of areas for improvement and held the workshop in April 1999 to examine the current method, present ideas to advance the approach, and come to some conclusions relative to new research and development directions. The resulting workshop report is presented in the document as Report 2, entitled, *Workshop Report: The Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems.* Finally, EPA scientists have used the information from the April 1999 workshop to develop a number of conclusions and recommendations relative to this area of research and to develop a conceptual approach to performing a cumulative risk assessment. This information is presented in the document as Report 1, entitled, *EPA Conclusions and Conceptual Approach for the Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems.*

1.2. PURPOSE

The objective of this Task Order was to coordinate the external peer review of the **Research Report: The Risk Assessment of Mixtures of Disinfection Byproducts (DBPs) for Drinking Water Treatment Systems**. The document was reviewed by seven experts selected by Versar because of their specific experience in drinking water treatment engineering, chemistry, risk assessment, toxicology, epidemiology, statistical modeling/uncertainty analysis, and exposure assessment. The seven peer reviewers are listed below:

1.2. Mr. Phillipe Daniel, CDM - Drinking water treatment engineering and chemistry.
1.3. Dr. Lynne Haber, TERA - Carcinogenicity, developmental/reproductive toxicity, and mixtures risk assessment methodology.
1.4. Dr. Jay Nuckols, Colorado State University - Epidemiology, exposure modeling, and drinking water treatment engineering/chemistry.
1.5. Dr. Shesh Rai, St. Jude Children's Hospital - Statistical modeling/uncertainty analysis and epidemiology.
1.6. Dr. Venkat Rao, DynCorp - Carcinogenicity, developmental/reproductive toxicity, and mixtures risk assessment methodology.
1.7. Dr. John Reif, Colorado State University - Epidemiology.
1.8. Dr. Charles Wilkes, Wilkes Technologies - Exposure modeling, statistical modeling/uncertainty analysis.

This document details the comments provided at the 2-day workshop held in Cincinnati, OH on June 20 - 21, 2000. The sections that follow are organized according to the charge questions and/or the chapters of the report.

2. CHARGE TO THE PEER REVIEWERS AND WORKSHOP AGENDA

This section presents the charge questions posed to the peer reviewers in 2.1 and the workshop agenda in 2.2.

2.1. EPA'S CHARGE MEMO AND QUESTIONS

The external review of this document has the primary goal of evaluating Report 1 on EPA's conclusions and conceptual approach. This is the portion of the document that can and will be changed based on what the reviewers discuss and recommend. This report requires careful review for accuracy and soundness of conclusions. Both the pre-meeting report (Appendix I) and Report 2 are final documents that cannot be changed, but are included to provide background information and detailed descriptions of the data and methods either used by EPA or proposed during the workshop. In addition to critiquing Report 1, the peer reviewers are also invited to comment on the data, methods and discussions presented in the entire document or to add text on new information and perspectives that are not covered by the document. The summary report of the external review comments generated by this contractual review will be added as Appendix II of the document prior to its final clearance.

EPA recognizes that review of this document requires a multi-disciplinary panel of scientists. EPA expects the peer reviewers to focus their comments on sections of the document that discuss material relative to their areas of expertise, but also to comment on the overall methodology and approaches to the risk assessment to the best of their abilities. For a quick overview of the scientific questions, it is suggested that the peer reviewers read over the charge to the April 1999 workshop participants (introductory material to Report 2). EPA expects the reviewers to have read the document prior to attending the meeting and to come prepared to discuss its scientific strengths and weaknesses. EPA scientists are not planning to make presentations of the material in the document, but will be in attendance at the meeting to clarify and answer questions. The peer review panel is required to write an initial draft peer review report that is due to EPA by the end of the 2nd day of the meeting.

Q 1. Is the introductory material in sections 1 and 2 of Report 1 clearly and concisely written, so that the DBP mixtures problem is well defined, the logic behind approaching this as a mixtures risk assessment is sound, and the current state of the science is understandable and correct?

Q 2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer

effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Q 3. Should the toxicity of unidentified DBPs or of identified DBPs for which little or no data exist be incorporated into the risk assessment? If so, what are the most scientifically appropriate ways to estimate the potential health risks?

Q 4. How can EPA integrate both epidemiologic and toxicologic data into the risk assessment? Are the expert judgment methods discussed in the document (section 3.1. of Report 1 and discussions in Report 2) an appropriate way to incorporate data from each of these disciplines?

Q 5. Given the information in section 3 of Report 1, is the conceptual model for the cumulative risk assessment, shown in section 4 of Report 1, a scientifically sound approach to the DBP mixtures problem? Are there better alternatives to this approach? Are important considerations missing, inaccurately portrayed, or not fully developed?

Q 6. Are the areas of research specified in section 5 of Report 1 as future research directions clearly stated, appropriate as next steps and complete? Should anything be added or deleted?

Q 7. Do the reviewers know of any newer data or methods that EPA has not considered, but should be aware of in order to improve this risk assessment? Specifically address advancements in dose-response modeling, analytical chemistry, exposure characterization, mixtures risk assessment methods, probabilistic techniques, quantitative structure activity relationships, and methods for estimating risk for the unidentified DBPs.

Q 8. What is the reviewers' overall evaluation of the scientific content, readability and utility of the entire document? Are there suggestions relative to structure or content that would improve the quality of the document?

2.2. WORKSHOP AGENDA

Peer Review of *Research Report: Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems*

June 20-21, 2000

June 20, 2000 Tuesday

8:00-8:30 Registration/Check In

8:30-8:40 Welcome
Terry Harvey, U.S. EPA/NCEA

8:40-8:50 Welcome, Meeting Structure, Objectives, Introduction of Panel
David Bottimore, Versar, Inc.

8:50-9:10 Background on the Document: Etiology, Purpose, Approach
Linda Teuschler, EPA/NCEA-Cin

9:10-9:20 Overview of the Charge
David Bottimore, Versar, Inc.

9:20-10:30 Initial Overall Assessment of the Document; Major Points for Consideration During the Peer Review Meeting
Discussion Leader: David Bottimore
Expert Panel Members (5-10 minute summaries from each person)

Q 8. What is the reviewers' overall evaluation of the scientific content, readability and utility of the entire document? Are there suggestions relative to structure or content that would improve the quality of the document?

10:30-10:45 Break

10:45-11:45 Chapters 1 and 2 - Introduction and Current State of the Science
Discussion Leader: Phillipe Daniel

Q 2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Discussion Leaders: Charles Wilkes and Jay Nuckols

Q 3. Should the toxicity of unidentified DBPs or of identified DBPs for which little or no data exist be incorporated into the risk assessment? If so, what are the most scientifically appropriate ways to estimate the potential health risks?

Discussion Leader: Venkat Rao

Q 4. How can EPA integrate both epidemiologic and toxicologic data into the risk assessment? Are the expert judgment methods discussed in the document (section 3.1. of Report 1 and discussions in Report 2) an appropriate way to incorporate data from each of these disciplines?

Discussion Leader: John Reif

2:45-3:00 Break

3:00-4:00 Chapter 4 - Conceptual Model for a Cumulative Risk Approach
Discussion Leader: Lynne Haber

Q 6. Are the areas of research specified in section 5 of Report 1 as future research directions clearly stated, appropriate as next steps and complete? Should anything be added or deleted?

Q 7. Do the reviewers know of any newer data or methods that EPA has not considered, but should be aware of in order to improve this risk assessment? Specifically address advancements in dose-response modeling, analytical chemistry, exposure characterization, mixtures risk assessment methods, probabilistic techniques, quantitative structure activity relationships, and methods for estimating risk for the unidentified DBPs.

5:00-5:30 Summation of Issues; Plans for Report Writing
David Bottimore, Versar, Inc.

June 21, 2000 Wednesday

8:30-12:00 Final Discussions by the Expert Panel; Development of Recommendations for Revisions
Facilitator: David Bottimore, Versar, Inc.

1:00-5:00 Report Writing; Preliminary Draft of Peer Review Workshop Report - due to EPA by Close of Business

3. COMMENTS IN RESPONSE TO EPA CHARGE

This section presents detailed comments that were presented at the peer review workshop. In general, the reviewers felt that the report was well done and that with moderate revisions, it is suitable for publication. In addition, many suggestions were provided on how to make the report more complete and useful for readers. Particularly, almost all the reviewers felt that the document needs a clearly stated purpose and scope. Several individuals suggested minor reorganization of the report to present certain information in a less fragmented manner.

This section is organized according to the charge questions and/or the chapters of the report. Specifically, while most of this section is organized according to the 8 charge questions presented previously, some of the discussion at the workshop deviated from the charge questions and, instead, focused on providing comments according to the report chapters and subsections (Table 3-1). The reviewers recognized the sometimes overlapping nature of the questions and chose (especially for Chapter 3 of the report) to organize the discussion and comments in this manner. Therefore, the following subsections are presented in the following manner:

Table 3-1. Crosswalk of Report Sections, Charge Questions, and Sections of the DBP Report

Section of This Report	Charge Question No.	Section of DBP Report # 1
3.1	8	All
3.2	1	1 & 2
3.2.1	1	1
3.2.2	1	2
3.3	2	All of Section 3
3.3.1	4	3.1
3.3.2	2 & 4	3.2
3.3.3	3	3.3
3.3.4	2	3.4
3.3.5	2	3.5
3.3.6	2	3.6
3.3.7	2	3.7
3.4	5	4
3.5	6	5
3.6	7	All

Subsections present comments and suggestions in the following format (1) summary, (2) organizational comments, (3) content comments, and (4) specific comments.

3.1. Q8 - *OVERALL EVALUATION* (ALL SECTIONS DBP REPORT)

Q8. What is the reviewers' overall evaluation of the scientific content, readability and utility of the entire document? Are there suggestions relative to structure or content that would improve the quality of the document?

Summary: In response to Question 8, there was a nearly unanimous call for clarification on the purpose of the report and for more information on the context in which the document fits. Similarly, clarification is needed on the scope of the Report 1 document and its relationship to the appendices. Overall, there was general agreement that a cumulative risk assessment approach is an appropriate method for addressing this issue. However, many reviewers believed that further analyses and presentation of the epidemiological, toxicological, and exposure data are needed so the approach is based on the "state of the science." Of particular note was the call for an expand discussion of exposure assessment, such as the need to account for the variety of DBP mixtures that are likely to be found nationwide. With these changes and some editing (e.g., minor changes to the organization and wording of certain sections) the document would be a helpful tool for directing future work in this area.

Organization Comments: Considerable discussion addressed the organization and outline for the document, particularly with respect to the relationship between the report and the appendices. For the most part the reviewers agreed with the current organization, however suggestions were made on select sections. In a few cases, the case was made to either pull text up from the appendices or to move detailed discussions back to an appendix so as not to interrupt the flow of the report.

Content Comments: In response to Question 8, there was a nearly unanimous call for clarification on the purpose/scope of the report and for more information on the context in which the document fits. The reviewers felt that the document addresses very important and complex issues, but that it needs to be revised in a manner that provides a better picture of the role of the report (and associated efforts) in EPA's vision for the future. Included in the suggestion was the need for clarification on the relationship of the Report 1 document to the appendices and the possible need to "pull up" some of the details from the appendices to flesh out the technical aspects of the document. One reviewer suggested that the document be reorganized to follow a risk management/decision making paradigm that might more directly influence current rulemaking efforts and regulatory decision-making.

Overall, there was general agreement that a cumulative risk assessment approach, using the response addition and relative potency factor approach, is an appropriate method for addressing this issue. However, many reviewers believed that improved analysis and

presentation of the epidemiological, toxicological, and exposure data are needed so the approach is based on the "state of the science." Included in these suggestions was the recommendation that some of the wording of the epidemiology sections be edited and that discussion be clarified. For example, discussion addressed the need for new epidemiology studies to evaluate effects in the context of specific DBPs of interest (e.g., brominated compounds). There was discussion about effects of DBPs for endpoints (e.g., liver and kidney effects) that may not have been identified to date by epidemiology.

Several reviewers commented that EPA should expand the discussion of exposure assessment. Included here is the need for the risk assessment to account for the variety of DBP mixtures that are likely to be found nationwide. Better data are needed on DBPs in drinking water at the tap to incorporate into the assessment. Furthermore, the reviewers stated that the risk assessment approach should account for the formation of brominated and mixed chloro-/bromo- compounds when different technologies and different source water characteristics are considered. The reviewers also stated the need to include inhalation and dermal exposure routes into the risk assessment. Accordingly, more extensive toxicity data for the effects of these chemicals via these exposure routes will be needed in the future. Comments called for sensitivity analyses to be performed on the risk assessment approach to determine those parameters that may be the most important risk drivers. From this analysis, priorities can be set on those issues that will have the greatest impact on the risk.

Several reviewers commented that the document could use a thorough editing. Furthermore the organization and wording of certain sections of the document should be improved. More detailed recommendations follow below.

3.2. Q1 - *INTRODUCTION* AND *CURRENT STATE OF THE SCIENCE* (SECTIONS 1 AND 2 DBP REPORT)

Q1. Is the introductory material in sections 1 and 2 of Report 1 clearly and concisely written, so that the DBP mixtures problem is well defined, the logic behind approaching this as a mixtures risk assessment is sound, and the current state of the science is understandable and correct?

3.2.1. *Introduction* (Section 1 DBP Report).

Summary: This section of the document needs significant revision to more concisely present the problem and outline the scope of this document.

Organization Comments: Significant changes in Section 1 of the report are advised. A revised outline would include:

1. Drinking water: sources, treatments, distribution systems à mixtures of compounds (DBPs) of potential health significance (i.e., consequence of low-level risk over large population).

2. Regulations: previous, current, future. Issues of concern.
3. Relationship between Office of Water and NCEA.
4. Purpose of the report: to guide further development of this effort to support regulatory decision-making
5. Context of this effort: previous efforts and reports
6. Report overview

Content Comments: Risk management alternatives, principal questions relevant to regulatory decision-making, and the schedule by which specific information can be furnished needs to be added. The reviewers also suggested the following changes. Move epidemiology discussion into Section 2. As presently written, epidemiology discussions are scattered throughout the document (e.g., pages 1-2, 1-5, 1-7, and 1-14). These should be streamlined and combined to provide more cohesive discussion. In addition, the language should be more neutral i.e., not using terms such as used on 1-2 of only relatively weakness, questionable, and entirely dismissed and the discussion more balanced. Further comments on epidemiology are presented under the comments in Section 3.3.1.

Specific Comments:

I. Risk characterization discussion/outline on page 1-1 needs expansion and clarification.
II. Alternative hypothesis discussion on page 1-2: #2 is unclear.
III. Add the potential for an unidentified constituent being responsible for the response in epidemiology studies (e.g., could NDMA be such a compound?).
IV. The hypothesis of certain vulnerable populations resulting in the observed response should be noted (e.g., insulin signaling pathway hypothesis with DCA as made by Dr. Richard Bull).
V. Since this is a report on DBPs, the benefits of disinfection do not need to be discussed (or neutrally framed within the compartive risk framework).

3.2.2. *Current State of the Science (*Section 2 DBP Report).

Summary: Significant changes are advised.

Organization Comments: A revised outline would include:

I. Objective
II. Risk paradigm
III. Hazard identification and dose response: discussion of endpoints and lines of evidence
    a. Cancer
        – Description
        – Epidemiology
        – Animal toxicology
        – Mechanistic toxicology
        – In vitro toxicology

b. Reproductive/Developmental
   - Description
   - Epidemiology
   - Animal toxicology
   - Mechanistic toxicology
   - In vitro toxicology

c. Other
   - Epidemiology
   - Animal toxicology
   - Mechanistic toxicology
   - In vitro toxicology

d. Impact of exposure routes

IV. Exposure assessment

V. Risk characterization method

In addition, material that is introduced in Section 2 should be more fully explained at this point rather than repeated and expanded later. For example, information on exposure is introduced in Section 2, but not fully explained until Section 3. The document would probably be clearer and less redundant if this information is presented once, and then Section 3 discusses the outstanding questions. Or consider another example, reproductive/developmental discussion in Section 3.4 should be moved/introduced in Section 2.

Content Comments:

I. Information on toxicology and epidemiology is diffused – it should be consolidated in a concise format and brought up-to-date.

II. Concordance: Clarify what is meant with respect to site, type, and doses. Why should we expect to see concordance? Non-concordance discussion must be far more specific: e.g., site, type, histology, dose. Dose discrepancies are one element. Concordance and non-concordance: limitations of studies? Expected non-concordance?

III. Epidemiology discussion: need better appreciation for nature of environmental epidemiology studies: difficulty of determining causation, the need to view results in the context of other mixture studies. It is not unusual to find low risks from many epidemiology studies.

IV. A preferable epidemiology summary statement is found in Report 2 at 2-1 though this section still needs updating.

V. The issue of consistency of findings in epidemiological studies should be stated accurately. For bladder cancer, there is consistent evidence from interview-based

studies that there is an increase in risk associated with long term exposure to chlorinated water. This comes from 5 case control studies and 1 cohort study. There is inconsistency with respect to the sub-populations where the effect is observed; i.e., men and women, smokers and non-smokers. For colon and rectal cancer, the findings are based on fewer studies, and are inconsistent because some studies show an effect an some do not. For the reproductive epidemiology data, there are relatively few studies. Since several individual outcomes are assessed, the database is sparse with respect to specific outcomes; e.g., neural tube defects. Among those studies examining common outcomes (low birth weight, intrauterine growth retardation, developmental defects) the findings are inconsistent. It is not clear how factors such as exposure misclassification and differences in the constituents of the DBP mixture may have affected the results of these studies. It is not clear whether residual confounding, not considered by investigators, could have biased the results.

VI. The single sentence at 1-5, para 2 is accurate but could be expanded to reflect the state of the science by summarizing the evidence for cancer and reproductive outcomes separately. On page 1-14, the findings from the epidemiological studies are discussed briefly and reference is made to Appendix C of Appendix 1. Table 5 of Report 1 is focused only on cancer. There are no summary data provided for human reproductive studies although the toxicological data for reproductive effects is summarized and incorporated into the report (Tables 2 & 3). This is an obvious omission. The results of reproductive studies should be incorporated into a table and the database updated to include recent publications not included in the report or appendices. On page1-14, par. 2, additional references are needed for human studies of reproductive endpoints and are provided below. The statement concerning cancer and odds ratios is incorrect, poorly worded and requires modification.

VII. Table 5 requires revision. The Doyle study (1997) contained only 2 cases of bladder cancer in the exposed group (43 overall). It is highly questionable whether this study should be used to draw any inferences about bladder cancer. Footnote (b) refers to the Iowa studies. The cases in these Iowa studies are independent of each other, defined by site; there is some overlap among controls.

VIII. Exposure assessment discussion should indicate evolution of DBPs from treatment to tap; show how different mixtures result according to source water characteristics, treatment technology, and final disinfectant type. Indicate importance of different human exposure pathways, not just oral.

IX. Need better introduction to Section 2.4.1. Instead of focusing on one option, several alternatives should be described first before the discussion turns to selecting one over the others. For example, discuss additivity, synergism, and antagonism (e.g., use additivity figure) and provide illustration of options (e.g., response addition vs dose addition). The discussion of alternative methods is important. Should the illustrative treatment example drawn from Report 2 be an appendix?

Specific Comments:

1. While Table 1 represents the current status of assessments, almost all of the assessments in Table 1 are in the process of being updated by the Office of Water and by ORD, and the document should note that, so that the reader will know to look for updated values. A separate table of current/ongoing assessments of DBPs would be useful. This information could be obtained from the Office of Water.

2. While the formaldehyde result reported in Table 1 is consistent with IRIS, there may be more recent information.

3. Since the purpose of Tables 2 and 3 is unclear and the data are not essential to the argument, it may be advisable to either delete these tables or to move the LOAELs/NOAELs to an appendix. Several reasons why it can be misleading to present this detailed quantitative information include: **(a)** Except for the NTP (1997) study, all of the HAN studies were conducted using a tricaprylin vehicle, and this vehicle alone can cause increased post-implantation loss and soft tissue malformations (Christ et al., 1995, 1996; Smith et al., 1989a). For example, when TCAN was administered in corn oil, the NOAEL was 35 mg/kg-day and the LOAEL was 55 mg/kg-day for developmental toxicity, based on increased post-implantation loss and a number of types of malformations, in contrast to an AEL of 15 mg-kg-day for TCAN in tricaprylin in the same study (Christ et al., 1996). (As noted in Table 2, 7.5 mg/kg-day was a LOAEL and 1 mg/kg-day was a NOAEL in another study conducted with tricaprylin.) Additional information is in a recent update to the Drinking Water Criteria Document on HANs. **(b)** It is unclear whether the table is intended to list (all of) the available toxicity data (as stated), or whether only the study identifying the critical effect for each chemical is shown. Additional abstracts and *in vitro* studies are available, but were not included in this list. If the document authors wish to retain these tables, they should either update the text, just provide qualitative information on reproductive/developmental effects of the HANs and haloacetic acids, or leave it in an appendix with all the appropriate caveats.

4. While standard deviations of IRIS data presented in Tables 1-3 are not readily available, such information would be useful to obtain for uncertainty analysis.

5. It would be useful to supplement Table 6 with information on other DBPs (or classes of DBPs) found in drinking water, to give a sense of what the universe of DBPs is like. DBPs outlined in Table 6 should be expanded to note brominated analogues (and mixed bromochloro species). Reporting the values on a molar basis in the text would also be helpful. Finally, note that Figure 1 is only an example and not representative of all waters or treatment technologies – it is for chlorination and chloramination of a moderate bromide containing water.

6. Precursors (pages 1-4 and 1-5): should either refer to inorganic or bromide but not both.

7. In vivo studies of mixtures were limited by concentration effects (i.e., salt limitations) and should be noted (1-5).

8. On page 1-9, line 2: Section 2.3 of Report 2 does not list or refer to the hundreds of potential DBPs. It would be better to Section 3.3 of the current report, which lists DBPs, or refer to specific table(s) in report 2 to give the reader a sense of the range of DBPs. The list of DBPs evaluated by QSAR in Appendix B.3 of the pre-meeting report is also informative for providing the range of DBPs identified beyond those listed in tables 1 and 2 of the main report.

9. The notion of dose additivity for complex mixtures (1-9) has been widely used for low concentration components and should be referenced (i.e., these observations are consistent with other studies and other expert groups).

10. On pages 1-12 and 1-13: It is difficult to compare the studies because of the multiplicity of units used. It would help the reader to report the units used by the authors, and then to report the doses in standardized units.

11. On page 1- 14, lines 4-5: Unclear. Are the words data on missing?

12. In discussing the three factors on 1-17 and 1-19 there was no analysis of which factors were likely to be most important (e.g., is bioavailability refer to fate in treatment and distribution or to likelihood of human metabolism).

13. Response addition methodology (page 1-22) should examine the mixtures associated with the risk management alternatives and scenarios of concern to see which issues are amenable to the proposed analysis.

14. The example (1-23) focused on one water and did not evaluate a final chloramination scenario that would be a likely regulatory alternative.

15. It would be useful to present Figure 2 here, rather than later in the document (page 1-23).

16. Expand discussion to include stochastic characterization of input data.

3.3. OVERALL SECTION 3 (SECTIONS 3.1-3.7 DBP REPORT)

Q2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

General Comments: Chapter 3 is a summary of EPA's priority conclusions and recommendations arising primarily from the April 1999 Workshop. As such, Chapter 3 should be renamed to "EPA's Major Conclusions and Recommendations based on the April 1999 Workshop." The introduction to the chapter should include a discussion of the Workshop, and be framed addressing issues and problems raised in the "state of science" discussion from Chapter 2, clearly discussing what EPA accepted, what was rejected, and the reasons. "State of science" information in Chapter 3 should be moved to Chapter 2. The recommendations given in Chapter 3 regarding gathering additional data should be evaluated and prioritized using techniques such as sensitivity analysis. Models and methods recommended in Chapter 3 should be validated where possible.

Structure:

* Use charge questions as format for formulation of report
* Move "state of science" information from EPA Workshop report to Chapter 2
* Chapter 3: keep as summary of how 1999 workshop was used to formulate recommendations
* Chapter 3 should be framed as addressing issues and problems raised in Chapter 2 being clear what EPA accepted (or not) and why;
* Every recommendation should be evaluated (for example, sensitivity analysis) and prioritized.
* Validation of exposure models should be addressed

3.3.1. Q4 - *Integration of Epidemiologic and Toxicologic Data* (Section 3.1 DBP Report).

Q4. How can EPA integrate both epidemiologic and toxicologic data into the risk assessment? Are the expert judgment methods discussed in the document (section 3.1. of Report 1 and discussions in Report 2) an appropriate way to incorporate data from each of these disciplines?

Summary: The proposed risk assessment will incorporate data from toxicologic studies in laboratory animals and epidemiologic studies of human populations. This section of the report focuses on integrating these two data sources and raises several issues with respect to expert judgement, concordance in findings between animal and human studies, sensitive subpopulations, and meta-analysis.

Organization Comments: The section provides rationale for integrating the epidemiologic and toxicologic data, followed by a series of bullet-form recommendations based on the 1999 workshop. Unlike the remainder of the section, where recommendations for the risk assessment are made directly, the recommendations in 3.1 take the form of recommendations for further research and should be moved to Section 5. Although some recommendations are clearly topics for further research, others are reasonable recommendations for immediate implementation. The bullets should be separated according to this scheme.

Content Comments: In this section, and elsewhere in the document, the point is raised that the data from toxicologic studies and epidemiologic studies lack concordance (1-27). This statement requires clarification and further documentation in the report. Concordance between groups of studies can be evaluated at several levels (eg., with respect to organ system involvement, site of lesion, histopathologic characterization or tumor type, and with respect to dose or concentration of xenobiotic required to produce the observed effect). There is concordance between epidemiologic and toxicologic data at several levels. There is evidence of carcinogenicity, effects on reproductive and developmental endpoints, and to some extent, for specific disorders such as urinary tract cancer and fetal growth parameters. There is organ system concordance between findings of kidney cancer in rodents and bladder cancer in humans and between hepatotoxic effects of THMs in animals and of chloroform in case studies and occupational studies in humans. There is concordance between the finding of full litter resorption and evidence of increased risk for spontaneous abortion in human studies (Walker et al., 1998). The lack of concordance may be largely a matter of administered (animal) or estimated (human) dose. The failure to find a given effect at a particular dose across species may reflect several factors as pointed out in the first paragraph on 1-28.

Integration of the epidemiological and toxicological data, at a minimum, requires that the insufficiency and incompleteness of the toxicological approach be recognized. The traditional toxicological approach focuses on individual contaminants thereby falling into the trap EPA's Science Advisory Board has recently warned against: risk management decisions that focus on the reduction of particular risks rather than on the reduction of total risks (EPASAB, 1999 and 2000 – discussions on *Integrated Environmental Decision Making in the 21st Century).* That is the burden of this NCEA effort.

The reviewers found that the recommendation to pursue the use of expert judgement in setting bounds for human risk and establishing probabilities for specific risk estimate from published epidemiological studies had merit. The paper by Evans (1994) on bladder cancer risk and long-term consumption of chlorinated water provides an example of the approach. The expert judgement process should be pursued because it may (1) aid in regulatory process, (2) dampen bias, (3) expand the literature database, and help to generate hypotheses and identify knowledge gaps. The caveats are that (1) the proper instrument is selected, and (2) a panel of qualified, unbiased experts can be identified. The approach could be applied to several categories of risk assessment (ie tox-epi data integration, exposure assessment). The publication of additional studies of high quality on this topic provide a dataset that could be used to explore the utility of expert judgement as suggested in the report. Expert judgement could be used to select the appropriate literature base, refine the questions to be asked based on the data available, and identify knowledge gaps in each category of interest. Expert judgedment approaches should include face-to-face discussions so that the benefit of learning from other experts and building from each others' knowledge base can be realized.

The issue of sensitive subsets of populations of animals and humans should be defined further. As written, this appears to apply to demographic variables such as age, gender and race and their equivalents in rodents. This concept should be kept separate from the issue of susceptibility markers such as genetic polymorphisms (e.g., GST

enzymes, acetylation) which should form the basis of an additional research recommendation for integrating human and animal data.

The recommendations concerning meta-analysis should be rephrased to reflect the intent of the authors. It appears from the earlier report that there may be compelling reasons to avoid meta-analysis, or at minimum, to be extremely judicious in potential application of this technique. The panel concurs with this view, and recommends that the recommendations on 1-29 be re-written to reflect EPA's position. If meta-analysis is recommended as a technique to be used in risk assessment, the framework should be outlined briefly. If meta-analysis is not recommended, the text should be revised accordingly and the recommendation deleted.

Further in the report (3-2), the issue of incorporating biomarkers into human studies is raised. The issue of biomarkers should be included here as a recommendation as well. Identification and validation of suitable biomarkers of exposure and effect would be another important means to integrate epidemiologic and toxicologic data on a dose-response basis.

3.3.2. Q2 - *Improvements in Exposure Characterization* (Section 3.2 DBP Report).

Q2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Summary: The exposure characterization methods presented in the report were very general. The description of these methods needs to start with a global description of the current state of exposure assessment techniques, including a discussion of exposure assessment priorities and each method's strengths and weaknesses. Recognizing that the focus of this document is not on exposure assessment, a judgment needs to be made regarding the level of detail. The authors may wish to include a general review, and cite appropriate technical publications that discuss in greater detail these methods. Depending upon the level of detail the authors choose to address exposure assessment within the document, a fairly detailed discussion of the necessary data, parameter values, and other factors that influence the exposure may be appropriate, including a discussion of the current state of knowledge for the parameter and data needs.

Exposure assessment in the context of risk assessment from DBPs should include characterization of water quality, biomarkers (future research necessary), all potential routes of exposure, and factors related to water-use activity and environment for the study population.

Characterization of Water Quality: The draft report mentions that the range of DBP concentrations are important, but other than treatment practices, does not discuss factors that influence these concentrations. The authors should consider a general overview of the important processes that occur as a result of disinfection, and between the treatment plant and the tap. Possible topics include the characteristics of the water supply, alternative treatment processes, changes in DBP concentrations as it flows through the distribution

system, the effect of seasonal variations in water quality and temperature, and the effect of point of use devices (eg, water filters, storage in hot water tanks, etc). Specific comments from the panel on this topic were as follows:

1. Different treatment technologies will create mixtures that are qualitatively and quantitatively different. What is most important is that the DBP we are reasonably sure will be formed by certain technologies are as completely accounted for as possible.

2. The report states that "the range of individual DBP concentrations within the distribution system over the etiological relevant time period" should be incorporated in developing exposure models for risk assessment. Current state of the science demonstrates that each of these variables is mutually exclusive that is, while one may be able to discern individual DBPs for a specific utility at a specific (and narrow, ie maybe seasonal) period of time; it is a daunting task to define this exposure variable over a sufficient geographic region (within a utility or across a set of utilities), and to capture a sufficient study population for the necessary statistical power to differentiate relative risk. This problem is compounded if the etiological time period is a matter of years. Furthermore, current science on this issue has only dealt with THM speciation, and not even began to address the other DBPs identified as potentially toxic by this report).

3. The report states that ICR data should be used to characterize DBP mixture "exposures". ICR is composed of quarterly samples (at best composite over a day, but most likely grab samples) at the Point of Entry from the WTP to the distribution system, and approximately 4 other locations in the distribution system. The dataset is restricted to utilities with a service population greater than 100,000; Therefore, the data set is composed of a sample size of six measurements at each location over an 18 month period in the late 1990's. While the dataset may be very useful from a regulatory standpoint in characterizing DBP occurrence in this subset of large utilities (approximately 250 utilities out of an estimated 60,000 utilities that serve the people of the USA); it does little to assist in defining potential exposure to individuals over a etiological relevant time period for an epidemiological study. The exception might be a retrospective reproductive or developmental epidemiological study design in the service population for one or more of the participating utilities. It is a shame that a prospective study could not have been incorporated into the ICR study plan.

4. The report recommends that "for cancer, annual exposure estimates [based on utility water quality] may be required". I have never understood this logic for exposure reconstruction in cancer epidemiology. Let us assume the most simplest of scenarios, where all participants in an epidemiological study of cancer live at the same location for their entire lives, and the DBP production by their respective water utility was consistent over this time period. Spatial and/or temporal variation in DBP concentrations could result in a significant variation over each annual cycle during the "etiological relevant time period" for some fraction of the study population, depending on the geographic extent of the study. Classifying the population according to the annual average could introduce significant misclassification of exposure if peaks in exposure are relevant to risk. The annual average classifies the population towards the "central tendency", where the tails of exposure

distribution across the study population are lost, and exposure classification is toward a mean value. Misclassification of exposure that is nondifferential by disease status biases the risk estimate towards the null, thus true associations between a disease and an exposure may be missed or underestimated.

5. In my opinion, the most important contribution that USEPA could make toward improvements in exposure characterization are missing from this report. That is (1) to work with health scientists in estimating historic levels of DBPs in a specific set of utilities in order that a definitive epidemiological study can be conducted and, perhaps more importantly, (2) to support collection of DBP monitoring data that could be used in a prospective epidemiological study.

6. The exposure characterization necessarily needs to start with an understanding of the DBP concentrations in the water supply. It is likely not sufficient to take measurements at the treatment facility and at system nodes. Rather, the reactions that occur in the system are likely to be important, as they are a function of the duration of time spent in the distribution system, the temperature, the constituents in the water supply, and a variety of other variables. For example, the time the water spends in the water heater and water-use activities that occur after the water sits in the water heater for long periods need to be considered. The DBP concentrations are likely at their highest after extended storage in the water heater, and inhalation exposure to the volatile constituents may be larger than currently predicted. This may also be true of dermal exposure to lesser volatile DBPs.

7. On mixture characterization methods, studying reproducible disinfection scenarios on a range of bromide-TOC matrices should have a high priority.

8. When predictive models are used to reconstruct water quality at the tap (or other unit of analysis in an epi study, ie census block group), validation of models should be addressed.

Biomarkers:

1. The report states that "biomarkers of exposure should be used in future analytical epidemiological studies", and that "it is critical to include all exposure routes". While the researchers that have been doing this work may agree, the report would be much stronger if it made specific recommendations as to how to achieve these objectives, rather than broad brush statements of needs, which we are all aware of already.

2. The incorporation of biomarkers of exposure, susceptibility and effect into epidemiological studies should be added in the list of research recommendations
3. Use of biomarkers as endpoints [in epidemiological studies] could be coordinated with similar studies in animals for risk assessment purposes .

Route of exposure:

1. Despite the sentence on 1-28, para 1 regarding differences in metabolism of DBPs that are ingested and inhaled or dermally absorbed, the issue of route of exposure

was not treated satisfactorily in earlier accompanying work. The risk characterization reported in Appendix 1 relied on a single exposure pathway. EPA must resolve the issue of multiple routes of exposure to volatile DBP in further risk assessment work for the findings to be credible.

2. The recommendation to account for multi-route exposures when doing DBP risk assessment (1-30) is appropriate.

3. Research topics should include the development of pharmacokinetic models to be used to evaluate route-specific uptake for different classes of DBPs and related issues.

4. The issues of exposure pathways and route specific exposure were not adequately addressed. While mentioning the other routes, the risk characterization dealt only with the ingestion route. The inhalation and dermal routes have been shown to be important by several publications (ILSI, Exposure to Contaminants in Drinking Water, Ed Stephen S. Olin, 1998). A discussion on factors influencing each route of exposure should address topics such as route specific factors and chemical volatility.

5. Validation of exposure models should be addressed

Activity patterns / environment:

1. A discussion of the important behavioral and environmental issues affecting exposure should be included. Possible discussion topics include a discussion of water-use behavior, building characteristics, inter-occupant behavior, various water-use devices, and historical exposures.
2. The activities of other family members are known to impact the exposure of a given individual (e.g., when consecutive showers are taken, the second shower is expected to give a substantially larger dose than the first shower). Several technical papers have been written analyzing this impact. However, there are very few studies of family-type activity patterns.

3. There are issues with estimating long-term exposure when chronic endpoints are of concern. Current exposure models deal with exposure under a given set of conditions, but little work has been done to address a population's historical exposures.

4. Validation of exposure models should be addressed

3.3.3. Q3 - *Unidentified DBPs* (Section 3.3 DBP Report).

Q3. Should the toxicity of unidentified DBPs or of identified DBPs for which little or no data exist be incorporated into the risk assessment? If so, what are the most scientifically appropriate ways to estimate the potential health risks?

Summary: External peer review and discussion on the unidentified DBPs may be grouped under the following categories:

Content Comments:

1. Approaches to chemical characterization and classification of DBPs
2. Analytical and modeling techniques to include unidentified DBPs in hazard analysis
3. QSTR as a predictive tool for unidentified QSTR.
4. Summary of the ILSI workshop

Specific Comments:

1. Approaches to Classification of DBPs: The peer review group considered theClassification of DBPs in to Group A, B, and C categories as reasonable approach. However, subgrouping of known and identified halogenated DBP (Group A) into Cl^- and Br^- compounds was suggested as even better from a risk assessment and management point of view. In this regard, more effort in identifying unknown DBPs based on additional analytical studies was considered necessary. No other specific recommendations were made on this topic.
2. Unidentified DBPs: Most of the discussion was focused on the approaches to handling the unidentified halogenated DBPs (Group B). Development of an approach using existing toxicity parameters such as the lethal dose (LD50, LD10, etc.) for known DBPs (Group A) to unknown DBPs (Group B) was suggested by some peer review group members. Studies to develop toxicity parameters for Group B DBPs as a whole may be another option, although there are mechanistic weaknesses in doing so. Some review group members suggested that a review of Group C (non-halogenated DBP) may be necessary at the drinking water consumption level, for it would provide the basis for the type of disinfection and the types and extent of DBPs.

3. QSTR as a Predictive Tool: A number of peer review members were of the opinion that quantitative structure toxicity relationship (QSTR) is perhaps best suited in to predict toxicity of Group B DBPs. Since QSTR is an iterative process evolving through continuo input of new data as a part of the model validation process, targeted tasks for QSTR should be identified to gain from this process. It was also suggested that the QSTR could just be focused on the Cl^-, Br^- and mixed Cl^-/Br^- groupings of the DBPs. Use of probabilistic techniques in handling uncertainties associated with unknown DBPs was discussed. In this regard, establishing bounds for the distribution of toxicity values (Group A) for known compounds was suggested as perhaps as the first step.

4. Summary of ILSI Workshop: Review group suggested either moving the ILSI workshop summary to the Appendix or get the information integrated to the document. The format as is reads repetitive and covers topics not related to the section.

3.3.4. Q2 - *Risk Assessment of Developmental and Reproductive Effects* (Section 3.4 DBP Report).

Q2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Summary: The general approach was considered appropriate and valid, but significant additional explanation of the approach and rationale for the approach is needed.

General comments:

- Additional information needs to be provided, either in this section or earlier in the document, qualitatively walking through the "illustrative example." This includes discussing the reason for the choice of endpoints, basics of how the modeling was done, and the rationale for key choices made in the calculations. For example, the text should address the potential for other non-cancer effects resulting from exposure to DBPs (including issues of whether the epidemiology studies show that other effects would not be expected, or whether these endpoints have just not been adequately evaluated) and discuss why the document focuses on reproductive/developmental effects. The document should also address the rationale for using no-threshold risk models for reproductive/developmental endpoints (which have traditionally been considered noncancer effects for which a threshold of toxicity exists). This discussion should include both the biological basis for the possible absence of a threshold, and the practical reasons for assuming a threshold.

- The panel did not see a need to link endpoints such as low birth weight to such serous effects as infant mortality.

- Data modeled do not need to be quantalized. A hybrid continuous benchmark dose model (which models continuous data, but expresses the BMD in terms of increased risk) could be used.
- If multiple chemicals act via the same mode of action, the exposure concentration for each individual chemical could be below the threshold for that chemical, but one might expect that an effect could result from exposure to the resulting mixture. The text at the top of page 40 should address this possibility.

Specific Comments:

P. 40, line 2: This should be the exposure concentrations were *below* the threshold estimate (or threshold above the exposure concentration).

3.3.5. Q2 - *Risk Assessment of Carcinogenic Effects* (Section 3.5 DBP Report).

Q2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Summary: External peer review and discussion on the carcinogenic risk assessment for DBPs may be grouped under the following categories:

Content Comments:

1. Concordance (or the lack of it)
2. Threshold Issue
3. Mechanistic Information
4. Summary of ILSI Workshop

Specific Comments:

1. Concordance (or the lack of it): The information provided on this topic under this section was considered insufficient by the review team. Differences in concordance of tumor sites could as well be due to differences in the experimental procedures, type of animal used, etc. Lack of concordance in tumor sites may not have anything to do with the more substantial issue on the concordance between experimental and epidemiological evidence. This issue requires clarification.

2. Threshold Issue: Threshold issue stems both from (a) possibility of the presence of threshold and (b) extrapolation (if it is present) to all DBPs. It is unclear if there is a threshold for carcinogenic effects of DBPs (carcinogenic species). A clear determination is first needed before this concept is applied to other DBPs. Some peer review members suggested whether QSTR may have an application on the threshold issue, although such an application is possible only for the known DBPs (Group A) with data on carcinogenicity. No changes were recommended to this section under this chapter.

3. Mechanistic Information: Mechanistic information is a fundamental requirement to develop a robust risk assessment approach. However, it is unclear how this requirement could be met with chemical mixtures. The sentence (page 43) needs modification to better reflect this fundamental shortcoming with mixtures. Note on the epidemiological and statistical modeling should be deleted from this sentence and include separately.

4. Summary of ILSI Workshop: Review group suggested either moving the ILSI workshop summary to the Appendix or get the information integrated to the document. The format as is reads repetitive and covers topics not related to the

section.

3.3.6. Q2 - *Uncertainty and Variability* (Section 3.6 DBP Report).

Q2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Summary: It is suggested that EPA incorporate more quantative analysis of uncertainty and variability into the risk assessment for DBP.

General Comments: This section deals with uncertainty analysis associated with risk due to exposure to contaminated water. In general risk is calculated using two random variables: potency and exposure. The variables potency and exposure can further broken down to more variables. Usually, these variables are referred as risk factors, and also input factors. Thus, if we can identify all the factors that are used to build up a model for risk, these risk factors will be random variables due to many reasons: extrapolating from high dose in the laboratory studies to the lower levels of exposure experienced by humans, laboratory animal data translated to humans, route of exposure, make up of the population.

Many risk assessors feel that these risk factors are subject to subject to uncertainty and variability. But, there has been some confusion in the past how to distinguish between variability and uncertainty. It was felt, however, important to distinguish between variability and uncertainty. This report does not clearly define the rules to distinguish between these two types of variabilities.

Having identified the risk factors, variabilities and uncertainties in them, one can use either our analytical results to approximate the distributions of risk or simulate using Monte Carlo techniques. The purely Monte Carlo can be very time consuming and may not result to a good approximation if the number of risk factors is very large. The analytical results lead to estimating average risk and confidence intervals for risks for a general population as well as a subset of the general population. The results of the uncertainty analysis used do not provide estimates of the confidence intervals.

To address the quantitative uncertainty analysis in a probabilistic risk model, I briefly outline the following approach.

“Recently the focus in risk assessments has moved from obtaining point estimates of risk to characterizing the entire distribution of risk (Bartlett *et al*, 1996). For such practices, it is important to distinguish between uncertainty (lack of knowledge about the value of a particular parameter or variable) and variability (variation among individuals in the population of interest). Rai, Krewski and Bartlett (1996) and Rai and Krewski (1998) have proposed a general framework for characterizing uncertainty and variability in general

as well as multiplicative risk models. They have also proposed a general framework for a rigorous integrated approach to uncertainty analysis. The methods allow for complex interrelationships between subsets of risk factors in multivariate models. Partitioning of total uncertainty in risk due to uncertainty, due to variability and due to individual risk factors, proposed in our papers, is very useful for predicting risk more precisely in a subset of a population. Krewski, Rai, Zilienski and Hopke (1999) and Rai, Bartlett and Krewski (2000) have considered practical examples: cancer deaths due to radon exposure in U.S. homes; and for guidelines in drinking water, respectively."

The suggested uncertainty analysis can be easily applied to the risk models (equations 1, 3, and 4) given in section 4 for a known form of the function f.

Model uncertainty is another issue that needs to be discussed. For example, dose-response relationship may depend on the type of function one may use. In this regard, the techniques of quantitative uncertainty analysis need to be extended.

When lognormal distributions are proposed for risk factors, the geometric standard deviations (GSD) are assumed to be 10 for many risk factors. I am assuming that the geometric means are assumed to be 1. Introducing a such type of uncertainty/variability is very subjective.

Future Work: Following Krewski et al. (1999), one can extend models 1, 3 and 4 of section 2.4 to define life time relative risk and population attributable risk due to exposure to contaminated water. One can also perform uncertainty analysis for life time relative risk and population attributable risk.

References:

Bartlett, S., Richardson, G.M., Krewski, D., Rai, S.N. and Fyfe, M. (1996). Characterizing uncertainty and variability in risk assessment - conclusions drawn from a workshop. *Human and Ecological Risk Assessment*, 1, 221-231.

Krewski, D., Rai, S.N., Zielinski, J. and Hopke, P.K (1999). Characterization of uncertainty and variability in residential radon cancer risks. *The Annals of the New York Academy of Sciences.* 895, 245-272.

Rai, S.N., Krewski, D. and Bartlett, S. (1996). A general framework for the analysis of uncertainty and variability in risk assessments. *Human and Ecological Risk Assessment*, 2, 972-989.

Rai, S.N. and Krewski, D.(1998). Uncertainty and variability analysis in multiplicative risk models *Risk Analysis*, 18, 37 - 45.

Rai, S.N., Bartlett S. and Krewski, D. (2000). Probabilistic risk assessment and its applications to drinking water guidelines. *Human and Ecological Risk Assessment*. Submitted.

3.3.7. Q2 - *Mixtures Risk Characterization Methods* (Section 3.7 DBP Report).

Q2. In section 3 of Report 1, has EPA identified the most important issues to work on and resolve under these seven research areas (sections 3.1-3.7, with background information in Report 2)? Specifically address issues related to concentration data, exposure estimates, dose-response information for both cancer and noncancer effects, treatment of unidentified DBPs, choices among mixtures risk characterization methods, and handling of uncertainty and variability.

Summary: External peer review and discussion on the mixtures risk characterization methods for DBPs may be grouped under the following categories:

Content Comments:

1. Difficulties with the Approach
2. Approach Based on Dose Addition
3. Sufficiently Similar Mixtures" Approach
4. "Defined Mixtures" Approach
5. Summary of ILSI Workshop

Specific Comments:

21. Difficulties with the Approach: The peer review group acknowledged the inherent difficulties with the mixtures risk characterization methods. These difficulties particularly apply to DBPs because of the tremendous structural diversity among Group A-C DBPs. No specific suggestion for modification of this section (page 50-51) was made.

22. Approach Based on Dose Addition: Work group members pointed out that the dose addition approach is based on the dioxin toxicity assessment approach and may not apply in this case due to multiplicity of biological mechanism of action. No specific recommendations were made for modification. Need a line or two on the shortcomings of this approach for DBP.

23. "Sufficiently Similar Mixtures" Approach: Based on a representative group of DBPs consistently generated (or detected) in disinfection process. The cluster of similar DBPs may then be used as the representative cluster in risk assessment. No specific suggestions were made by the group.

24. "Defined Mixtures" Approach: This approach uses the groups of DBPs detected in the drinking water. No recommendations were made by the group.

25. Summary of ILSI Workshop: The summary of the workshop under this section was considered relevant and generally focused on the mixtures risk assessment methods. This section may stay as is in the report.

A general observation was made by a few workgroup members that interactive effects (synergistic, antagonistic, promotional) of mixtures of DBP requires some discussion. There are several publications citing binary combinational effects leading to

synergistic effects among some of the more well known DBPs.

3.4. Q5 - CUMULATIVE RISK ASSESSMENT CONCEPTUAL MODEL APPROACH (SECTION 4 DBP REPORT)

Q5. Given the information in section 3 of Report 1, is the conceptual model for the cumulative risk assessment, shown in section 4 of Report 1, a scientifically sound approach to the DBP mixtures problem? Are there better alternatives to this approach? Are important considerations missing, inaccurately portrayed, or not fully developed?

Summary: Overall, the approach was considered a valid one. The panel recommended that there be significant additional explanation of a number of areas, either in this chapter or earlier in the document. This includes explanation of the different approaches considered, more thoroughly walking through the rationale for the RPF and how mode of action needs to be taken into account in applying it, and more complete use of examples.

Organizational Comments: Much of the material in 4.1 relates to issues that should be discussed in more detail earlier in the document (e.g., the issue of concordance between experimental animal and human data). Those issues may not need to be raised again in this section.

Content Comments:

1. Each of the mixtures risk characterization methods addressed should be explained, either here or earlier in the document. A text box may be an appropriate way to do this.

2. The definition of cumulative risk should be presented in the introduction, rather than in Section 4.2.

3. Section 4.2 should note that the issue of time-variation in exposure and the resulting impact on risk is not addressed by the approach presented.

4. Clarify that this section is aimed specifically at presenting an approach for evaluating RPFs (and then cumulative risk) from exposure to DBPs.

5. Section 4.2.1: Significant additional explanation of the approach would be useful. For example, more explanation of the assumptions behind RPF and how the RPF relates to evaluation of mode of action is needed. More explanation of the use of the index chemical would be useful. The example in Table 8 was very useful, but more text is needed to explain that table (e.g., explanation of the last column and of how the final risk was calculated). The text also needs to explain that similar approaches would be used for developmental/reproductive risk, building on the illustrative example in the pre-meeting report.

6. It was suggested that the issue of extrapolation from experimental animals to humans (e.g., scaling factors, dosimetry) be noted.
7. The text about Table 7 should explain how the data set characteristics are used in the RPF approach (i.e., in the choice of index chemical).

8. Section 4.2.2 should address how the source water and treatment approach influences the composition of the unidentified DBPs (as addressed elsewhere in these comments).

9. Section 4.2.3 should discuss in greater detail the possible options for combining the results from evaluation of subclasses. An example or examples would enhance clarity. In particular, issues and options related to evaluating risk from multiple endpoints, and from the same endpoint via multiple modes of action should be presented.

10. It was noted that the time issue and exposure patterns can be taken into account in both the dose-response assessment (in how the exposure pattern influences the tissue dose), and directly in the exposure assessment. A sensitivity analysis could help focus research on these issues.

11. The suggestion was made that casting the mixtures question into a risk management context may allow comparison of treatment alternatives by analyzing the relative occurrence concentrations. Compounds that occur at equivalent concentrations under different treatment conditions can effectively be "zeroed" out of the analysis (since they would not affect the difference in risk resulting from different treatment alternatives). Efforts can then focus on constituents that vary significantly in concentration from technology to technology.

12. It may be useful to address (at least in a broad sense, or to note as area for future research) how one would incorporate the risk from carcinogens with nonlinear dose-response curves (or thresholds), and the risk for noncancer endpoints other than reproductive/developmental ones.

Specific Comments:

1. The suggestion was made to not call it a "cumulative relative potency factor approach." It is a RPF approach applied in a cumulative manner.

2. Consider whether the term multinomial or multivariate analysis is more appropriate.

3. P. 57: Rather than assuming Monte Carlo simulations will be used, the document should take into account the possibility that other probabilistic approaches (addressed in the comments in the Section 3.6, uncertainty and variability) may be used.

4. P. 57, last paragraph: The proposed tasks and approach are good.

5. Figure 4 needs to be explained more.

6. In equations 1, 2, 4, and 5, C_m should be notated as C_{mk}, since it also depends on the index chemical k.

7. P. 60, 7 lines from bottom: awkward sentence

8. The title in Figure 5 should be modified. The figure relates to mode of action, but does not shown any specific mode of action.

9. P. 62, last line: delete both uses of "single" to make sentence clearer.

10. Table 8 should note that the RPF is unitless.

11. P. 71, sentence after equation 4: the notation of "s" and "j" is confusing in this sentence and should be removed.

3.5. Q 6 - *FUTURE RESEARCH NEEDS* (SECTION 5 DPB REPORT)

Q 6. Are the areas of research specified in section 5 of Report 1 as future research directions clearly stated, appropriate as next steps and complete? Should anything be added or deleted?

Summary: A number of suggestions were made regarding additional useful areas of research, as listed below. Several recommendations were also made regarding clarifying or improving the language on research needs contained in sections of the report.

Organizational Comments: One commenter suggested adding another subsection, 5.5.

Content Comments: Comments addressed both the existing text on future research directions and suggested additional items that were raised during discussion at the workshop. These edits and additions are noted below, organized by the sections subsections. Please note that some of the specific changes also relate to content changes

3.5.1. *Methods Research* (Section 5.1 DBP Report).

Specific Comments:

1. In the first bullet, modify to state (new text in italics) "Investigate use of expert judgment *and expert systems* approaches for integrating toxicologic and epidemiologic data in the same risk assessment *and for filling data gaps.*

2. Explore use of biomarkers of exposure and effects.

3. Include discussion concerning research on DBPs in transgenic animals, exploration of genetic polymorphisms as markers of susceptibility in experimental animals, and incorporation of biomarkers of susceptibility into molecular epidemiologic studies in humans to explore gene-environment interactions.

4. EPA should check the use of "multinomial." Is it being used in an appropriate manner? Should this be multivariate?

5. Methods should be developed to investigate linking exposure modeling with PBPK models.

6. Efforts should be made to identify/characterize DBPs at the point of entry to the water system and at the tap (and throughout the distribution system, to better understand the processes that influence formation/transformation).

7. Explore impacts of point of use devices, such as water filters and water heaters.

8. Better characterize the occurrence, exposure, and toxicity of unidentified DBPs at the treatment plant and at the tap.

3.5.2. *Research on Cumulative Relative Potency Factor (CRPF)* (Section 5.2 DBP Report).

Specific Comments:

1. Change title to Research on Application of a Relative Potency Factor Approach for Cumulative Risk Assessment

2. Add ..."including type of halogen" to the end of bullet #1.

3. Conduct *in vitro* studies validating the mixtures risk assessment approach and studies to validate and extend QSTR analyses.

4. Explore addressing other toxicity endpoints in research on cumulative risk approach.

5. Explore way to validate the predictions provided by the relative potency factor approach.

6. Move the last bullet in 5.2 to section 5.1 (methods research)

7. First bullet: "Define subclasses of DBPs based on exposure route, chemical structure (*e.g., type of halogen substitution*)..."

3.5.3. *Epidemiology Research* (Section 5.3 DBP Report).

Specific Comments:

1. Reword the first bullet in a more neutral manner: For example, "Explore sources of bias... (recognizing the potential for bias in both directions).

2. Break the first bullet into three bullets: continue...to decrease...determine the feasibility of...

3. Clarify the third bullet what is meant by susceptibility of response?

4. Explore the incorporation of data on genetic polymorphisms into epidemiology studies and in identification of sensitive subpopulations.

5. Design epidemiology studies so that a wide range of exposures can be evaluated (preferably in separate exposure groups) and dose-response analyses can be conducted. Explore utility of evaluating other noncancer endpoints in epidemiology

studies. For example, retinol binding protein (RBP) in urine or liver enzymes in serum (e.g., SGOT, SGPT) could be used to evaluate effects on the kidney and liver, respectively.

6. The potential application of biomarkers for risk assessment might be explored, although the issue arises of definition of an adverse level of effect. (Latter issue discussed in context of threshold, not in context of research area).

3.5.4. *Development of Toxicologic Data* (Section 5.4 DBP Report).

1. Develop methods for whole mixtures toxicity testing

2. In the 3rd bullet, chage “and” to “to” (...to enrich the database...)

3. The fourth bullet needs to be reworded/clarified. It is too vague as written

4. In the first bullet on page 1-78, consider changing the word “statistical” to “probabalistic.”

5. The second bullet on page 1-78 should be broken into 2 bullets. Also, the list of toxic endpoints, because it probabaly is not comprehensive, ought to be changed to list a few, then add etc. or start list with e.g., reproductive...

6. Also on 2nd bullet on page 1-78, emphasis might be placed on developing methods to intrepret DBP data from existing test systems, in addition to investigating new short-term toxicicity tests.

3.5.5. Suggestion for adding NEW section 5.5 in the DBP Report - Improved integration, responsiveness and accountability for rulemaking efforts).

1. Develop interdisciplinary advisory group including an epidemiologist, a toxicologist, chemist, engineer, statistician and rule-making representative.

2. Meet w/Office of Water to determine opportunities to provide relevant and timely information to NCEA.

3. Periodic progress reviews w/ Office of Water

3.6. Q7 - NEW DATA (OVERALL DBP REPORT)

Q7. Do the reviewers know of any newer data or methods that EPA has not considered, but should be aware of in order to improve this risk assessment? Specifically address advancements in dose-response modeling, analytical chemistry, exposure characterization, mixtures risk assessment methods, probabilistic techniques, quantitative structure activity relationships, and methods for estimating risk for the unidentified DBPs.

Recommendations on new data and methods, discussed by the reviewers during the workshop, were presented throughout this document (see sections 3.1 to 3.5).